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# Unusual Fragmentation of Trimethylsilylated Enols Derived from *m*- and *p*-Hydroxyacetophenones

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**When 4-hydroxyacetophenone is treated with MSTFA the corresponding bis-trimethylsilylated enol ether (1a) is obtained. The mass spectrum of 1a is characterized by a $[M-1]^+$ base peak. Extensive deuteration experiments revealed that the hydrogen is mainly removed from a ring position, but originates also to some extent from the side chain (methylidene group) and even to a very small amount from the hydrogens of the methyl groups of the enolic trimethylsilyl group. A mechanism for this fragmentation behaviour is formulated.**

## INTRODUCTION

During the investigation of compounds occurring in the roots of stinging nettle (*Urtica dioica*) a phenolic fraction was obtained. This fraction was derivatized with MSTFA (*N*-methyl-*N*-trimethylsilyltrifluoroacetamide) in order to allow a gas chromatographic analysis of the trimethylsilyl derivatives. One of these peaks showed the mass spectrum reproduced in Figure 1.

Further investigations revealed that this spectrum corresponds to the trimethylsilyl enol ether of the trimethylsilylated 4-hydroxyacetophenone (**1a**). The formation of trimethylsilyl ethers of enols is a well known reaction of ketones treated with basic silylating reagents.[1]

In the same phenolic fraction the bis-trimethylsilylated derivative of 4-hydroxy-3-methoxyacetophenone (**2**) was detected too[2] as well as the same derivative from 3-hydroxyacetophenone (**3**). Both compounds **2** and **3** show similar, albeit less strong $[M-1]^+$ ions in their mass spectra. Hence, this behaviour seems typical for various acetophenone trimethyl silenol ethers.

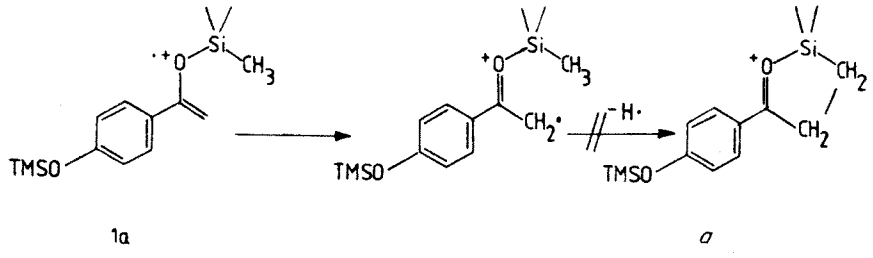
## RESULTS AND DISCUSSION

The high intensity of the $[M-1]^+$ ion in the spectra of the bis-trimethylsilyl enol ethers **1a**, **2** and **3** is unexpected. The first assumption was that this hydrogen loss may be the result of a cyclization reaction by abstraction of one hydrogen from the enolic $(CH_3)_3Si$-group to produce the ion *a* (Scheme 1).

This was excluded by the mass spectrum of the deuterated compound **1b** which showed still a $[M-1]^+$ base peak and not a $[M-2]^+$ peak. A $[M-1]^+$ peak was also present in the spectrum of compound **1c**, carrying two $(CD_3)_3Si$-groups (Table 1).

The spectrum of the di-deuterated compound **1d** shows, besides the $[M-1]^+$ peak, only a small peak (20% relative intensity) at $[M-2]^+$. This experiment proves that one or several hydrogens located at the aromatic ring must be involved in the formation of the $[M-1]^+$ ion. Thus, the ring di-deuterated compounds **1e** and **1f**, and also the tetradeuterated compound **1g**, were synthesized. The mass spectra of the ring di-deuterated compounds **1e** and **1f** are rather similar. Both show about the same ratio of $[M-1]^+$ and $[M-2]^+$ ions ($[M-2]^+$ about 50% of $[M-1]^+$ = base peak) after correction for insufficient deuteration and isotope contribution, indicating the approximate equivalence of all the ring hydrogens during the hydrogen elimination reaction. This is confirmed by the spectrum of **1g** with a $[M-2]^+$ base peak. Even the hexadeuterated compound **1h** shows a small $[M-1]^+$ peak, indicating exchange reactions between the hydrogens of the trimethylsilyl groups and deuterium atoms before fragmentation.

