min. in a water bath maintained at 60–65°. The reaction mixture was cooled to room temperature and diluted with anhydrous ether (5 ml.); an excess of pyrrolidine (0.8 ml.) was added. After stirring at room temperature for 30 min. excess solvent was removed on the steam bath and the product isolated by preparative vapor phase chromatography.[15] The following retention times were observed: N-acetylpyrrolidine, 8 min.; N-*n*-propionylpyrrolidine, 9 min.; and N-*n*-valerylpyrrolidine, 23 min. using an oven temperature of 150° and helium pressure of 10 p.s.i. The isotopic purity of the products was at least 98% d_2 species.[17]

Mass Spectrometry in Structural and Stereochemical Problems. LXXV.[1] Occurrence of Alkyl Rearrangements in the Fragmentation of Some Formaldehyde Acetals[2]

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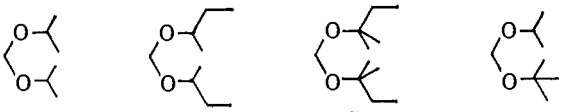
The mass spectra of a series of formaldehyde acetals of primary, secondary, and tertiary alcohols, and phenol, have been recorded. Deuterium labeling and high resolution mass spectrometry demonstrated the operation of three distinct alkyl rearrangement mechanisms, each involving elimination of formaldehyde. Plausible pathways for the formation of all other principal ions are presented.

Introduction

Although the mass spectra of a wide range of acyclic acetals are on record,[4,5] few attempts,[6,7] have been made to rationalize the fragmentations mechanistically. No studies on deuterium-labeled acetals have been reported at all, whereas ketals have received extensive scrutiny.[8] The first new spectrum obtained in this work, that (Figure 4) of di-*t*-butoxymethane (I), excited immediate interest owing to the presence of an appreciable (29% relative intensity) peak corresponding to the loss of 45 mass units. It was subsequently shown by a combination of deuterium labeling and high-resolution techniques that this fragment ion arose

I a

in a rearrangement involving alkyl migration,[9] resulting in expulsion of a formaldehyde molecule from the M − 15 α-cleavage product *a*. In view of the paucity of rigorously demonstrated alkyl rearrangements—in contrast to the virtually ubiquitous hydrogen rearrangements—induced by electron impact, it was deemed important to examine the scope and mechanism of the alkyl-transfer reaction noted in the acetal I. Indeed, completely analogous rearrangements were uncovered in other formaldehyde acetals of secondary and tertiary alcohols (compounds II–V). It is interesting



II III IV V

to note that neither the dithioacetal VI (Figure 16) nor the ether VII (Figure 17) showed any analogous M − (15 + 46) or M − (15 + 28) peaks, respectively. Two other groups of formaldehyde acetals could be

VI VII

classified, on the basis of direct loss of formaldehyde from the molecular ion. The first of these included the primary alcohol derivatives VIII, IX, and X, and the second, the half-acetals of phenol XI, XII, and XIII. In addition, other modes of fragmentation proposed[7] for acetals in general were confirmed by the deuterium-labeling results.

(1) Paper LXXIV: A. M. Duffield and C. Djerassi, *J. Am. Chem. Soc.*, 87, 4554 (1965).

(2) Financial assistance from the National Institutes of Health (Grant No. GM-06840 and AM-04257 to Stanford University) of the U. S. Public Health Service and Lucidol Divisions, Wallace and Tiernan, Inc., Buffalo, N. Y. (to Aarhus University), are gratefully acknowledged.

(3) Postdoctoral Research Fellow, 1964–1965.

(4) (a) W. H. McFadden J. Wasserman, J. Corse, R. E. Lundin, and R. Teranishi, *Anal. Chem.*, **36** 1031 (1964); (b) R. A. Friedel and A. G. Sharkey, *ibid.*, **28**, 940 (1956).

(5) "Catalog of Mass Spectral Data," American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., Spectra No. 1089–1101, 1111–1122.

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

(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 3.

(8) (a) Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 3727 (1964); (b) G. von Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *Steroids*, **2**, 475 (1963); (c) H. Audier, J. Bottin, A. Diara, M. Fétizon, P. Foy, M. Golfier, and W. Vetter, *Bull. soc. chim. France*, 2292 (1964); (d) H. Audier, A. Diara, M. de Durazo, M. Fétizon, P. Foy, and W. Vetter, *ibid.*, 2827 (1963); (e) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day Inc., San Francisco, Calif., 1964, Chapter 18.

(9) For a recent and fully documented example of electron impact induced alkyl (methyl) migration, see F. Komitsky, Jr., J. E. Gurst, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 1398 (1965).

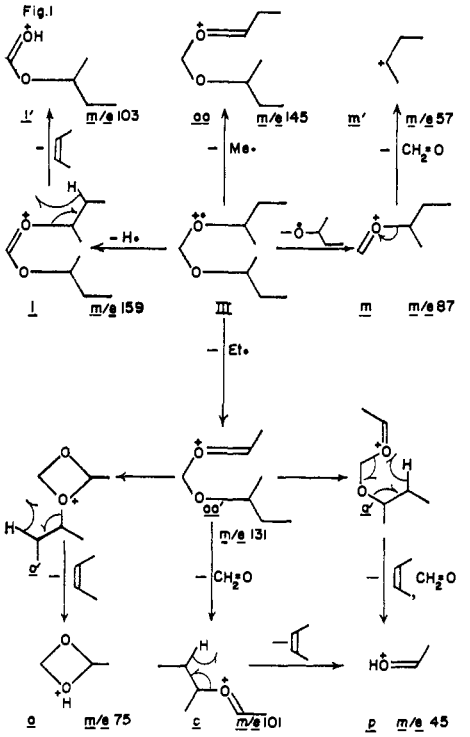


Figure 1. Fragmentation of di-*sec*-butoxymethane (III).

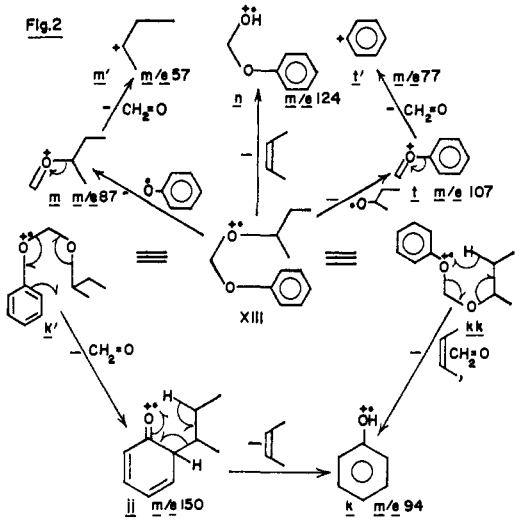
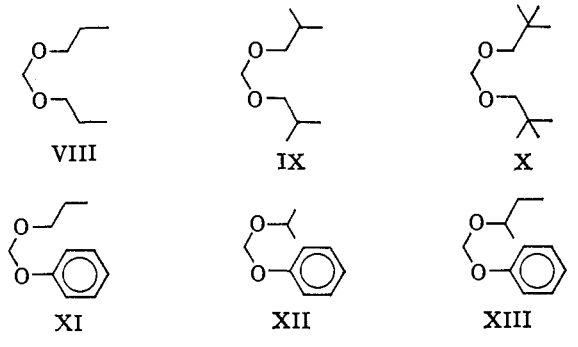


Figure 2. Fragmentation of *sec*-butoxyphenoxymethane (XIII).

The fragmentations of III and XIII are shown in Figures 1 and 2, some deuterated acetals in Figure 3, and mass spectra in Figures 4–29.



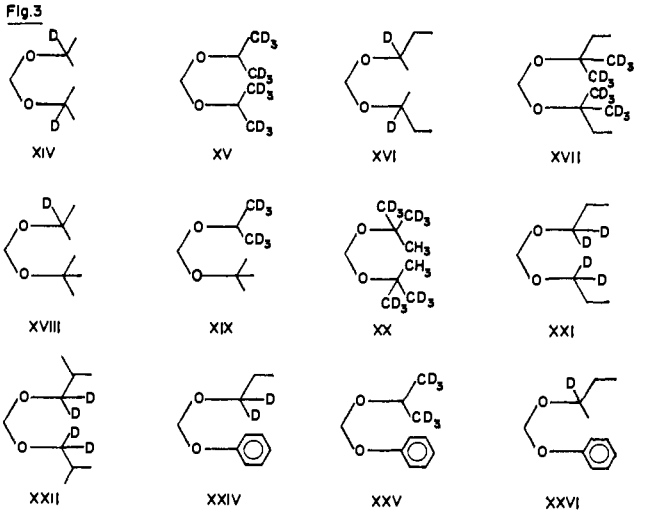


Figure 3. Deuterated acetals.

