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A Mass Spectrometric Study of the Dimethyl Ester Trimethylsilyl Enol Ether Derivatives of Some 3-Oxodicarboxylic Acids

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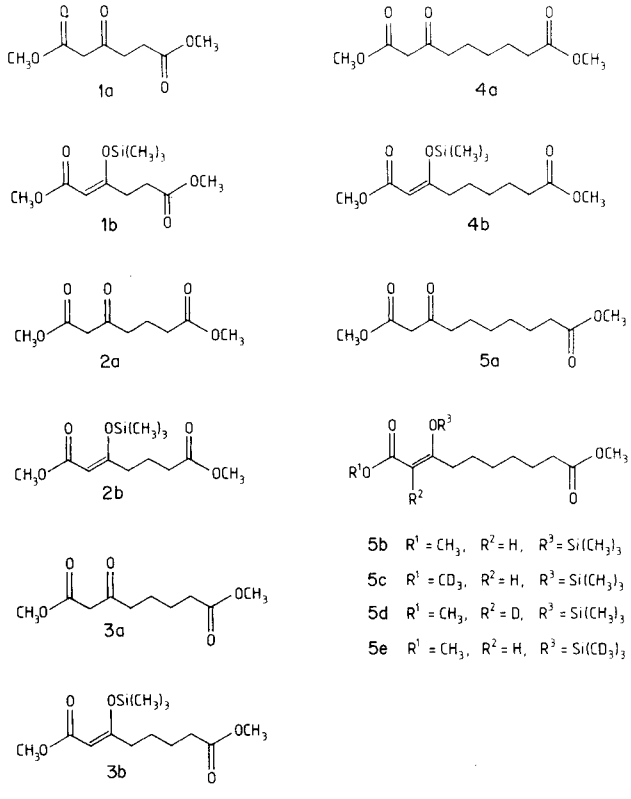
The fragmentation pathways for the dimethyl ester trimethylsilyl enol ether derivatives of some 3-oxodicarboxylic acids have been found by using *B/E* and B^2/E linked scans, collisional activated decomposition and isotope substitution techniques. The trimethylsilyloxy group strongly directs the decomposition processes, and induces a fragmentation pattern that intimately reflects the structure of the compounds.

INTRODUCTION

During the metabolism of dicarboxylic acids in man, a number of different dicarboxylic acid derivatives are conceivably formed and excreted in the urine.[1] Whereas some of the proposed metabolites, e.g. 3-hydroxydicarboxylic acids, have been known for a number of years,[2-4] the formation of 3-oxodicarboxylic acids has only recently been confirmed.[5] The latter group of metabolites was detected as the corresponding dimethyl 3-trimethylsilyloxy-2-alkenedioates, by combined gas chromatography/mass spectrometry using the selective and sensitive multiple ion detection technique. A major reason for the successful application of this technique was the mass spectra resulting from the electron impact (EI) ionization of the silylated diesters which displayed a number of high-intensity peaks with high mass. We have therefore investigated the mass spectral properties of a number of such compounds more closely, and discovered that their mass spectra contain characteristic peaks due to the individual compounds as well as significant peaks due to this class of compounds.



EXPERIMENTAL

Instrumentation

EI mass spectra were recorded on a VG MicroMass 7070H double-focusing mass spectrometer using either a direct inlet system (inlet temperature, 100-180 °C) or a Hewlett-Packard 5710 gas chromatograph equipped with a CP Sil 5 CB (Chrompack) fused silica capillary column (25 m × 0.22 mm i.d.). The injector port temperature was 250 °C and the oven temperature was programmed from 120 to 240 °C at a rate of 6 °C min^{-1} after a start delay of 2 min. The ion source temperature was 220 °C and the ionization energy was 70 eV, except for the low-temperature spectra which were recorded at 150 °C and 15 eV. Metastable transitions were obtained by *B/E* and B^2/E linked scanning using a VG linked-scan unit. Collisional activated decomposition (CAD) spectra were recorded by making a *B/E* linked scan of the compound of interest while holding the pressure in the collision cell at approximately 1 Torr. Data were obtained and processed on a VG 2050 data system.

