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AN INVESTIGATION INTO THE MECHANISM OF GAS-PHASE TAUTOMERISM USING MASS SPECROMETRY

OXAZOLIDINES AND β-DIKETONES

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Abstract—Ring-chain tautomerism in 4,4-dimethyl-2-phenyloxazolidine and some aryl-substituted derivatives and keto-enol tautomerism in acetylacetone has been studied by a mass spectrometric method in which the concentration of each species involved in the tautomeric equilibrium is defined in terms of the abundance of a fragment ion uniquely associated with that species. From the effects of changes in source temperature at constant inlet temperature, and inlet temperature at constant source temperature, it is concluded that oxazolidine ring-chain tautomerism in the gas phase is an intramolecular process (which may involve wall collisions) while keto-enol tautomerism in acetylacetone is probably also unimolecular. Approximate values of enthalpy differences have been obtained and are comparable to those found in non-polar solutions. Changes in the spectra of aryl-substituted 2-phenyl-oxazolidines reflect the same trend towards more of the open form with electron-donating substituents as is observed in solution.

INTRODUCTION

TAUTOMERIC equilibria are commonly studied using NMR, IR and other spectroscopic methods, but since these procedures are normally less conveniently applied to gaseous systems than to solutions, relatively little work has appeared on gas-phase tautomerism.[1] A start has been made[2] in the application of mass spectrometry to gaseous tautomeric equilibria and in this investigation the method is further developed and extended.

Two years ago it was reported[2] that the enthalpy change for the keto-enol tautomerism in β-diketones could be determined by introducing the compound into the heated inlet system of a mass spectrometer, varying the temperature of the inlet system and monitoring the change in ratio of two daughter ions associated exclusively with the keto and with the enol form, respectively. At about the same time we started to employ this principle in the study of the ring-chain tautomerism[3] manifest by oxazolidines, one of us having previously studied this process in solution.[4, 5] Larsen and co-workers[2] are to be credited with initiating a new type of application of mass spectrometry, but they met several difficulties in their study, chiefly the very small temperature range (26°) available to them. There was also some question as to the correctness of their assumption regarding the effect of source temperature and their assignments of fragment ions to tautomeric forms. For these reasons we have included a reinvestigation of acetylacetone with our study on the oxazolidines.

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RESULTS AND DISCUSSION

The mass spectrum (Fig. 1) of 4,4-dimethyl-2-phenyloxazolidine (**1**) includes six primary fragment ions which can potentially be associated with either the cyclic or linear form of the molecular ion (**1a** and **1b**, respectively). Elementary principles of mass spectral fragmentation demand that the M^{+}-$^{\cdot}OH$ ion be associated with the chain form and that the M^{+}-$C_6H_5^{\cdot}$ ion be associated (at least mainly) with the ring

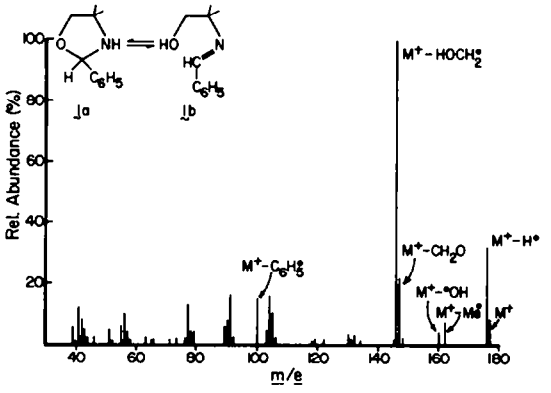

FIG. 1 Mass spectrum (70 eV) of the ozazolidine (1); not corrected for ^{13}C isotopic contributions

form; furthermore it is probable that the M^{+}-$H^{\cdot}$* and the M^{+}-CH_2O ions arise from the closed form and the M^{+}-$^{\cdot}CH_2OH$ ion from the open form. Supporting evidence for these assignments comes from the spectrum of the *O*-(or *N*) d_1-analog (**2**). This compound was prepared, *in situ*, by exchange with D_2O in the ion source, and in its spectrum M^{+}-H, M^{+}-$^{\cdot}CH_2OH$, and M^{+}-$^{\cdot}OH$ become M^{+}-$H^{\cdot}$, M^{+}-$^{\cdot}CH_2OD$, and M^{+}-$^{\cdot}OD$, respectively. Hence, with an error of probably no more than a few percent, five of the six† fragment ions in question can be assigned exclusively as indicators of the concentrations of one or other form of the molecular ion. This system is therefore well-suited to the study which follows, as multiple checks on the relative proportions of the two forms are built into the compound.

