# Mass Spectrometry in Structural and Stereochemical Problems. CCXVII.<sup>1</sup> Electron Impact Promoted Fragmentation of *O*-Methyl Oximes of some $\alpha,\beta$ -Unsaturated Ketones and Methyl Substituted Cyclohexanones

YOUNUS M. SHEIKH, RAYMOND J. LIEDTKE, A. M. DUFFIELD, AND CARL DJERASSI Departments of Chemistry and Genetics, Stanford University, Stanford, California 94305

Received February 15, 1972

Deuterium labeling and high resolution mass spectrometry have been utilized to delineate the modes of mass spectrometric fragmentation of O-methyl oximes of  $\alpha,\beta$ -unsaturated ketones and methyl substituted cyclohexanones.  $\alpha,\beta$ -Unsaturated ketone and 2- and 4-methylcyclohexanone O-methyl oxime ether derivatives fragment upon electron impact in a manner reminiscent of the carbonyl derivatives from which they were prepared. However, several fragmentation sequences characteristic of the O-methyl oxime ether group were observed.

Le marquage au deutérium et la spectrométrie de masse à haute résolution ont été utilisés pour décrire le spectre de fragmentation des oximes O-méthylés de cétones  $\alpha,\beta$  insaturées et de cyclohexanones substituées par le méthyle. La cétone  $\alpha,\beta$  insaturée et les dérivés de la méthyl-2 et -4 cyclogexanone oxime O-méthyle éther se fragmentent lors de l'impact électronique, de façon semblable aux dérivés carbonylés à partir desquels ils ont été préparés. Cependant, plusieurs séquences de fragmentation caractéristiques du groupe oxime O-méthyl éther ont été observées. [Traduit par le journal]

Canadian Journal of Chemistry, 50, 2776 (1972)

O-Methyl oxime ether derivatives have found extensive use in g.c. and g.c./m.s. studies of relatively complex molecules (1). Recent publications (2) described for the first time the electron impact sponsored fragmentation processes of O-methyl oxime ethers. The present paper extends the knowledge of the mass spectral fragmentation behavior of this class of compound to  $\alpha,\beta$ -unsaturated ketones and methyl substituted cyclohexanone derivatives and defines, using deuterium labeling, some of the rearrangement processes accompanying their fragmentation.

## O-Methyl Oxime Ethers of Aliphatic α,β-Unsaturated Ketones

Prominent molecular ions are an important and useful feature of the mass spectra (see for example Figs. 1-4) of the O-methyl ether oxime derivatives of the  $\alpha,\beta$ -unsaturated ketones

$$\begin{array}{c} N-OCH_{3} \\ R-C-C=CH-R'' \\ R' \end{array}$$

$$\begin{array}{c} I \quad R=R'=R''=CH_{3} \\ 2 \quad R=C_{2}H_{5}; R'=H; R''=CH_{3} \\ 3 \quad R=CH_{3}; R'=H; R''=n-C_{3}H_{7} \\ 4 \quad R=CH_{3}; R'=H; R''=n-C_{4}H_{9} \\ 5 \quad R=CH_{3}; R'=H; R''=n-C_{5}H_{11} \\ 6 \quad R=CH_{3}; R'=H; R''=n-C_{6}H_{13} \end{array}$$





examined. Loss of a methyl radical from the molecular ion of 1 could involve either the two alkyl branches or the methyl group of the oxime ether function. Deuterium labeling  $(1, R = CD_3)$ established that 10% of the methyl lost in this fragmentation arose from C-1. Since ions due to  $M - CH_3$  occur in the spectra of compounds 1-6 the most likely position for the remaining loss of  $CH_3$  in 1 is the O-methyl oxime ether group (formation of a) but other sources not completely eliminated include the alkyl chains of 1-6. The facile expulsion of the methyl ether entity in aliphatic  $\alpha,\beta$ -unsaturated ketone Omethyl ether oxime derivatives (see Figs. 1-4) should be contrasted to the behavior observed (2) with the same derivative of aromatic aldehydes and ketones in which this process was not observed.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.