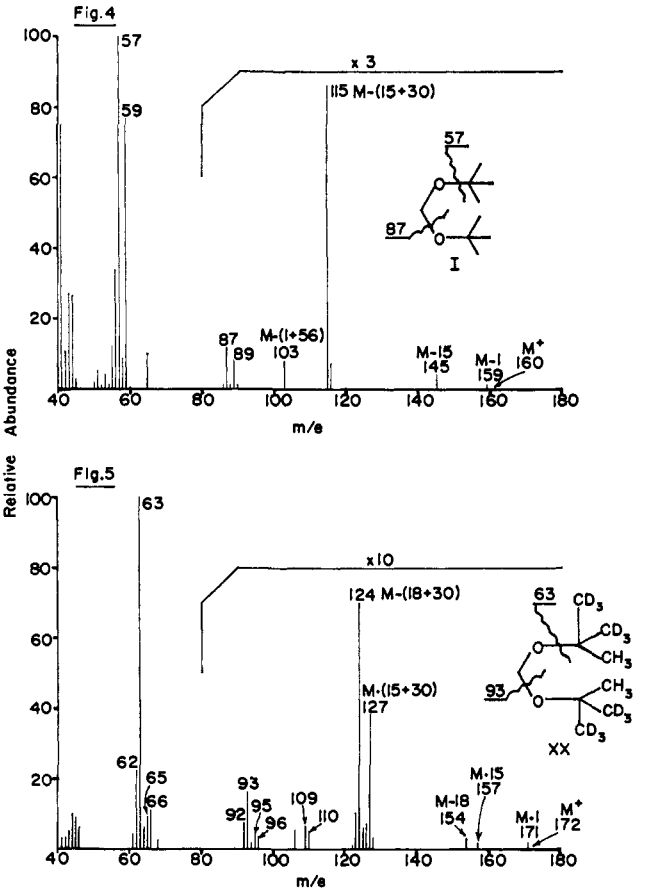
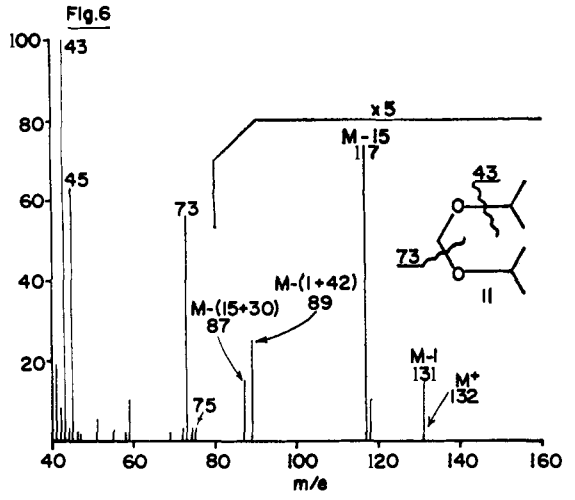


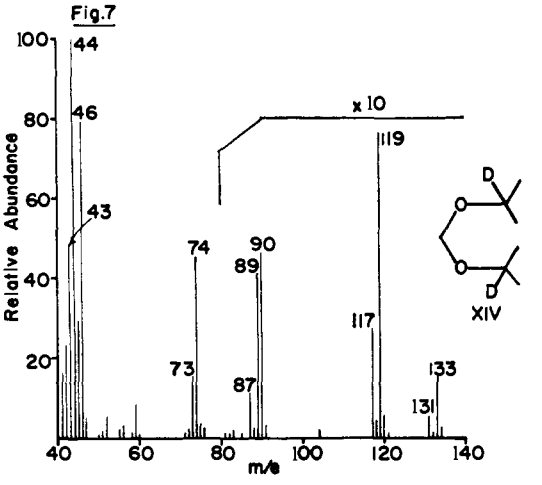
Figure 4. Mass spectrum of di-*t*-butoxymethane (I).
Figure 5. Mass spectrum of d_{12}-di-*t*-butoxymethane (XX).

Synthesis of Acetals

Di-*t*-butoxymethane was synthesized according to the method of Jansson.[10] In all other cases, the compounds studied were prepared by equilibration of a slight excess of the requisite alcohol with paraformaldehyde in ethanol-free chloroform with *p*-toluenesulfonic acid as catalyst. Yields of the symmetrical acetals were good, except with 1,1-dimethylpropanol, presumably owing to competing dehydration. Mixed

(10) I. Jansson, *Suomen Kemistilehti*, 37B, 19 (1964).





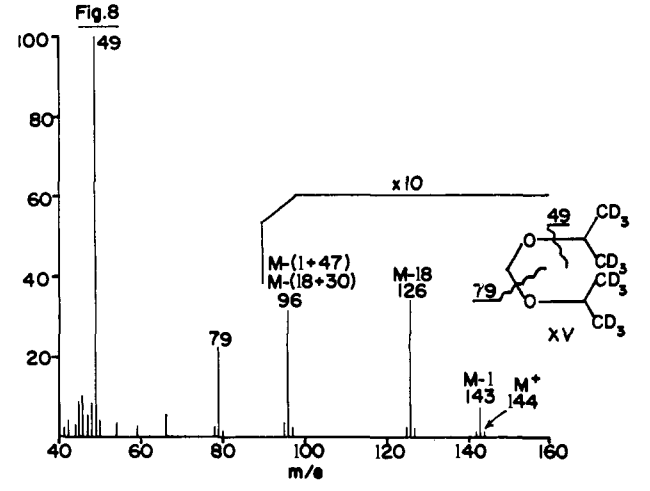
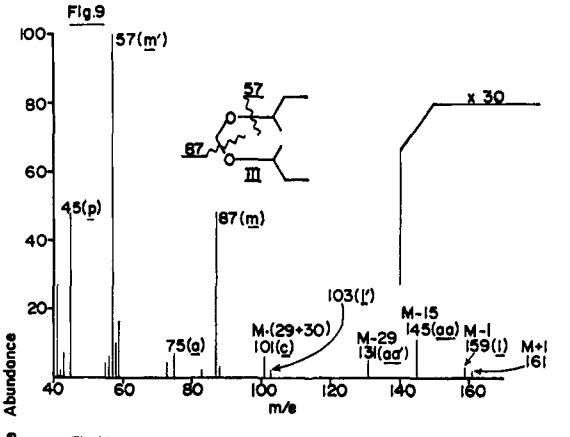


Figure 6. Mass spectrum of diisopropoxymethane (II).
Figure 7. Mass spectrum of d_2-diisopropoxymethane (XIV).
Figure 8. Mass spectrum of d_6-diisopropoxymethane (XV).

acetals were made similarly, but in moderate to poor yields, by equilibration of equimolar proportions of each alcohol and paraformaldehyde. Products were separated and purified by vapor phase chromatography, and their structure and deuterium content checked by n.m.r. spectrometry. Deuterium-labeled[11] alcohols were conveniently prepared as follows: 2-d_1-propan-

(11) For a summary of current methods for the introduction of deuterium into organic molecules, see ref. 8e, Vol. 1, Chapter 2.



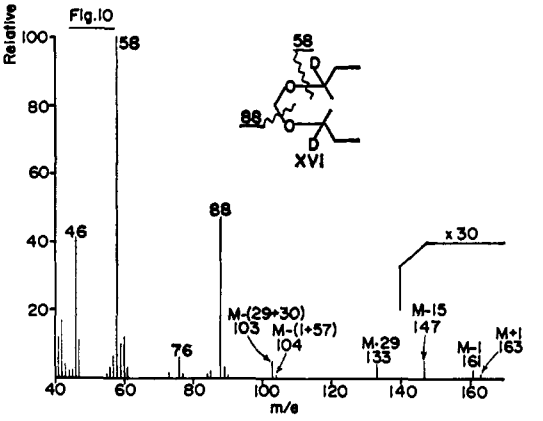
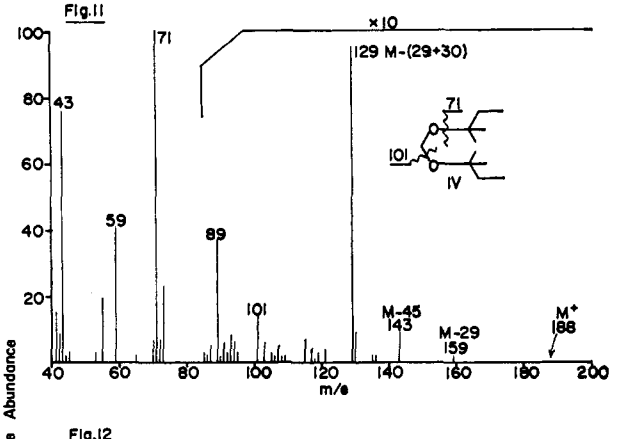


Figure 9. Mass spectrum of di-*sec*-butoxymethane (III).
Figure 10. Mass spectrum of d_2-di-*sec*-butoxymethane (XVI).