^1H NMR (89.55 MHz) and ^{13}C NMR (22.50 MHz) spectra were obtained on a JEOL FX 90 Q spectrometer at 29 °C. The samples, with tetramethylsilane (TMS) as internal reference, were 5-10% by weight in $CDCl_3$ which also provided the deuterium signal for the NMR field lock. The spectra were run with a spectral width of 1000 and 6000 Hz, respectively, and a pulse width of

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45°. The ^{13}C NMR spectra were accumulated with a pulse repetition time of 5 s and the ^{13}C NMR C-H decoupling was achieved by a broad-band decoupling pulse at 89.55 MHz. The chemical shift values are in ppm downfield to TMS.

The infrared spectra were recorded on a Shimadzu IR-435 infrared spectrophotometer as liquid film.

Reference compounds

Dimethyl 3-oxohexanedioate (**1a**) was purchased from Fluka AG, Buchs, Switzerland.

Dimethyl 3-oxodecanedioate (5a). Dimethyl 3-hydroxydecanedioate (0.62 g, 2.5 mmol) was prepared according to the literature[6] and oxidized by pyridinium chlorochromate[7] (0.65 g, 3 mmol) in dry dichloromethane (5 cm^3) at ambient temperature for 18 h. The black reaction mixture was diluted with dry ether (10 cm^3), and the organic phases were filtered through Florisil. The residue was decanted three times with dry ether before the combined organic phase was evaporated under reduced pressure: this gave 0.48 g (79%) of compound **5a**. ^1H NMR: δ 1.06-1.85(8H, m), 2.30(2H, t), 2.53(2H, t), 3.42(2H, s), 3.65 (3H, s), 3.72(3H, s). ^{13}C NMR: δ 23.3, 24.7, 28.7, 28.8, 34.0, 42.9, 49.0, 51.3, 52.2, 167.6, 174.0, 202.4. IR(cm^{-1}): 1735(s), 1715(s), 1430(m).

Dimethyl 3-oxoheptanedioate (2a), dimethyl 3-oxooctanedioate (3a) and dimethyl 3-oxononanedioate (4a). These compounds were prepared in the same way from the corresponding dimethyl 3-hydroxyalkanedioates, giving yields ranging from 67 to 77%. All compounds gave IR spectra identical to that of compound **5a**. ^1H NMR—**2a**: δ 1.4-1.8(2H, m), 2.3-2.8(4H, m), 3.46(2H, s), 3.66(3H, s), 3.70(3H, s). **3a**: δ 1.3-1.8(4H, m), 2.3-2.8(4H, m), 3.46(2H, s), 3.66(3H, s), 3.73(3H, s). **4a**: δ 1.1-1.8(6H, m), 2.32(2H, t), 2.56(2H, t), 3.44(2H, s), 3.66(3H, s), 3.74(3H, s). ^{13}C NMR—**2a**: δ 20.8, 34.1, 41.8, 49.0, 51.7, 52.3, 167.6, 173.4, 201.8. **3a**: δ 22.9, 24.4, 33.7, 42.5, 49.0, 51.4, 52.3, 167.6, 173.6, 202.1. **4a**: δ 23.1, 24.7, 28.5, 33.9, 42.7, 49.0, 51.4, 52.3, 167.6, 173.9, 202.3.

α-Methyl-d_3-ω-methyl 3-hydroxydecanedioate (6). Activated zinc dust (0.65 g, 10 mmol) was suspended in a dry mixture of benzene and ether (5:1, 25 cm^3). A mixture of methyl-d_3 bromoacetate[6] (1.56 g, 10 mmol) and methyl 8-oxooctanoate (1.72 g, 10 mmol) was then added, and the resulting solution was refluxed for 3 h. The reaction mixture was quenched by addition of 10% sulphuric acid (15 cm^3), the layers were separated, and the organic phase was washed with dilute sulphuric acid, water and aqueous sodium hydrogencarbonate before drying (magnesium sulphate). Compound **6** was obtained 95% pure (GC) in 75% yield by evaporation of the solvent. ^1H NMR: δ 1.2-1.8(8H, m), 2.2-2.5(6H, m), 3.43(1H, s), 3.66(3H, s), 4.0(1H, m). ^{13}C NMR: δ 24.9, 25.3, 29.1, 29.2, 30.1, 36.6, 41.2, 51.4, 68.1, 173.3, 174.1.