#### SHEIKH ET AL.: MASS SPECTROMETRY. CCXVII

41(C3H<sup>+</sup>70% - 12.3 100 N-OCH3 и С-сн=снсн<sub>з</sub> Per C2H3N 307 Cent 2 80 98 127 (M) 56(C3H6N\*92%) Total Albundonce 8.0 60 112 Ionization Relative 40 4.0 M 20 \* 40 120 140 eс 80 ıдо m/e







Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.



A characteristic fragmentation of the species **a** occurs by the elimination of water (metastable ion observed in all instances) and one representation for the product ion, using 1 as an example, is **b**, m/e 94 (Scheme 1). In the trideuterio derivative (1,  $R = CD_3$ ) most (80%) of the label was retained.

The ion of mass 96  $(M - OCH_3)$  in the mass spectrum (Fig. 1) of 1 is moved predominantly to m/e 99 in the corresponding trideuterated analog (1, R = CD<sub>3</sub>). This ion, assigned structure c, m/e 96, is envisaged as arising from a four-centered reaction in which the methoxyl radical attached to nitrogen is expelled. The species c decomposes by the elimination of a methyl radical (metastable ion observed) and the product is rationalized in terms of d, m/e 81. Only 60% of the ion yield at m/e 81 in Fig. 1 was located at m/e 84 in the spectrum of the tri-



FIG. 4. Mass spectrum (70 eV) of 6. (a) Mass spectrum (15 eV) of 6.

CANADIAN JOURNAL OF CHEMISTRY, VOL 50, 1972



deuterated compound 1 ( $\mathbf{R} = CD_3$ ) indicating that other modes of formation of m/e 81 exist. One possibility, which accounts for 25% of the ion yield, is depicted by  $\mathbf{1} \rightarrow \mathbf{d}'$ , m/e 81 (Scheme 2).

The ion of mass 86  $(M - CH_3CN)$  in the spectrum (Fig. 1) of 1 is analogous to the low abundance ion of mass 72  $(M - C_2H_5CN)$ observed in the mass spectrum (Fig. 2) of the ethyl analog 2. These processes presumably occur by a four-centered transition state (for instance  $1 \rightarrow e$ , m/e 86) (see Scheme 3). The CD<sub>3</sub> analog of 1 ( $R = CD_3$ ) surprisingly indicated that 70% of the trideuteriomethyl label was eliminated while loss of CHD<sub>2</sub>CN (15%), CH<sub>2</sub>DCN (40%), and CH<sub>3</sub>CN (11%) contributed to the overall process. Clearly some hydrogen-deuterium exchange must precede the formation of e. One rationalization for H-D scrambling is depicted by  $1 \rightarrow 1a$ . Further loss of a methyl radical from e serves as the origin for the ion  $(97\% C_4H_7O^+)$  of mass 71 in Fig. 1. In the CD<sub>3</sub> analog of 1 (R = CD<sub>3</sub>) the peak in question is distributed between m/e 71, 72, and 73. This indicates that further randomization of the label occurs prior to the formation of a species which we represent as **f**, m/e 71.

High resolution mass spectrometry established the composition of m/e 55 in the mass spectrum (Fig. 1) of 1 as 88% C<sub>4</sub>H<sub>7</sub><sup>+</sup>; 10% C<sub>3</sub>H<sub>5</sub>N<sup>+</sup>, and 2% C<sub>3</sub>H<sub>3</sub>O<sup>+</sup> while the corresponding ion in the ethyl analog (2, Fig. 2) at m/e 41 consisted of C<sub>3</sub>H<sub>5</sub><sup>+</sup> (70%) and C<sub>2</sub>H<sub>3</sub>N<sup>+</sup> (30%). The hydrocarbon ions can be interpreted as arising from the alkenyl portions of 1 and 2 respectively.

