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Original Article

Formation of $[M-H]^+$ of 4-Substituted-1-(methoxymethyl)benzene Derivatives under Positive Fast Atom Bombardment Ionization

Shizuyo Horiyama[1] and Motohiro Shizuma[2]

[1]School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, 11–68 Koshien Kyuban-cho, Nishinomiya, Hyogo 663–8179, Japan
[2]Osaka Research Institute of Industrial Science and Technology, 1–6–50, Morinomiya, Joto-ku, Osaka 536–8553, Japan

The appearance of the characteristic peak of the hydride-eliminated molecule $[M-H]^+$ under a positive ion mode (positive) fast atom bombardment (FAB) ionization condition and liquid-assisted secondary ion mass spectrometry (LSIMS) conditions is known for some compounds and the mechanism of its formation has been investigated. In this study, we investigated the formation mechanism of the hydride-eliminated molecule $[M-H]^+$ from 4-substituted-1-(methoxymethyl)benzene under a positive FAB ionization condition. The mass spectra of 4-methoxy-1-(methoxymethyl)benzene (**1**), 4-methoxy-1-(methoxymethyl-d_2-)benzene (**1**-d_2), and 4-methoxy-1-(methoxymethyl-d_3)benzene (**1**-d_3) were measured under the positive FAB conditions. $[M-H]^+$ was observed for **1** and **1**-d_3, and $[M-D]^+$ for **1**-d_2, indicating that the site of hydride elimination was the methylene of the 1-(methoxymethyl) moiety. Since $[M-H]^+$ was hardly observed under the conditions of positive electron ionization and positive chemical ionization in the gas phase, the hydride elimination is a reaction specific to positive FAB ionization. To examine the contribution of the 4-substituent to the hydride elimination reaction, the mass spectra of (methoxymethyl)benzene (**2**) and 4-nitro-1-(methoxymethyl)benzene (**3**) were measured using the positive FAB. The ordering of the relative peak intensity of $[M-H]^+$ for $[M+H]^+$ in the FAB mass spectra was **1** > **2** > **3**, and the results suggest that the electron-donating power of the substituents is an important factor in the formation of $[M-H]^+$.

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1. INTRODUCTION

Matrix-assisted fast atom bombardment (FAB) ionization, one of the soft ionization techniques, was first used in organic mass spectrometry (MS) in the 1980s and has become an effective ionization method for highly polar compounds. In the positive FAB ionization method, protonated molecules $[M+H]^+$ are typically formed, and $M^{+\cdot}$ and $[M-H]^+$ may appear for some classes of organic compounds, leading researchers to speculate on the mechanism of formation of these molecules.

Paul *et al*. investigated the mechanism of FAB ionization by comparing the mass spectra obtained using FAB ionization with those obtained using other ionization techniques, such as electron ionization (EI), chemical ionization (CI), and electrospray ionization, for compounds with specific structures. In a paper published in 1993, the mass spectra obtained by EI, CI, and FAB ionization of the cyclic acetal, 2-phenyl-1,3-dioxolane, and its deuterated analogs were compared to provide information on the ionization process.[1)] Mass-analyzed ion kinetic energy spectrometry (MIKES) has confirmed that the $[M-H]^+$ ion observed by the EI and CI methods of gas-phase ionization originates from the elimination of $H^{\cdot}$ from $M^{+\cdot}$ and that $[M-H]^+$ is not formed from $[M+H]^+$. In addition, the FAB ionization method has been reported to include both EI and CI processes because the fragment ions appearing in the FAB mass spectrum contain cleavage ions similar to those ionized by EI and CI. Mass spectrometric analysis of 4-alkyl-2-phenyl-1,3-dioxolane-2-*d* showed that the probability of hydrogen elimination at position 2 was higher than that at positions 4 and 5 and that the probability of hydrogen elimination depends on the functional group at position 4. In another study of liquid-assisted secondary ion mass spectrometry (LSIMS) analysis, the $[M-H]^+$ was produced in the LSIMS method,

