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Mass Spectrometry in Structural and Stereochemical Problems. CCXXXVIII.[1] The Effect of Heteroatoms upon the Mass Spectrometric Fragmentation of Cyclohexanones

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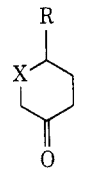
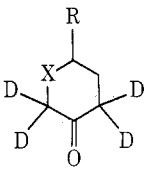
In continuation of our work on determining whether the fragmentation of bifunctional compounds reflects the summation of the behavior of each functionality or gives rise to new patterns, we discuss the fragmentation patterns of tetrahydropyran-3-one (**1**), tetrahydrothiopyran-3-one (**3**), two N-substituted 3-piperidones (**5**, **7**), and their respective 6-methyl congeners **2**, **4**, **6** and **8**. High-resolution mass spectra, metastable defocusing experiments, and the mass spectra of the 2,2,4,4-tetradeuterio analogs of **1**–**8** are used in the interpretation. Dramatic differences in the fragmentation of **1**–**8** are observed compared to the fragmentation of the monofunctional analogs, cyclohexanone, 4-methylcyclohexanone, and the parent heterocycles. These findings emphasize the importance of gathering information on fragmentation of difunctional compounds.

In the course of a study on the influence of heteroatoms on the circular dichroism of certain six-membered heterocyclic ketones containing a methyl group at position 6,[3] we observed that the mass spectra of these compounds appeared to differ substantially from the spectra of the corresponding monofunctional analogs. Our motive for examining the spectra was to determine to what extent, if any, the spectra of compounds **1**–**8** reflected the modes of fragmentation of the monofunctional analogs cyclohexanone, 4-methylcyclohexanone, and the corresponding six-membered heterocycles. This study was also motivated by our interest in extensions of our artificial intelligence program for interpretation of mass spectral data.[4] The operation of this program depends on the existence of a knowledge base covering the spectral behavior of molecules and there is a paucity of mass spectral data on model difunctional compounds.

The mass spectra of aliphatic difunctional compounds display features resulting from fragmentations that are uncharacteristic of monofunctional analogs.[5-9] An investigation of the fragmentation of 4-hydroxycyclohexanone uncovered a rearrangement process involving remote functional group interaction,[10] a process which does not occur in either cyclohexanol or cyclohexanone. With the exception of lactones[11,12] and lactams,[13] there has been no careful examination of six-membered keto heterocycles containing oxygen or nitrogen as the heteroatom. The fragmentation of 4-thiacyclohexanone and its oxide and dioxide have been discussed.[14] Although the oxides display fragmentations paralleling those for cyclohexanone, 4-thiacyclohexanone fragments along different pathways.

This paper is concerned with a study of the mass spectra of compounds **1**–**8** and their 2,2,4,4-tetradeuterio analogs **9**–**16**.





Compd	X	R	Compd	X	R
1	O	H	9	O	H
2	O	CH_3	10	O	CH_3
3	S	H	11	S	H
4	S	CH_3	12	S	CH_3
5	NCH_3	H	13	NCH_3	H
6	NCH_3	CH_3	14	NCH_3	CH_3
7	NC_2H_5	H	15	NC_2H_5	H
8	NC_2H_5	CH_3	16	NC_2H_5	CH_3

Tetrahydropyran-3-ones (1, 2). The mass spectrum of tetrahydropyran itself is characterized by loss of an α hydrogen, α cleavage with loss of formaldehyde, and expulsion of a methyl radical involving an α carbon with a hydrogen transfer.[15a,16-18a] The mass spectrum of 2-methyltetrahydropyran, the analog of **2** lacking the carbonyl group, has not been published, but those of other α-alkylated tetrahydropyrans have been presented.[19,20] We have obtained both low- and high-resolution mass spectra of 2-methyltetrahydropyran. Instead of the strong $[M - 1]^+$ ion observed for tetrahydropyran, there is now encountered the expected intense $[M - 15]^+$ ion (base peak). While the relative intensities vary somewhat, the remainder of the spectrum (masses and elemental compositions) of 2-methyltetrahydropyran closely resembles that of tetrahydropyran.

The spectrum[21a] of 4-methylcyclohexanone, the analog of **2** lacking the ring oxygen atom, is characterized by an

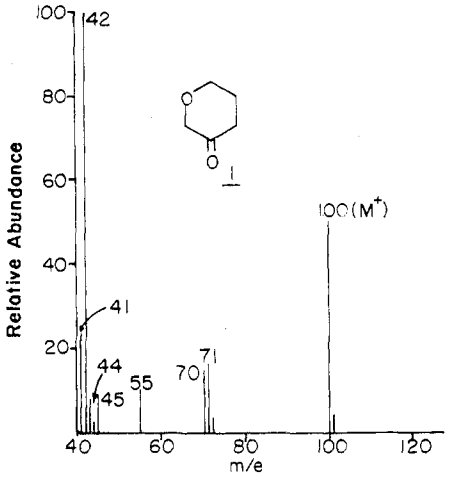


Figure 1. Mass spectrum of tetrahydropyran-3-one (1).

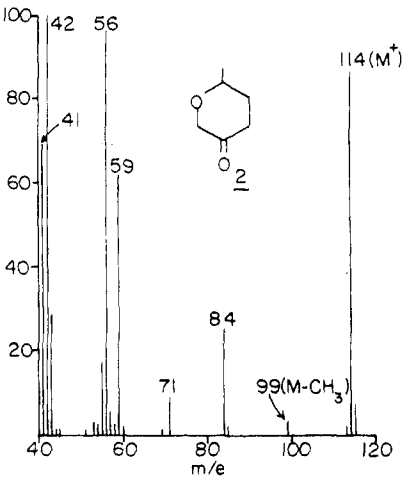


Figure 2. Mass spectrum of 6-methyltetrahydropyran-3-one (2).

intense ion at m/e 55 (base peak) accompanied by other abundant ions at m/e 41, 42, 69, and 70.