The mass spectrum of the parent oxazolidine (**1**) was run in the following ways: (i) sample introduced *via* the heated inlet system, system temperature constant, source temperature varied, (ii) sample introduced *via* the heated inlet system, system temperature varied, source temperature constant and, (iii) sample introduced by direct insertion at varying source temperatures. The results of method (iii) paralleled those of method (i) and will not be detailed since the sample introduction rate was much more difficult to control. Major interest centers on the differences in the results obtained by methods (i) and (ii). Figs 2 and 3 respectively, show the results of varying inlet system and source temperatures. The abundances of ions which represent the

* Loss of $H^{\cdot}$ from the ring form involves benzylic cleavage as well as α-cleavage to *two* heteroatoms, it should dominate over methine $H^{\cdot}$ loss from the chain form.

† Loss of Me could reasonably come from either form although results of the temperature variation studies implicate the closed form (*vide infra*).

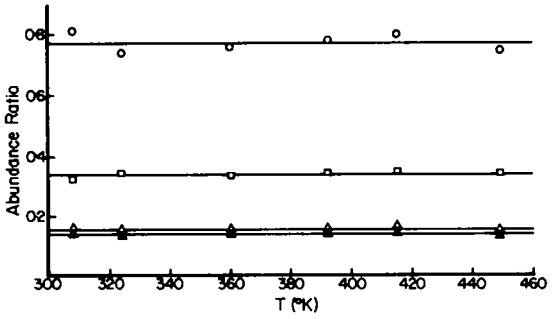

FIG 2. Effect of variation of inlet system temperature upon the spectrum of compound 1 (source 75°). ○ = $M^+ - H^\cdot/M^+ - {}^\cdot CH_2OH$; □ = $M^+ - C_6H_5^\cdot/M^+ - CH_2OH$; △ = $M^+ - CH_2O/M^+ - {}^\cdot CH_2OH$; ▲ = $M^+ - CH_3^\cdot/M^+ - {}^\cdot CH_2OH$

closed form of the molecule (M^+-$H^\cdot$, M^+-CH_2O, and M^+-$C_6H_5^\cdot$) are in each case plotted against M^+-$^\cdot CH_2OH$ (representing the open form) to obtain a representation of the relative proportions of closed to open forms with variation in temperature. It is evident that these ratios do not vary when source temperature is held constant, even when the inlet system temperature *is changed by* 200°, indeed, the whole spectrum remains sensibly constant during this process. Conversely, small changes in source temperature cause appreciable changes in these ratios. The simplest interpretation of the data of Figs 2 and 3 comes from a consideration of the sample pressure at different