*Correspondence to: Shizuyo Horiyama, *School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, 11–68 Koshien Kyuban-cho, Nishinomiya, Hyogo 663–8179, Japan,* e-mail: horiyama@mukogawa-u.ac.jp

whereas in CI spectra with ammonia $[M+H]^+$ shows as the main species while $[M-H]^+$ is absent. From the above, it has been reported that the production pathways of the two ionization methods are different and that the production of $[M-H]^+$ in LSIMS may be due to the condensed phase ionization processes.[2] Furthermore, the formation of $[M-H]^+$ of perhydro-3a,6a,9a-triazaphenalene under FAB ionization and LSIMS was reported in detail by Paul *et al*. in 1995.[3] The observation that the prominent $[M-H]^+$ signal in the FAB mass spectrum was absent in the CI mass spectrum suggested that the formation of $[M-H]^+$ in the FAB ionization process is not due to gas phase terms, and the ionization in the FAB method was proposed to be a beam-induced process. In 1994, Nakata *et al*. studied in detail the influence of the structure and functional groups of organic compounds (aromatic amines, benzophenones, and biphenyls) on the formation of $M^{+\cdot}$ and $[M+H]^+$, appearing under FAB ionization conditions.[4] In this case, $M^{+\cdot}$ appears characteristically in the FAB mass spectra of these compounds. The authors compared the FAB and CI mass spectra of several compounds, such as 4-hydroxybiphenyl, and found intense $[M+H]^+$ peaks with weak $M^{+\cdot}$ peaks in the CI mass spectra. From these results, the author indicated that ionization under FAB conditions using a matrix is different from ionization in a gas-phase CI processes, as previously reported by Paul *et al*. In 1996, Takayama *et al*. reported that, in the case of Trolox and α-tocopherol, the formation of molecule-related ions $[M+H]^+$, $M^{+\cdot}$, and $[M-H]^+$ under FAB conditions with a matrix occurs in the condensed phase as compared to EI and CI in the gas phase.[5] They also reported that this reaction was a reactive interaction that depended on the properties of the analyte and matrix molecules and that the most similar phenomenon in CI was the abstraction of hydride.[5,6] However, they also pointed out that it was difficult to identify the site of hydride elimination. Thus, it can be said that the formation of $[M-H]^+$ in FAB was one of the characteristics of the ionization method and depended on the chemical properties of the analyte[6]; however, there were many unknowns, such as the site of hydride elimination.

Recently, we measured a mass spectrum of a monosaccharide, 2-propen-1-yl 6-deoxy-2-*O*-[(4-methoxyphenyl)methyl]-α-L-galactopyranoside,[7] using positive FAB ionization, and the molecular related ions appeared as $[M-H]^+$ (Fig. S1). In general, the positive FAB mass spectra of carbohydrates showed the molecular-related ion peak as $[M+Na]^+$,[8,9] but in this case $[M-H]^+$ appeared instead. Paul *et al*. reported the appearance of $[M-H]^+$ in the positive ion LSIMS mass spectra of the α-methoxy ($-O-CH_3$) and *O*-benzyl ($-CH_2-O-CH_2-C_6H_5$) modifications of 2-deoxy-D-ribofuranose.[2] Since this compound has the same partial structures of α-methoxy and *O*-benzyl structure as reported by Paul *et al*.,[2] we hypothesized that their common chemical structures were the cause of the formation of $[M-H]^+$.

In this study, the mass spectra of 4-methoxy-1-(methoxymethyl)benzene (**1**), which corresponds to the common structure, were measured to investigate the site of hydride elimination and the important factors in the formation of $[M-H]^+$. The deuterated compound **1**-d_2, in which two deuterium atoms were introduced into the methylene group of **1**, was synthesized and analyzed by the FAB ionization method. The mass spectra of compounds **1** and **1**-d_2 were obtained using gas phase ionization methods (EI and CI) and compared with the positive ion FAB mass spectra. The contribution of the methoxy group at position 4 of compound **1** to the reaction of formation of $[M-H]^+$ observed in the FAB mass spectrum was examined. For this purpose, compound **2** with a hydrogen atom at position 4, and compound **3**, with a nitro group at position 4 were characterized by FAB mass spectrometry. The structures of compounds **1**–**3** are shown in Fig. 1. The formation of $[M-H]^+$ and the contribution of the 4-substituent to the reaction and fragmentation were discussed with reference to the results of the density functional theory (DFT) calculations.