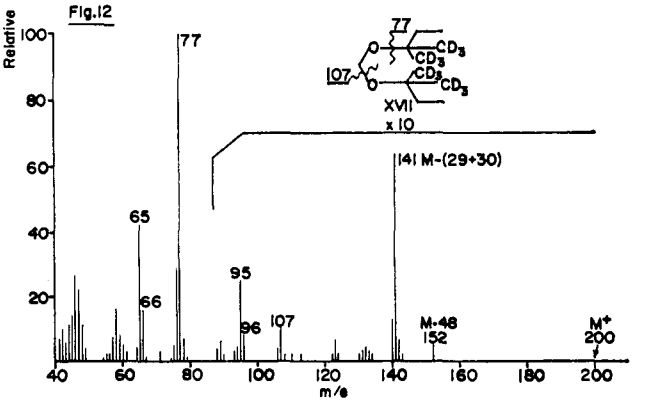
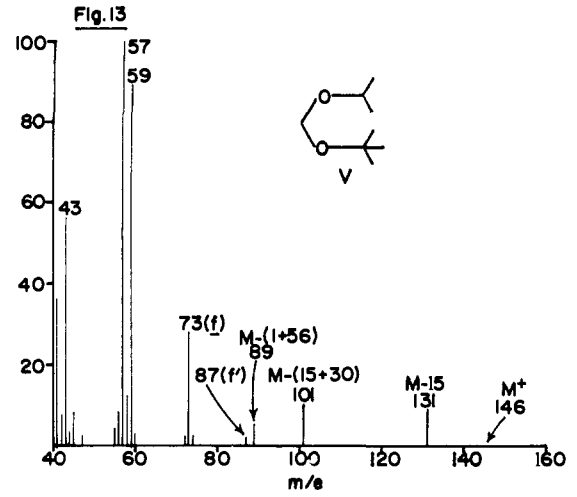
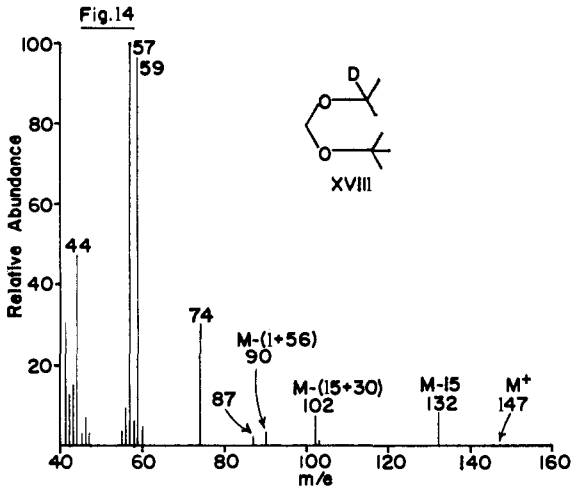


Figure 11. Mass spectrum of di-*t*-amyloxymethane (IV).
Figure 12. Mass spectrum of d_{12}-di-*t*-amyloxymethane (XVII).





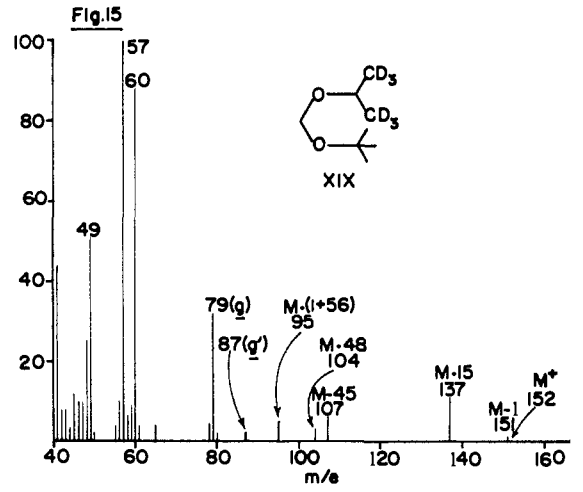


Figure 13. Mass spectrum of isopropoxy-*t*-butoxymethane (V).
Figure 14. Mass spectrum of d_1-isopropoxy-*t*-butoxymethane (XVIII).
Figure 15. Mass spectrum of d_6-isopropoxy-*t*-butoxymethane (XIX).

2-ol, 2-d_1-butan-2-ol, 1,1-d_2-propan-1-ol, and 1,1-d_2-2-methylpropan-1-ol by lithium aluminum deuteride reduction of the corresponding ketone or carboxylic acid. 1,1,1,3,3,3-d_6-Propan-2-ol was obtained from lithium aluminum hydride reduction of d_6-acetone, and 1,1,-1,3,3,3-d_6-2-methylpropan-2-ol and 1,1,1,3,3,3-d_6-2-ethylpropan-2-ol were synthesized from the same

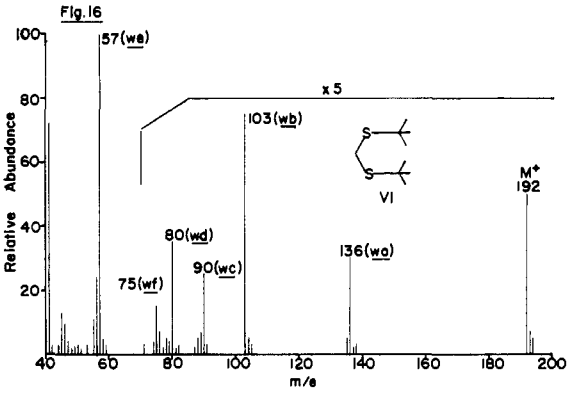


Figure 16. Mass spectrum of bis(*t*-butylmercapto)methane (VI).

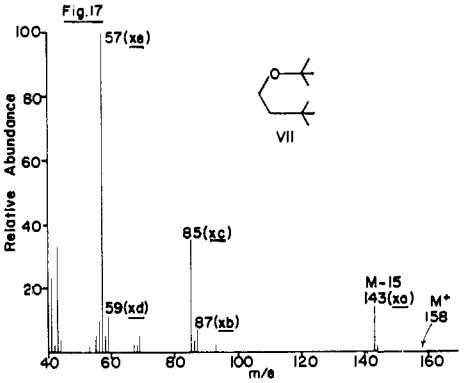


Figure 17. Mass spectrum of *t*-butyl-3,3-dimethylbutyl ether (VII).

starting material by use of the appropriate Grignard reagent. All deuterated acetals contained at least 90% of the designated number of deuterium atoms, except compound XIV, which by n.m.r. was 71% deuterated, and by mass spectrometry contained 71% d_2, 4% d_1, and 25% d_0 species. Since the isotopic content did not affect the mechanistic conclusions, no isotopically purer sample was prepared. Compound VI was prepared from methylene chloride and *t*-butylmercaptan and compound VII from the reaction of *t*-butyl perbenzoate with the Grignard reagent of 1-chloro-3,3-dimethylbutane.

The M − (R + 30) Rearrangement

This process is exemplified further by diisopropoxymethane (II), whose mass spectrum (Figure 6) exhibits a peak at *m/e* 87 [M − (15 + 30)], that moves completely to *m/e* 89 (M − 45) and *m/e* 96 (M − 48) in the deuterated acetals XIV (Figure 7) and XV (Figure 8), respectively. In the case of di-*sec*-butoxymethane (III), the rearrangement peak appears (Figure 9) only at *m/e* 101 [M − (29 + 30)]; no M − 45 peak [M − (15 + 30)] is apparent. This observation can readily be rationalized, since the M − 15 species (Figure 1, *aa*) has a relative abundance of only 0.3%, whereas the M − 29 ion (Figure 1, *aa'*) is, as expected, more intense (5%). Deuteration as in XVI results (Figure 10) in the quantitative shift of the M − 59 peak to *m/e* 103. A precisely analogous situation obtains with di-*t*-amyloxymethane (IV), where M − 59 (*m/e* 129) again is observed (Figure 11). The labeled compound XVII (Figure 12) has the rearrangement