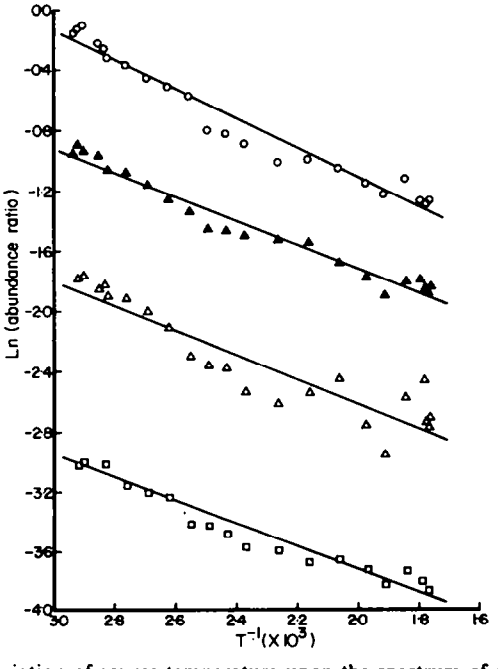

FIG 3. Effect of variation of source temperature upon the spectrum of compound 1 (inlet system 35°), semi-log plot. Symbols as in Fig. 2. For clarity, ordinate of the $M^+ - CH_3^\cdot$ plot is offset +1·0 units, that of the $M^+ - C_6H_5^\cdot$ plot −2·0 units

points in the instrument. Inter-molecular collisions can occur only in the inlet system ($\sim 10^{-3}$ torr) and not in the source ($\sim 10^{-6}$ torr), yet it is the source temperature which determines the position of ring-chain equilibrium. Hence the reactions which establish equilibrium must be unimolecular.

A detailed examination of the effects of varying source temperature brings out these facts: (i) the M^{+}-$CH_3^{\cdot}$ ion appears to arise predominantly from the closed form, since it gives a plot against M^{+}-$^{\cdot}CH_2OH$ similar to that observed for other closed-form ions. (ii) The M^{+}-$^{\cdot}OH$ ion, should bear a constant abundance ratio to M^{+}-$^{\cdot}CH_2OH$, but it varies considerably. No explanation can be offered for this fact but it may be noted that this ion behaves anomolously throughout the series of compounds (*vide infra*) and that it is the least abundant of the fragment ions of interest. (iii) The measure of agreement found using different ions to represent the closed form is best seen from the similarity in the slopes of the curves in the log ratio *vs* T^{-1} plots (Fig 3). Note, too, that in each case the curve shapes show similar non-random deviations from linearity;* correlation coefficients vary from 0·925 to 0·984.

Since the abundance of each characteristic ion is proportional to the concentration of one tautomeric form, the ratio of ion abundances is proportional to the equilibrium constant,

$$\text{hence, ln (abundance ratio)} = \ln K + k$$

$$\text{but } \ln K = \frac{-\Delta H}{RT} + k^{1},$$

$$\text{hence ln (abundance ratio)} = \frac{-\Delta H}{RT} + k^{11},$$

where k, k^{1}, and k^{11} are constants. Considering the lack of information regarding some of the factors operating to give plots such as Fig 3 this data can only be used to obtain a crude indication of enthalpy differences. Among the unknown factors is the possibility of some molecular ion isomerization and operation of a normal temperature effect upon the fragmentation of each species individually.† The ΔH values for the chain $\rightleftharpoons$ ring process in compound **1** are, from Fig 3, $-1{\cdot}61 \pm 0{\cdot}13$, $-1{\cdot}52 \pm 0{\cdot}08$, $-1{\cdot}59 \pm 0{\cdot}06$, and $-1{\cdot}93 \pm 0{\cdot}09$, giving an average value of $\Delta H_{gas} = -1{\cdot}7 \pm 0{\cdot}1$ kcal mole^{-1}. A duplicate determination at a different time, using a rebuilt ion source, gave an average value of $-2{\cdot}0$ kcal mole^{-1}. These values should be compared with those found[4] for the same reaction in CCl_4 solution ($-1{\cdot}15$ kcal mole^{-1}) and for the neat liquid ($-4{\cdot}0$ kcal mole^{-1}). While it is not possible to determine the equilibrium constant from the mass spectral data it is nevertheless true that the two forms of the molecular ion are associated with comparably abundant fragment ions and K probably differs from unity by less than an order of magnitude. This value is similar to those found for non-polar solutions, e.g., $K_{311^{\cdot}} = 1{\cdot}71$ in CCl_4.[4]

Further evidence that the tautomerism in the gas phase resembles that in non-polar solution can be found by comparing the spectra of the ring-substituted derivatives

* The results of Fig 3 are those of a typical experiment, but the general curve shape was the same in other runs and was also observed for the aryl-substituted compounds.