α-Methyl-d_3-ω-methyl 3-oxodecanedioate (7). This compound was prepared in 69% yield from compound **6** as described for compound **5a**. ^1H NMR: δ 1.2-1.8(8H, m), 2.31(2H, t), 2.54(3H, s), 3.44(2H, s), 3.67(3H, s). ^{13}C NMR: δ 23.3, 24.8, 28.7, 28.8, 34.0, 42.9, 49.1, 51.4, 167.7, 174.1, 202.4.

Dimethyl 2,2-d_2-3-oxodecanedioate (8). This compound was prepared by dissolving compound **5a** in a mixture of 5% deuterium chloride in deuterium oxide. The reaction was monitored by ^1H NMR spectroscopy by observing the disappearance of the singlet at 3.44 ppm. Compound **8** was then isolated by extracting the solution three times with ether, drying (magnesium sulphate) and evaporation of the ether under reduced pressure.

Methyl 2,2-d_2-3-oxobutanoate (10a). Compound **10a** was synthesized in the same manner as compound **8**, starting with methyl acetoacetate.

Silylation

Dimethyl 3-trimethylsilyloxy-2-hexenedioate (**1b**), dimethyl 3-trimethylsilyloxy-2-heptenedioate (**2b**), dimethyl 3-trimethylsilyloxy-2-octenedioate (**3b**), dimethyl 3-trimethylsilyloxy-2-nonenedioate (**4b**), dimethyl 3-trimethylsilyloxy-2-decenedioate (**5b**), α-methyl-d_3-ω-methyl 3-trimethylsilyloxy-2-decenedioate (**5c**), and dimethyl 2-*d*-3-trimethylsilyloxy-2-decenedioate (**5d**) were obtained as 1:1 *E*/*Z* mixtures by treating compounds **1a**, **2a**, **3a**, **4a**, **5a**, **7** and **8**, respectively, with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) containing 1% trimethylchlorosilane. Unreacted BSTFA was removed in a stream of dry nitrogen, and the dimethyl 3-trimethylsilyloxy-2-alkenedioates were immediately analysed on the mass spectrometer. Methyl 3-trimethylsilyloxy-2-butenoate (**9**) and methyl 2-*d*-3-trimethylsilyloxy-2-butenoate (**10**) were prepared similarly from methyl acetoacetate and compound **10a**, respectively.

Compound **5a** was in addition silylated with *N*,*O*-bis(tri(methyl-d_3)silyl)acetamide(d_{18}-BSA) yielding dimethyl 3-tri(methyl-d_3)silyloxy-2-decenedioate (**5e**).

RESULTS AND DISCUSSION

Silylation of the dimethyl 3-oxoalkanedioates gives both the *E* and *Z* forms of the dimethyl 3-trimethylsilyloxy-2-alkenedioates in a ratio of approximately 1:1. Separation of the silyl enol ether isomers is readily achieved on an apolar capillary column. The EI mass spectra of each isomer displayed the same fragments, although the intensity of some ions differed between the isomers.

The mass spectra of all the dimethyl 3-trimethylsilyloxy-2-alkenedioates as *E*/*Z* mixtures (Fig. 1) contain a number of peaks due to fragments resulting from the same processes. This is evident since some fragments have the same *m*/*z* values in all spectra whereas other fragments appear with mass differences of 14 u as expected for a series of homologues. The fragmentation processes are therefore discussed for one compound only, namely, dimethyl 3-trimethylsilyloxy-2-decenedioate (**5b**).

