gaseous ^{13}C-enriched carbon dioxide (100 ml, 52% ^{13}C enriched). After destruction of the excess Grignard reagent with saturated ammonium chloride solution at −40°, work-up in the usual manner[22] gave the labeled benzoic acid (0.52 g). This was converted to benzyl-1-^{13}C bromide as outlined above which was then utilized to prepare XII.

Mass Spectrometry in Structural and Stereochemical Problems. CLXXXIII.[1] A Study of the Electron Impact Induced Fragmentation of Aliphatic Aldehydes[2]

Raymond J. Liedtke[3] and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received July 24, 1969*

Abstract: In spite of the importance of the aldehyde functionality in organic chemistry, no investigation of the mass spectral behavior of aliphatic aldehydes has as yet been performed using the techniques of isotopic labeling, exact mass measurement, and metastable peak analysis. The present study, utilizing hexanal and all of its possible deuterated analogs as substrates as well as several pertinent labeled heptanals, has shed new light on the electron impact induced behavior of aliphatic aldehydes. Several interesting observations have been made, including the origin of the hydrogen atoms in the loss of water (Tables III and IV), the multiple, and yet not indiscriminate, expulsion of ethylene (Schemes I and II), the apparent nonspecificity of the "McLafferty" rearrangement leading to an ionized olefin (Scheme IV), and the reciprocal hydrogen transfer (Scheme VI) associated with the loss of a propyl radical.

A major program has been initiated in our laboratories directed toward the use of artificial intelligence computer techniques in the interpretation of mass spectra.[4] The first stages of this research program involved the establishment of necessary "rules" for computer-assisted mass spectral interpretation of simple monofunctional compounds, aliphatic ketones having been selected as an initial test case.[4b] Much information is known concerning the electron impact induced fragmentation pathways of ketones,[5] and these data made the successful formulation of rational rules possible. In the course of continuing work, attempts were made to extend these computer techniques to the interpretation of aliphatic aldehyde mass spectra, but it soon became obvious that serious gaps existed in our knowledge concerning the fragmentation patterns of such compounds. Although Gilpin and McLafferty[6] have documented over 10 years ago numerous straight chain aldehyde mass spectra, no high-resolution measurements, low voltage measurements, metastable peak analyses, or isotopic labeling studies have been performed in the intervening years—a surprising state of affairs considering the importance of the aldehyde functionality. Anticipating the results of our study, several earlier assumptions concerning electron impact induced aldehyde fragmentation have now been shown to be erroneous. Other proposed fragmentation mechanisms, formerly based only on speculation, have now been substantiated by experimental evidence.

This work, then, describes a systematic investigation of mass spectral aliphatic aldehyde fragmentation pathways. The powerful techniques of deuterium labeling, high-resolution mass measurement, and defocusing metastable peak determination[7] all proved essential to the achievement of the goals of this project. Hexanal (I) and its six deuterium-labeled analogs were chosen as suitable substrates for preparative considerations and because the chain length seemed sufficiently long so as to be typical of other aliphatic aldehyde systems. Certain deuterium-labeled analogs of heptanal (II) were also synthesized to confirm and clarify several results initially observed in the mass spectra of the labeled hexanals.

Discussion of Results

The mass spectra at 70 eV and at nominal 12 eV of hexanal (Figures 1 and 2) and heptanal (Figures 3 and 4) are reproduced. Only a very weak molecular ion is observed for each aldehyde, even at low voltage. In the mass spectrum of hexanal an $M - 1$ ion (m/e 99) is present but its abundance is small (less than one-half that of the molecular ion), and a pressure-dependent $M + 1$ ion (m/e 101) can also be observed. Two very prominent peaks, m/e 44 and m/e 56, are seen at high voltage. It should be noted that while the m/e 44 peak (associated with a McLafferty rearrangement[5])

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[1] For paper CLXXXII, see R. T. Gray and C. Djerassi, *J. Org. Chem.*, in press.

[2] Financial support from the National Institutes of Health (Grant No. AM-04257) is gratefully acknowledged. The purchase of the CH-4 mass spectrometer was made possible by NASA (Grant No. NGR-05-020-004).

[3] National Institutes of Health Predoctoral Fellow.

[4] (a) J. Lederberg, G. L. Sutherland, B. G. Buchanan, E. A. Feigenbaum, A. V. Robertson, A. M. Duffield, and C. Djerassi, *J. Am. 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.*, in press.

[5] For a detailed and up to date coverage see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 3.

[6] J. A. Gilpin and F. W. McLafferty, *Anal. Chem.*, **29**, 990 (1957).

[7] (a) K. R. Jennings, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davies, Ed., United Trade Press, London, 1967, p 105; (b) T. W. Shannon, T. E. Mead, C. G. Warner, and F. W. McLafferty, *Anal. Chem.*, **39**, 1748 (1967).

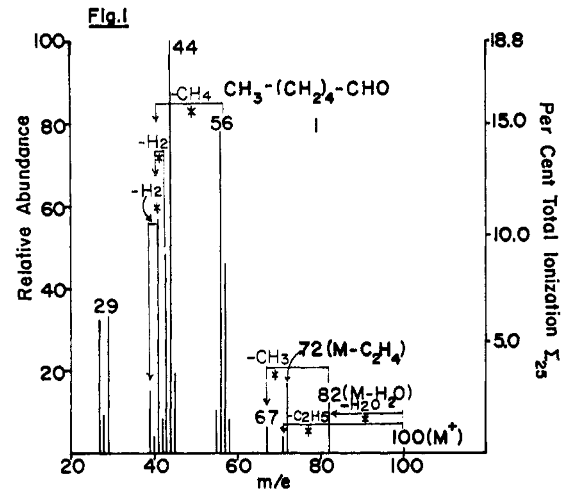

Figure 1. Mass spectrum of hexanal at 70 eV.

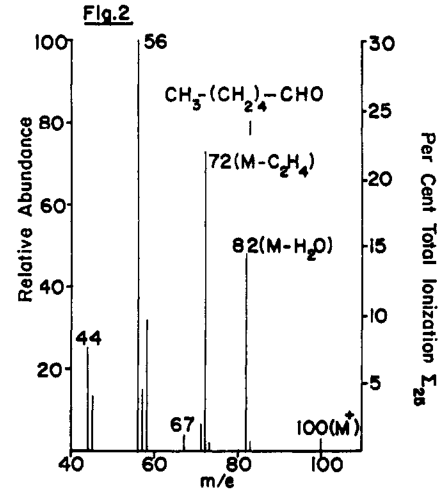

Figure 2. Mass spectrum of hexanal at 12 eV.