† Both should be relatively minor effects, see ref 6 for ion tautomerism (in another system) and ref 7 for discussions of temperature effects. "Normal temperature effects" refers to the effect of source temperature upon the internal energies of the individual species as opposed to the effect upon the equilibrium constant.

of compound **1**. From Table 1 it can be seen that the equilibrium constant for the gas-phase process varies with substituent in the same direction as occurs in solution. Thus there is a general tendency for the abundances (compared to $M^{+}\cdot-{}^{\cdot}CH_2OH$) of $M^{+}\cdot-CH_3^{\cdot}$ and $M^{+}\cdot-Ar^{\cdot}$ to decrease with increasing electron donating-power of substituents. If, as for compound **1**, these ion abundances represent the concentration

TABLE 1. RELATIVE ABUNDANCES OF SELECTED IONS IN THE MASS SPECTRA OF ARYL-SUBSTITUTED DERIVATIVES OF THE OXAZOLIDINE **1**[a]

Substituent	[Ring]/[chain] Soln[b]	Substituent σ^{+}[c]	[Ring]/[chain] M^{+}	M^{+}-1	M^{+}-30	M^{+}-Ar$^{\cdot}$	M^{+}-15	M^{+}-17
mNO_2 (**3**)	4·00	0·67	1	22	19	26	33	2·5
*m*Cl (**4**)	2·72	0·40	4	22	15	27	9·5	6
*p*Cl (**5**)	2·16	0·11	7	28	14	15	8	4
*m*MeO (**6**)	1·96	0·05	9	24	9	21	5	1·5
H (**1**)	1·71	0	3	23	9	17	7	4
*p*Me (**8**)	1·18	−0·31	5	19	7	10	13	1·5
*p*MeO (**9**)	0·66	−0·78	5	21	3	3	3	1·5
pNMe_2 (**10**)	0·21	−1·7	1	21	10	3	2	2·5

[a] Abundances are relative to $M^{+}\cdot-{}^{\cdot}CH_2OH$ = 100%. Data were obtained by direct insertion at 150° and are corrected for ^{13}C isotopic contributions

[b] CCl_4 solution, see ref 5

[c] Values from C. D. Ritchie and W. F. Sager, *Progress Phys. Org. Chem.* **2**, 323 (1964)

of the ring form, and $M^{+}\cdot-{}^{\cdot}CH_2OH$ represents that of the chain form, then stabilization of the chain form by electron-donating substituents occurs here as in solution. Some departures from the general trends are observed when the substituent can fragment to give an ion of the same mass as the characteristic ions. In addition, the $M^{+}\cdot-{}^{\cdot}OH$ process is not well-behaved, as was observed earlier in the variable temperature study on the parent oxazolidine. It will also be noted that the abundance of the $M^{+}\cdot-H^{\cdot}$ ion shows essentially no variation down the series. This is probably because the substituent effect upon the loss of $H^{\cdot}$ from the cyclic form of the molecular ion balances the substituent effect upon the tautomeric equilibrium. (Increasing contributions from imino hydrogen loss may also occur down the series).

The *m*-nitro and *p*-dimethylamino compounds, **3** and **10**, representing the extremes in ring/chain ratios in solution and the gas phase, were examined for temperature effects by introduction through the reservoir system. Inlet system temperature had no effect on the spectra exept that, at high temperatures (> 170°) thermal dehydration occurred. This is illustrated in Fig 4, for compound **3**; an $M^{+}\cdot$-18 ion appeared in the spectrum just at the temperature where the deviation from linearity commenced. No $M^{+}\cdot$-18 ion was observed when the source temperature was raised and that of the inlet system kept low. The effects of source temperature are illustrated for the *p*-dimethylamino (**10**) in Fig 5. These compounds (**3** and **10**) were difficult to get into the heated inlet system and hence a smaller range of temperatures could be covered. Very approximately, ΔH values (chain = ring) are −3·2 kcal mole^{-1} and −2·3 kcal mole^{-1} for **3** and **10**, respectively. Although the greater negative value for the