The abundant ion of mass 68 in the spectrum





(Fig. 2) of **2** owes its genesis (mestastable ion recognized) to the loss of ethylene (high resolution) from the ion  $\mathbf{c}', m/e 96$  (M - OCH<sub>3</sub>). This process could be rationalized in terms of a five-membered transfer of hydrogen to nitrogen  $(\mathbf{c}' \rightarrow \mathbf{g})$  (Scheme 4). Protonated acetonitrile (**h**, R = CH<sub>3</sub>) and propionitrile (**h**, R = C<sub>2</sub>H<sub>5</sub>) ions respectively account for the appearance of charged fragments of mass 42 and 56 in the mass spectra (Figs. 1 and 2) of 1 and 2. These conclusions are in agreement with the results from high resolution mass spectrometry.

$$R - C = NH$$
  
; 1,  $R = CH_3$ ,  $m/e$  42  
2,  $R = C_2H_5$ ,  $m/e$  56

The effect of substituting an alkyl chain for the methyl group  $(\mathbb{R}^n)$  can be gauged from the mass spectra (Figs. 3 and 4) of compounds 4 and 6 which contain an *n*-butyl and *n*-hexyl chain respectively. In the case of the *n*-hexyl derivative (6) extensive deuterium labeling has made possible the presentation of plausible fragmentation pathways.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.

The molecular ions of compounds (3-6) are abundant (see for instance Figs. 3 and 4) while the M - 15 species is of reduced ion yield. The expulsion of a methyl radical from the parent species of these compounds is ascribed in 50%yield to a process analogous to that postulated for the formation of **a** since equal losses of  $CD_3$ and  $CH_3$  were observed in the spectrum of 6a. On lowering the ionizing voltage to 15 eV loss of  $CH_3$  was twice as frequent in **6***a* as loss of  $CD_3$ . The low ion yield resulting from the elimination of  $CD_3$  in 6a should be contrasted to the situation observed (3) for the parent  $\alpha,\beta$ saturated ketone (7) where expulsion of C-1 accounted for the origin of the base peak at 12 eV.



**6**a

The loss of a methoxyl radical from the molecular ions of the alkyl substituted derivatives (3-6) is explicable by a process analogous to that suggested for the formation of ion c. The ion of mass 137  $(M - CH_4NO)$  by high resolution) in the mass spectrum (Fig. 4) of 6is accompanied by metastable ion formation. indicating the molecular ion to be its precursor, and similar expulsions are observed in the mass spectra of 3, 4, and 5. Deuterium labeling in the *n*-hexyl derivative indicated that hydrogen was eliminated from C-6 (0.55), C-7 (0.20), and a combined total of 0.25 from C-1 and -3. This process, using the *n*-hexyl analog 6 as example, would yield j, m/e 137 (see Scheme 5). A metastable ion established a parent-daughter relationship between j and the species of mass 81 which we designate as  $\mathbf{k}$ . High resolution mass spectrometry confirmed the loss of  $C_4H_8$ in this process since the ion of mass 81 was composed of  $C_6H_9^+$  (60%),  $C_5H_7N^+$  (33%), and  $C_5H_5O^+$  (7%).

The peak at m/e 126 is the base peak in the spectra (see for instance Figs. 3 and 4) of the C-4 alkyl substituted methoxy oximes (3-6)studied. The results obtained from deuterated analogs of 6 are consistent with the assignment of structure **m**, m/e 126 to this ion. At low ionizing voltages (15 eV) the ion m remains the base peak (see Fig. 4a) and it should be noted that a similar process ( $\gamma$ -cleavage) generated an abundant ion in the mass spectra of the  $\alpha,\beta$ unsaturated ketones (3) from which the methoxy oximes were prepared. Loss of methanol from **m** (verified by a metastable ion) affords the fragment o, m/e 94 and high resolution mass spectrometry established this ion's composition as 97%  $C_6H_8N^+$  and 3%  $C_7H_{10}^+$ . Deuterium labeling indicated that only 0.30 of one hydrogen atom (see Scheme 6,  $\mathbf{m} \rightarrow \mathbf{0}$ ) originated from





C-6 together with a total of 0.25 from C-1 plus C-3. This result indicates essentially a random loss of hydrogen in the formation of the species of mass 94 from that of mass 126.