Insufficient deuteration required an approximate correction of the peak intensities of **1e** and **1f** in the molecular ion region. This was achieved by using **1a** as a standard.




1a *a*

**Scheme 1.** First assumed elimination of hydrogen from the enolic $(CH_3)_3SiO$-group.

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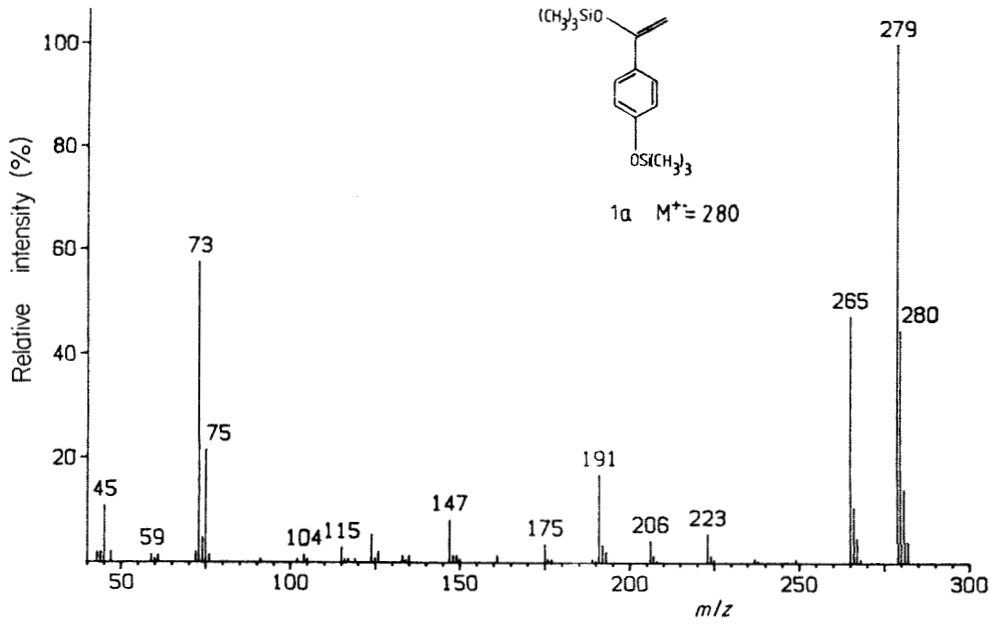
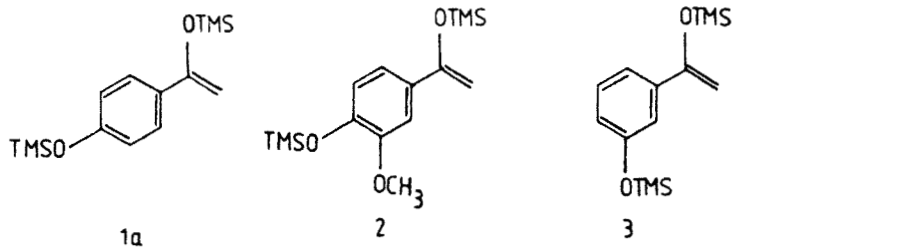



