

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Mass Spectrometry in Structural and Stereochemical Problems. XLIII.¹ Mass Spectrometric Fragmentation of Isohexyl Bromide and Five Deuterated Derivatives

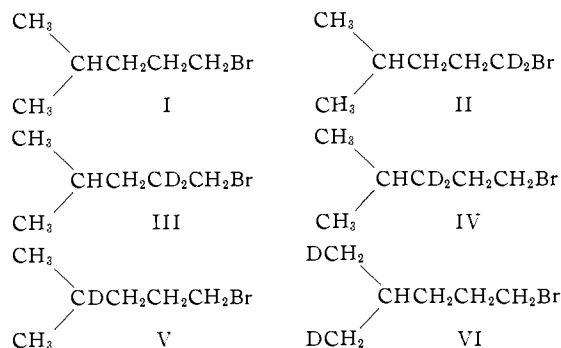
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A detailed interpretation of the mass spectrum of isohexyl bromide has been made possible by a study utilizing five labeled analogs in which all the nonequivalent hydrogen atoms have been replaced by deuterium.

Introduction

As a result of our synthetic program to obtain cholestan-16-ones selectively deuterated in the side chain,²



we had available 4-methylpentyl bromide (I) and its 1,1-*d*₂- (II), 2,2-*d*₂- (III), 3,3-*d*₂- (IV), 4-*d*₁- (V), and 1'-*d*₁-4-methyl-5-*d*₁-pentyl (VI) analogs.

In view of the fact that only one study of deuterated alkyl bromides has hitherto been reported,³ it was of interest to determine the mass spectra of the isohexyl bromides I-VI in the hope of being able to extend our knowledge of the fragmentation processes of monohalogenated aliphatic compounds, which is mainly due to McLafferty.⁴

Discussion of Mass Spectral Fragmentation Processes

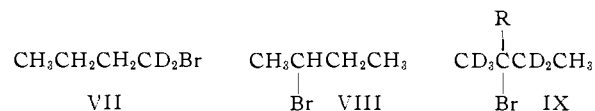
While the isotopic purity of the five deuterated analogs II-VI was known to be high from our studies of the mass spectra of cholestan-16-one² into which the labeled isohexyl skeletons had been incorporated, an independent calculation of this parameter was desirable. Since the molecular ion in the spectrum (Fig. 1) of isohexyl bromide is weak, the medium intensity M - Br ion (*m/e* 85) was chosen for this purpose. The analysis is complicated by the presence of the low intensity M - HBr ion at *m/e* 84. Since any M - Br fragment arising from *d*₁-contaminant in II, III, IV, and VI or *d*₀-contaminant in V will overlap with the M - HBr ion in these compounds, it is first necessary to establish any shifts of the dehydrohalogenated fragment. The mass spectra of the six bromides in the region of the M - Br ion are given in Table I, the intensity of the C₆-H₁₃⁺ fragment being arbitrarily taken as 100.

If a specific source of hydrogen were involved in the loss of hydrogen bromide, then a shift of the 5% M - HBr peak to M - DBr would be detectable. The absence of such a shift suggests that the hydrogen atom may be abstracted in a random fashion, but, owing to the low intensity of the peak, quantitative calculations are impossible. It must be stated that the loss of hydrogen halide from alkyl halides can be most conveniently studied in chlorides where the loss of hydrogen chloride

TABLE I
MASS SPECTRA OF ISOHEXYL BROMIDE AND ITS DEUTERATED
ANALOGS IN THE REGION OF THE M - Br ION

Compound	<i>m/e</i> values						
	82	83	84	85	86	87	88
I	2	2	5	100	7		
II			1	2	12	100	7
III			1	2	11	100	7
IV			1	1	6	100	6
V		1	1.3	2	100	6	
VI				2	8	100	7

is much more pronounced.⁴ Thus, McFadden³ encountered a similar difficulty in 1,1-*d*₂-butyl bromide (VII) in which he could only conclude that involvement of hydrogen from C-1 was not "significant."