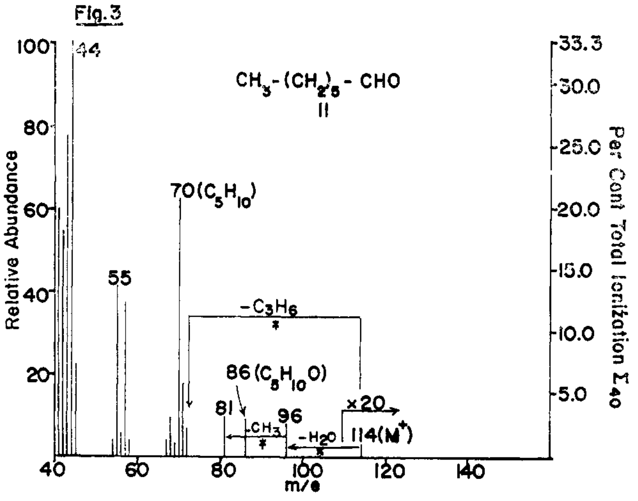

Figure 3. Mass spectrum of heptanal at 70 eV.

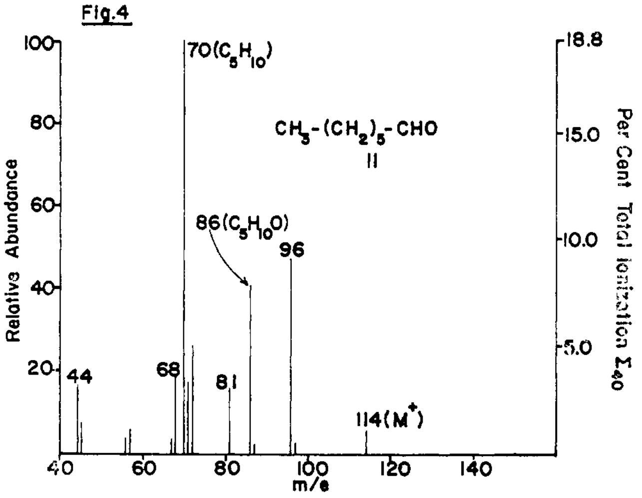

Figure 4. Mass spectrum of heptanal at 12 eV.

is the most important one in the 70-eV spectrum (Figure 1), at low voltage (Figure 2) the *m/e* 56 peak (olefin ion) becomes dominant. Similar observations hold for the heptanal mass spectra (Figures 3 and 4), the corresponding prominent peaks being *m/e* 44 and *m/e* 70. The important peaks were analyzed by high-resolution mass measurements to separate isobaric hydrocarbon and oxygen-containing ions (Tables I and II). Exact mass measurement played an indispensable role in the analysis of the mass spectra of the deuterated aldehydes. The complexity of the problem is evident from inspection of the *m/e* 40–45 and *m/e* 55–58 regions in the hexanal mass spectrum (Figure 1 and Table I). Using this information and the peak shifts in the mass spectra of the deuterated compounds,

Table I. High-Resolution Mass Measurements of Hexanal (I) Peaks

Peak	Composition	
m/e	70 eV	12 eV
29	21% CHO, 79% C_2H_5	
42	22% C_2H_2O, 78% C_3H_6	
43	11% C_2H_3O, 89% C_3H_7	
44	100% C_2H_4O	100% C_2H_4O
45	100% C_2H_5O	100% C_2H_5O
55	9% C_3H_3O, 91% C_4H_7	
56	100% C_4H_8	100% C_4H_8
57	67% C_3H_5O, 33% C_4H_9	50% C_3H_5O, 50% C_4H_9
58	100% C_3H_6O	100% C_3H_6O
71	83% C_4H_7O, 17% C_5H_{11}	83% C_4H_7O, 17% C_5H_{11}
72	100% C_4H_8O	100% C_4H_8O

Table II. High-Resolution Mass Measurements of Heptanal (II) Peaks

Peak	Composition	
(*m/e*)	70 eV	12 eV
29	18% CHO, 82% C_2H_5	
42	2% C_2H_2O, 98% C_3H_6	
43	7% C_2H_3O, 93% C_3H_7	
44	100% C_2H_4O	100% C_2H_4O
45	100% C_2H_5O	100% C_2H_5O
55	4% C_3H_3O, 96% C_4H_7	100% C_4H_7
56	100% C_4H_8	100% C_4H_8
57	87% C_3H_5O, 13% C_4H_9	89% C_3H_5O, 11% C_4H_9
58	100% C_3H_6O	100% C_3H_6O
70	100% C_5H_{10}	100% C_5H_{10}
71	40% C_4H_7O, 60% C_5H_{11}	34% C_4H_7O, 66% C_5H_{11}
72	100% C_4H_8O	100% C_4H_8O
85	88% C_5H_9O, 12% C_7H_{11}	88% C_5H_9O, 12% C_7H_{11}
86	100% $C_5H_{10}O$	100% $C_5H_{10}O$

Table III. Mass Distribution of the M − H_2O Ion in Deuterated Analogs of Hexanal

		Transfer of M − H_2O peak[a]		
	Isotopic purity	A (70 eV)	B (70 eV)	B (15 eV)
1-d_1	99% d_1	83 (100%)		
2,2-d_2	92% d_2	84 (91%)	82 (90%)	82 (94%)
	8% d_1	83 (9%)	81 (10%)	81 (6%)
3,3-d_2	97% d_2	84 (20%)	84 (14%)	84 (20%)
	3% d_1	83 (61%)	83 (70%)	83 (63%)
		82 (19%)	82 (16%)	82 (17%)
4,4-d_2	95% d_2	84 (51%)	84 (46%)	84 (46%)
	5% d_1	83 (49%)	83 (54%)	83 (54%)
5,5-d_2	92% d_2	84 (71%)	84 (74%)	84 (73%)
	8% d_1	83 (29%)	83 (26%)	83 (27%)
6,6,6-d_3	98% d_3	85 (85%)	85 (92%)	85 (91%)
	2% d_2	84 (15%)	84 (8%)	84 (9%)

[a] Run A data were acquired with an Atlas CH-4 spectrometer (direct insertion on charcoal), while run B data were collected using an AEI MS-9 mass spectrometer (heated inlet). See also the Experimental Section.