**Figure 1.** EI mass spectrum of compound **1a**.

**Table 1. EI mass spectral data of compounds 1b–1h, 2 and 3**

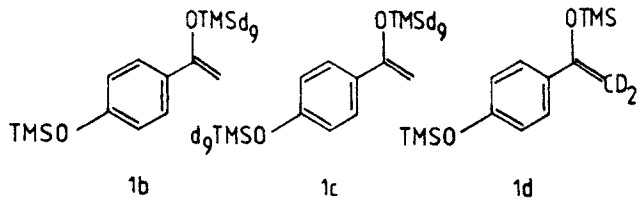
| Compound | $[M]^{+\cdot}$ | $[M-15]^+$ | Mass range *m/z* 250–300 (masses lower than 2% abundance are omitted) |
|---|---|---|---|
| **1b** | 289 | 274 | 291 (6), 290 (23), 289 (67), 288 (100), 287 (3), 275 (4), 274 (13), 273 (25), 272 (19), 271 (11). |
| **1c** | 298 | 283 | 300 (4), 299 (19), 298 (58), 297 (100), 296 (4), 283 (5), 282 (22), 281 (16), 280 (13). |
| ***1d*** | 282 | 267 | 284 (4), 283 (16), 282 (51), 281 (100), 280 (22), 279 (5), 268 (6), 267 (25), 266 (28), 265 (33). |
| **1e** | 282 | 267 | 284 (9), 283 (32), 282 (76), 281 (100), 280 (56), 279 (5), 269 (10), 268 (30), 267 (58), 266 (11). |
| **1f** | 282 | 267 | 284 (7), 283 (24), 282 (64), 281 (100), 280 (78), 279 (19), 269 (8), 268 (23), 267 (52), 266 (33), 265 (6). |
| **1g** | 284 | 269 | 286 (6), 285 (16), 284 (60), 283 (38), 282 (100), 281 (3), 271 (6), 270 (18), 269 (66), 268 (5). |
| **1h** | 286 | 271 | 288 (5), 287 (16), 286 (56), 285 (42), 284 (100), 283 (18), 282 (3), 272 (9), 271 (36), 270 (32), 269 (29). |
| | | | Mass range *m/z* 175–325 |
| **2** | 310 | 295 | 312 (3), 311 (10), 310 (39), 309 (29), 297 (3), 296 (9), 295 (41), 281 (6), 280 (16), 279 (62), 267 (5), 266 (2), 265 (10), 253 (4), 237 (2), 236 (2), 223 (3), 222 (4), 221 (22), 206 (5), 205 (4), 193 (3), 191 (5), 190 (5), 179 (3), 177 (3), 175 (2). |
| **3** | 280 | 265 | 282 (9), 281 (26), 280 (100), 279 (84), 267 (6), 266 (16), 265 (68), 249 (3), 224 (3), 223 (18), 207 (2), 206 (13), 193 (2), 192 (6), 191 (35), 190 (2), 189 (2), 176 (2), 175 (8). |




Owing to isotope effects the loss of deuterium is generally not comparable to the loss of hydrogen, except in a specific elimination process.[3]

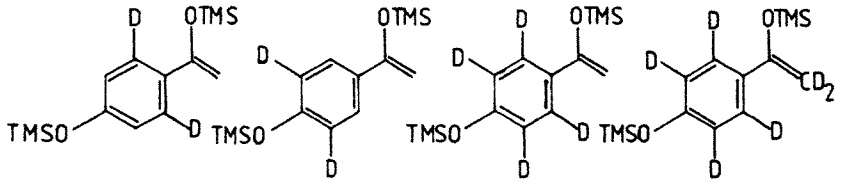
Therefore, the $[M-15]^+$ ion in **1a** (loss of a methyl group) was used as reference, which does not interfere with the ring deuteration. The intensity ratio between the isotopic peaks of $[M-15]^+$ was calculated from the spectrum of **1a** and used for the correction of the $[M-15]^+$ peaks of **1e** and **1f** taking the peak at lowest *m/z* for the least deuterated compound (Table 2).

In the $D_2$-deuterated compounds **1e** and **1f** the deuterium atoms can be assumed to be in the correct positions, but a distinct statement of the amount of equivalence during the elimination step at the four posi-




1b 1c 1d

$d_9TMSO- = (CD_3)_3SiO-$




1e 1f 1g 1h

**Table 2. Approximated deuterium insertion for compounds 1e and 1f**

| | | | | |
|---|---|---|---|---|
| **1e** | | $D_1$[a] | $D_2$ | $D_3$ |
| | | 15%[b] | 67% | 18% |
| **1f** | $D_0$ | $D_1$ | $D_2$ | $D_3$ |
| | 9% | 37% | 46% | 8% |