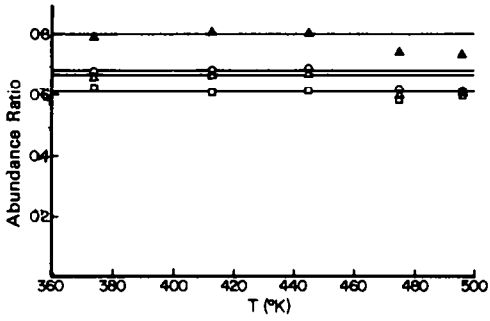

FIG 4. Effect of variation of inlet system temperature upon the spectrum of compound **3** (source 95°). Symbols as in Fig. 2, except that □ = $M^+ - Ar^{\cdot}/M^{+\cdot} - {}^{\cdot}CH_2OH$

nitro derivative is in line with expectation, that for the amino derivative is lower than a consideration of Table 1 leads one to expect.

Three supplementary experiments relating to the oxazolidine tautomerism were performed. First, the effect upon the oxazolidine spectra of doubling source pressures was tested. As expected no changes could be detected. Second, differences were sought in direct insertion spectra when the oxazolidines were deposited on the probe from solutions of different polarity (CCl_4 and MeOH were used, and compounds **1**, **3**, and **10** were tested). The open/closed ratios for **1** in these two solvents differ by a factor of 18,[4] hence if this difference were maintained as the compound sublimed from the probe, differences in spectra with solvent could be expected unless gaseous unimolecular tautomerism were to occur. No differences were observed for any of the three compounds. The third supplementary experiment concerned the effect of varying source temperature upon the 18 eV spectra of compound **1**. Van't Hoff plots, similar to those obtained at 70 eV, resulted although the amount of scatter was greater.

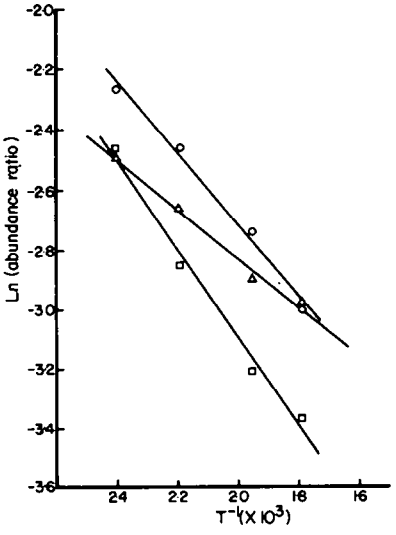

FIG 5. Effect of variation of source temperature upon the spectrum of compound **10** (inlet system 110°). Symbols as in Fig. 4

In marked contrast to the behavior of the oxazolidines (1 to 10) it has been reported[2] that the spectrum of acetylacetone shows pronounced variations with heated inlet temperature. We have also observed changes with inlet temperature but, in addition, found that large changes accompany independent variation of source temperature, in contrast to a previous assumption.[2]

It is very difficult to assign fragment ions to particular tautomeric forms of acetylacetone and the assignments of Lamir *et al.*[2] are, at first sight, surprising. They assigned the $M^{\ddagger}$-Me$^{\cdot}$ ion to the enol form of the molecular ion and the $M^{\ddagger}$-CH_2CO and $M^{\ddagger}$-CO ions to the keto form. It seems unlikely that the keto form will not undergo substantial loss of a Me radical. In an effort to make the necessary association of ions and forms the enol methyl ether of acetylacetone was prepared. Its mass spectrum shows ions of $\approx 0{\cdot}3\%$ relative abundance at the nominal masses of $M^{\ddagger}$-CO and $M^{\ddagger}$-CH_2CO[8] and therefore sheds no light on the problem. Implicit evidence on the relationships between tautomeric forms and fragment ions comes from the variable temperature studies. These suggest that $M^{\ddagger}$-CO and $M^{\ddagger}$-CH_2CO arise, probably exclusively, from the same (keto) form, with $M^{\ddagger}$-$CH_3^{\cdot}$ probably due to both keto and enol forms, although the latter may well be predominant.[9]