The molecular ion was observed in all spectra, and the intensity decreased from 3.6% in compound **1b** to

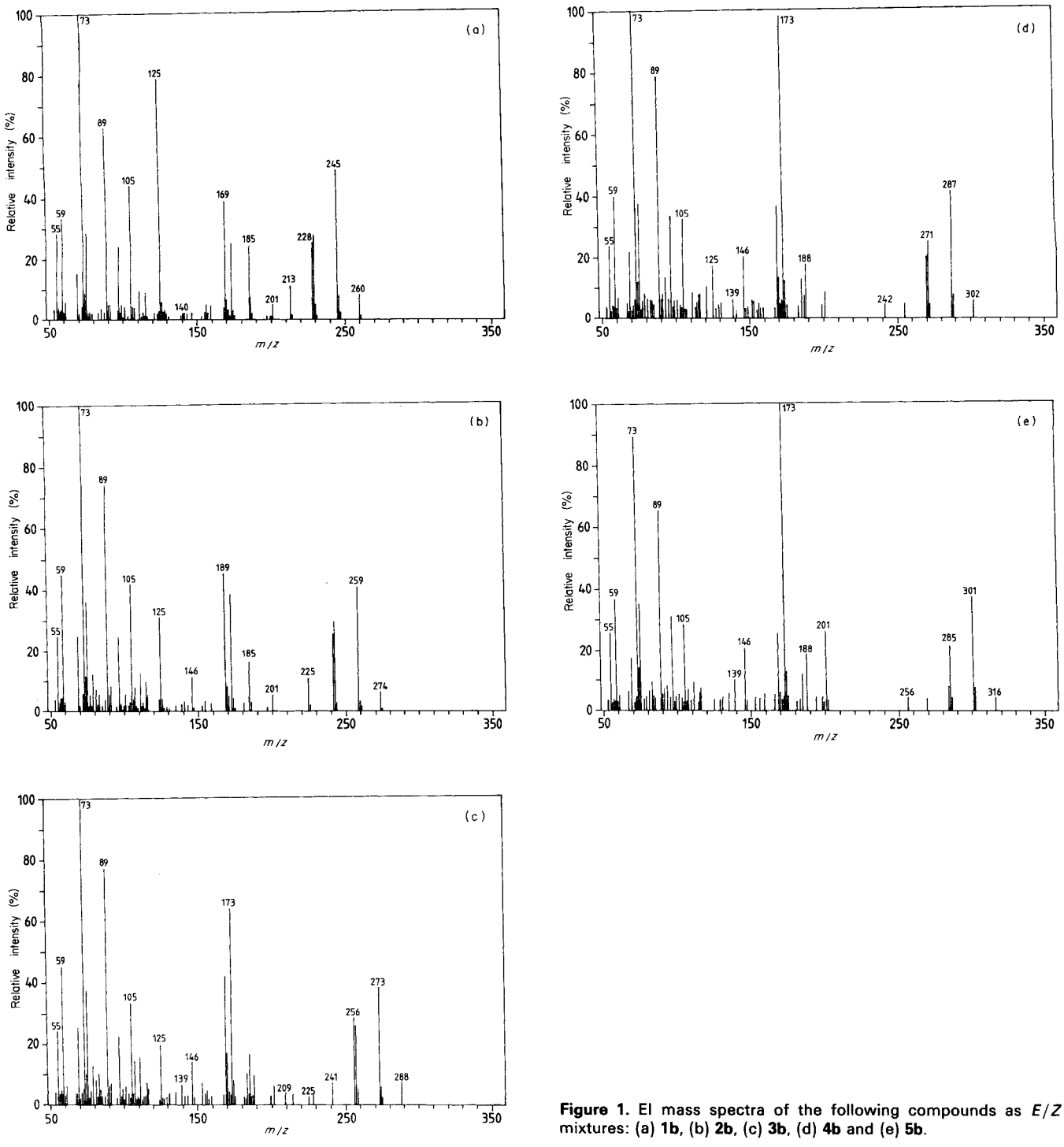


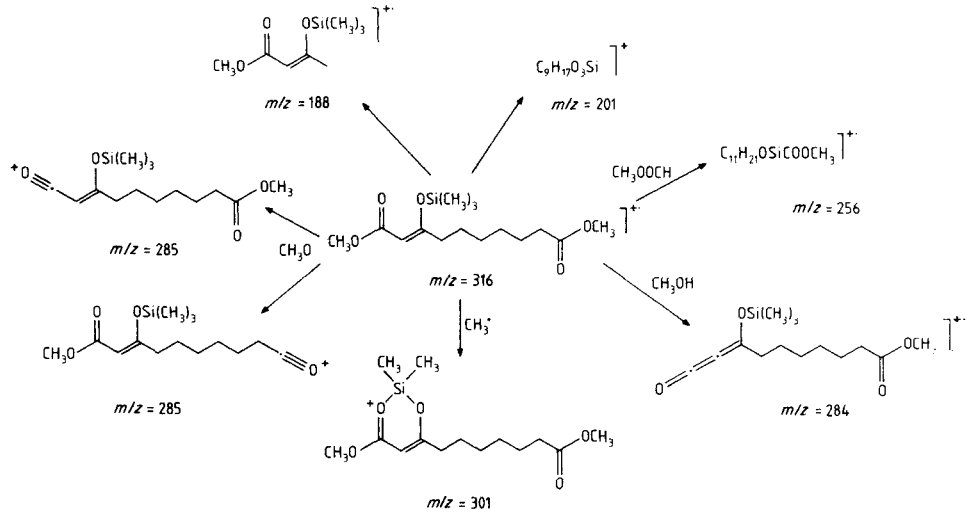
Figure 1. EI mass spectra of the following compounds as *E*/*Z* mixtures: (a) **1b**, (b) **2b**, (c) **3b**, (d) **4b** and (e) **5b**.

1.2% in compound **5b**. This finding is in contrast with the corresponding dimethyl 3-trimethylsilyloxyalkanedioates,[6] where no molecular ion was observed even at low ionization potentials.

The presence of a number of fragmentation directing functional groups renders a large number of different primary fragmentation processes available to the molecular ion(s) (Scheme 1). The metastable processes from the molecular ion include loss of a methyl radical from the trimethylsilyloxy group, loss of methoxy radicals and methanol from the ester group(s), and loss of methyl formate. Probable non-metastable primary processes are the formation of *m*/*z* 201 and 188 and the trimethylsilyl ion *m*/*z* 73.