Table IV. Mass Distribution of the M − H_2O Ion in Deuterated Analogs of Heptanal

		Transfer of M − H_2O peak	
	Isotopic purity	70 eV	15 eV
2,2-d_2	92% d_2	98 (95%)	98 (93%)
	8% d_1	97 (5%)	97 (7%)
3,3-d_2	97% d_2	98 (35%)	98 (34%)
	3% d_1	97 (55%)	97 (60%)
		96 (10%)	96 (6%)
4,4-d_2	98% d_2	98 (42%)	98 (42%)
	2% d_1	97 (58%)	97 (58%)
6,6-d_2	92% d_2	98 (81%)	*a*
	8% d_1	97 (19%)	
7,7,7-d_3	98% d_3	99 (94%)	99 (94%)
	2% d_2	98 (6%)	98 (6%)

[a] The 15-eV spectrum of this compound was not measured.

plausible rationalizations for the most important fragmentation routes can now be offered.

M − 18 and M − 33 Ions. The ion of mass 82 (M − 18) in the mass spectrum of hexanal arises by the elimination of water from the molecular ion, subsequent ejection of a methyl radical then yielding the ion of mass 67 (M − 33). Analogous transitions produce peaks at *m/e* 96 and *m/e* 81, respectively, in the mass spectrum of heptanal (Figures 3 and 4). Abundant metastable peaks are observable for these processes. Such a prominent loss of water in aldehydes contrasts with the virtual absence of such a process in aliphatic ketones[8] and hence can be considered a useful differentiating criterion between these two classes of carbonyl compounds. Therefore, it is of particular interest to establish the source of the hydrogen atoms eliminated in the dehydration process and to compare the results with those recorded in the literature[9] for the electron impact induced dehydration of primary alcohols. The data obtained from measuring the shift of the M − H_2O peak in the mass spectra of the deuterium-labeled analogs of hexanal and heptanal are listed in Tables III and IV. It is seen that some transfer of deuterium occurs in each of the labeled analogs of hexanal except the 1-d_1 compound. Interestingly, the major site of transfer is C-3 indicating that at least one of the hydrogen migrations proceeds preferentially through a five-membered transition state. In fact, in the mass spectra of hexanal-3,3-d_2 and heptanal-3,3-d_2, a significant peak is observed at M − 20, corresponding to elimination of D_2O. Hydrogen atoms further removed from the aldehyde functionality serve as progressively less important sources of the water hydrogen atoms, thus showing that while partial hydrogen–deuterium randomization could possibly be a contributing factor to the labeling data, preferential ring size in the transition state is of obvious importance. Hydrogen–deuterium randomization in aliphatic ketones has received much recent study[10] and has been shown to occur in several straight chain ketones. In the case of hexanal-3,3-d_2, metastable transitions in the second field free region of the MS-9 mass spectrometer are observable for elimination of DHO and H_2O, while no metastable peak is seen for ejection of D_2O even though the M − H_2O and M − D_2O peaks are of identical intensity in the mass spectrum. This could be interpreted as indicating that several distinct processes are, indeed, occurring.

The transfer of two hydrogen atoms from one methylene group is not without precedent. The mass spectrum of ethyl *n*-hexyl ether contains a peak involving transfer of two hydrogen atoms from the hexyl chain such that the charged species formally corresponds to $C_2H_5O^+H_2$. Deuterium labeling has demonstrated[11] that the major source of both transferred hydrogen atoms is C-5 of the hexyl chain.

The result outlined above coupled with the observation of metastable peaks corresponding to the elimination of H_2O in the mass spectrum of both hexanal (*m/e* 67.2) and heptanal (*m/e* 80.7) demonstrate conclusively that the process is not a thermal phenomenon but rather an electron impact promoted process, which becomes noticeably more prominent at low ionizing voltage (Figures 2 and 4). In contrast to these data, the loss of water in aliphatic alcohols has been shown to involve specifically (>90%) the γ-hydrogen atom in the cases of several primary alcohols.[9d,e]

The ion of mass 67 produced by expulsion of a methyl radical from the M − H_2O ion (*m/e* 82) retains some deuterium in each of labeled hexanals (the same phenomenon is observed in the mass spectra of the labeled heptanals). Hence, a nonspecific loss of hydrogen must be involved. This fact and the low intensity of the *m/e* 67 peak do not justify further speculation on the nature of this process.

M − 28 and M − 29 Ions. The *m/e* 72 peak in the mass spectrum (Figure 1) of hexanal, which is particularly prominent at low voltage, was shown (Table I) by high-resolution mass measurement to have the composition C_4H_8O (100%), and therefore corresponds to the elimination of ethylene from the molecular ion. A metastable transition (first field free region) was observed for the process using the defocusing technique.[7] Ex-

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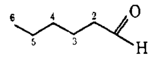
[8] Long-chain aliphatic ketones exhibit a minute M − H_2O peak [A. N. H. Yeo and D. H. Williams, *Org. Mass Spectrosc.*, **2**, 331 (1969)] which does not increase in intensity at low voltage (unpublished observations in our laboratory).

[9] (a) W. H. McFadden, M. Lounsbury, and A. L. Wahrhaftig, *Can. J. Chem.*, **36**, 990 (1958); (b) W. H. McFadden, D. R. Black, and J. W. Corse, *J. Phys. Chem.*, **67**, 1517 (1963); (c) C. G. McDonald, J. S. Shannon, and G. Sugowdz, *Tetrahedron Letters*, 807 (1963); (d) W. Benz and K. Biemann, *J. Am. Chem. Soc.*, **86**, 2375 (1964); (e) S. Meyerson and L. C. Leitch, *ibid.*, **86**, 2555 (1964).

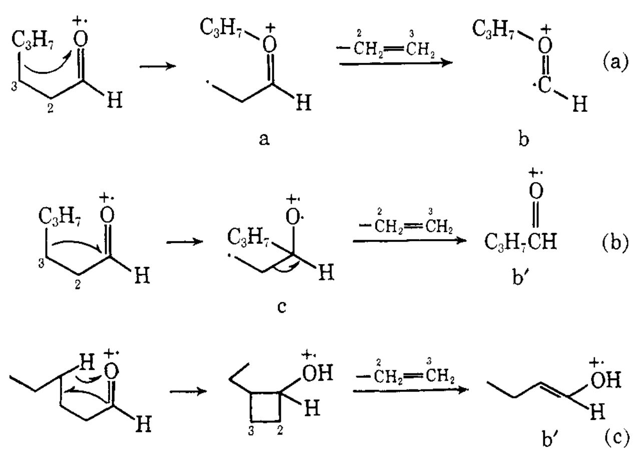
[10] (a) W. Carpenter, A. M. Duffield, and C. Djerassi, *ibid.*, **90**, 160 (1968); (b) A. N. H. Yeo and D. H. Williams, *ibid.*, **91**, 3582 (1969).