TABLE 2. MASS SPECTRUM OF ACETYLACETONE AS A FUNCTION OF INLET TEMPERTATURE[a]

Ion	(MS9) Temperature Range	Abundance (%)	(RMU-6) Temperature Range	Abundance (%)
M^+	300 → 480	69 → 62	340 → 513	85 → 92
$M^{\ddagger}$-CH_3	300 → 480	82 → 75	340 → 513	100 → 100
$M^{\ddagger}$-CO	340 → 480	1·4 → 2·3	340 → 513	0·9 → 7·6
$M^{\ddagger}$-CH_2CO	340 → 480	1·6 → 5·3	340 → 513	0·7 → 4·4
CH_3CO^+	300 → 480	100 → 100	340 → 513	37 → 70

[a] Ion abundances relative to base peak, *m/e* 43 in MS9, *m/e* 85 using RMU-6. All temperatures in °K. Source temperature was 65° in the MS9 and 95° in the RMU-6.

From the results of Table 2 it is seen that changes in the temperature of the heated inlet system have a relatively minor effect on the spectrum of acetylacetone, although the low abundance rearrangement ions, $M^{\ddagger}$-CO and $M^{\ddagger}$-CH_2CO are relatively much changed. These results do not seem to require the inference that the position of tautomeric equilibrium in the source is controlled by inlet temperature as has been suggested.[2] The changes in $M^{\ddagger}$-CO and $M^{\ddagger}$-CH_2CO could be partly due to normal temperature effects (see above).

The effects of changes in source temperature at constant (30°) inlet temperature are illustrated in Fig 6. The constancy of the $M^{\ddagger}$-CO/$M^{\ddagger}$-CH_2CO ratio (not illustrated) suggests the cogenesis of these ions from just one tautomeric form. The plots of $M^{\ddagger}$-$CH_3^{\cdot}$ against either of the rearrangement ions show near-linear portions covering wide temperature ranges. This suggests that this tautomerism, like that occuring between oxazolidine and the corresponding Schiff base, also occurs by a unimolecular mechanism. The deviations from linearity observed in Fig 6 probably reside in two factors: (i) at high temperatures thermal eliminations of CH_2CO and CO could occur in the source, this should depress the abundance ratios, as observed;

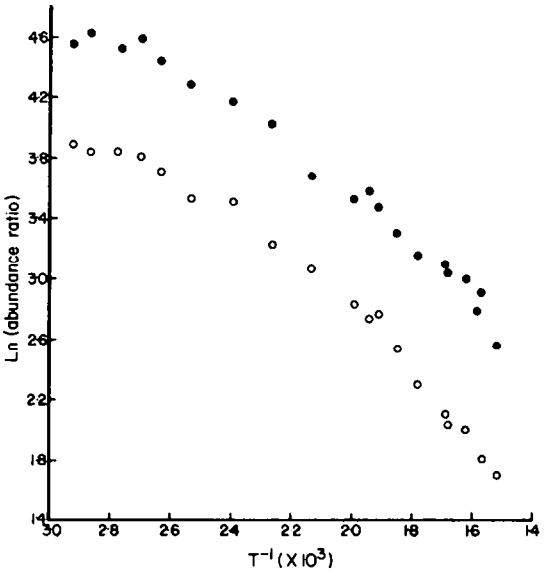

FIG 6. Effect of variation of source temperature upon the spectrum of acetylacetone (inlet system 30°). ○ = $M^+ - CH_3^{\cdot}/M^+ - CH_2CO$; ● = $M^+ - CH_3^{\cdot}/M^+ - CO$. For clarity, ordinate of the $M^+ - CO$ plot is offset +1·0 units

(ii) M^+-$CH_3^{\cdot}$ probably does not arise from just one tautomeric form. The value of ΔH_{gas} indicated by the data of Fig 6 (~ -3 kcal mole^{-1}) is in broad agreement with literature values ($-2{\cdot}4$ and $-2{\cdot}06$ kcal mole^{-1}).[1, 10]

CONCLUSIONS

The situation in acetylacetone is complex, in particular, the results cannot simply be explained by a bimolecular tautomerization process, occurring in the heated inlet system but not in the source, which a reading of Zamir *et al.*[2] would suggest. Our results imply that in the gas phase, keto-enol tautomerism in acetylacetone involves wall collisions and/or occurs by a (four-centered) intramolecular mechanism.* Since this process occurs in the source it overrides any prior tautomerization which may occur in the heated inlet system.