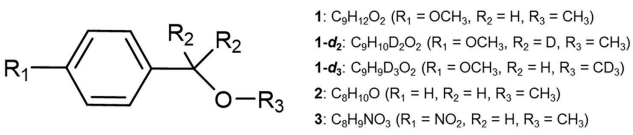

Fig. 1. Compounds **1**–**3**.

2. EXPERIMENTAL

2.1 Materials

The commercial product of (4-methoxybenzyl) methyl ether (4-methoxy-1-methoxymethylbenzene, **1**) (TCI, Tokyo, Japan) was used without further purification. 4-Methoxy-1-(methoxymethyl-d_2)benzene (**1**-d_2) and 4-methoxy-1-(methoxy-d_3-methyl)benzene (**1**-d_3) were prepared using methyl 4-methoxybenzoate (TCI, Tokyo, Japan) and 4-methoxybenzyl alcohol (TCI), respectively (see Supplemental Information, SI). Benzyl methyl ether (methoxymethylbenzene) (**2**) was purchased from TCI (Tokyo, Japan). 4-Nitro-1-methoxymethylbenzene (**3**) was prepared *via* etherification with 4-nitrobenzyl alcohol (TCI, Tokyo, Japan) (see SI).

The matrices for FAB ionization, glycerol (GLY), and *m*-nitrobenzyl alcohol (NBA) were purchased from TCI (Tokyo, Japan). Liquid chromatography-mass spectrometry (LC-MS) grade water and methanol were obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). The other reagents and solvents were analytical reagent grade and were used without further purification.

2.2 MS conditions

The FAB and EI experiments were performed on a JMS-700 double-focusing mass spectrometer (JEOL Ltd., Tokyo, Japan). The ion acceleration voltage was 10 kV. The fast atom xenon beam used was generated from xenon ions, which were accelerated to 5 keV. The FAB gun emission current was 1 mA. NBA and glycerol were used as the liquid matrices. The EI-MS ionization energy was 70 eV and the current was 300 μA.

GC-EI and CI experiments were performed on a GCMS-TQ8050 NX (Shimadzu, Co., Kyoto, Japan) using the following parameters: mode, Q3 scan mode; capillary column, SH-I-5Sil MS (length, 30 m; inner diameter, 0.25 mm; thickness, 0.25 μm); carrier gas, helium; time program, 50°C, 3 min, 20°C/min, 300°C, 14.5 min; ion source temperature, 200°C; interface temperature, 250°C; mass range for EI, *m/z* 35–600; mass range for CI, *m/z* 60–600; and reaction gas, isobutane.

2.3 DFT calculation

DFT calculations were performed using the Material Studio 2019 system (BIOVIA) on a Windows Workstation. The