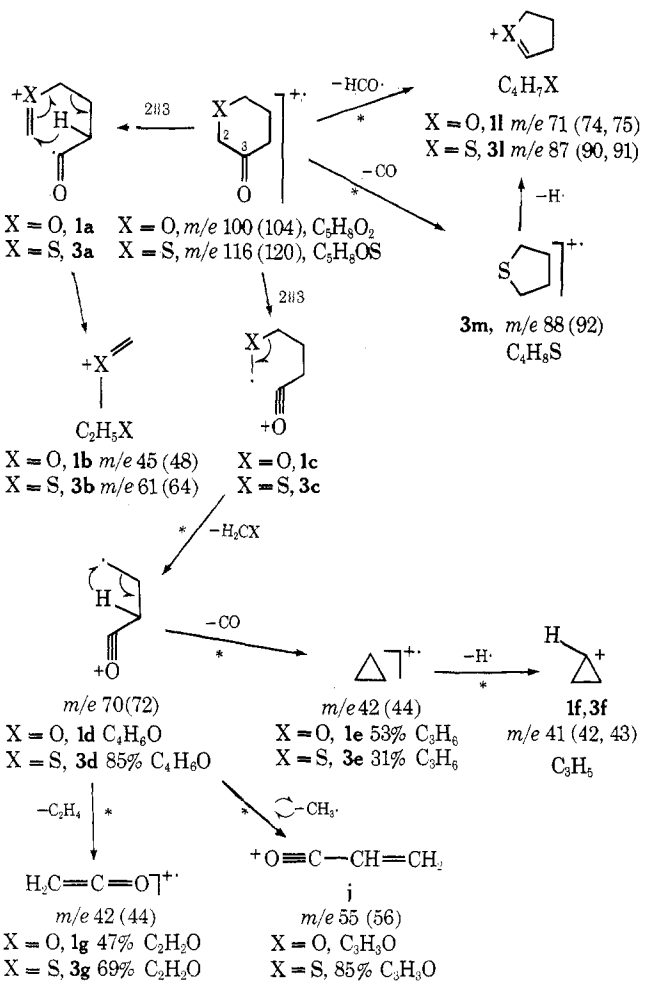
The mass spectra of the tetrahydropyran-3-ones (**1**, **2**) do not resemble the spectra of tetrahydropyran and 2-methyltetrahydropyran; there is no significant $[M - 1]^+$ ion (m/e 99) for tetrahydropyran-3-one (**1**) (Figure 1). The intensity of the $[M - 15]^+$ peak (m/e 99) in the spectrum (Figure 2) of 6-methyltetrahydropyran-3-one (**2**) is less than 5% that of the base peak (m/e 42). Also the mass spectra of **1** and **2** bear little resemblance to the spectrum[21a] of 4-methylcyclohexanone when mechanisms proposed for fragmentation of the last are considered.[21b]

We rationalize the major features of the spectra of **1** and **2** in terms of two primary fragmentation processes involving initial scission of the 2,3 bond as summarized in Schemes I and II. Mass numbers in parentheses refer to the analogous ion in the spectra of the d_4 analogs **9** and **10**, respectively. Peak shifts are essentially quantitative (>85%) unless otherwise noted. Asterisks refer to transitions supported by metastable ions observed in either the first[22] or second field-free region. The nominal masses noted in all Schemes are comprised >95% of ions of the indicated elemental composition unless otherwise noted.

Scission of the 2,3 bond with charge retention on the heterocyclic oxygen yields molecular ions **1a** (Scheme I) and **2a** (Scheme II) of **1** and **2**. Ions **1b** and **2b** result from decomposition of molecular ions **1a** and **2a** through a hydrogen transfer step involving a hydrogen atom at C-4 (six-membered transition state) as shown in Schemes I and II.

Scission of the 2,3 bond with charge retention on the keto moiety yields the molecular ions **1c** (Scheme I) and **2c** (Scheme II) of **1** and **2**. This step is analogous to the initial ring opening in the fragmentation of cyclohexanone.[23] This step in the case of cyclohexanone is followed by either hydrogen rearrangement from the α carbon and subsequent fragmentation yielding m/e 55 (C_3H_3O), the base peak, or decomposition yielding an abundant ion of mass 42 (predominantly C_3H_6).[23] Although ions of mass 55 and 42 in the spectra of **1** and **2** are observed, accurate mass measurements and metastable defocusing data indicate that the subsequent decompositions of ions **1c** and **2c** do not parallel the decomposition noted[23] for cyclohexanone. Instead, we observe ions **1c** and **2c** decomposing *via* expulsion of the heterocyclic oxygen along with C-2, as formaldehyde, yielding ions **1d** and **2d** (Schemes I and II). We depict the structures of **1d** and **2d** as open-chain radical ions with knowledge that they may exist in several