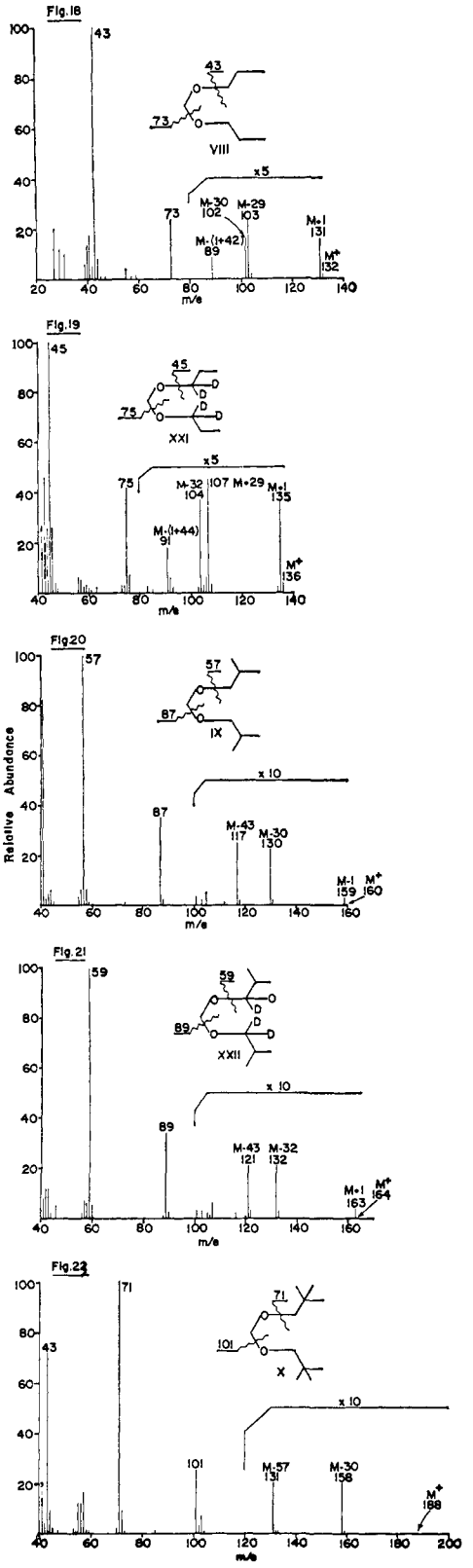


Figure 18. Mass spectrum of di-*n*-propoxymethane (VIII).
Figure 19. Mass spectrum of d_4-di-*n*-propoxymethane (XXI).
Figure 20. Mass spectrum of bis(2-methylpropoxy)methane (IX).
Figure 21. Mass spectrum of d_4-bis(2-methylpropoxy)methane (XXII).
Figure 22. Mass spectrum of bis(2,2-dimethylpropoxy)methane (X).

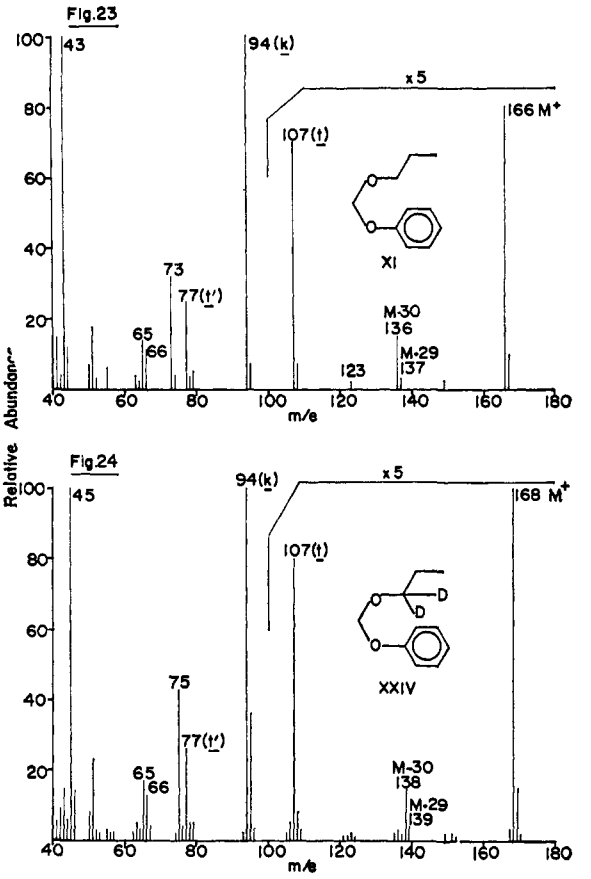
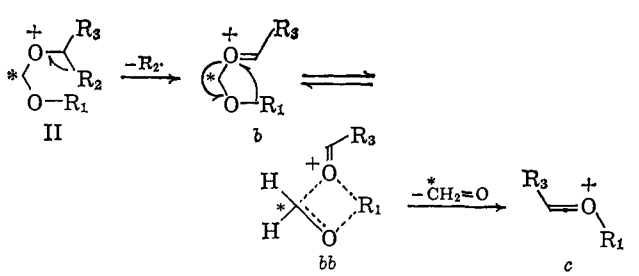


Figure 23. Mass spectrum of *n*-propoxyphenoxymethane (XI).
Figure 24. Mass spectrum of d_2-*n*-propoxyphenoxymethane (XXIV).

peak at *m/e* 141 (M − 59). In the mixed isopropyl–*t*-butyl acetal V (Figure 13), *m/e* 101 corresponds to M − (15 + 30), which moves to *m/e* 102 (M − 45) in the monodeuterated analog XVIII (Figure 14). The recognition of a metastable ion at *m/e* 79.2 ($102^2/132 = 78.9$) provides additional support for this rearrangement path. The d_6 derivative XIX (Figure 15) has peaks at both *m/e* 107 (M − 45) and *m/e* 104 (M − 48) in the expected intensity ratio of 3:2. The partially labeled di-*t*-butoxymethane XX also shows (Figure 5) both M − 45 (*m/e* 127) and M − 48 (*m/e* 124) peaks, in the predictable ratio of 1:2. High-resolution mass measurements[12] established the composition of the rearrangement ion from acetal III as exclusively $C_6H_{13}O^+$.

This evidence unequivocally demonstrates that the central carbon atom of the acetal, with both of its attached hydrogen atoms, together with one adjacent oxygen atom, is eliminated from the M − R_2 α-cleavage product (b). The mechanism of this rearrangement is



(12) Performed by Dr. L. Dolejš, on an A.E.I. MS-9 double-focusing instrument, with apparent resolution of 1 part in 15,000.

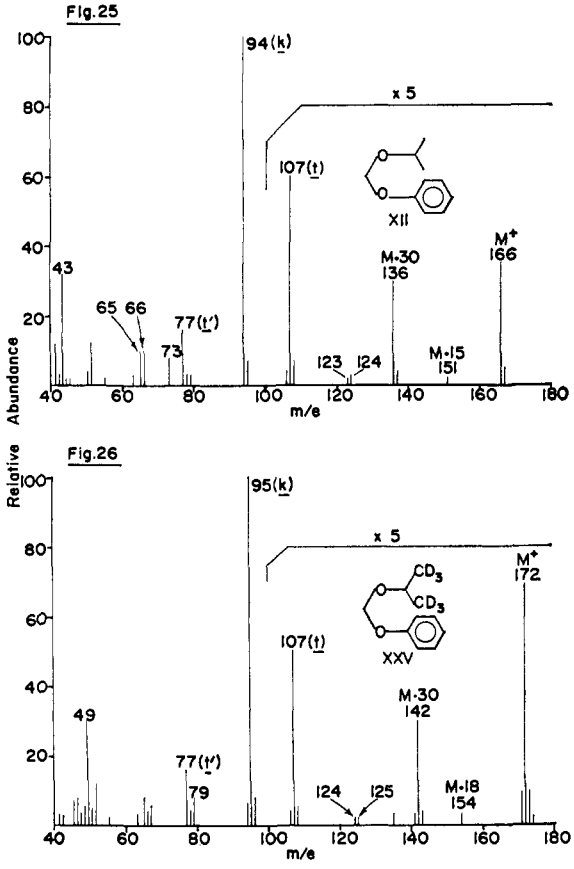


Figure 25. Mass spectrum of isopropoxyphenoxymethane (XII).
Figure 26. Mass spectrum of d_6-isopropoxyphenoxymethane (XXV).

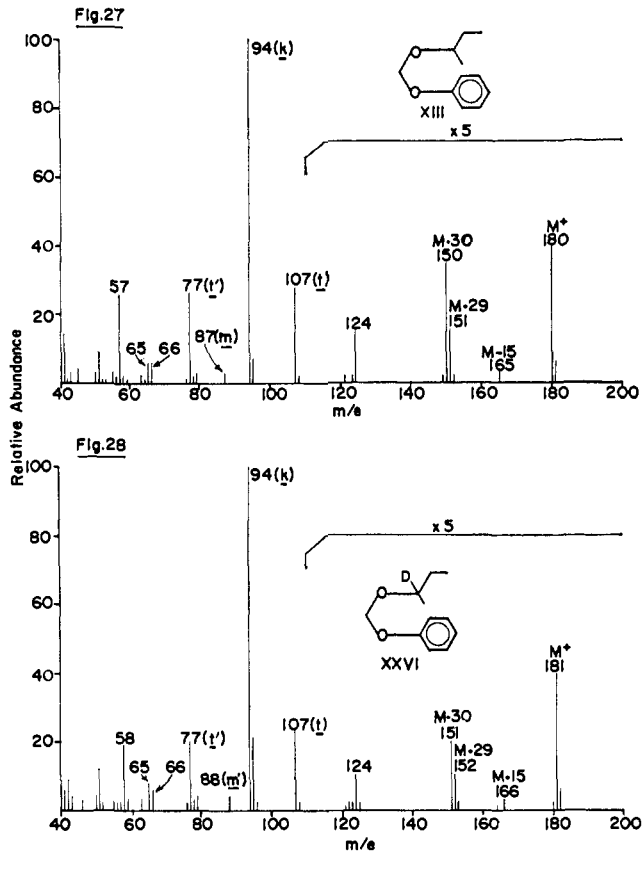


Figure 27. Mass spectrum of *sec*-butoxyphenoxymethane (XIII).
Figure 28. Mass spectrum of d_1-*sec*-butoxyphenoxymethane (XXVI).