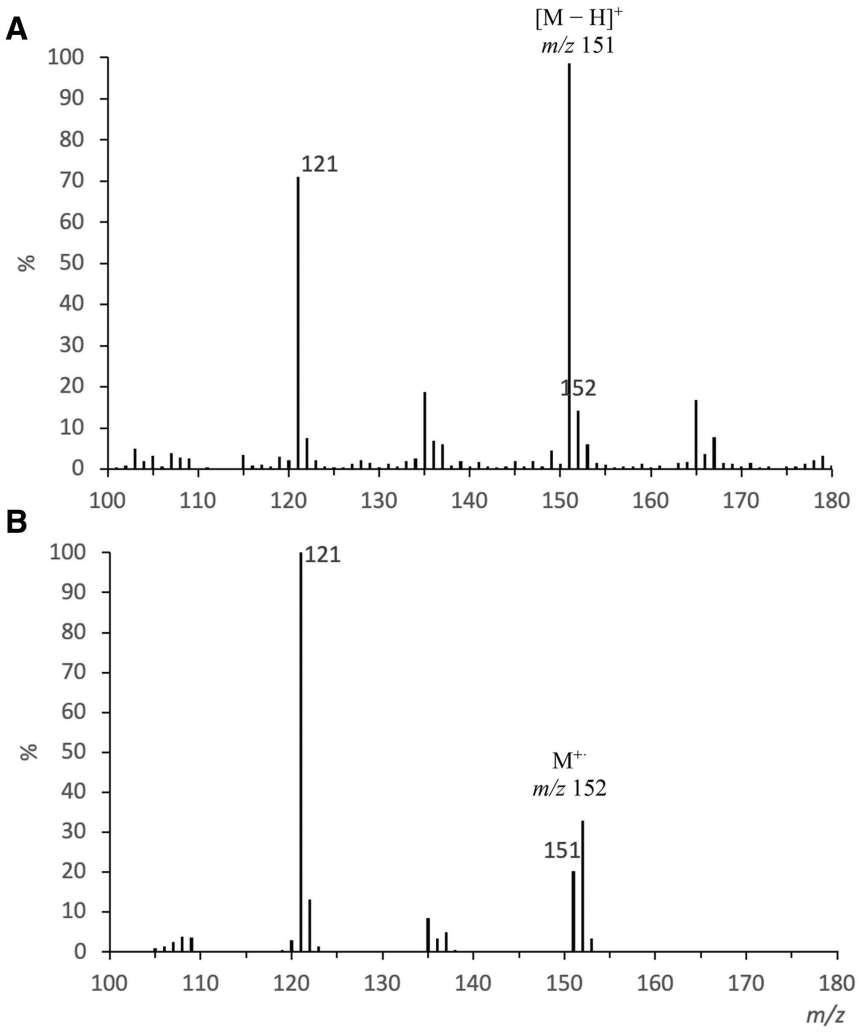

Fig. 2. (**A**) Positive ion mode FAB (glycerol) and (**B**) EI mass spectra of compound **1**. FAB, fast atom bombardment; EI, electron ionization.

initial structures of compounds **1**–**3** were built in the visualizer module handled on the system and optimized by the DMol3 module (function, B3LYP; SCF set, DNP).[10–19] The transition state (TS) search and optimization were carried out using DMol3 with complete linear synchronous transit (LST)/quadratic synchronous transit (QST) (density function/level, GGA/PBE; basis function, DNP 4.4; convergence calculation, thermal smearing).[20]

3. RESULTS AND DISCUSSION

3.1 Mass spectral analysis of 4-methoxy-1-(methoxymethyl)benzene (1)

Using FAB and EI MS, we analyzed compound **1**. The ion peak *m/z* 151 was observed in the FAB mass spectrum of compound **1** (molecular weight (MW): 152) in positive ion mode (Fig. 2A), while the peak of $[M–H]^-$ at *m/z* 151 was detected in negative ion mode (Fig. S2). In the EI mass spectrum, the molecular ion $M^{+\cdot}$ appeared at *m/z* 152 (Fig. 2B). These results indicate that the MW of this compound is 152 and that the peak at *m/z* 151 in the FAB mass spectrum of positive ion mode was $[M–H]^+$.