In a previous publication (3) concerned with the mass spectral fragmentation of  $\alpha,\beta$ -unsaturated ketones we observed the expulsion of acetone from the molecular ion of 7 to be a significant process at 70 eV and the second most intense fragmentation (86% relative abundance) at 12 eV. The analogous fragmentation in the case of the O-methyl oxime ether (6) would generate the species **p**, m/e 96 and **q** would be the neutral molecule (O-methyloxime of acetone) eliminated (see Scheme 7). High resolution mass spectrometry confirmed the composition of  $\mathbf{q}$ , m/e 87 but no ion corresponding to  $\mathbf{p}$  was observed.<sup>2</sup> The appearance of  $\mathbf{q}$  in the *O*-methyl ether oxime derivatives can be attributed to charge localization on the nitrogen atom. The sources of hydrogen in this double hydrogen rearrangement (formation of  $\mathbf{q}$ ) were determined (from the mass spectra of  $\mathbf{6b}$ ,  $\mathbf{6c}$ , and  $\mathbf{6d}$ ) to be: C-5 (0.35), C-6 (0.40), and C-7 (0.55). In the case of the ketone 7 the values for hydrogen transfer leading to acetone elimination and the formation of a hydrocarbon ion

<sup>&</sup>lt;sup>2</sup>The composition of the ion of mass 96 in Fig. 4 was determined to be 84%  $C_6H_{10}N^+$  and 16%  $C_6H_8O^+$ . The nitrogen-containing component at this ion yield could arise from the loss of formaldehyde (CH<sub>2</sub>O) from the species **m** but no metastable ion was found to support this contention.





FIG. 5. Mass spectrum (70 eV) of 8.

species were C-5 (0.50), C-6 (0.80), and C-7 (0.30) (3).

The ions below mass 80 in the four alkyl O-methyl ether oximes investigated (3-6) do not appear to contain any ions of appreciable diagnostic utility and no discussion of their possible geneses will be presented.

Except for the presence of an abundant molecular ion, the mass spectra of *O*-methyl oxime ethers of  $\alpha$ , $\beta$ -unsaturated ketones offer no diagnostic advantages, as compared to the ketones from which they are derived, in interpretation because of the large number of fragment ions observed.

# O-Methyl Oximes of 2- and 4-Methylcyclohexanone

The base peak in the mass spectra (Figs. 5 and 6) of 2-methyl and 4-methylcyclohexanone *O*-methyl oxime (8 and 9) and of cyclohexanone *O*-methyl oxime (2*a*) corresponds to their respective molecular ions. This behavior is in contrast to cyclohexanone oxime where the parent ion attains only 20% relative abundance (4). Loss of a methyl radical from the parent ions of 8 and 9 yields low abundance ions which are rationalized as arising from loss of the *O*-methyl group.

Loss of 28 a.m.u. (ethylene) from the molecular ion of 8 and 9 yields the peak at m/e 113 in Figs. 5 and 6. Deuterium labeling (8*a*) indicated

D

NOCH<sub>3</sub>

80

CH,

D

NOCH<sub>3</sub>

8

CH<sub>3</sub>



FIG. 6. Mass spectrum (70 eV) of 9. (a) Mass spectrum (15 eV) of 9.

that for the 2-methyl isomer 50% of the ethylene expropriated originated from C-5 and -6 allowing the rationalization  $\mathbf{8} \rightarrow \mathbf{r}$ , m/e 113 to be presented (Scheme 8). The remaining source of extruded ethylene could be explained by  $\beta$ -fission of the molecular ion (see  $\mathbf{8} \rightarrow \mathbf{s}$ , m/e 113) followed by homolytic fission of the C<sub>3</sub>—C<sub>4</sub> bond. This process has analogy with that found to operate in the extrusion of ethylene from cyclohexanone oxime (4).