Formation and fragmentation of *m*/*z* 301

The *m*/*z* 301 fragment is formed from $M^{+\cdot}$ (Scheme 2) by expulsion of a methyl radical from the trimethylsilyl moiety, a process also observed during EI ionization of the analogous dimethyl 3-trimethylsilyloxyalkanedioates.[6] The origin of the methyl group was confirmed by substituting the TMS group with a TMS-d_9



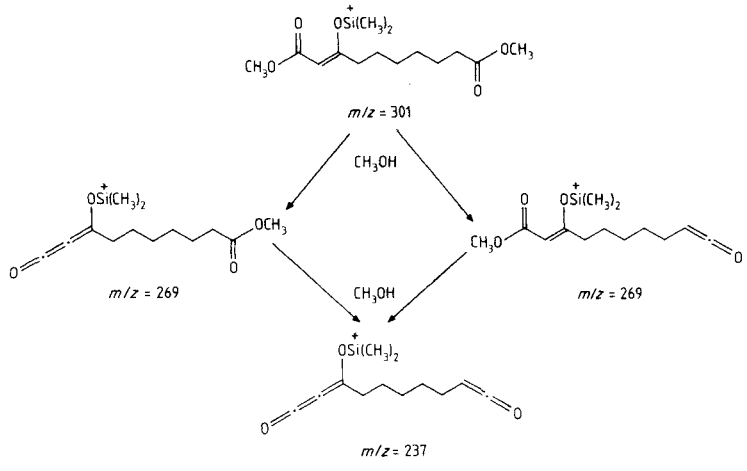
Scheme 1. Primary fragmentation processes from the molecular ion of compound **5b**.

m/z	Fragment ion
316	$M^{+\cdot}$
301	$[M-CH_3^{\cdot}]^+$
285	$[M-CH_3O^{\cdot}]^+$
284	$[M-CH_3OH]^{+\cdot}$
269	$[M-CH_3^{\cdot}-CH_3OH]^+$
256	$[M-CH_3OOCH]^{+\cdot}$
252	$[M-2\times CH_3OH]^{+\cdot}$
240	$[M-CH_3OH-CO_2]^{+\cdot}$
237	$[M-CH_3^{\cdot}-2\times CH_3OH]^+$
201	$[C_9H_{17}O_3Si]^{+\cdot}$
194	$[M-CH_3OH-(CH_3)_3SiOH]^{+\cdot}$
188	$[C_8H_{16}O_3Si]^{+\cdot}$
173	$[C_7H_{13}O_3Si]^+$
169	$[C_8H_{13}O_2Si]^{+\cdot}$
105	$[C_4H_{13}OSi]^+$

Scheme 2. Metastable transitions in the 1st FFR in compound **5b**.