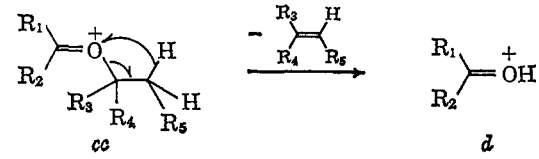
envisaged as proceeding through a four-center cyclic transition state *bb*, and furnishing the oxonium ion *c*.

Table I shows that in accordance with the proposed mechanism, the per cent total ionization (Σ_{40}) for the rearrangement peak increases with the expected trend of increasing migratory aptitude of the alkyl group (*i.e.*, tertiary > secondary) up to R_1 = *t*-butyl. The subsequent decrease in Σ_{40} when R_1 = *t*-amyl can be reasonably attributed to the larger steric requirements of that bulky group, producing excessive crowding on approaching the transition state. This simple treatment neglects the effect of any further decomposition of the rearrangement ion *c*, which would certainly be expected to include elimination of a neutral olefin molecule,[6,7,13] (*e.g.*, Figure 1, $c \rightarrow p$).

Table I. Extent of Rearrangement with Different Alkyl Groups

OR_1 / OR_2	R_1	R_2	Ion *c* *m/e*	Ion *c* Σ_{40}
II	Isopropyl	Isopropyl	87	1.3
III	*sec*-Butyl	*sec*-Butyl	101	2.0
V	Isopropyl	*t*-Butyl	101	2.6
I	*t*-Butyl	*t*-Butyl	115	6.6
IV	*t*-Amyl	*t*-Amyl	129	2.9

(13) Recent work in these laboratories has shown (C. Djerassi and C. Fenselau, *J. Am. Chem. Soc.*, submitted for publication) that β-hydrogen transfer from similar M − R α-cleavage products in ethers is only the preferred process when no alternative hydrogen (α, γ, δ) is available for transfer.



The spectrum (Figure 12) of the labeled acetal XVII shows that the rearrangement ion (*cc*, $R_1 = R_2 = R_3 = R_4 = CD_3$; $R_5 = CH_3$) decomposes into two charged species of mass 65 (*d*, $R_1 = R_2 = CD_3$) and mass 66 (*d*, $R_1 = R_2 = CD_3$; H = D), in the ratio of 2.6:1 (see Table II). Allowing for an isotope effect[14a] (discrimination against deuterium) of approximately 0.9 (but neglecting possible γ-transfer from R_5 = Me in *cc*), there still remains a sevenfold preference for transfer of secondary over primary

Table II. Effect of Substitution on Further Decomposition of Rearrangement Ion (*cc*)

Acetal	R_1	R_2	R_3	R_4	R_5	Ion *d* *m/e*	Ion *d* %
II	H	Me	H	Me	H	45	63
III	H	Me	H	Me	Me	45	48
I	Me	Me	Me	Me	H	59	77
IV	Me	Me	Me	Me	Me	59	41
V	H	Me	Me	Me	H	45	8
	Me	Me	Me	H	H	59	89

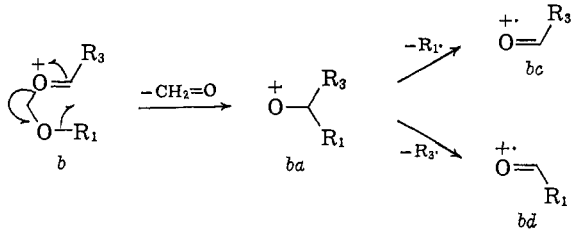
(14) (a) D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 284 (1964); (b) D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *ibid.*, **81**, 643 (1959).

hydrogen to the oxonium ion (*cc*) in the olefin elimination. This result is in marked contrast to the simple statistical effect of primary *vs.* secondary hydrogen noted[14b] in the pyrolysis of *t*-amyl acetate. The values of Σ_{40} for the M − (R + 30) rearrangement in Table I for R_1 = *sec*-butyl (III) and *t*-amyl (IV) may therefore be relatively underestimated.

Inspection of the transition state *bb* may also shed light on the previously mentioned failure of both the dithioacetal VI and the ether VII to undergo a similar rearrangement. The larger van der Waal's radius[15] of sulfur (1.85 Å.) compared with oxygen (1.40 Å.) means that transannular nonbonded repulsions between the two heteroatoms on approaching a four-center cyclic transition state will set in earlier in the dithioacetal VI, so that bridging and migration by R_1 is prevented. The ether case may indicate the desirability of having lone electron pairs on the atom originally bonded to the migrating group R_1 (CH_2 in ether; O in acetals), possibly to facilitate charge dispersion in a positively charged transition state.

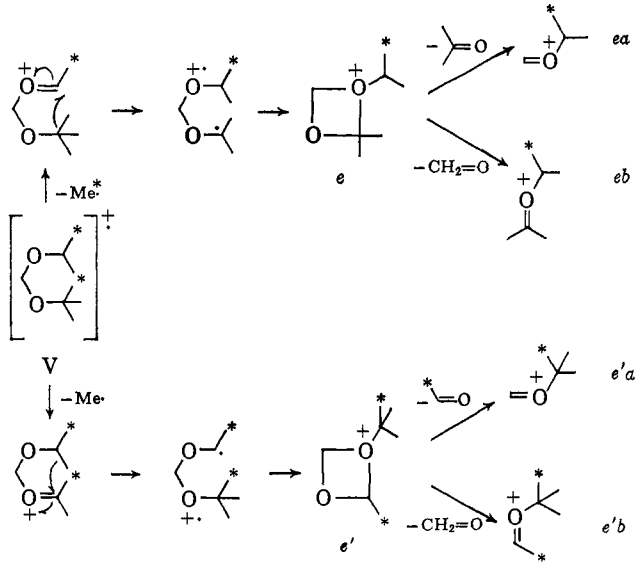
Two alternative mechanisms merit consideration for the M − (R + 30) rearrangement.

Mechanism i



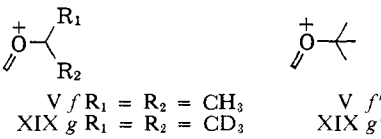
However, species *ba* would be of higher energy than *c*, and ready loss of R_1 and R_3 to afford ions *bc* and *bd*, respectively, would be expected. No peaks corresponding to the higher mass fragment *bd* have been observed.

Mechanism ii



Starred methyl groups are CD_3 in compound XIX.

The presence of cyclic intermediates *e* and *e'* in this scheme demands the two subsequent decomposition modes shown for each. The two species of mass 73 (*ea*) and 87 (*e'a*) are identical with the main α-cleavage products of (unlabeled) V (*f* and *f'*, see Figure 13), and fragment ions of mass 101 (*eb*, *e'b*) are isobaric. In the labeled material XIX, however, the four ions should appear at *m/e* 76 (*ea*), 104 (*eb*), 90 (*e'a*), and 107 (*e'b*), while the α-cleavage products *g* and *g'* correspond to mass 79 and 87, respectively. Complete



absence of peaks at *m/e* 76 and 90 in the mass spectrum (Figure 15) of XIX rule out operation of this mechanism in this instance.

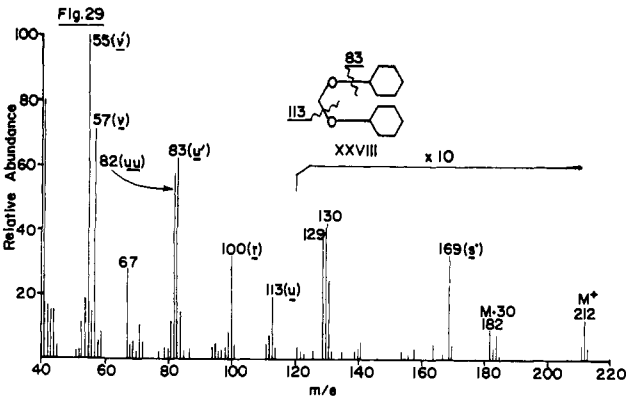


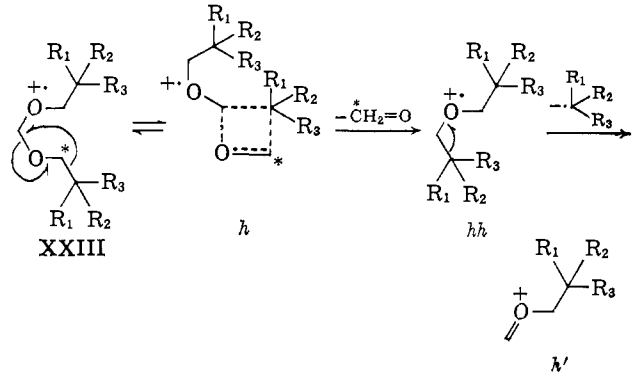
Figure 29. Mass spectrum of bis(cyclohexoxy)methane (XXVIII).