In contrast the 4-methyl derivative (9) expelled ethylene by a more complex route since 40%of this species' yield involved the loss of a single deuterium atom from the parent ion of 9a. The remaining 60% of this ion contribution could arise by a process similar to that depicted



2782

Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.



by  $\mathbf{8} \rightarrow \mathbf{r}$  but the presence of an M – 29 ion in the unlabeled compound ruled against a quantitative answer being presented. In contrast to the process  $8 \rightarrow s$ , suggested for the loss of ethylene from 2-methylcyclohexanone O-methyl oxime, the elimination of propene from the parent ion of 9 yielded only a low (3%) relative abundance, see Fig. 6) intensity ion of mass 99.

The ion of mass 110  $(M - OCH_3)$  in the mass spectra of 8 and 9 (Figs. 5 and 6) requires no discussion. However, both of these compounds, as did the O-methyl ether oxime of cyclohexanone (2a), eliminate 41 a.m.u.  $(C_3H_5)$  from

Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.

their respective molecular ions. In the case of the 2-methyl derivative (8) 55% of the ion in question arose from loss of C-6, -5, and -4 (less one hydrogen atom) while the remainder (45%)could be explained by loss of C-5, -4, and -3 (less one hydrogen atom). These results are explicable by invoking an initial  $\alpha$ -cleavage (path A) or  $\beta$ -cleavage (path B) of the molecular ion relative to the imine bond (Scheme 9).

If the rationalization depicted as path A occurred by fission of the  $C_1$ — $C_2$ , bond of 8 the peak at m/e 86 (M – C<sub>4</sub>H<sub>7</sub>) in Fig. 5 would result (Scheme 10). However, no more than 50%









SCHEME 10

of this ion's (w) yield can arise from this process since only this portion was displaced to m/e 88 in the spectrum of 8*a*. The proximity of other ions did not allow an indication of the remaining disposition of this peak in the spectrum of 8*a*.

The loss of 55 a.m.u.  $(C_4H_7)$  in the mass spectrum (Fig. 6) of 9 occurred by the following two fragmentations as shown from the mass spectrum of 9a where this ion was located at m/e 90 (55%,  $\beta$ -cleavage) and m/e 88 (45%,  $\alpha$ -cleavage).



Loss of  $C_5H_8$  (high resolution) from the molecular ion of 9 generates (Fig. 6) a fragment of mass 73 and this species remains prominent at low ionizing (15 eV) voltages (see for instance Fig. 6a). This ion was located at mass 75 (60%) and mass 76 (40%) in the tetradeuterio derivative 9a. The rationalizations ( $9 \rightarrow x$ , m/e 73 by paths A and B) explain the distribution of the fragment x at m/e 75 (path A) and m/e 76 (paths A and B) in the spectrum of the labeled analog 9a (Scheme 11).

Analogous rationalizations to  $9 \rightarrow x$ , m/e 73



(paths A and B) can be applied to the formation of the ions of mass 73 and 87 in the mass spectrum (Fig. 5) of 8. The former was shifted to m/e 76 in 70% yield in the trideuterio analog (8a) while m/e 87 was located at m/e 89 (70%) in the spectrum of this labeled derivative.