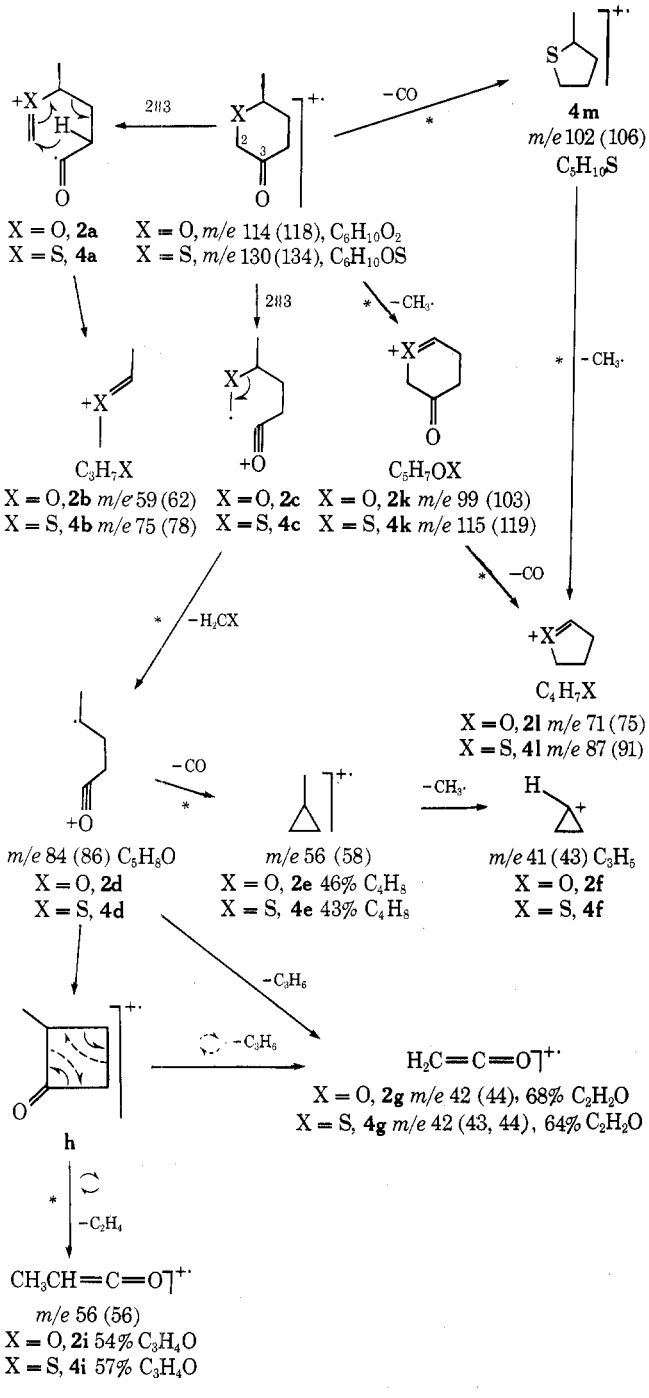
Scheme I
Fragmentation of Tetrahydropyran-3-one (1) and Tetrahydrothiopyran-3-one (3)



forms. Subsequent decompositions of **1d** and **2d** support alternative structures (see below).

Ions **1d** and **2d** decompose along similar pathways (Schemes I and II), each of which is supported by data from metastable defocusing experiments. Expulsion of CO from **1d** and **2d** yields ions **1e** (C_3H_6) and **2e** (C_4H_8). High-resolution examination of m/e 56 and 58 in the spectrum of *2,2,4,4-d*$_4$-6-methyltetrahydropyran-3-one (**10**) showed that the oxygenated contributor to m/e 56

Scheme II
Fragmentation of 6-Methyltetrahydropyran-3-one (2) and 6-Methyltetrahydrothiopyran-3-one (4)



(C_3H_4O) remained unshifted, while the hydrocarbon contributor (ion **2e**) shifted to m/e 58 (98% $C_4H_6D_2$). Subsequent decomposition of ions **1e** and **2e**, arbitrarily depicted as cyclopropyl structures, yields ions **1f** and **2f**.

Although both ions **1d** and **2d** show loss of C_2H_4, the spectra of the deuterated analogs **9** and **10** indicate that different mechanisms are operative. We compared the low-resolution spectra of **1** and **9** and found that m/e 42 shifts predominantly to m/e 44. Thus both contributors to m/e 42 in the spectrum of **1**, $C_2H_2O\cdot^+$ and $C_3H_6\cdot^+$, retain two deuterium atoms in the fragmentation of **9**. This supports loss of C-5 and C-6 as ethylene, with C-4 retained in ion **1g**, and indicates little prior cyclization to a cyclobutanone ion (see below) which would eliminate either C-5 and C-6 or C-4 and C-5 in equal amounts. The analogous process in the fragmentation of 6-methyltetrahydropyran-3-one (**2**) is loss of C_3H_6 to yield the oxygenated contributor to m/e 42, ion **2g**. By examination of the peak shifts in *2,2,4,4-d*$_4$-6-methyltetrahydropyran-3-one (**10**) at high resolution we found that the C_2H_2O contributor shifted primarily to m/e 44 (C_2D_2O). The hydrocarbon contributor remained ⅔ unshifted while ⅓ shifted to m/e 43 (C_3H_5D). The former observation could result from simple loss of propylene from ion **2d** to yield **2g**, or expulsion of propylene from ion **h** (Scheme II, see below).

Loss of ethylene from ion **2d** appears to proceed *via* initial cyclization to the substituted cyclobutanone (ion **h**, Scheme II). The high-resolution experiment mentioned previously in connection with ion **2e** indicated that the remaining ion of mass 56 in the spectrum of **10** is comprised of $C_3H_4O\cdot^+$. We rationalize these observations as expulsion of C-4 and C-5 as ethylene from ion **h** as shown in Scheme II.[24,25] Ion **2i**, comprising C-3, C-6, and the keto oxygen and methyl group, results.

Origins of other important ions in the spectra of **1** and **2** are summarized in Schemes I and II.