The M − 30 Rearrangement

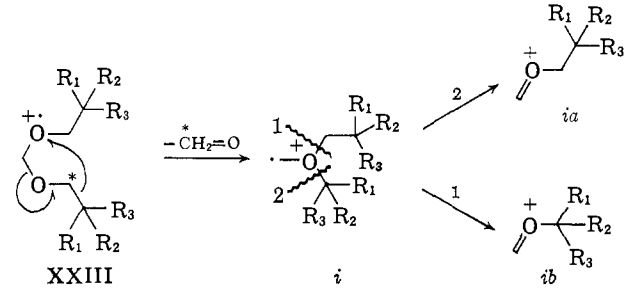
(*i*) *Acetals of Primary Alcohols.* Di-*n*-propoxymethane (VIII) (Figure 18) and the two related acetals IX (Figure 20) and X (Figure 22) all display significant M − 30 peaks in their spectra, of approximately the same relative intensity as their respective M − 29, M − 43, and M − 57 α-cleavage products.[16] In the deuterated analogs XXI (Figure 19) and XXII (Figure 21), exclusive shift to M − 32 is apparent, while high-resolution mass measurements[12] on acetal VIII confirmed the constitution of the M − 30 ion as $C_6H_{14}O^+$. *These data are only consistent with expulsion of formaldehyde from the molecular ion [rather than M − (1 + 29)], the carbon atom involved this time being the former α-carbon atom of the alcohol.* The proposed mechanism (XXIII → *h* → *hh*) predicts the formation of symmetrical ether intermediates (*hh*), and in the case of acetal VIII (XXIII, $R_1 = R_2 = H$; R_3 = Me) receives some support from the close similarity between the spectrum of VIII below *m/e* 73, and that of di-*n*-propyl ether[6] (*hh*, $R_1 = R_2 = H$; R_3 = Me). Alkyl migration by way of a cyclic transition state such as *h* should be reflected in the relationship between per cent total ionization (Σ_{40}) for the rearrangement peak and the migratory aptitude of the migrating group. However, the relative facility for further decomposition of the ether intermediate *hh* (*e.g.*, by α-cleavage to *h'*)

(15) L. Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell University Press, Ithaca, N. Y., 1959, p. 260.

(16) Reference 5 gives M − 29 (and M − 43) peaks for acetal IX, but no M − 30; the spectrum of VIII is correctly reported,[4] however. Di-*n*-butoxymethane[5] apparently does not show an M − 30 peak, and the operation of this rearrangement seems to be reduced in acetaldehyde acetals.[4,5]



will also increase in the same order (VIII < IX < X), and, from the correlation obtained (Table III), this latter process appears dominant. Generally lower Σ_{40} values for this rearrangement compared with the M − (R + 30) process (Table I) also reflect this phenomenon. A conceivable alternative mechanism was also considered, involving alkyl migration on to oxygen, rather than carbon. Expected further fragmentation of the odd-electron species *i* should generate ions *ia* (identical



with the main α-cleavage product of XXIII) and the lower homolog *ib*. In no instance was any peak corresponding to *ib* observed.

Table III. Extent of Rearrangement with Different Alkyl Groups

$CH_2(-OCH_2-\underset{R_3}{\overset{R_1}{C}}-R_2)_2$

				—Ion *hh*—		—Ion *h'*—	
	R_1	R_2	R_3	*m/e*	Σ_{40}	*m/e*	Σ_{40}
VIII	H	H	Me	102	1.1	73	13.3
IX	H	Me	Me	130	0.8	87	13.6
X	Me	Me	Me	158	0.6	101	23.9

The quantitative shift of *m/e* 73 (VIII, Figure 18) to 75 (XXI, Figure 19) and of *m/e* 87 (IX, Figure 20) to 89 (XXII, Figure 21) rules out incursion of the M − (R + 30) rearrangement in this group of acetals.

(*ii*) *Mixed Alkyl Aromatic Acetals.* In the three examples studied, the M − 30 peak (XI, *m/e* 136 in Figure 23; XII, *m/e* 136 in Figure 25; XIII, *m/e* 150 in Figure 27) moves to *m/e* 138 (XXIV, Figure 24), *m/e* 142 (XXV, Figure 26), and *m/e* 151 (XXVI, Figure 28), respectively, in the deuterated analogs, and thus still corresponds to M − 30. These results clearly indicate an M − 30 [rather than M − (1 + 29)] process, and show that, as with the M − (R + 30) rearrangement, the methylene group of the original formaldehyde is also expelled in this instance. A cyclic mechanism is again envisaged, proceeding *via* a six-membered transition state (*j*), or the alternative four-center array, by analogy with similar fragmentation paths proposed for phenetole[17-19] (loss of ethylene) and benzyl methyl ether[19] (loss of formaldehyde).

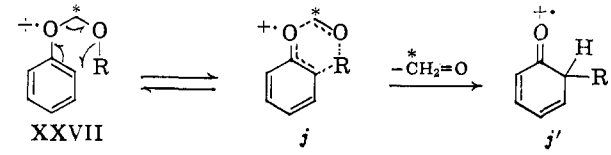


Table IV shows again a good correlation between expected order of migratory aptitude of group R and Σ_{40} for the rearrangement peak. Facile decomposition of ion *j'* would be predicted, however, particularly by the elimination of a neutral olefin molecule, giving rise to ionized phenol (*k*, *m/e* 94), which is responsible for the base peak in all spectra of this class (Figure 2, *jj* → *k*). A further source of *m/e* 94 (*e.g.*, Figure 2, *kk* → *k*) is discussed in a following section. No M − (R + 30) rearrangement occurs in this series.

Table IV. Extent of Rearrangement with Different Alkyl Groups

		—Ion *j'*—	
$PhOCH_2OR$	R	*m/e*	Σ_{40}
XI	*n*-Propyl	136	0.7
XII	Isopropyl	136	2.2
XIII	*sec*-Butyl	150	2.5

General Acetal Fragmentat ons

Molecular Ion Region. With the alkyl-aromatic acetals, the molecular ion is relatively intense (Figures 23–28), while only a weak M − 1 (and occasionally M + 1)[4,5] peak is characteristic for the dialkyl compounds.

α-Cleavage Products. Taking di-*sec*-butoxymethane (III) as a typical example (Figures 1 and 9), the conjugated M − 1 structure[7] *l* is supported by remaining (Figure 10) at M − 1 in the labeled compound XVI (as well as in XIV, Figure 7, and XXI, Figure 19). As previously mentioned, the M − 29 species (*aa'*) is considerably more abundant than M − 15 (*aa*), and this situation is equally apparent in acetals IV (Figure 11) and XIII (Figure 27). The principal α-cleavage product (*m*) results through loss of alkoxy radical[6,7] from the molecular ion, and appears at *m/e* 87. Completely analogous fissions produce peaks in the mass spectra of acetals II (Figure 6), V (Figure 13), VIII (Figure 18), XI (Figure 23), and XII (Figure 25) at *m/e* 73; in I (Figure 4), V (Figure 13), IX (Figure 20), and XIII (Figure 27) at *m/e* 87; in IV (Figure 11) and X (Figure 22) at *m/e* 101; and in XI (Figure 23), XII (Figure 25), and XIII (Figure 27) at *m/e* 107. Quantitative shifts in all deuterated analogs support these assignments.

Decomposition of α-cleavage product *m* (Figure 1), with loss of formaldehyde, furnishes the alkyl carbonium ion *m'*, which characteristically appears 30 mass units lower. Corresponding ions are invariably

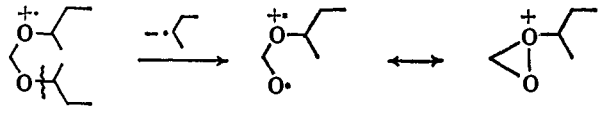
(17) See ref. 7, pp. 177, 178.
(18) F. W. McLafferty, *Anal. Chem.*, 31, 2072 (1959).
(19) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 116.

responsible for the base peak in these formaldehyde dialkylacetal spectra. Appropriate metastable peaks displayed by compounds III, VIII, IX, X, XVI, and XXII provide strong evidence for this fragmentation path, although simultaneous formation of the alkyl carbonium ion by heterolysis of a C–O bond in other species[6] (*e.g.*, M^+, M − 1) is not ruled out. The relative intensities of the hydrocarbon portions (see Table V) of *m/e* 73 and 87 (14:1) and *m/e* 43 and 57 (1:3) in the spectrum (Figure 13) of the isopropyl-*t*-butyl acetal V are in agreement with the proposed scheme. High-resolution mass spectrometry[12] utilizing selected acetals (Table V) shows that such peaks (*m/e* 43, 57) are not always homogeneous.