Quantitative conclusions were, however, possible for 2-bromobutane (VIII) from a study of the 1,1,1,3,3-*d*₅- (IX, R = H) and 1,1,1,2,3,3-*d*₆- (IX, R = D) analogs.³ The results showed that more than 86% of the hydrogen came from that attached to C-2 or C-4 and, of this, more than 73% involved only hydrogen on C-4; *i.e.*, 1,3-elimination predominated. However, while no such specificity is immediately evident in the present case, a remarkable feature is apparent in the M - HBr region of the spectrum of the 4-*d*₁-analog V: reference to Table I shows that any loss of HBr (*m/e* 85) or DBr (*m/e* 84) is, at the most, only 40% of the corresponding loss occurring in the parent. It must be concluded that replacement of the tertiary C-4 hydrogen by deuterium in isohexyl bromide inhibits the formation of the C₆H₁₂⁺ ion. It is therefore reasonable to postulate that in the parent bromide, hydrogen from C-4 is mainly involved in the loss of hydrogen bromide and that the steric requirements of the process are radically affected by substitution of deuterium for hydrogen. This hypothesis gains credence in view of the fact that discrimination against deuterium in a specific rearrangement process in the mass spectra of methyl butyrate and its γ -mono-, di-, and trideuterio analogs has been observed.⁵ This effect was attributed to the greater strength of the carbon-deuterium bond, although the smaller van der Waals radius of deuterium compared with hydrogen may be an additional factor. The isotope effect in the bromide must be much greater than that in the ester (0.88 atom of deuterium per atom of hydrogen). A plausible mechanism for the loss of HBr is shown below, a "fishhook" representing a one-electron shift and a full arrow representing a two-electron shift.^{5a}

(1) Paper XLII: J. A. Joule and C. Djerassi, *J. Chem. Soc.*, in press.

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

(3) W. H. McFadden and M. Lounsbury, *Can. J. Chem.*, **40**, 1965 (1962).

(4) F. W. McLafferty, *Anal. Chem.*, **34**, 2 (1962), and references cited therein.

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

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

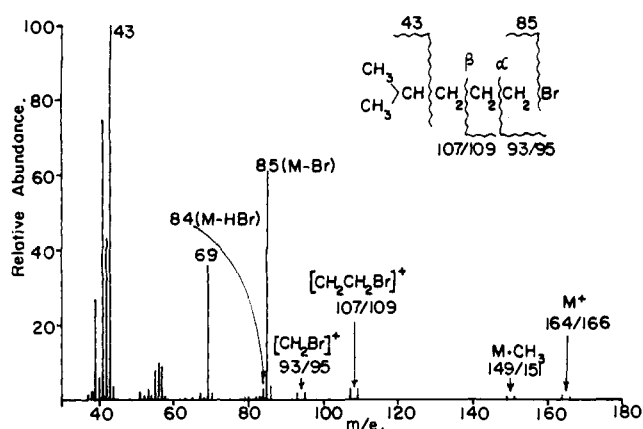
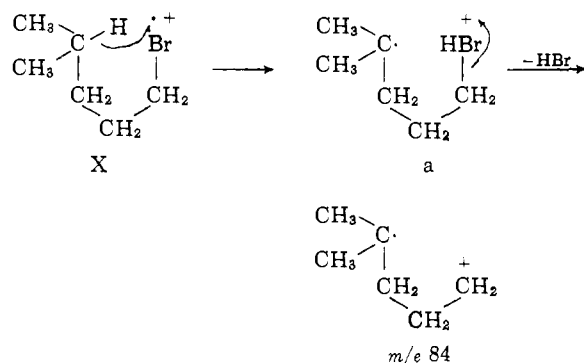


Fig. 1.—Mass spectrum of isohexyl bromide.