The considerable similarities between ΔH values and substituent effects on the oxazolidine ring-chain tautomerism in the gas phase and those in non-polar solution in no way require that the detailed mechanisms involved be similar. Indeed, further speculation on these mechanisms would be premature.

With data on two completely different tautomeric processes in hand some comments can be made on the merits of the mass spectromeric method, particularly *vis-a-vis* nuclear magnetic resonance. In terms of providing thermodynamic quantities mass spectrometry is very restricted, equilibrium constants cannot be obtained and enthalpy differences are only approximate. An important advantage of this approach,

* A referee has suggested that the most plausible mechanism is an intramolecular process *assisted* by wall collisions.

however, is the fact that some insight into the mechanism (molecularity) of the tautomerization process can be obtained. In most systems assignment of tautomer-specific fragment ions should be possible, although labeled analogs may be required.

EXPERIMENTAL

Except for the data of Table 1, mass spectra were determined on samples introduced through the heated inlet system. An AEI MS9 spectrometer was used throughout except as noted in Table 2, where an Hitachi RMU-6 was used. Standard conditions for the MS9 were 70 eV ionizing voltage, 100 μA trap current, 8 kV accelerating voltage and indicated source pressure $< 10^{-6}$ torr. Source temperature was measured using a thermocouple attached to the ion block, inlet temperature by a thermocouple mounted against the glass reservoir. Standard conditions for the RMU-6 were 70 eV ionizing voltage, 30 μA trap current, 2·5 kV accelerating voltage and indicated source pressure $\sim 10^{-6}$ torr.

Relative ion abundances represent the average of four repetitive scans for the experiments in which inlet temperature was varied and single scans when source temperature was varied. Errors are probably less than 2% for the abundant fragment ions but approach 5% for the less abundant.

Most of the compounds used were prepared in connection with another study.[5] Acetylacetone was a purified (gc) commercial sample (Aldrich) and its methyl ether was prepared by a standard method.[11]

REFERENCES

[1] J. Powling and H. J. Bernstein, *J. Am. Chem. Soc.* **73**, 4353 (1951)
[2] L. Zamir, B. S. Jensen and E. Larsen, *Org. Mass Spectrom.* **2**, 49 (1969)
[3] For a review on ring-chain tautomerism see P. R. Jones, *Chemical Rev.* **63**, 461 (1963)
[4] J. V. Paukstelis and R. M. Hammaker, *Tetrahedron Letters* 3557 (1968)
[5] J. V. Paukstelis and L. L. Lambing, *Ibid.* 299 (1970)
[6] J. K. MacLeod, J. B. Thompson and C. Djerassi, *Tetrahedron* **23**, 2095 (1967)
[7] [a] G. Remberg, E. Remberg, M. Spiteller-Friedmann and G. Spiteller, *Org. Mass Spectrom.* **1**, 87 (1968);
[b] A. Cassuto, *Advan. Mass Spectrom.* **2**, 296 (1963);
[c] J. Jullien and J. M. Pechine, *Org. Mass Spectrom.* **4**, 325 (1970)
[8] Compare with N. Schamp and M. Vandewalle, *Bull. Soc. Chim. Belges* **75**, 539 (1966)
[9] N. Schamp, M. Vandewalle and M. Francque, *Ibid.* **76**, 528 (1967)
[10] W. Strohmeier and I. Höhne, *Z. Naturforschg*, **7b**, 184 (1952)
[11] R. Chong and P. S. Clezy, *Tetrahedron Letters* 741 (1966)