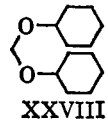
Table V. High-Resolution Mass Measurements[12] of *m/e* 43 and 57 Peaks in Some Acetals

	Composition, %			
	m/e 57		*m/e* 43	
Acetals	C_4H_9	C_3H_5O	C_3H_7	C_2H_3O
VIII	...	..	~99	~1
II	...	..	55	45
III	77	23	...	...
V	100	..	67	33

Other Rearrangement Fragmentations. Formal loss of one alkyl group can be represented either as M − (1 + olefin) (Figure 1, $l \rightarrow l'$), or as (less probably)



IV $\rightarrow$ *n* $\leftrightarrow$ *n'*. Although β-hydrogen transfer[13] onto the fully developed oxonium ion of M − 1, with concomitant olefin expulsion, has been accepted,[6,7,20] deuterium-labeled substrates are required for definite discrimination between the two mechanisms. Thus, acetals II (Figure 6), V (Figure 13), and VIII (Figure 18) afford analogous peaks at *m/e* 89; I (Figure 4) and III (Figure 9) at *m/e* 103; and XXVIII (Figure 29) at *m/e* 129. High-resolution mass measurements[12] on acetals II and VIII confirmed the composition of the



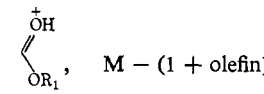
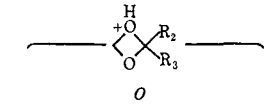
XXVIII

m/e 89 ion as $C_4H_9O_2^+$. In the corresponding deuterium-labeled compounds, the rearrangement peak shifts to *m/e* 91 (XXI, Figure 19); 104 (XVI, Figure 10); 90 (XVIII, Figure 14); 95 (XIX, Figure 15); 96 (XV, Figure 8); and 109, 110 (XX, Figure 5). The last two results are clearly in favor of an M − (1 + olefin) mechanism, as in Figure 1, $l \rightarrow l'$. It is of interest to note that acetal IX does not undergo this rearrangement, despite the presence of two tertiary β-hydrogen atoms.

In the aromatic series, acetals XII (Figure 25) and XIII (Figure 27) suffer olefin loss directly from the molecular ion (*e.g.*, Figure 2, XIII $\rightarrow$ *n*), generating peaks at *m/e* 124. All three acetals XI (Figure 23), XII (Figure 25), and XIII (Figure 27) also have small peaks at *m/e* 123, which corresponds to M − (1 + olefin) as in the dialkyl series. In the deuterated analog XXV (Figure 26), shifts to *m/e* 124 (M − olefin) and *m/e* 125 [M − (1 + olefin)] provide firm evidence for these assignments.

A homologous series of peaks at *m/e* 61, 75, and 89 ($C_nH_{2n+1}O_2$) in acetal mass spectra have been ascribed[4] to fragmentation of hemiacetals, but these fragments obviously are identical with M − (1 + olefin) ions. In (formaldehyde) acetals of secondary and tertiary alcohols, a second isomeric series of low abundance was encountered (Table VI, *o*), which for the same acetal always contained fewer carbon atoms. As examples, acetals II and III have a peak at *m/e* 75, and I and IV at *m/e* 89. High resolution[12] established the formulation of IV (*o* in Figure 1) as $C_3H_7O_2^+$. With labeled analogs, the corresponding peak shifted to *m/e* 76 (XVI, Figure 10); 95, 96 (XVII, Figure 12); and 92, 93, 95, 96 (XX, Figure 5), which is entirely consistent with the mechanism proposed in Figure 1, $aa' \rightarrow o' \rightarrow o$.

Table VI

	 M − (1 + olefin)				
Acetal	R_1	*m/e*	R_2	R_3	*m/e*
II	Isopropyl	89	H	Me	75
III	*sec*-Butyl	103	H	Me	75
I	*t*-Butyl	103	Me	Me	89
IV	*t*-Amyl	117	Me	Me	89

m/e 45 and 59 Ions. Relatively intense (see Table II) peaks occur in the spectra of dialkylacetals II, III, and V at *m/e* 45, and I, IV, and V at *m/e* 59. Their genesis is visualized from the M − (R + 30) rearrangement ion (Figure 1, $c \rightarrow p$), and from the α-cleavage M − R species (Figure 1, $aa' = a' \rightarrow p$). Both paths are subject to the same considerations and are indistinguishable by deuterium labeling, the sole difference being sequential or concerted loss, respectively, of formaldehyde and olefin from the M − R fragment (Figure 1, aa'). The latter process involves a cyclic six-membered transition state, with accompanying transfer of γ-hydrogen[21–23] (McLafferty rearrangement), and leads to an *m/e* 45 ion (Figure 1, *p*) identical with that supposedly[6,7] produced by fragmentation of isopropyl ethers. This view is completely substantiated by the observed shifts with the corresponding deuterium-labeled compounds. For example, *m/e* 45 becomes 49 (XV, Figure 8), 46 (XVI, Figure 10); and *m/e* 59 becomes 59 (XVIII, Figure 14), 60 (XIX, Figure 15), 65, 66 (XVII, Figure 12), and 62, 63, 65, 66 (XX, Figure 5).

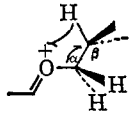
(20) See ref. 19, p. 129.

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

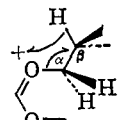
(22) F. W. McLafferty in "Determination of Organic Structures by Physical Methods," Vol 2, Academic Press Inc., New York, N. Y., 1962, pp. 129–149.

(23) C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Am. Chem. Soc.*, 87, 817 (1965), and references cited therein.

Thus formaldehyde acetals can generate *m/e* 45 and 59 fragments,[6,7] but with relative abundance generally less[4,5] than in the case of acetaldehyde and propionaldehyde acetals, where an M − (OR + olefin) process[7] usually provides the base peak. For example, *m/e* 45 is the most intense peak in the mass spectrum of diethoxyethane,[4] di-*n*-propoxyethane,[4] and di-*sec*-butoxyethane,[5] and *m/e* 59 is most intense in diethoxypropane.[4] Once more diisobutoxyacetals are anomalous, *m/e* 45 for the acetaldehyde derivative (analogous to formaldehyde derivative IX) being only 37% of the base peak. The pretransition state array *q* for this rearrangement closely resembles that (*q'*) for M − (1 + olefin) in the formaldehyde acetal IX (which latter process is not observed). Inspection of Dreiding models indicates that eclipsing of the two β-



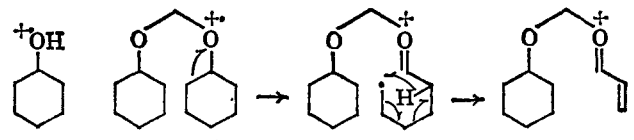
q



q'

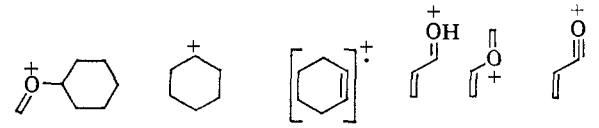
methyl groups with the two α-hydrogen atoms may hinder attainment of a coplanar assembly.

A probable alternative genesis of the *m/e* 94 (base peak) species *k* (ionized phenol) found in the spectra (Figures 23–28) of the aromatic series of acetals is envisaged as *kk* → *k* (Figure 2). The labeled compounds do not distinguish between this path, and *k'* → *jj* → *k* (Figure 2), but appropriate metastable ions in the spectra of acetals XII and XIII are evidence for the second stage (Figure 2, *jj* → *k*) of stepwise elimination of formaldehyde and olefin. Ions of *m/e* 65 and 66 result from further fragmentation of *k*.[24] Operation of a process analogous to *kk* → *k'* in the case of bis(cyclohexoxy)methane (XXVIII) results in the elimination of cyclohexene and formaldehyde with the production of ionized cyclohexanol (*r*) at *m/e* 100. α-Cleavage in the ring followed by the usual[25] cyclohexanol type hydrogen rearrangement (XXVIII → *s* → *s'* is proposed to account for *m/e* 169 (Figure 29)).