Tetrahydrothiopyran-3-ones (3, 4). The fragmentation pathways of the tetrahydrothiopyran-3-ones (**3**, **4**) are very similar to those observed for the tetrahydropyran-3-ones (**1**, **2**). The most important difference is the increased abundance of ions retaining the heterocyclic atom, sulfur, in the former compounds, with diminished intensities of ions arising from loss of thioformaldehyde in a process corresponding to **1c** and **2c** → **1d** and **2d** (Schemes I and II). This may be the result of the increased Lewis basicity of the sulfur atom in **3** and **4** relative to the heterocyclic oxygen atom in the case of **1** and **2**.[26] Similar to our observations concerning the spectra of tetrahydropyran-3-ones, introduction of a keto group as in tetrahydrothiopyran-3-ones (**3**, **4**) leads to spectra that bear little resemblance to those of analogous compounds such as tetrahydrothiopyran[15b,18b] and the related 2-methyl-, 3-methyl-, and 4-methyltetrahydrothiopyrans.[15c,e,18b] The spectra of **3** and **4** are presented in Figures 3 and 4.

Scission of the 2,3 bond of **3** and **4** with charge retention on the sulfur moiety yields the molecular ions **3a** and **4a** (Schemes I and II) which in turn decompose in a manner completely analogous to the decomposition of ions **1a** and **2a**.

Scission of the 2,3 bond with charge retention on the keto functionality is followed by elimination of thioformaldehyde, analogous to elimination of formaldehyde from ions **1c** and **2c** (Schemes I and II). Subsequent decompositions of ions **3d** and **4d** parallel the decomposition of ions **1d** (Scheme I) and **2d** (Scheme II).

Although the ketotetrahydrothiopyrans **3** and **4** display ions analogous to **11** and **21**, Schemes I and II (loss of hydrogen or methyl radical, respectively, accompanied by loss of carbon monoxide), the course of the fragmentation is somewhat different. Both ketotetrahydrothiopyrans **3** and **4** display [M − CO] peaks at m/e 88 for tetrahydrothiopyran-3-one (**3**) and m/e 102 for 6-methyltetrahydrothiopyran-3-one (**4**). The loss of carbon monoxide would be expected to produce the tetrahydrothiophene radical ion **3m** and the 2-methyltetrahydrothiophene radical ion **4m**. Ion **3m** loses a hydrogen radical and ion **4m** a methyl radical, yielding ion of m/e 87 (C_4H_7S) and ions **31** and **41** (Schemes I and II). It is interesting to note in contrast that the abundant ion at m/e 88 (M − 28) in the spectrum of 4-thiocyclohexanone[14] arises from loss of C_2H_4 rather than CO.[27]

Common to both spectra (Figures 3 and 4) are peaks at m/e 45 (CHS), 46 (CH_2S), and 60 (C_2H_4S). Ions of this type have been shown previously to originate from a tetrahydrothiophene radical ion, *e.g.*, **3m**, **4m**.[28] The shifts of peaks in the spectra of the tetradeuterio analogs (**11**, **12**) are complex, consistent with previously published re-

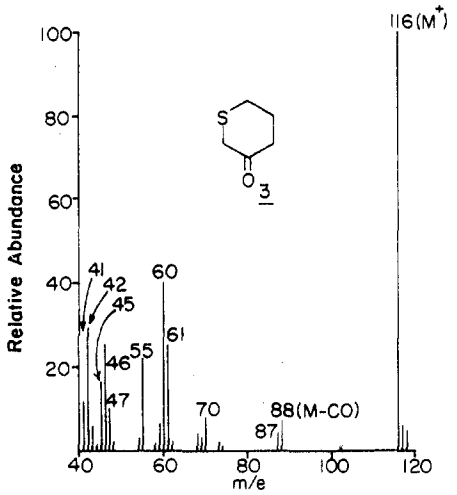


Figure 3. Mass spectrum of tetrahydrothiopyran-3-one (3).

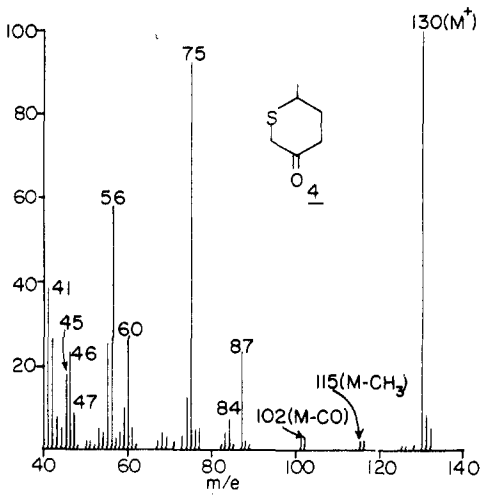


Figure 4. Mass spectrum of 6-methyltetrahydrothiopyran-3-one (4).

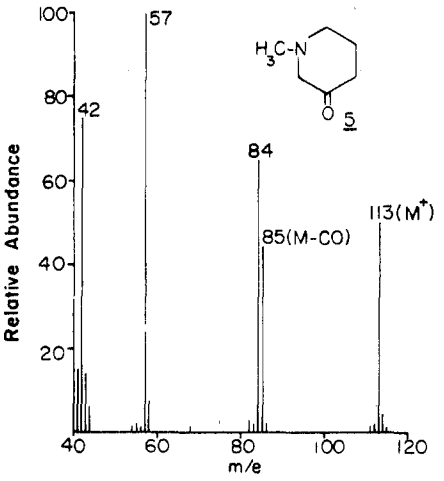


Figure 5. Mass spectrum of 1-methyl-3-piperidone (5).