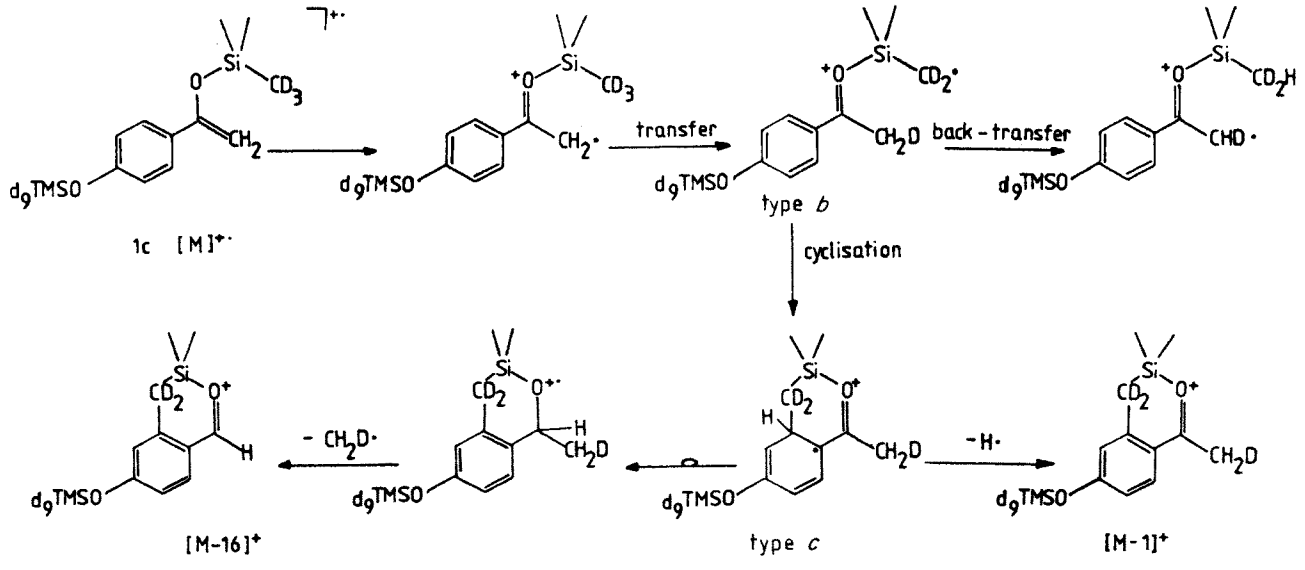
[a] $D_x$ = number of deuterium atoms inserted.
[b] $x$% = percentage of each compound in the mixture.

tions of the aromatic ring would require a deuteration grade of more than 95%.

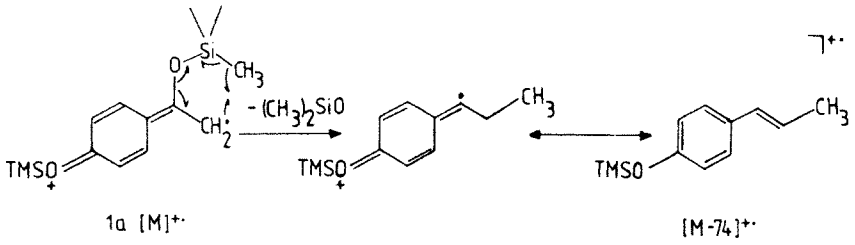
Nevertheless we must conclude that the hydrogen abstraction from **1a** is a complicated process involving mainly the aromatic hydrogens, to a lesser extent hydrogens from the methylidene group, and only in minute amounts those from the trimethylsilyl groups.

Furthermore, the spectra demonstrate that the loss of a methyl group $[M-15]^+$ does not only occur from the trimethylsilyl groups, but also involves the $CH_2$-group together with a hydrogen atom from the enolic trimethylsilyl group. In fact each trimethylsilyl group contributes about 25% and the methylidene group about 50% to this reaction. Obviously in the latter elimination reaction hydrogen-transfer reactions are involved, as may be deduced from the spectra of the partly deuterated compounds **1b**, **1c**, **1d** and **1h** showing $[M-16]^+$, $[M-17]^+$ and $[M-18]^+$ peaks (Table 1). A possible reaction sequence is formulated in Scheme 2.