[11] W. Carpenter, A. M. Duffield, and C. Djerassi, *ibid.*, **89**, 6164 (1967).

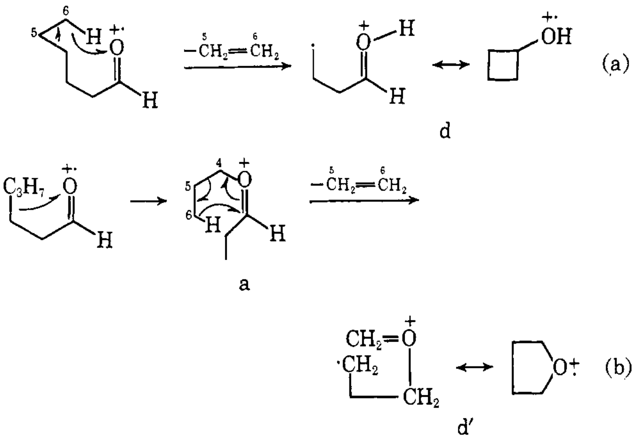
Table V. Origin of Ethylene Loss (m/e 72) in Hexanal Mass Spectrum

Compound 	Carbon eliminated as ethylene, %		
	70 eV	15 eV	12 eV
2,2-d_2	80	78	77
3,3-d_2	81	82	79
4,4-d_2	0	0	0
5,5-d_2	25	22	22
6,6,6-d_3	22	18	18

Scheme I



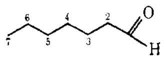
Scheme II



amination of the data obtained from the spectra of the deuterated hexanals (Table V) leads to the interesting conclusion that C-2 and C-3 are eliminated as a unit as are C-5 and C-6, whereas C-4 is not at all implicated. Possible mechanistic rationalizations consistent with these data are shown in Schemes I and II. An advantage of Schemes Ia and Ib lies in their simplicity, fission of the 3–4 bond with transfer of an alkyl fragment to either oxygen (a) or carbon (c), followed by elimination of carbon atoms 2 and 3 as ethylene leading to either b or b′. Other more complex processes involving cyclic intermediates can, of course, also be envisioned, a typical example being depicted in Scheme Ic. The probable intervention of a cyclic intermediate[11a] (Scheme Ic), at least to a partial extent, is supported by the observation in our laboratory that the principal features of the mass spectrum of 2-ethylcyclobutanol, notably the loss of ethylene, are in accord with those of the hexanal mass spectrum. A cyclobutanol intermediate is not, however, involved in the important McLafferty rearrangement exhibited by α-branched aldehydes and ketones upon electron impact.[12]

Scheme II illustrates two representations for the experimentally demonstrated retention of one of the terminal hydrogen atoms of hexanal in the ejection of the terminal two carbon atoms as ethylene. Analogous processes occur in the mass spectrum of heptanal producing the ion of mass 86. Data collected from deuterated analogs of heptanal (Table VI) clearly show that ejection of the terminal two carbon atoms as a unit becomes less favorable relative to C-2,C-3 elimination with increasing chain length.

Table VI. Origin of Ethylene Loss (m/e 86) in Heptanal Mass Spectrum

Compound 	Carbon atom eliminated as ethylene, %	
	70 eV	15 eV
2,2-d_2	98	98
3,3-d_2	93	92
4,4-d_2	0	0
6,6-d_2	6	[a]
7,7,7-d_3	8	8

[a] The 15-eV spectrum of this compound was not measured.

The complexities of the problem do not allow a choice between Schemes IIa and b based solely on the data at hand, but examination of the effect of alkyl substitution on both the above two pathways of olefin elimination could prove interesting. Even though the exact details of the process are not known, the different structures (b, b′, d, d′) for the fragment ion could conceivably be differentiated by ion cyclotron resonance spectrometry in the manner accomplished recently for certain fragment ions of aliphatic ketones.[13] Irrespective of the detailed structure of the M − 28 ion, it is of interest to compare the loss of ethylene observed in the present instance with that seen in the spectra of alkyl cyanides.[14] In the case of n-hexyl cyanide 75% of the ethylene eliminated from the molecular ion was found to include the terminal carbon atoms with only 20% encompassing C-2 and C-3. One of the factors responsible for these quantitative differences in the origin of the eliminated ethylene may be the difference in the geometry of the ionized aldehyde *vs.* the ionized cyano functionality.

The m/e 71 peak (M − 29) comprises only about 1% of the total ion current in the mass spectrum of hexanal both at high (Figure 1) and low (Figure 2) voltage. Exact mass measurements show this fragment to arise predominately (83%) from ejection of an ethyl radical and only slightly (17%) from loss of a formyl radical. In the latter process the C-1 hydrogen is involved specifically as shown in the mass spectrum of hexanal-

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(11a) Note Added in Proof. Through a private communication from Dr. Catherine Fenselau (Johns Hopkins University) we have learned that C. Fenselau, J. Young, S. Meyerson, W. Landis, E. Selke, and L. Leitch, *J. Am. Chem. Soc.*, **91**, 6847 (1969)) have reached the same conclusion by studying labeled hexanals and heptanals.

(12) C. A. Brown, W. H. Faul, A. F. Gerrard, R. L. Hale, and R. Liedtke, submitted for publication.

(13) (a) J. Diekman, J. K. MacLeod, C. Djerassi, and J. D. Baldeschweiler, *J. Am. Chem. Soc.*, **91**, 2069 (1969); (b) G. Eadon, J. Diekman, and C. Djerassi, *ibid.*, **91**, 3986 (1969).

(14) W. Carpenter, Y. M. Sheikh, A. M. Duffield, and C. Djerassi, *Org. Mass Spectrosc.*, **1**, 3 (1968).