This cyclic process is identical with those presented to explain similar phenomena in alcohols.⁶



Removal of one of the lone pair electrons from bromine to yield the molecular ion X is reasonable in view of the fact that the ionization potential of alkyl bromides (e.g., methyl bromide, 10.5 e.v.^{7a}) is smaller than that of the corresponding hydrocarbon (e.g., methane, 14 e.v.^{7b}). The second step, X → a, transfer of a hydrogen radical in a six-membered transition state with the generation of a tertiary radical, is also a common process in mass spectrometric fragmentation.⁸

Returning now to Table I for the purpose of calculating the isotopic purity of the samples, it can be seen that the intensity of the (M - Br) + 1 ion is 6–7% of the M - Br ion in all the bromides. Hence, the d_2 -compounds (II, III, IV, VI) do not contain any d_3 -species and the d_1 -compound V does not contain any d_2 -species, because the isotope peak due to the M - Br fragment is 6.6%. Since it has been established that there is no appreciable loss of DBr from the 1,1- d_2 - (II), 2,2- d_2 - (III), 3,3- d_2 - (IV), and the 1'- d_1 -4-methyl-5- d_1 - (VI)-derivatives, the percentage of d_1 -contaminant in these materials can be obtained by subtraction of the M - HBr peak in isohexyl bromide (5% in Table I) from the respective M - HBr peaks (12, 11, 6, and 8% in Table I). The 4- d_1 -analog is of necessity at least 98% pure (and very probably purer), its high percentage purity being compatible with its mode of preparation from the hydrolysis of the sodio derivative of a malonate ester by deuterium oxide (99.7% purity).² In contrast, in the other labeled derivatives, deuterium was incorporated by lithium aluminum deuteride reduction of either tosylates (VI) or acids (II, III, IV).²

(6) W. H. McFadden, M. Lounsbury, and A. L. Wahrhaftig, *Can. J. Chem.*, **36**, 990 (1958).

(7) (a) V. H. Dibeler and R. M. Reese, *J. Research Natl. Bur. Standards*, **64**, 127 (1955); (b) L. G. Smith, *Phys. Rev.*, **51**, 263 (1937).

(8) See for example, W. Vetter, P. Longvialle, F. Khung-Hui-Laine, Q. Khwong-Hui, and R. Goutarel, *Bull. soc. chim. France*, 1324 (1963).

The isotopic purity of the deuterated isohexyl bromides are summarized in Table II, where the figures represent maximum isotopic impurity levels. For purposes of comparison, the isotopic purities of the derived cholestan-16-ones² are given in the last column of Table II. It is obviously not permissible that the isotopic purity of these ketones be greater than those of the corresponding bromides. It can be seen that the 2,2- d_2 -derivative III and the terminally labeled bromide VI do not fall within this criterion of consistency, and even here the anomaly would be resolved by as little as 1% error in each figure.

TABLE II
ISOTOPIC PURITY (%) OF DEUTERATED ISOHEXYL BROMIDES

	d_0	d_1	d_2	Purity in derived 16-ones, ² %
II		6	94	88
III		6	94	95
IV		1	99	93
V	≥ 98			99
VI		3	97	99

Having established the isotopic purity of the bromides, a general discussion of the fragmentation pattern follows, and finally a detailed analysis of rearrangement ions is given.

It can be seen from reference to Fig. 1 that the base peak in the spectrum of I is at m/e 43. The shifts of this peak (m/e 44 in the 4- d_1 -analog V, and m/e 45 in the 1',5- d_2 -analog VI) establish that it is predominantly due to the terminal isopropyl group. The necessary rupture of the 3–4 bond is independent of the halogen atom since McLafferty has shown⁴ that bromine does not enhance cleavage of alkyl chains beyond the 1–2 bond. This carbon-carbon fission at branched centers is a characteristic feature of hydrocarbon spectra, to which the spectra of halides containing large alkyl chains do in fact approximate.⁴ The proximity of the m/e 41 and 42 ions makes it impossible to speculate as to whether any double rearrangement is involved in the formation of this fragment. These m/e 41 and 42 fragments must correspond to $C_3H_5^+$ and $C_3H_6^+$, respectively, but in the presence of three abundant ions differing only by unit mass one cannot establish the origins of these ions.