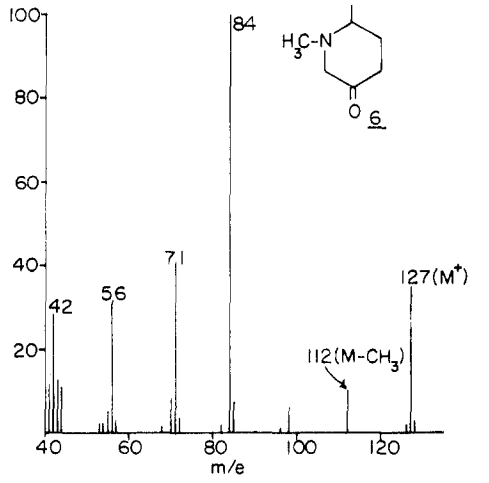


Figure 6. Mass spectrum of 1,6-dimethyl-3-piperidone (6).

ports.[28] Metastable defocusing of m/e 60 in the spectrum of **3**, for example, shows m/e 88 (ion **3m**) as a progenitor. Similar ions in the spectrum of **4** could arise by analogous but necessarily more complex pathways.

3-Piperidones (5–8). The fragmentation patterns of the 3-keto substituted piperidines (**5–8**) are characterized by the relative absence of ions that contain the oxygen atom. The mass spectra of the 3-ketotetrahydropyrans (**1**, **2**) and to a lesser extent the 3-ketotetrahydrothiopyrans (**3**, **4**) displayed several important ions that we ascribe to processes directed by and retaining the 3-keto oxygen atom. The absence of such ions in the spectra of **5–8** is presumably a further manifestation of the order of increasing Lewis basicity O < S < N.[26] However, although the oxygen atom is not retained to an important extent in the charged species resulting from fragmentation of **5–8**, the presence of the keto group dramatically influences the course of fragmentation of these compounds as compared with N-substituted piperidines.

The spectrum of piperidine is characterized by an intense $[M - 1]^+$ ion (base peak) and several other important ions resulting from loss of small hydrocarbon radicals and neutral molecules.[29,30] The spectrum of *N*-methylpiperidine is very similar to that of piperidine with a peak shift of 14 amu. The mass spectrum of 2-methylpiperidine displays an intense $[M - CH_3]^+$ ion corresponding to the $[M - 1]^+$ ion of piperidine. We also recorded the high-resolution mass spectra of other analogs of **5–8**, 1,2-dimethyl- and 1-ethyl-2-methylpiperidine. The mass spectrum of 1,2-dimethylpiperidine is characterized by an intense $[M - CH_3]^+$ ion (base peak).[31] The remainder of the spectrum resembles that of *N*-methylpiperidine, with ions of the same elemental composition but of lower abundance. The mass spectrum of 1-ethyl-2-methylpiperidine is also characterized by an intense $[M - CH_3]^+$ ion (base peak) presumably primarily due to loss of the C-2 methyl group, as the remainder of the spectrum resembles that of 1,2-dimethylpiperidine, with a peak shift of 14 amu.

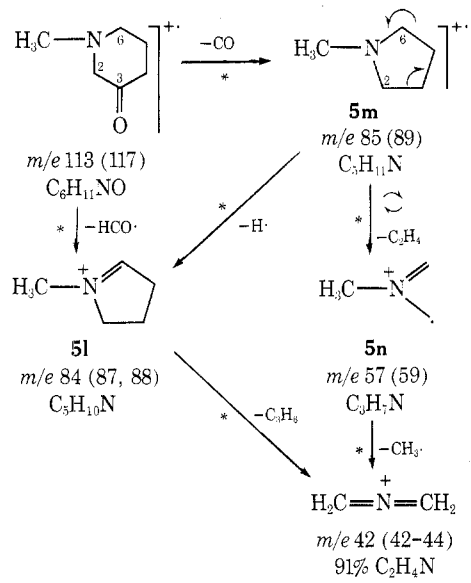
The introduction of a keto group at C-3 yields compounds whose mass spectra cannot be explained by processes depicted for the analogous piperidines. The mass spectrum of 1-methyl-3-piperidone (**5**) is presented in Figure 5. The absence of an important $[M - 1]^+$ ion is notable. Rather, expulsion of the keto group as carbon monoxide yields the abundant ion **5m** of mass 85 (Scheme III). Subsequent loss of a hydrogen radical, or a one-step loss of HCO, both supported by metastable defocusing, yields ion **5l** (m/e 84).

The resulting decomposition of ions **5l** and **5m** closely parallels the decomposition of the molecular ion of *N*-methylpyrollidine;[29] the spectra below m/e 86 are quite similar. We have summarized the processes in Scheme III.

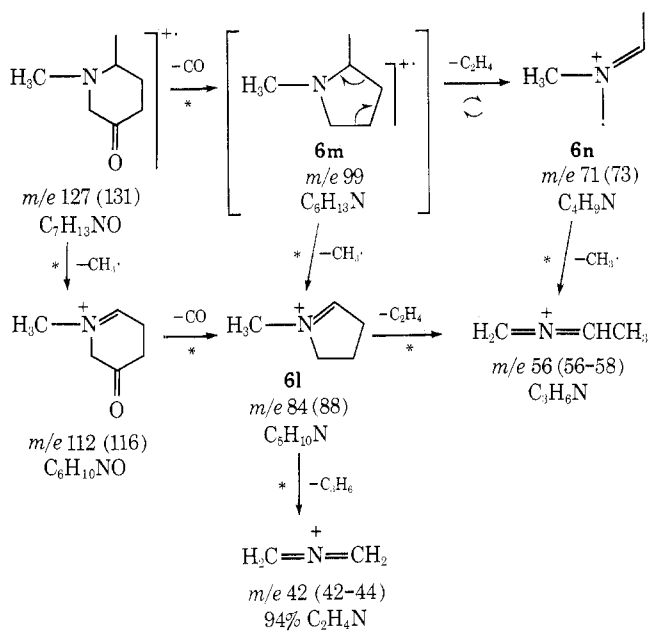
The mass spectrum of 1,6-dimethyl-3-piperidine (**6**) is presented in Figure 6. The fragmentation of **6** is similar to that suggested for **5**. The processes are summarized in Scheme IV.