1-d_1. The percentage of formyl radical loss drops to 12% of total peak intensity in the 70-eV and nominal 12-eV mass spectra (Figures 3 and 4) of heptanal in which the M − 29 peak is similarly of minor importance. Labeling data (70 eV) indicate expulsion of an ethyl radical from the terminal carbon atoms of hexanal to the extent of roughly 60% and involves to a somewhat smaller degree (40%) the C-2 and C-3 atoms. This latter process must involve a hydrogen transfer if the ethyl radical is eliminated directly from the molecular ion. A possible alternative mode of formation involves loss of a hydrogen radical from an *m/e* 72 precursor; however, no metastable transition is observed for such a pathway either in the first or second field free regions of the MS-9 spectrometer. In the case of *n*-hexyl cyanide a large metastable peak is observed for the corresponding loss of a hydrogen radical from the M − 28 ion.[14]

***m/e* 55, 56, 57, and 58 Peaks (Hexanal).** The most significant fragment of this group is the ion of mass 56 which (Table I) is entirely hydrocarbon (C_4H_8) in nature. Indeed, this ion is responsible for the base peak of the low voltage hexanal mass spectrum (Figure 2), accounting for 30% of the total ion current. At 70 eV (Figure 1), the *m/e* 56 peak is second in abundance only to the peak (*m/e* 44) associated with the McLafferty rearrangement. The corresponding ion of mass 70 is of similar importance in the high and low voltage heptanal mass spectra (Figures 3 and 4). Formally, the genesis of this olefin ion involves β cleavage with hydrogen transfer, that is a McLafferty rearrangement with the charge remaining on the alkene fragment. Indeed, the process has been depicted in this manner as shown in Scheme III.[15] However, examination of the data (Table VII) obtained from the mass spectra of the deuterated hexanals demonstrates that this process is apparently not of the site-specific McLafferty rearrangement type. Transfer of a γ- or δ-hydrogen atom is the dominant process, each being equally favored at 70 eV, and together accounting for 81% of the total transfer. Therefore, Scheme IV rather than Scheme III constitutes a more realistic representation for the genesis of the M − 44 ion. Specific hydrogen transfer after partial hydrogen randomization[10] along the alkyl chain is an alternative possibility.

Scheme III

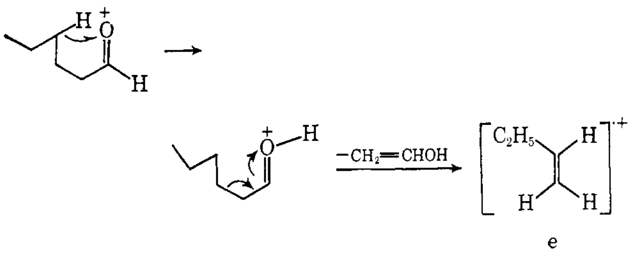
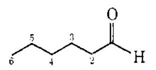
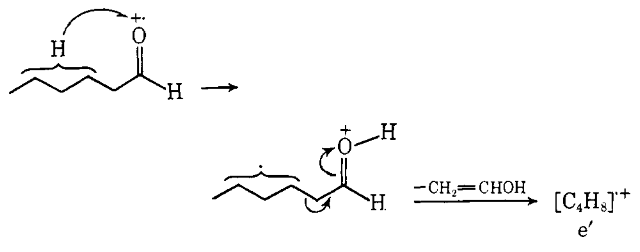


Table VII. Mass Distribution in *m/e* 56 Peak Group (Labeled Hexanals)

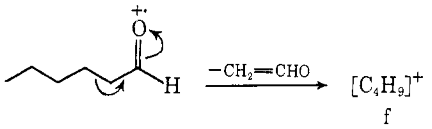
Compound 	Relative abundance, %	
	70 eV	15 eV
2,2-d_2	56 (100%)	56 (100%)
3,3-d_2	57 (7%)	57 (7%)
	58 (93%)	58 (93%)
4,4-d_2	57 (41%)	57 (31%)
	58 (59%)	58 (69%)
5,5-d_2	57 (40%)	57 (46%)
	58 (60%)	58 (54%)
6,6,6-d_3	58 (7%)	58 (7%)
	59 (93%)	59 (93%)

Scheme IV



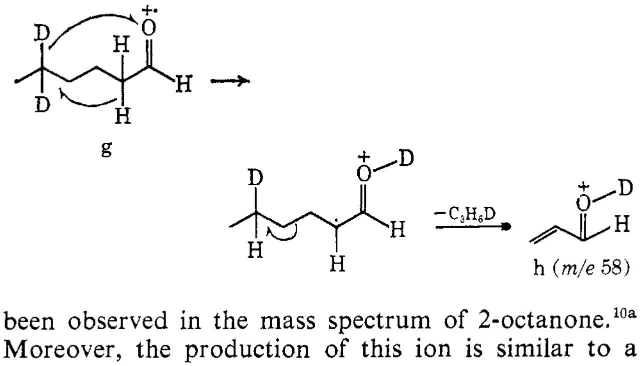
A second β-cleavage process but without hydrogen migration is shown in Scheme V and leads to the butyl ion radical f (*m/e* 57). This is a much less favored process than that leading to the *m/e* 56 peak, accounting for less than 1% of the total ion current in the 70-eV mass spectrum of hexanal (33% of *m/e* 57 peak). The peak shifts in the mass spectra of the deuterated hexanals are in accord with Scheme V.

Scheme V



The major component (67%) of the *m/e* 57 peak in the hexanal mass spectrum (Figure 1) is $C_3H_5O^+$, formally due to loss of a propyl radical from the molecular ion. Because of the overlap of this peak with the oxygen-containing *m/e* 58 peak in the mass spectrum of several of the deuterated hexanals, no precise calculations of peak shifts are given. However, qualitative conclusions can be drawn. A significant amount, greater than 50%, of the propyl radical loss cannot arise from simple fission of the β,γ-linkage, but must occur with reciprocal hydrogen transfer. A majority of this reciprocal hydrogen transfer involves positions 5 and 2 whereas the hydrogen atoms attached to C-4 and C-6 are implicated to a much smaller degree. The major process is illustrated in Scheme VI. An analogous process has been observed in the mass spectrum of 2-octanone.[10a] Moreover, the production of this ion is similar to a reciprocal hydrogen transfer process shown to be operative in the genesis of the important *m/e* 301 peak in the

Scheme VI



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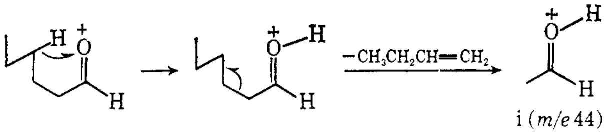
(15) See ref 5, p 132.

mass spectrum of cholestan-16-one[16] and in simpler monocyclic analogs.[17]

The *m/e* 58 peak in the hexanal mass spectrum (Figure 1) corresponds formally to a "McLafferty plus 14" ion.[10a,18] Because of the multiple peak overlapping mentioned above and the low intensity of this ion at high voltage, the site specificity of this process could not be determined. Finally, brief mention may be made of the weak *m/e* 55 peak (Figure 1) which disappears completely in the low voltage spectrum (Figure 2). Judging from metastable peak evidence (Table IX), at least a portion of this ion arises by hydrogen ejection from an *m/e* 56 precursor.

m/e **44 Peak.** The *m/e* peak results from β-cleavage with hydrogen transfer to the charge-retaining C_2H_4O fragment. The site specificity of this hydrogen transfer is confirmed by the mass spectrum of hexanal-4,4-d_2 and heptanal-4,4-d_2 (>90% γ-hydrogen migration) and the reaction is therefore a typical McLafferty rearrangement[5] (Scheme VII), which is in marked contrast to the β cleavage with nonspecific hydrogen transfer and charge retention on the olefinic fragment (*m/e* 56) (Scheme IV). The intervention of this second sequence (Scheme IV) and its dominance at low voltage over the McLafferty rearrangement (Scheme VII) are an intriguing and significant difference in the behavior of aldehydes and ketones.