The M - Br (m/e 85) ion was used for the calculation of isotopic purities and needs no further comment except to note that loss of the isolated heteroatom is usually an important feature of the spectra of alkyl bromides and iodides.⁴ The ion at m/e 69 is a very interesting one and corresponds to the loss of methyl and hydrogen bromide, which is a common process in alkyl bromides containing up to six carbon atoms and usually gives rise to ions of medium intensity. Although it is plausible that this fragment arises through loss of a methyl group from the M - HBr ion (m/e 84, Fig. 1), loss of methane from the M - Br ion (m/e 83, Fig. 1), or alternatively elimination of hydrogen bromide from the M - CH_3 ion (m/e 149/151, Fig. 1), no metastable peaks are evident to support any of these processes. The m/e values of this ion in six bromides are indicated in Table III. The figures are corrected for the isotopic purity of the deuterated analogs and the M - CH_3 Br ion is arbitrarily taken as 100 in each case, except for VI, where M - CH_3 DBr is taken as 100, since the almost complete shift of m/e 69 in I to m/e 70 in VI necessitates the loss of a terminal methyl group in this fragmentation.

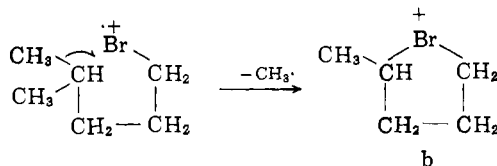
However, there is a significant loss (5%) of d_2 from the analog labeled at C-1 (II). This necessitates that 5% of the M - CH_3 Br ion does not involve loss of a terminal methyl group, which is corroborated by the approxi-

TABLE III
 SOURCE OF HYDROGEN ATOM LOST IN $M - CH_2Br$ ION

Compd.	m/e					Deuterium transferred (%)		Atoms deuterium transferred (d_1)
	67	68	69	70	71	d_1	d_2	
I	4	1.5	100	6	1
II			10	14	100	10.5	5.0	0.10(5)
III			5	20	100	15.5	0.8	.15(5)
IV			5	33	100	24.0	0.7	.24(0)
V	4		12	100		9.509(5)
VI	3		10	100	11	23.423(5)
(3 × 7.8)						Total		0.83

mately 5% intrinsic m/e 71 value in VI (after allowing for the abundance of ^{13}C in m/e 70). The total loss of d_1 (0.83 atom) is consistent with the operation of a small isotope effect. In view of the almost random loss of hydrogen, it would seem profitless to propose specific mechanisms. However, it has been suggested³ that saturated parent molecule ions randomize H and D slowly (relative to the bond break), but unsaturated parent ions or fragment ions exchange rapidly (relative to their decomposition). Since the data seem to indicate loss of a terminal CH_3 with very little rearrangement and loss of HBr in which H and D have almost statistically exchanged, the order of decomposition seems to be loss of CH_3 followed by loss of HBr.

Four low intensity doublets are evident in the high mass region of the spectrum (Fig. 1). These ions must therefore contain the heteroatom, since bromine consists of two stable isotopes, ^{79}Br and ^{81}Br , in approximately equal amounts. The doublet at m/e 164/166 is the molecular ion, while the ion at m/e 149/151 corresponds to loss of a methyl group. The shift in this latter fragment to m/e 150/152 in the terminally labeled d_2 -analog VI establishes that an end-of-chain methyl group is lost. McLafferty⁴ has proposed that this type of process occurs with the formation of a five-membered cyclic ion b.



When such a five-membered ion is substituted, as in the present case, it is usually only of low intensity.⁴ This generalization is satisfied here, as is also the one requiring that cyclic ions will be of low abundance in the presence of prominent $M - Br$ ions.