The decomposition of ions **6l** and **6m** closely parallels the decomposition of ions **5l** and **5m** (Schemes III and IV),

Scheme III
Fragmentation of 1-Methyl-3-piperidone (5)



Scheme IV
Fragmentation of 1,6-Dimethyl-3-piperidone (6)



yielding peaks shifted by 14 amu. We infer the pathways indicated in Scheme IV for the creation and destruction of ion **6m** on the basis of metastable defocusing experiments, peak shifts in the spectrum of *2,2,4,4-d*$_4$-1,6-dimethyl-3-piperidone (**14**), and analogy with compound **5**; no significant peak at *m/e* 99 is observed in the normal mass spectrum.

The mass spectrum of 1-ethyl-3-piperidone (**7**, Figure 7) arises from fragmentations closely related to those described for 1-methyl-3-piperidone (**5**). The pattern is complicated somewhat by the presence of the *N*-ethyl group, which can undergo α cleavage resulting in loss of a methyl radical. As in the case of **5** and **6**, fragmentation of **7** (Scheme V) is dominated by initial processes involving expulsion of carbon monoxide.

Our interpretation of the spectrum of 1-ethyl-6-methyl-3-piperidone (**8**, Figure 8) is complicated by the fact that loss of a methyl radical alone or in concert with other processes can occur from either the *N*-ethyl or the 6-methyl group. None of our experimental techniques permits differentiation between these two possibilities, as we labeled

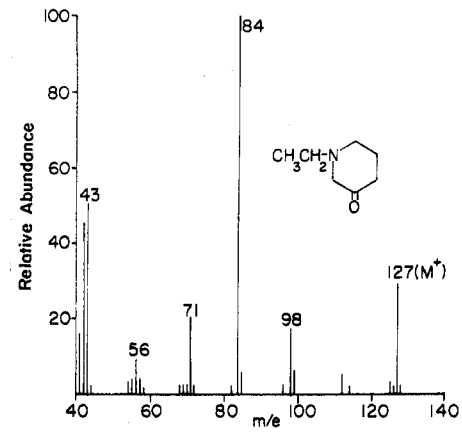


Figure 7. Mass spectrum of 1-ethyl-3-piperidone (**7**).

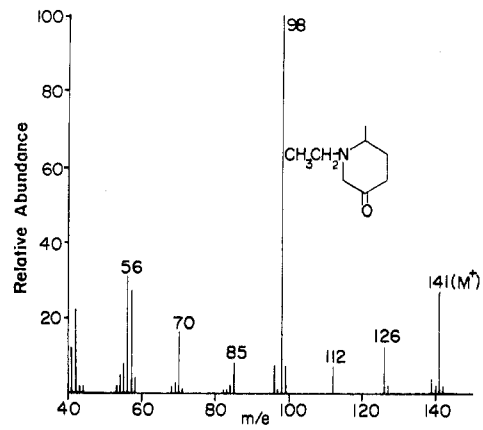
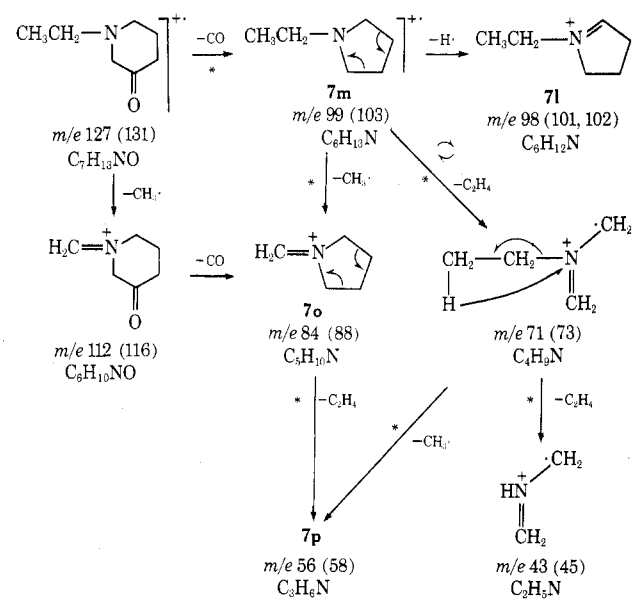


Figure 8. Mass spectrum of 1-ethyl-6-methyl-3-piperidone (**8**).

Scheme V
Fragmentation of 1-Ethyl-3-piperidone (7)



neither methyl group. Our comparison of the spectra of **5** and **6** revealed that loss of the 6-methyl group played an important part in the fragmentation of **6**. On the other hand, the similarity of the fragmentation patterns of **7** and **8** (Figures 7 and 8) argues against an important influence of the C-6 methyl group in the fragmentation of **8**. Rather than speculate about the details of the fragmentation pathways, we wish only to mention some important

points. Although the abundance of m/e 113 ($M\cdot^+ - CO$) is negligible in the normal mass spectrum (Figure 8), metastable defocusing experiments support the importance of this ion in fragmentation pathways leading to the abundant ions of mass 98 ($M\cdot^+ - CO - CH_3$ and $M\cdot^+ - CH_3 - CO$) and 85 ($M - CO - C_2H_4$). Thus, again we observe the importance of initial expulsion of carbon monoxide resulting in a substituted pyrrolidine molecular ion which subsequently undergoes fragmentation characteristic of this species.