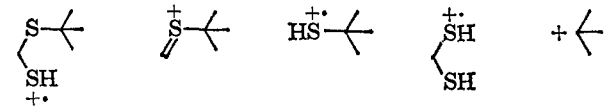
r XXVIII *s* *s'*

Cyclohexene may also result by electron impact on XXVIII from an M − (1 + olefin) mechanism, giving a charged species analogous to *l'* (Figure 1) of mass 129. As in the aromatic series, $M^+ > M - 1$, and *m/e* 130 is assigned to an M − olefin ion, while *m/e* 67 is attributed to the M − 15, species arising from further decomposition of cyclohexene[26] (*uu*). Other fragments are identified below, but without any high resolution evidence.



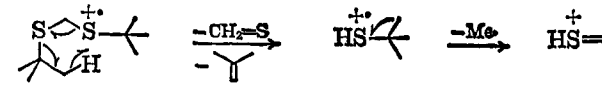
u *m/e* 113 *u'* *m/e* 83 *uu* *m/e* 82 *v* *m/e* 57 *v'* *m/e* 55

In the mass spectrum (Figure 16) of the dithioacetal VI the following ions can be assigned, using the natural



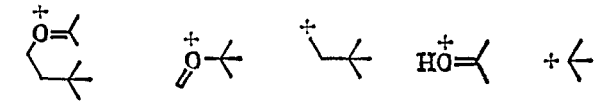
wa *m/e* 136 *wb* *m/e* 103 *wc* *m/e* 90 *wd* *m/e* 80 *we* *m/e* 57

abundance of ^{34}S as a guide. The molecular ion is characteristically more intense[7] than with the oxygen analogs, and no M − 1 species is apparent. The M − olefin process operates twice,[7] affording sequentially *wa* and then *wd*, while *wc* can also conceivably arise from the molecular ion. The *m/e* 75 peak is tentatively attributed to the sulfur analog (*wf*) of the dialkylacetal fragment *m/e* 59 (*d*, Table II), which in this instance is more likely to come directly from *wc*, rather than from an (absent) M − 15 ion.



VI *wc* *wf*

The principal peaks in the spectrum (Figure 17) of the ether VII can be plausibly accounted for in similar manner.



xa *m/e* 143 *xb* *m/e* 87 *xc* *m/e* 85 *xd* *m/e* 59 *xe* *m/e* 57

Experimental Section[27]

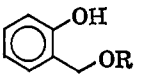
Bis(t-butylmercapto)methane (*VI*). Sodium *t*-butylmercaptide in ethanol was allowed to react with methylene chloride and gave a 73% yield of the title compound, b.p. 92–93° (10 mm.); $n^{20}D$ 1.4910 (lit.[28] b.p. 99–101° (13 mm.); $n^{15}D$ 1.4901).

t-Butyl 3,3-Dimethylbutyl Ether (*VII*). The ether was prepared in 75% yield from 3,3-dimethylbutylmagnesium chloride[29] and *t*-butyl perbenzoate according to a general procedure,[30] b.p. 55° (24 mm.), $n^{20}D$ 1.4054. *Anal.* Calcd. for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.87; H, 14.11.

d_4-Di-n-propoxymethane (*XXI*). (a) Propionic acid was dried by heating under reflux with 5% its weight of propionic anhydride, followed by fractional distillation, b.p. 140–141°. Conventional reduction with lithium aluminum deuteride in anhydrous ether afforded an 84% yield of 1,1-d_2-propan-1-ol, b.p. 97°.

(24) T. Aczel and H. E. Lumpkin, *Anal. Chem.*, 32, 1819 (1960).
(25) See ref. 7, Chapter 2.
(26) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, in press.
(27) All low-resolution mass spectra were obtained by Mr. J. W. Smith, using a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer equipped with an all-glass inlet system heated to 200°. The ionizing energy was maintained at 70 e.v., and the ionizing current at 50 μa. N.m.r. measurements were performed by Mr. D. McMillen with a Varian A-60 spectrometer, employing carbon tetrachloride as solvent, and tetramethylsilane as internal reference. Analyses were made by Dr. A. Bernhardt, Mulheim, Germany.
(28) H. J. Backer and P. L. Stedehouder, *Rec. trav. chim.*, 52, 437 (1933).
(29) 1-Chloro-3,3-dimethylbutane was supplied by Pharmacia Ltd., Uppsala, Sweden.
(30) C. Frisell and S.-O. Lawesson, *Org. Syn.*, 41, 91 (1961).

(b) 1,1-d_2-Propanol (0.30 g., 4.8 mmoles) and paraformaldehyde (0.07 g., 2.3 mmoles) were heated under reflux in ethanol-free chloroform (10 ml.) overnight, together with a few small crystals of *p*-toluenesulfonic acid. No attempt was made to azeotropically remove any water formed. The reaction was cooled and washed with sodium carbonate and then sodium chloride solutions. The solvent was removed under reduced pressure, and the crude product bulb-distilled at 50° (25 mm.), furnishing 0.39 g. (59%) of impure acetal. Gas chromatography was used to quantitatively separate acetal XXI (retention time 2.7 min. on 6-ft. 20% SE-30 on Chromosorb P column at 90°) from residual 1,1-d_2-propanol (retention time 1.0 min.). Essentially this same procedure, commencing from purified reactants, was used for all other acetals prepared in this work. Purity was established for each compound by gas chromatographic analysis, the mass spectrum, and especially the highly characteristic n.m.r. spectrum coupled with integrated proton count.



XXIX

As an example of n.m.r. assay, di-*n*-propoxymethane (VIII) had the following spectral data (all chemical shifts are quoted in δ values, TMS = 0): 4.53 (2-proton singlet), 3.40 (4-proton triplet), 1.48 (4-proton multiplet), 0.92 (6-proton triplet). The d_4-analog XXI had resonances at 4.53 (2-proton singlet), 1.50 (4-proton quartet), 0.92 (6-proton triplet). No other absorption was detected. The aromatic acetal XII exhibited peaks at 7.00 (5-proton multiplet), 5.14 (2-proton singlet), 3.95 (1-proton multiplet), 1.15 (6-proton doublet). The corresponding d_6-compound XXV absorbed at 7.00 (5-proton multiplet), 5.15 (2-proton singlet), 3.93 (broad 1-proton singlet). These data, together with infrared spectral evidence, exclude the alternative formula XXIX for the aromatic acetals.

Mass Spectra of Nucleic Acid Derivatives. Pyrimidines

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The mass spectra of pyrimidine, 2-aminopyrimidine, uracil, 6-methyluracil, thymine, 1,3-dimethyluracil, dihydrouracil, dihydrothymine, cytosine, 5-methylcytosine, 5-hydroxymethyluracil, and the corresponding deuterated compounds have been obtained. Molecular ions were observed for all compounds. Fragmentation patterns characteristic of the position and nature of substituents and of the extent of unsaturation of the pyrimidine ring were interpreted in each case with the aid of metastable peaks and deuterium labeling. Interpretations were often facilitated by recording spectra at low electron beam energies in addition to the standard 70 e.v. The mass spectra of these compounds can serve as useful models for determination of the structures of chemically or biologically modified pyrimidines or their nucleosides.

Introduction

Mass spectra of compounds containing the pyrimidine ring were first obtained by Biemann and McCloskey,[3] who studied the naturally occurring nucleosides by time-of-flight mass spectrometry. They observed molecular ion peaks and fragmentation corresponding principally to cleavage of the purine- or pyrimidine ribose bond, with the production of both ribose and purine or pyrimidine ions, and to fragmentation of the ribose moiety of each compound. The potential utility of the double-focusing mass spectrometer for structural studies on chemically modified pyrimidines, including the products of photochemical addition of aromatic hydrocarbons to these compounds,[4] has prompted us to study the mass spectra of a series of substituted pyrimidines, chiefly those of the nucleic acids. The small amount of sample required, the ease with which the spectra are obtained, and the specificity of the fragmentation patterns observed all suggest that the mass spectra of these compounds can serve as useful models with which the spectra of chemically or biologically altered pyrimidines could be compared to assist in structure elucidation.

The observation of peaks due to metastable ion transitions provided proof of the origins of ions produced in many fragmentation processes.[5] These transitions involve the decomposition of an ion of mass m_1 to form another ion of mass m_2 plus a neutral fragment in the field-free region of the spectrometer, and are recorded as broad peaks of low intensity at m/e values m^* given by the relation[6] $m^* = (m_2)^2/m_1$.

The high ionization voltage of 70 e.v. which is commonly used in mass spectrometry is sometimes necessary to obtain reproducible spectra, but this voltage often results in high-energy fragmentation processes which may involve extensive rearrangements. It is generally difficult to write mechanisms for such processes, and they are usually of less interest for structure

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(3) K. Biemann and J. A. McCloskey, *J. Am. Chem. Soc.*, **84**, 2005 (1962); K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 351–354.
(4) J. M. Rice, *J. Am. Chem. Soc.*, **86**, 1444 (1964).
(5) Ionic fragmentation processes do not always give rise to metastable peaks, however, and failure to observe these peaks does not prove that such reactions do not occur.
(6) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960, p. 252.