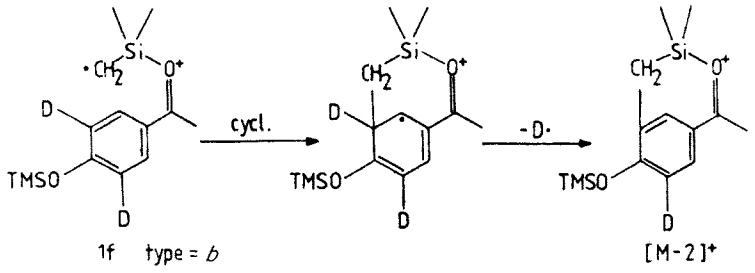
Another characteristic fragment ion at $[M-74]^+$ corresponds to the loss of $(CH_3)_2$ SiO, confirmed by high-resolution data. In the mass spectrum of the $D_9$-deuterated compound **1b** a similar fragment indicat-



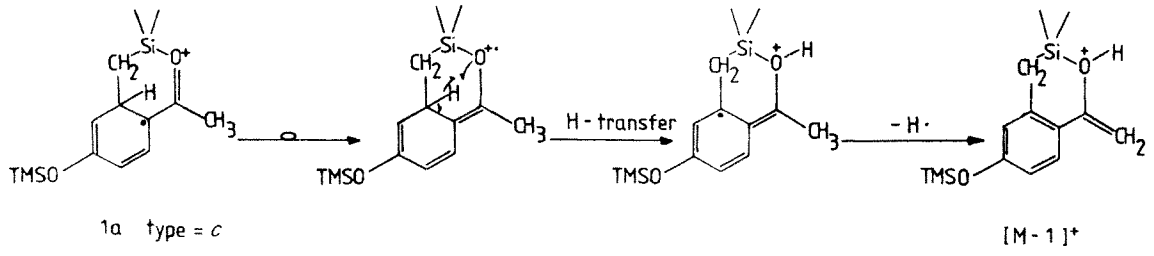

**Scheme 2.** Suggested mechanism for the loss of a methyl group form the enolic methylidene group.




**Scheme 3.** Transfer of a methyl group and loss of $(CH_3)_2SiO$.




**Scheme 4.** Possible elimination of hydrogen via a seven-membered ring.




**Scheme 5.** Elimination of hydrogen from the enolic methylidene group.

ing the loss of $(CD_3)_2$ SiO is observed. The reaction may occur via the shift of a methyl group as shown in Scheme 3.

The elemental composition of the ion at $[M - 57]^+$ in **1a** was confirmed by high-resolution data. This fragment is formed by the loss of a methyl radical and ketene.[4]

The intermediate *c* postulated in Scheme 2 may explain the loss of one of the ring hydrogens in the *ortho* position to the original acetophenone molecule by reformation of the aromatic ring. But this intermediate does not explain the loss of one of the hydrogens in the *meta*-position. Given that the intermediate *b* (Scheme 2) not only attacks position 2 and 6 but also position 3 and 5 of the aromatic ring by formation of a seven-membered ring; which should be sterically possible, the losses of the hydrogens in position 3 and 5 would be equally probable (Scheme 4).

A small amount of hydrogen originating from the $CH_2$-group may be eliminated as outlined in Scheme 5.

This example again demonstrates the need of extensive labelling experiments to clarify the degradation reactions of aromatic compounds, whilst the exact fragmentation pathway cannot be fully revealed without more detailed investigation.

## EXPERIMENTAL

The mass spectra were run under EI-conditions on a Varian MAT 312 double-focusing mass spectrometer connected with a Varian 370 gas chromatograph. The ionization energy was 70 eV at an ion-source temperature of 250 °C. A WCOT-glass capillary column (length: 25 m) coated with OV-101 was used for gas chromatography. High-resolution mass spectrometry was performed on a Finnigan MAT 8500 mass spectrometer under EI-conditions using the direct inlet probe. The ionization energy was 70 eV at an ion-source temperature of 250 °C. Data acquisition was obtained with a MAT SS 300 data system.

$^1$H-NMR spectra were measured on a Bruker AM 500 NMR-spectrometer in $CDCl_3$ as a solvent.

$D_2O$, $CH_3OD$ and $DCl/D_2O$ were used in 98% purity (Aldrich, Steinheim). $(CD_3)_3SiCl$ was obtained from MSD Isotopes (Montreal, Canada) in 98% purity. The other chemicals used were commercially available from EGA, Aldrich (Steinheim) and Merck-Schuchardt (Hohenbrunn).