Conclusions

Our results indicate that, in these relatively simple, difunctional systems, few fragmentation processes occur that directly reflect processes occurring in the monofunctional analogs. Thus, considerable work remains to be done to provide the necessary knowledge base for either manual or computer-based interpretation of mass spectra based on empirical rules for the mass spectral fragmentation of other bifunctional cyclic molecules in which the heteroatoms are in close proximity to each other.

Experimental Section

Low-resolution mass spectra were obtained on an A.E.I. MS-9 mass spectrometer at 15 and 70 eV. The high-resolution mass spectra were obtained on a Varian MAT 711 mass spectrometer. Defocusing studies were performed in the first field-free region of the MS-9 mass spectrometer.[32] Infrared specra were obtained using Perkin-Elmer Model 700 or Model 420 recording spectrophotometers and measured as films. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer. In all cases deuteriochloroform was employed as solvent and tetramethylsilane (δ 0.00 ppm) as internal reference.

All samples were collected on an Aerograph Model 200 gas chromatograph equipped with a thermal conductivity detector using helium at a flow rate of 40–50 ml/min. The tetrahydropyranones and tetrahydrothiopyranones were run on 10 ft × 0.25 in. aluminum columns containing 15% Carbowax 20M Chromosorb W a/w 80/100 mesh and the piperidones on 10% SE-30 on Chromosorb W a/w 80/100 mesh. Deuteration was accomplished using a special column of KOD/Carbowax 6000 according to previously published procedures.[33] In general, 300 μl of deuterium oxide was injected in 50-μl portions prior to an injection and an additional 100 μl (2 × 50 μl) of deuterium oxide between each injection of ketone.

2-Methyltetrahydropyran. A commercial sample (Aldrich) was purified on a 15% Carbowax 20M column with an oven temperature of 130°: mass spectrum [70 eV) m/e (rel intensity) 100 (21, M^+), 85 (100, $M - CH_3$), 71 (11, C_4H_7O), 67 (5, C_5H_7), 59 (6, C_3H_7O), 57 (8, 70% C_4H_9, 30% C_3H_5O), 56 (34, C_4H_8), 55 (18, 98% C_4H_7), 45 (17, C_2H_5O), 44 (7, C_2H_4O), 43 (41, 87% C_2H_3O, 13% C_3H_7), 42 (19, 95% C_3H_6), 41 (48, C_3H_5).

Tetrahydropyran-3-one (1). To a cooled solution of 0.750 g of 3-hydroxytetrahydropyran[34] in 60 ml of acetone, Jones reagent[35] was added until the orange color persisted for 1–2 min at room temperature. After addition of 2-propanol to decompose the excess reagent, water was added to dissolve the chromium salts and the acetone was removed under vacuum. The aqueous solution was saturated with sodium chloride and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the chloroform was removed under vacuum. A pure sample of **1** was collected on 15% Carbowax 20M at an oven temperature of 175°: ir (neat) 1720 (C=O), 1100 cm^{-1} (COC); nmr δ 4.03 (s, 2, CH_2-2), 3.53 (t, 3, J = 6 Hz, CH_2-6), 2.57 (m, 2, CH_2-4), 1.81 (m, 2, CH_2-5).

Anal. Calcd for $C_5H_8O_2$: M^+, 100.0524. Found: M^+, 100.0525.

2,2,4,4-Tetradeuteriotetrahydropyran-3-one (9). The ketone **1** was passed once through a KOD/Carbowax 6000 column at 175°, producing **9** containing 19% d_3 and 81% d_4.

2,2,4,4-Tetradeuterio-6-methyltetrahydropyran-3-one (10). 6-Methyltetrahydropyran-3-one (**2**)[3] was passed once over the KOD/Carbowax 6000 column at 180°, producing **10** containing 15% d_3 and 85% d_4.

2,2,4,4-Tetradeuteriotetrahydrothiopyran-3-one (11). Tetrahydrothiopyran-3-one (3)[36] was passed once through the KOD/Carbowax 6000 column at 190°, producing **11** containing 11.4% d_3 and 88.6% d_4.

2,2,4,4-Tetradeuterio-6-methyltetrahydropyran-3-one (12). 6-Methyltetrahydrothiopyran-3-one (4)[3] was passed once through the KOD/Carbowax 6000 column at 190° producing **12** containing 1.6% d_2, 16.4% d_3, and 82% d_4.

1,2-Dimethylpiperidine. A solution containing 0.8 g of 2-methylpiperidine, 20 ml of ethanol, 6 ml of 36% formaldehyde, and 250 mg of 10% Pd/C was stirred over hydrogen at atmospheric pressure until no further uptake of hydrogen occurred. After the catalyst was filtered off, the filtrate was acidified with dilute hydrochloric acid and the solvent was removed under vacuum. The residue was washed with ether, dissolved in water, made basic with 20% potassium hydroxide, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the chloroform was removed under vacuum. A pure sample[37] was collected on 10% SE-30 at 115°: mass spectrum (70 eV) m/e (rel intensity) 113 (15, M^+), 112 (8, $M - H$), 98 (100, $M - CH_3$), 84 (3, $C_5H_{10}N$), 70 (12, C_4H_8N), 57 (14, C_3H_7N), 42 (23, 96% C_2H_4N).