The two remaining doublets at m/e 93/95 and 107/109 correspond to α - and β -cleavage^{5a} of the alkyl chain, respectively (see Fig. 1). The first process usually gives rise to ions of low abundance in the spectra of alkyl bromides and is formally analogous to the simple α -cleavage occurring in alcohols,⁹ amines,¹⁰ and ketones.¹¹ Examination of the spectrum of the 1,1- d_2 -analog II indicates that there is some rearrangement of one and two hydrogen atoms in each direction in the present case. However, the loss of deuterium from the $[CD_2Br]^+$ fragment only prevails to the extent of 0.24 atom (12% transfer of one deuterium atom and 6% transfer of two deuterium atoms) and for such a small peak it is impossible to establish the source of hydrogen which is, of necessity, returned of the charge-retaining fragment. It should be noted that this result does not differ

(9) C. S. Cummings and W. Bleakney, *Phys. Rev.*, **56**, 787 (1940).

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

(11) A. G. Sharkey, J. L. Schultz, and R. A. Friedel, *ibid.*, **28**, 934 (1956).

markedly from that of McFadden and Lounsbury,³ who established that approximately 15% exchange of deuterium for hydrogen takes place during the α -cleavage in 1,1- d_2 -butyl bromide (VII).

However, the extent of rearrangement associated with β -cleavage is considerably greater. The mass spectra of the six bromides in the region of the $[CH_2-CH_2Br]^+$ ion, corrected for isotopic abundances and with the unrearranged ion containing ^{79}Br arbitrarily taken as 100, are reproduced in Table IV.

 TABLE IV
 SOURCE OF HYDROGEN REARRANGEMENT IN $[CH_2CH_2Br]^+$ ION

Compound	m/e values							
	105	106	107	108	109	110	111	112
I	7	7	100	8	91	3	3	
II			24	22	100	29	75	3
III			35	67	100	67	68	3
IV	5	9	100	63	100	55	11	
V	6	9	100	30	86	27	2	
VI	7	5	100	24	91	22	2	
Deuterium lost, %								
		d_1		d_2		Atoms lost		
II		11		12.5		0.36		
III		32		15		0.62		
						Total lost		
						0.98		
Deuterium gained, %								
		d_1		d_2		Atoms gained		
IV		32		5		0.42		
V		28		..		0.28		
VI		21		..		0.21		
						Total gain		
						0.91		

The results show that the β -cleavage is associated with the transfer of approximately one deuterium atom in each direction. The agreement between total loss and total gain is very close, as it should be if one assumes that any isotope effect will have the same value for all C-D bonds. Despite the participation of all hydrogen atoms in the rearrangement process, those attached to C-2 and C-3 are involved to the greatest extent. While this may seem reasonable in view of the proximity of these hydrogens to the site of bond rupture, such processes will always necessitate the breaking of two or three bonds of the same carbon atom (C-2 or C-3). Clearly, the generally fruitful concept that fragmentation will occur with the genesis of the most stable organic intermediates^{5a,12,13} is not applicable to the formation of this ion. In contrast to the present instance, β -cleavage of 1,1- d_2 -butyl bromide (VII) upon electron impact has been shown to proceed without loss of deuterium from C-1.³

Experimental

The syntheses of the deuterated isohexyl bromides have previously been described.² The samples so obtained were purified by preparative gas-liquid chromatography (Wilkins Aerograph Instrument, Walnut Creek, Calif.) on a 20% silicone rubber column operating at 60°, the retention time of the halides being approximately 5 min.

The mass spectra were measured with a CEC 21-103C mass spectrometer equipped with a heated all-glass inlet system (200°). The ionizing energy was maintained at 70 e.v. and the ionizing current at 50 μ a.

Acknowledgment.—Financial support by the National Institutes of Health (Grants No. AM-04257 and 5TI-GM-682) is gratefully acknowledged.

(12) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(13) F. W. McLafferty in "Determination of Organic Structures by Physical Methods," Vol. II, F. C. Nachod and W. D. Phillips, Ed., Academic Press, Inc., New York, N. Y., 1962, p. 113.