The prominent ions of mass 69 in Figs. 5 and 6 were shown to consist of (for 8)  $C_5H_9^+$  (92%),  $C_4H_7N^+$  (5%), and  $C_4H_5O^+$  (3%) and (for 9)  $C_5H_9^+$  (80%) and  $C_4H_7N^+$  (20%). The hydrocarbon contribution in each instance could arise (metastable ions observed) from the M – OCH<sub>3</sub> species (y, *m/e* 110) by the elimination of CH<sub>3</sub>CN and formation of  $C_5H_9^+$  (Scheme 12). As suggested previously (2*a*), and confirmed from this investigation of labeled methyl cyclohexanone *O*-methyl oxime ethers, their electron impact fragmentation processes are relatively complex with the formation of many ions which serve to complicate interpretation of these mass spectra.

## Experimental

Mass spectra were obtained by Mr. R. G. Ross with an



Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.

MS-9 mass spectrometer operating at 70 eV, 100  $\mu$ A trap current and an ion source temperature of 180°. Samples were introduced by the heated inlet system (150°) and low voltage measurements refer to nominal values only. High resolution mass measurements were obtained using the MS-9 mass spectrometer interfaced to the ACME computer system of the Stanford University Medical School. The hydrogen transfer processes determined by deuterium labeling are considered accurate to  $\pm 5\%$ .

Deuterated and non-deuterated  $\alpha,\beta$ -unsaturated ketones were either obtained commercially or prepared according to previously reported procedures (3).

#### Preparation of O-Methyloximes

The appropriate  $\alpha,\beta$ -unsaturated ketone or cyclic ketone (100 mg) in pyridine (0.2–0.3 ml) was warmed with methoxyamine hydrochloride (100 mg) to 80° for 15 min and then allowed to stand overnight. The reaction was worked up with ether in the usual way and a final purification was achieved by preparative gas chromatography over a 10% SE 30 on Gas Chrom W (60–80) column (1/4 in. × 10 ft).

#### Preparation of 8a and 9a

Can. J. Chem. Downloaded from www.nrcresearchpress.com by Santa Cruz (UCSC) on 11/11/14 For personal use only.

The appropriate cyclohexanone was exchanged twice in an excess of  $D_2O/NaOD$  for 2 days under reflux. The ketone was isolated by ether extraction and the exchange procedure repeated for an additional 2 days. The deuterated cyclohexanones were then converted to their *O*-methyl oxime derivatives as described above. The following isotopic purities were obtained: 8*a*, 92%  $d_3$ , 5%  $d_2$ , 3%  $d_1$ ; 9*a*, 94%  $d_4$ , 4%  $d_3$ , 2%  $d_2$ .

Financial support from the National Institutes of Health of the U.S. Public Health Service (Grant No. AM 04257 and GM 06840) and the National Aeronautics and Space Administration (NGR 05-020-004) is gratefully acknowledged.

- See for instance: H. M. FALES and T. LUUKKAINEN. Anal. Chem. 37, 955 (1965); M. G. HORNING, A. M. MOSS, and E. C. HORNING. Anal. Biochem. 22, 284 (1968); K. GREEN. Chem. Phys. Lipids, 3, 254 (1969); F. DRAY and I. WELIKY. Anal. Biochem. 34, 387 (1970); L. L. ENGEL, A. MUNTO NEVEILLE, J. C. ORR, and P. R. RAGGATT. Steroids, 16, 377 (1970); C. J. W. BROOKS and D. J. HARVEY. Steroids, 14, 283 (1970).
- (a) R. G. COOKS and A. G. VARVOGLIS. Org. Mass Spectrom. 5, 687 (1971); (b) B. S. MIDDLEDITCH and B. A. KNIGHTS. Org. Mass Spectrom. 6, 179 (1972).
- Y. M. SHEIKH, A. M. DUFFIELD, and C. DJERASSI. Org. Mass Spectrom. 4, 273 (1970).
- D. GOLDSMITH, D. BECHER, S. SAMPLE, and C. DJERASSI. Tetrahedron, Suppl. 7, 1945 (1966).
- 5. J. R. DIAS and C. DJERASSI. Org. Mass Spectrom. In press.