(compound **5e**); the peak corresponding to m/z 301 then appeared at m/z 307 which shows that the expelled radical contained three deuterium atoms. For the Z isomer, a cyclic structure of the m/z 301 ion can be envisaged, with the silicon atom as a bridge between the α-carbonyl oxygen and the enol ether oxygen. This is in accordance with observations of analogous cyclic ions in *o*-trimethylsilyloxyacetophenone.[8] The intensity of the $[M-15]^+$ ion of the isomer with shorter retention time is only half the intensity of the isomer with longer retention time. The Z isomer can easily gain a cyclic m/z 301 fragment structure, as pointed out above, whereas the E isomer has to isomerize to the Z isomer before a cyclic structure can be achieved. The isomerization process probably has a considerably lower frequency factor than the expulsion of the methyl radical, thereby making the isomerization rate determining, and the methyl elimination less feasible for the E isomer than the Z isomer. It is therefore probable that the E isomer is the isomer with shorter retention time. The existence of a common $[M-15]^+$ ion structure for the isomers is further supported by the fact that both the metastable and the CAD spectra are identical for the E and Z forms.

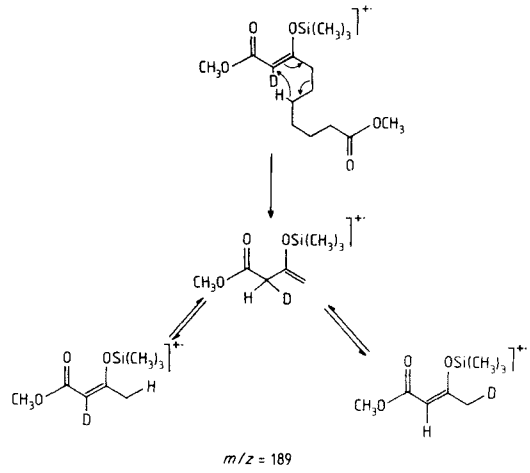
The even-electron species m/z 301 is degraded by two different metastable processes (Schemes 3 and 4). Both involve methanol elimination to m/z 269, but they differ in the origin of the methanol molecule being expelled. This was established by studying compound **5c**. The corresponding $[M-15]^+$ ion, m/z 304, which contains an α-methoxy-d_3 group instead of an α-methoxy group, eliminated CD_3OH and CH_3OH from the α-ester and



Scheme 3. Secondary fragmentation processes from m/z 301 from compound **5b**.

m/z	Fragment ion
319	$M^{+\cdot}$
304	$[M-CH_3^{\cdot}]^+$
288	$[M-CH_3O^{\cdot}]^+$
285	$[M-CD_3O^{\cdot}]^+$
284	$[M-CD_3OH]^{+\cdot}$
272	$[M-CH_3^{\cdot}-CH_3OH]^+$
271	$[M-CH_3^{\cdot}-CH_3OD]^+$
269	$[M-CH_3^{\cdot}-CD_3OH]^+$
256	$[M-CD_3OOCH]^{+\cdot}$
252	$[M-CD_3OH-CH_3OH]^{+\cdot}$
240	$[M-CD_3OH-CO_2]^{+\cdot}$
237	$[M-CH_3^{\cdot}-CD_3OH-CH_3OH]^+$
204	$[C_9H_{14}D_3O_3Si]^{+\cdot}$
194	$[M-CD_3OH-(CH_3)_3SiOH]^{+\cdot}$
191	$[C_8H_{13}D_3O_3Si]^{+\cdot}$
176	$[C_7H_{10}D_3O_3Si]^+$
169	$[C_8H_{13}O_2Si]^{+\cdot}$
108	$[C_4H_{10}D_3OSi]^+$

Scheme 4. Metastable transitions in the 1st FFR in compound **5c**.



Scheme 5. Formation of m/z 189 from compound **5b**.

the ω-ester moieties, respectively. The methanol elimination also occurred in the second field-free region (FFR): this is evident from a broad metastable peak located at m/z 240.5 (calc. 240.402). The m/z 269 ions both eliminate another molecule of methanol to m/z 237.