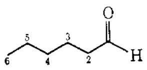
Scheme VII



i (*m/e* 44)

m/e **45 Peak.** The peak at *m/e* 45 in the mass spectra (Figures 1 and 3) of hexanal and heptanal corresponds to a "protonated McLafferty rearrangement" species already encountered in aliphatic acids[18] and ketones.[10,19] This mode of fragmentation is enhanced at low ionizing voltage. Predominant hydrogen transfer occurs from the γ and δ positions, involving six- and seven-membered transition states (Table VIII). The percentages quoted are considered accurate to no greater than ±5% since the neighboring *m/e* 44 peak hinders exact peak shift calculations. The values obtained at 70 and at 15 eV, however, do compare closely with each other. Similar labeling results have been obtained in the case of 2-octanone.[10a]

Table VIII. Mass Distribution of *m/e* 45 Peak in Deuterated Hexanals

Compound  	Relative abundance, %	
	70 eV	15 eV
3,3-d_2	45 (90%)	45 (90%)
	40 (10%)	46 (10%)
4,4-d_2	45 (10%)	56 (16%)
	46 (90%)	46 (84%)
5,5-d_2	45 (30%)	45 (26%)
	46 (70%)	46 (74%)
6,6,6-d_3	45 (82%)	45 (84%)
	46 (18%)	46 (16%)

m/e **29 Peak.** Attention has already been drawn in the earlier literature[6] to the fact that the *m/e* 29 peak in lower aldehyde mass spectra corresponds largely to the formyl cation (CHO^+) but that $C_2H_5^+$ ion predominates in the mass spectra of aldehydes with longer alkyl chains. Our high-resolution mass measurements (Tables I and II) with hexanal and heptanal confirm this conclusion.

Metastable Transitions. As part of this investigation metastable transitions of hexanal and heptanal were monitored in both the first and second field free regions of the AEI MS-9 mass spectrometer. Metastable transitions found for hexanal and heptanal in the second field region are depicted in Figures 1 and 3. Other metastable peaks were observed but competing processes made assignment equivocal. Transitions occurring in the first field free region of the MS-9 mass spectrometer are recorded for hexanal and heptanal in Tables IX and X.

Table IX. Metastable Transitions of Hexanal Occurring in the First Field Free Region at 70 eV

Daughter ion screened	Parent ions found
72	100
71	100
58	100, 73, 59
57	100, 72, 58
56	100, 57
55	83, 56
45	72
44	72, 45
43	71, 44
42	72, 70, 58, 57, 43
41	81, 69, 67, 59, 57, 56, 43

Table X. Metastable Transitions of Heptanal Occurring in the First Field Free Region at 70 eV

Daughter ion screened	Parent ions found
86	114
72	114, 87
71	114, 86
70	114, 71
68	114, 96, 86
57	86, 85, 72, 58
55	96, 83, 73, 70, 56
45	86, 46
44	86, 72, 45

Synthesis of Labeled Compounds. In general, the deuterated aldehydes used in this study were made from the corresponding alcohols which were in turn obtained by lithium aluminum hydride reduction of the appropriately labeled carboxylic acids. An exception was heptanal-3,3-d_2 which was synthesized by treating pentyl-1,1-d_2 bromide with the anion of 2-methyldihydro-1,3-oxazine, reduction with sodium borohydride, and hydrolysis.[20]

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(16) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 269 (1964).

(17) G. Eadon and C. Djerassi, *ibid.*, **91**, 2724 (1969).

(18) N. C. Rol, *Rec. Trav. Chim.*, **84**, 413 (1965).

(19) G. Spiteller, "Massenspektrometrische Strukturanalyse Organischer Verbindungen," Verlag Chemie, Weinheim, 1966, p 127.

(20) A. I. Meyers, A. Nabeya, H. Adickes, and I. R. Politzer, *J. Am. Chem. Soc.*, **91**, 763 (1969).

Hexanoic acid-6,6,6-d_3 was prepared as follows. Acetic-d_4 acid was reduced with lithium aluminum hydride in dry diglyme.[21] The labeled ethanol obtained was treated with H_2SO_4–HBr to form the bromide, and the alkyl chain was extended to six by successive diethyl malonate alkylations, hydrolyses, and decarboxylations. Conversion to hexyl-6,6,6-d_3 bromide and carbonation of the corresponding Grignard reagent gave heptanoic-7,7,7-d_3 acid.

Hydrolysis of diethyl methylmalonate in sodium deuteroxide followed by decarboxylation through addition of phosphorus trichloride gave propionic-2,2-d_2 acid.[22] Reduction, treatment with H_2SO_4–HBr, and diethyl malonate alkylation followed by hydrolysis and decarboxylation produced pentanoic 4,4-d_3 acid. Subsequent reduction, treatment with H_2SO_4–HBr, and carbonation of the corresponding Grignard reagent gave hexanoic-5,5-d_2 acid. Heptanoic-6,6-d_2 acid was prepared by treating the Grignard reagent prepared from hexyl-5,5-d_2 bromide with dry carbon dioxide.

The remaining labeled acids were similarly synthesized by reduction of the appropriate carboxylic acid with lithium aluminum deuteride and extension of the carbon chain when necessary by diethyl malonate alkylation and/or Grignard reagent carbonations.

Oxidation of the labeled alcohols was achieved with dimethyl sulfoxide together with sulfur trioxide (in the form of its pyridine complex) and triethylamine.[23] Each of the labeled alcohols was treated with N-methylisatoic anhydride in dry dioxane in the presence of potassium hydroxide.[24] The ester obtained was purified by thin layer chromatography and a mass spectrum obtained. Analysis of the molecular ion (base peak) gave the isotopic purity of the alcohol.