Synthesis of the labelled 4-hydroxyacetophenones **1e**, **1f** and **1g**:

(a) **Bromophenols**

3,5-Dibromophenol (**4**) was obtained from pentabromophenol by treatment with $AlCl_3$ in benzene.[5] After hydrolysation of the reaction mixture the product was extracted and recrystallized from cyclohexane.

**EI–MS (trimethylsilylated).** 326 (34), 324 (65), 332 (33), 311 (54), 309 (100), 307 (54), 235 (3), 230 (10), 228 (11), 215 (3), 213 (3), 205 (2), 203 (3), 201 (3), 155 (8), 154 (9), 153 (9), 109 (3), 137 (21), 109 (3), 107 (2), 91 (6), 75 (8), 74 (7), 73 (38), 63 (9), 45 (10).

**$^1$H-NMR ($CDCl_3$), $\delta$ (ppm).** 4.9–5.1 (br–s, 1H); 6.96 (d, 2H-*ortho*); 7.25 (t, 1H-*para*); m.p. 76–79 °C (uncorr.). Yield ~40%.

2,6-Dibromophenol (**5**) and pentabromophenol (**6**) were commercially available:

(b) **Deuterophenols**

The above mentioned bromophenols **4**, **5** and **6** were converted into the sodium salts and reduced in $D_2O$/NaOD using Cu–Al alloy ('Devarda' alloy).[6] After hydrolysation and isolation the products were acetylated without prior purification by acetic acid anhydride in NaOH/ice.[7] The compounds were purified by column chromatography on silica-gel 60 using cyclohexane: ethylacetate 4:1 as a solvent.

(c) **Deuterohydroxyacetophenones**

The Fries reaction was carried out in $CS_2$ with the acetylated phenols.[8] The resulting 2- and 4-hydroxy isomers were separated by fractionated crystallization from toluene or by preparative thin-layer chromatography on silica-gel $60PF_{254}$ (solvent cyclohexane: ethylacetate 1:1). The amount of deuteration was checked by $^1$H-NMR spectrometry and mass spectrometry and found to be about 95% for **1g**, 70% for **1e**, and 50% for **1f** (Table 2).

**$^1$H-NMR ($CDCl_3$), $\delta$ (ppm).** 2.58–2.60 (s, 3H), 6.95–6.99 (m, H-*meta*), 7.90–7.93 (m, H-*ortho*).

The exchange of the methyl protons in 4-hydroxyacetophenone was achieved in the usual manner by repeated heating of the sodium salt in $CH_3OD/NaOCH_3$ and removal of the solvent.[9] The amount of deuteration was greater than 97% (**1d**).

Trimethylsilylation was carried out in absolute THF with MSTFA (Macherey & Nagel, Düren). After standing of the mixture for 24 h at 40 °C the silenol ether was obtained nearly quantitatively (**1a**, **1d–1h**).

The selective insertion of the $(CD_3)_3Si$-group into the enol ether position was achieved by the reaction of the Li-enolate of 4-trimethylsilyloxyacetophenone (**7**) with $(CD_3)_3SiCl$ in THF (**1b**).[10]

The latter (**7**) was obtained by treating equimolar amounts of 4-hydroxyacetophenone and $(CH_3)_3SiCl$ in DMF and triethylamine [11] without excluding moisture during the isolation, for the silenol ether group is less stable under these conditions whilst the silyl ether group remains rather unchanged. The product was purified by distillation.

**EI–MS.** 209 (6), 208 (35), 194 (15), 193 (100), 151 (12), 149 (2), 135 (3), 133 (3), 123 (3), 91 (5), 89 (12), 75 (6), 73 (16), 45 (5), 43 (20).

**$^1$H-NMR ($CDCl_3$), $\delta$ (ppm).** 0.26 (s, 9H), 2.52 (s, 3H), 6.84 (d, 2H-*meta*), 7.84 (d, 2H-*ortho*). Yield = 45%.

The complete transformation of the hydroxyacetophenones to the bis-$D_9$-trimethylsilyl derivatives was achieved by the reaction of the compounds in dry DMF with $(CD_3)_3SiCl$ in the presence of triethylamine[11] for 5 h at 60 °C in a reacti vial. The dark mixture was centrifuged to remove precipitates and directly used for gas chromatography (**1c**).

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