Formation of m/z 256

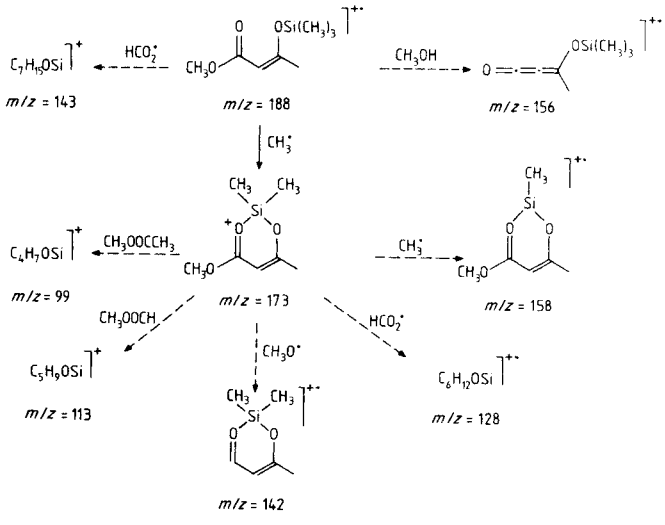
The m/z 256 is formed from $M^{+\cdot}$ by an elimination of methyl formate. This reaction takes place only in the α-ester moiety (Schemes 3 and 4) as borne out by isotope substitution experiments as outlined above. The m/z 256 ion has no metastable daughter ions.

Formation and fragmentation of m/z 201

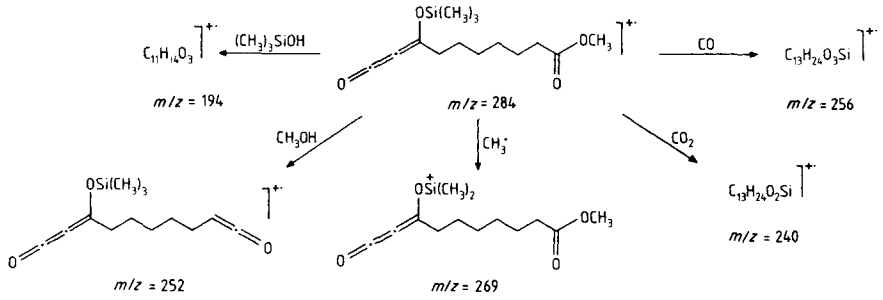
The m/z 201 ion possibly originates from $M^{+\cdot}$, but no metastable link between the molecular ion and m/z 201 could be established by B/E and B^2/E linked scan of the respective ions. The spectra of the isotope substituted analogues **5c**, **5e** and **5d** revealed that the fragment contained the α-methoxy group, a complete trimethylsilyl group and the hydrogen atom in position 2. The presence of an m/z 201 ion in all homologues (Fig. 1), together with its elemental composition $C_9H_{17}O_3Si$, determined by high-resolution mass spectrometry, strongly suggests its formation by a cleavage between C(5) and C(6) in the diester chain. The m/z 201 ion undergoes two metastable decomposition reactions: one is an elimination of methanol (from the former α-ester group) to m/z 169, which is observed in the 2nd FFR at m/z 142.1 (calc. 142.095); the other is a rearrangement forming protonated methyl trimethylsilyl ether at m/z 105.