Experimental Section

Mass spectra were obtained by Mr. C. Carroll on an Atlas CH-4 instrument using the E-4B ion source and direct insertion probe (samples absorbed on charcoal). Isobaric hydrocarbon and oxygen-containing peaks were separated by Mr. R. G. Ross using an AEI MS-9 double focusing instrument (heated inlet 150°, ion source temperature 180°) by medium resolution scanning (resolution 5000, 10% valley definition). Low-resolution aldehyde spectra were also obtained on the MS-9 spectrometer under the above conditions. Metastable transitions in the first field free region of the MS-9 were observed with the aid of the metastable defocusing technique.[7]

Deuterated Aldehydes. For each of the labeled aldehydes, oxidation of the corresponding alcohol was conveniently carried out as follows. A solution of pyridine–sulfur trioxide complex[25] (4.5 mmoles) in dry dimethyl sulfoxide (8 ml) was added to a mixture of the alcohol (1.5 mmoles), dimethyl sulfoxide (8 ml), and triethylamine (11 mmoles). The magnetically stirred reaction mixture was maintained at room temperature during the addition and subsequent 15-min reaction period. After acidification with 10% sulfuric acid, the reaction mixture was extracted (three times) with ether. The aldehyde was purified by vapor phase chromatography using a 10-ft, 0.2 in. diameter Carbowax 20M column (15% on 80–100 Chromosorb P, acid washed) using a flow rate of 50% maximum.

Hexanol-6,6,6-d_3. To 150 ml of dry diglyme in a 1-l. three-necked flask fitted with a dropping funnel, nitrogen inlet, and mechanical stirrer was added 9.5 g of lithium aluminum hydride. Next, 15 g of acetic-d_4 acid (dissolved in twice its volume of dry diglyme) was added to the stirred mixture dropwise over a period of 30 min. The ice bath was replaced with a heating mantle and the reaction mixture heated at 70° for 2 hr. The ice bath was restored and 162 g of diethylene glycol monobutyl ether was added (very cautiously at first to minimize foaming). The resulting ethanol-2,2,2-d_3 was distilled from the reaction mixture until the head temperature reached 160°. Redistillation gave 9.3 g (81% yield) of the labeled ethanol (bp 77–78°).

Hydrogen bromide (48%, 28 ml) and concentrated sulfuric acid (6.5 ml) were placed in a three-necked, 100-ml flask equipped with a dropping funnel, short-path distillation column, serum cap, and magnetic stirrer. The alcohol was added with a syringe and the flask heated (oil bath temperature 100°). The ethyl-2,2,2-d_3 bromide distilled out and was collected in a Dry Ice–acetone bath cooled flask. During this distillation concentrated sulfuric acid (11 ml) was added using the dropping funnel. After drying over magnesium sulfate, redistillation afforded 17.2 g of ethyl-2,2,2-d_3 bromide (84%), boiling at 37–38°.

In a nitrogen atmosphere, 3.8 g of metallic sodium was dissolved in 250 ml of absolute ethanol, and to this solution was added dropwise 26.4 g of diethyl malonate followed by 17.2 g of ethyl-2,2,2-d_3 bromide (magnetic stirring). The reaction was stirred at room temperature overnight and then heated under reflux for 2 hr. The ethanol was distilled from the reaction mixture and 34 g of potassium hydroxide in 35 ml of water slowly added. The solution was then heated under reflux for 4 hr. Ethanol was distilled from the reaction mixture until the head temperature reached 100°. The reaction mixture was cooled in an ice bath, 60 g of concentrated sulfuric acid in 90 ml of water added, and the mixture again heated under reflux overnight. The butyric-4,4,4-d_3 acid was steam distilled from the reaction mixture and extracted with ether.

The crude labeled butyric acid in ether was added dropwise to a well-stirred suspension of 16 g of lithium aluminum hydride in anhydrous ether at 0°. The reaction proceeded at room temperature overnight and was then heated under reflux for 2 hr. The excess lithium aluminum hydride was decomposed by the dropwise addition of 10% sulfuric acid. After ether extraction, the mixture was dried over anhydrous magnesium sulfate, filtered, and distilled yielding 5.3 g of butanol-4,4,4-d_3.

Treatment of the butanol-4,4,4-d_3 (5 g) with 48% hydrobromic acid and concentrated sulfuric acid in the usual manner gave 6 g of butyl-4,4,4-d_3 bromide. Alkylation with 5.8 g of diethyl malonate, followed by hydrolysis and decarboxylation as previously described, yielded 2.3 g of hexanoic-6,6,6-d_3 acid. Further reduction with lithium aluminum hydride as previously described yielded hexanol-6,6,6-d_3.

Hexanol-5,5-d_2. Deuterium labeling was accomplished using a procedure similar to that employed by Duffield, *et al.*[22] Sodium metal (20 g) was added over a period of 2 hr to 100 ml of deuterium oxide cooled to 0° and mechanically stirred. The solution was heated to reflux and 25 g of diethyl methylmalonate was added over a period of 45 min. After refluxing for another 5 hr, the ethanol was distilled out until head temperature reached 100°. The mixture was then cooled to 0° and phosphorus trichloride was slowly added over a period of 2 hr. After heating under reflux for 20 hr, the resultant acidic mixture was distilled almost to dryness, 25 ml of deuterium oxide added, and the process repeated. The combined distillate was continuously extracted with ether overnight and then dried over anhydrous magnesium sulfate. The ether solution was added to a slurry of lithium aluminum hydride (8 g) in anhydrous ether (200 ml), and the reaction allowed to proceed at 25° for 5 hr and then heated under reflux for 1 hr. Isolation in the usual manner using 10% sulfuric acid afforded 7 g of propanol-2,2-d_2.

Treatment of propanol-2,2-d_2 (9.3 g) with 48% hydrobromic acid (22 ml) and concentrated sulfuric acid (5.3 ml) in the usual fashion gave 10.4 g of propyl 2,2-d_2 bromide. Diethyl malonate alkylation (13.1 g), hydrolysis, and decarboxylation as previously described yielded after lithium aluminum hydride reduction and distillation 4.8 g of pentanoic 4,4-d_3 acid. Treatment with 11.8 ml of 48% hydrobromic acid and 3 ml of concentrated sulfuric acid gave pentyl-4,4-d_2 bromide (4.1 g). The Grignard reagent (780 mg of magnesium, 4 g of pentyl-4,4-d_2 bromide) was prepared in anhydrous ether in the usual manner. After cooling the reaction mixture to −78°, gaseous carbon dioxide was slowly bubbled through the vigorously stirred solution for 10 min. The mixture was then allowed to warm to room temperature. Isolation in the usual manner (10% sulfuric acid) and distillation yielded 2.2 g of hexanoic-5,5-d_2 acid. Lithium aluminum hydride reduction of 990 mg of hexanoic-2,2-d_2 acid afforded 700 mg of hexanol-2,2-d_2 after distillation.