1-Ethyl-2-methylpiperidine. A solution of 0.8 g of 2-methylpiperidine, 60 ml of acetone, and 1.5 ml of ethyl iodide was refluxed for 4 hr. The solution was taken to dryness under vacuum. The semisolid residue was dissolved in water, made basic with 20% potassium hydroxide, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate, filtered, and removed under vacuum. A pure sample[37] was collected on 10% SE-30 at 115°; mass spectrum (70 eV) m/e (rel intensity) 127 (12, M^+), 126 (5, $M - H$), 112 (100, $M - CH_3$), 98 (1, $C_6H_{12}N$), 84 (8, $C_5H_{10}N$), 71 (4, C_4H_9N), 56 (14, C_3H_6N).

1-Methyl-3-piperidone (5). A solution of 0.8 g of 3-hydroxypiperidine, 15 ml of ethanol, 250 mg of 10% Pd/C, and 6 ml of 36% formaldehyde was processed in the same manner as 1,2-dimethylpiperidine. The infrared spectrum of the unpurified reaction product was identical with that already published.[38] Without further purification the 1-methyl-3-piperidinol was dissolved in 20 ml of acetone and cooled, and 6 ml of Jones reagent[35] was added. The mixture was stirred for 4 hr over nitrogen at room temperature. It was cooled and 2-propanol was added until the orange color disappeared. Water was added to dissolve the chromium salts, and the acetone was removed under vacuum. The residue was made basic with 20% potassium hydroxide and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the chloroform was removed under vacuum. A pure sample of **5**[39] was collected on 10% SE-30 at 135°: ir 2875, 2780 (NCH_3), 1720 cm^{-1} (C=O); nmr δ 6.00 (s, 2, CH_2-2), 5.16 (m, 2, CH_2-4), 4.77 (s, 3, NCH_3), 4.67 (m, 2, CH_2-6), 4.13 (m, 2, CH_2-5).

Anal. Calcd for $C_6H_{11}NO$: M^+, 113.0840. Found: M^+, 113.0840.

2,2,4,4-Tetradeuterio-1-methyl-3-piperidone (13). A sample of **5** was passed twice through the KOD/Carbowax 6000 column at 185° producing **13** containing 22% d_2 and 78% d_3.

2,2,4,4-Tetradeuterio-1,2-dimethyl-3-piperidone (14). A sample of 1,2-dimethyl-3-piperidone (**6**)[3] was passed once through the KOD/Carbowax 6000 column, yielding **14** containing 6.3% d_2, 28.4% d_3, and 65.3% d_4.

1-Ethyl-3-piperidone (7). A solution of 0.8 g of 3-hydroxypiperidine in 60 ml of acetone and 1.5 ml of ethyl iodide was treated in the identical manner as in the synthesis of 1-ethyl-2-methylpiperidine. The unpurified 1-ethyl-3-piperidinol had the same infrared spectrum as published.[40] Without further purification the alcohol was dissolved in 20 ml of acetone, and 6 ml of Jones reagent[35] was added using the identical procedure described for the synthesis of **5**. A pure sample of **7**[41] was collected on 10% SE-30 at 140°: ir 2975, 2800, 1722 cm^{-1} (C=O); nmr δ 3.00 (s, 2, CH_2-2), 2.57 (m, 6, NCH_2CH_3, CH_2-4, CH_2-6), 2.33 (m, 2, CH_2-4), 1.83 (t, 3, J = 7 Hz, CH_3CH_2N).

Anal. Calcd for $C_7H_{13}NO$: M^+, 127.0997. Found: M^+, 127.1000.

2,2,4,4-Tetradeuterio-1-ethyl-3-piperidone (15). A sample of **7** was passed once through the KOD/Carbowax 6000 column at 180° yielding **15** containing 21.5% d_3 and 78.5% d_4.

2,2,4,4-Tetradeuterio-1-ethyl-6-methyl-3-piperidone (16). A sample of 1-ethyl-6-methyl-3-piperidone (**8**)[3] was passed once through the KOD/Carbowax 6000 column yielding **16** containing 24.5% d_3 and 75.5% d_4.

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Mechanism of Electron Impact Induced Elimination of Methylenimine from Dimethylamino Heteroaromatic Compounds[1]

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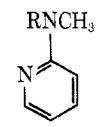
The characteristic expulsion of methylenimine from dimethylamino α-substituted N heterocycles was examined using models in which one methyl group is deuterium labeled, *e.g.*, 2-(*N*-methyl-*N*-methyl-d_3-amino)pyridine. Equal amounts of CD_2NH and CH_2ND are expelled, rather than CD_2ND and CH_2NH as expected from previously proposed mechanisms. A general mechanism is proposed in which the reaction is initiated by abstraction of methyl hydrogen by a charge-localized ring nitrogen, followed by skeletal rearrangement. Evidence from isomeric deazaadenosine derivatives suggests that N-7 rather than N-1 is the primary reactive site in N^6,N^6-dimethyladenine and related nucleosides. Complex hydrogen interchange reactions also occur during expulsion of methylenimine from analogous monomethyl-substituted heterocycles, but by a different reaction mechanism.

The expulsion of methylenimine is a common process observed in the mass spectra of many heteroaromatic compounds which bear methyl- or dimethylamino substituents,[2-15] *e.g.*, the simplest model **1**.[16,17] This structurally diagnostic reaction finds important use in the structural characterization of methylated purine bases or nucleosides, which often contain methyl- or dimethylamino groups. In the case of dimethylamino derivatives the mechanism of this reaction has been the subject of several investigations.[2-4,16,17] Eggers and coworkers postulated[2]



1a, R = H
b, R = CH_3

that expulsion of the elements of CH_3N from the base moiety of the puromycin nucleoside (**2**) occurs from the imidazole ring rather than the more obvious site at N^6.