Formation and fragmentation of m/z 188

Although no ancestor to m/z 188 could be found by a B^2/E linked scan, the ion probably originates from the molecular ion. The elemental composition $C_8H_{16}O_3Si$, and the presence of a complete trimethylsilyl moiety together with the α-methoxy group, suggest a structure similar to the molecular ion of methyl 3-trimethylsilyloxy-2-butenoate (**9**). This similarity is substantiated by examination of the CAD spectra of the m/z 188 fragment and the molecular ion from **9**, which are identical. A tentative rationale for the formation of the corresponding ion at m/z 189 from compound **5d** is included in Scheme 5. The mechanism involves a cyclic McLafferty-like rearrangement with a hydrogen transfer from C(6) to C(2) with a subsequent migration of the double bond. The double bond may isomerize back to the C(2)-C(3) position and thereby scramble the vinylic hydrogen. A similar process is observed in simple silyl enol ethers.[9] In order to investigate the scrambling process, the collision-induced elimination of methanol from the corresponding m/z 189 ion, obtained separately from compound **5d** and methyl 2-*d*-3-trimethylsilyloxy-2-butenoate (**10**), were studied. The results revealed that a considerable amount of the methanol was eliminated as CH_3OD. The CH_3OD is probably not formed by an 1,2-elimination,[10] and the deuterium atom thus originates from C(4) by a 1,4-elimination. This finding proves that scrambling of the vinylic hydrogen takes place in the m/z 189 ion irrespective of whether the ion originates from compound **5d** or **10**. The m/z 188 ion has



Scheme 6. Secondary fragmentation processes from m/z 188 and CAD (dashed arows) from m/z 188 and 173.



Scheme 7. Secondary fragmentation processes from *m/z* 284 from compound **5b**.

only one metastable daughter ion, *m/z* 173, formed by expulsion of a methyl radical from the trimethylsilyl group (Scheme 6). In addition, this reaction also takes place in the 2nd FFR: this is evident from an intense metastable peak located at *m/z* 159.25 (calc. 159.197). Collisional activation results in two more decompositions, namely, elimination of methanol to *m/z* 156 from the former α-ester moiety, and formation of *m/z* 143 by expulsion of a HCO_2 radical.

No metastable transitions from *m/z* 173 were observed, but a number of decompositions occurred by collision activation: loss of a methyl radical from the former trimethylsilyl moiety to *m/z* 158, loss of a methoxy radical to *m/z* 142 and loss of a HCO_2 radical to *m/z* 128. Furthermore, two even-electron species are eliminated, namely, methyl formate to *m/z* 113 and methyl acetate to *m/z* 99 (Scheme 6). The CAD spectra of *m/z* 173 from compounds **5b** and **9** are identical. It is also noteworthy that there are no differences in the CAD spectra of *m/z* 173 from the *E* and *Z* isomers of compound **5b**. The *m/z* 173 ion is therefore, most likely, the common cyclic ion structure for both the *E* and *Z* isomers.

Formation of *m/z* 285

The ions at *m/z* 285 are formed by a metastable loss of a methoxy radical from the molecular ion. This process can occur in both ester moieties (Scheme 1), as shown by isotope substitution experiments presented in Schemes 2 and 4. In contrast with the corresponding ions formed from dimethyl 3-trimethylsilyloxydecanedioate, none of the *m/z* 285 ions yielded any metastable decompositions.

Formation and fragmentation of *m/z* 284

The *m/z* 284 ion is formed by a metastable methanol elimination from the α-ester moiety in the molecular ion. Unlike the methoxy elimination from the molecular ion, this decomposition is seen in the 2nd FFR as a broad peak situated at *m/z* 255.3 (calc. 255.241). The *m/z* 284 ion can eliminate another molecule of methanol, or expel carbon monoxide and carbon dioxide to give *m/z* 252, 256 or 240, respectively (Scheme 7). Similar reactions have been observed with methylene ketenes in the gas phase at elevated temperatures.[11] The trimethylsilyl group in *m/z* 284 can expel a methyl radical forming *m/z* 269. The last mode of decomposition of *m/z* 284 is an elimination of trimethylsilanol to *m/z* 194.

CONCLUDING REMARKS

From the results discussed above, it is evident that the EI spectra of dimethyl 3-trimethylsilyloxy-2-alkenedioates is dominated by fragment ions due to the fragmentation directing power of the silyloxy moiety. Only a smaller amount of $M^{+\cdot}$ decomposes according to one or the other ester groups. This finding is in good agreement with results obtained by EI ionization of the corresponding saturated diesters, the dimethyl 3-trimethylsilyloxyalkanedioates.[6] However, the primary fragmentation processes differ considerably for the two types of compounds. The molecular ion of the unsaturated diesters are more stable and less prone to expel radicals than their saturated analogues. Furthermore, the characteristic α-cleavages adjacent to the trimethylsilyloxy group are observed for the saturated diesters only, and are completely absent in the presently investigated compounds.

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