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[21] L. Friedman and A. T. Jurewicz, *J. Org. Chem.*, **33**, 1254 (1968).

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

[23] J. R. Parikh and W. von E. Doering, *ibid.*, **89**, 5505 (1967).

[24] R. M. Teeter, *Anal. Chem.*, **38**, 1736 (1966).

[25] Purchased from the Eastman Chemical Co., Rochester, N. Y.

Other Deuterium-Labeled Compounds. Hexanol-4,4-d_2, hexanol-3,3-d_2, hexanol-2,2-d_2, hexanol-1,1-d_2, and heptanol-1,1-d_2 were prepared in a similar fashion and on a similar scale as the previously described deuterium-labeled compounds. Deuterium labeling was accomplished in each instance by reducing the appropriate carboxylic acid with lithium aluminum deuteride.[26] Heptanal-3,3-d_2 was prepared from pentyl-1,1-d_2 bromide by the method of Meyers, *et al.*[20]

Preparation of the *o*-N-Methylaminobenzoate Esters of the Deuterium-Labeled Compounds.[24] In the case of hexanol-3,3-d_2, N-methylisatoic anhydride (71 mg) was added to a mixture of 2 ml of dry dioxane, one-half pellet of potassium hydroxide (crushed), and hexanol-3,3-d_2 (42 mg). The mixture was heated (70°) for 10 min. After drying over magnesium sulfate and concentration, the product ester was purified by preparative tlc (ether-hexane 1:1). Mass spectrometry indicated the presence of 97% d_2 and 3% d_1 species. Similar procedure was followed for the other labeled alcohols.

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(26) Purchased from Karl Roth OHG, Karlsruhe, Germany.

Haller–Bauer Cleavage of Cyclopropyl Phenyl Ketones

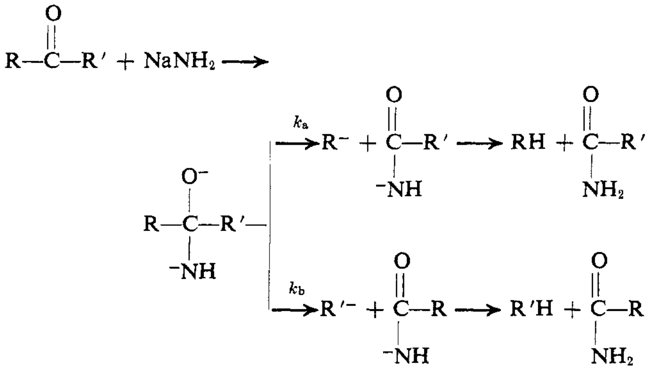
Carl L. Bumgardner and Kenneth G. McDaniel

Contribution from the Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607. *Received July 10, 1969*

Abstract: A number of cyclopropyl phenyl ketones substituted on the small ring were subjected to the Haller–Bauer reaction to resolve some inconsistencies in the literature and to learn more of the factors which determine the direction of cleavage. The results may be understood in terms of fragmentation to give the more stable carbanion intermediate except in the cases of (*Z*)-2-phenylcyclopropyl phenyl ketone and 1-methyl-2,2-diphenylcyclopropyl phenyl ketone. Steric relief appears to play an important role in these two examples. The original report of Haller and Benoist regarding the major products from cleavage of 1-methylcyclopropyl phenyl ketone is believed to be in error.

The cleavage of nonenolizable ketones with sodium amide, the Haller–Bauer reaction, has been known for some time and has been reviewed by Hamlin and Weston.[1] The reaction is believed to proceed by attack of amide ion on the carbonyl carbon giving rise to an intermediate which decomposes to yield ultimately a hydrocarbon and a carboxamide.[2]

Scheme I



As shown in Scheme I, if the groups originally attached to the keto carbonyl are different then cleavage may occur in two directions. Any preference for the mode of cleavage would be expected to be a reflection of the relative stability of the carbanions involved.[2,3]

Some apparent anomalies become obvious, however, when the results of substituted cyclopropyl phenyl ketone cleavages are examined. Haller and Beniost[4] reported that 1-methylcyclopropyl phenyl ketone underwent cleavage to give benzamide and a gas, presumably methylcyclopropane, both in unspecified yield. In the course of a study of the stereochemistry of cyclopropyl carbanions, Impastato and Walborsky[5] subjected 1-methyl-2,2-diphenylcyclopropyl phenyl ketone to sodium amide and isolated in high yield 1-methyl-2,2-diphenylcyclopropane. In contrast to these observations where benzamide and a cyclopropyl hydrocarbon were the major products, Piehl and Brown[6] noted that cleavage of 1-benzylcyclopropyl phenyl ketone led to 1-benzylcyclopropanecarboxamide in at least 56% yield. Their finding was later confirmed in this laboratory when the Haller–Bauer reaction was used as a step in the synthesis of phenylspiropentane.[7]

Hamlin and Biermacher[8] reported that 1-alkylcyclohexyl, 1-alkylcyclopentyl, and 1-alkylcyclobutyl phenyl ketones all gave mainly the corresponding 1-alkylcycloalkanecarboxamides.

To resolve some of these inconsistencies and to obtain information concerning factors which might influence the stability of cyclopropyl anions, we studied the Haller–Bauer cleavage of several substituted cyclopropyl phenyl ketones. The earlier work of Haller and Benoist[4] was also repeated so that their results could be placed on a quantitative basis.

Preparation of Ketones

1-Methylcyclopropyl phenyl ketone was prepared in 81% yield by treatment of cyclopropyl phenyl ketone with triphenylmethylpotassium followed by methyl

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(1) K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 1 (1957).

(2) (a) J. F. Bunnett and B. F. Hrutfiord, *J. Org. Chem.*, **27**, 4152 (1962); (b) G. W. Kenner, M. J. T. Robinson, C. M. B. Taylor, and B. R. Webster, *J. Chem. Soc.*, 1756 (1962).

(3) A. Streitwieser, Jr., and R. G. Lawer, *J. Amer. Chem. Soc.*, **87**, 5388 (1965).

(4) A. Haller and E. Benoist, *Ann. Chim.* (Paris), [9] **17**, 25 (1923).

(5) F. J. Impastato and H. M. Walborsky, *J. Amer. Chem. Soc.*, **84**, 4838 (1962).

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(8) K. E. Hamlin and U. Biermacher, *J. Amer. Chem. Soc.*, **77**, 6376 (1955).