3.2 Mass spectral analysis of 4-methoxy-1-(methoxymethyl-d_2)-benzene (1-d_2)

To elucidate the formation process of $[M–H]^+$ (*m/z* 151) in compound **1**, especially at the hydride elimination site, a deuterium-labeled compound (**1**-d_2) was synthesized by introducing deuterium into the methylene moiety of 4-methoxymethyl in compound **1**, and its FAB mass spectrum was then measured. In positive ion mode, $[M–D]^+$ *m/z* 152 was detected (Fig. 3A), which was 1 u higher than that of $[M–H]^+$ *m/z* 151 of compound **1** under the same conditions. In the EI mass spectrum, the molecular and fragment ions appeared at *m/z* 154 and 123, respectively (Fig. 3B). These results indicate that in positive FAB ionization, a deuterium anion is eliminated from the 1-methoxymethyl-d_2 moiety to form the $[M–D]^+$ ion in compound **1**-d_2. On the other hand, in the FAB mass spectrum of compound **1**-d_2 (MW: 154), the fragment ion at *m/z* 123 appeared at a mass value 2 u higher than that of compound **1** (*i.e.*, *m/z* 121). This indicates that the fragment ion of **1**-d_2 contains two deuterium atoms, suggesting that the fragment ion at *m/z* 121 of compound **1** contains a methylene ($–O–CD_2–$) of the 1-methoxymethyl moiety.

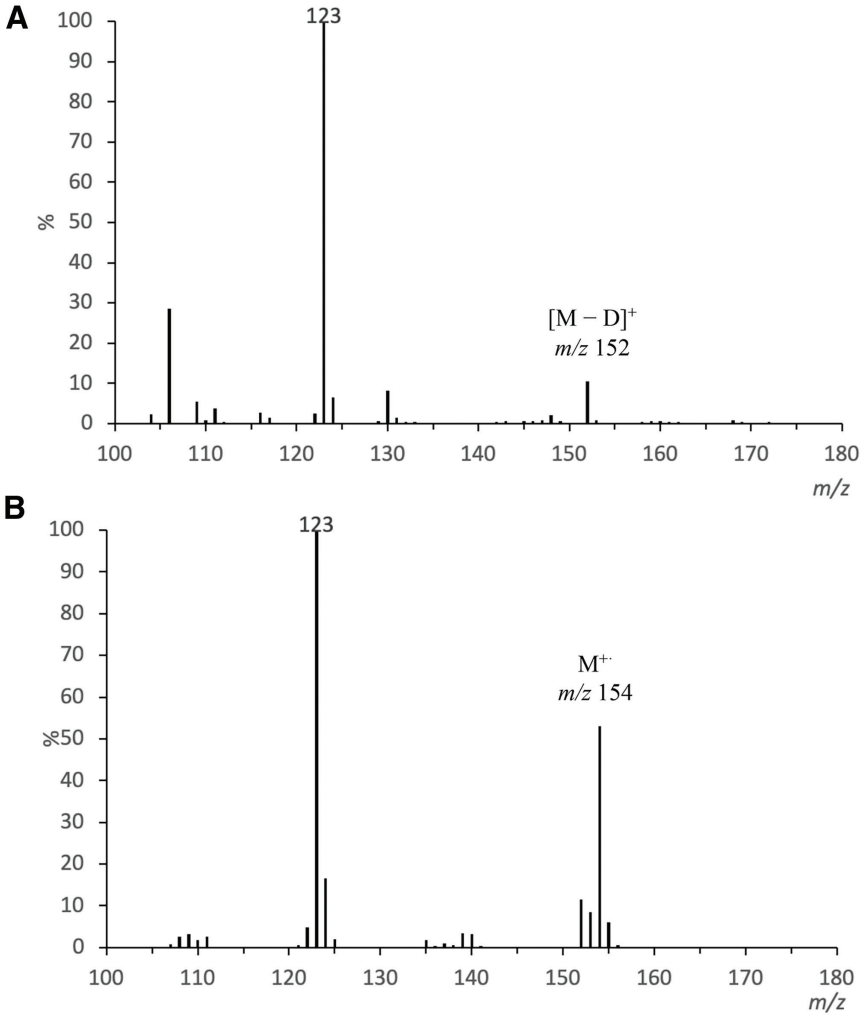

Fig. 3. (A) Positive ion mode FAB (without matrix) and (B) EI mass spectra of compound **1**-d_2. EI, electron ionization; FAB, fast atom bombardment.

3.3 Chemical ionization analysis of compounds 1 and 1-d_2

Compounds **1** and **1**-d_2 were analyzed using CI (reaction gas: isobutane), a gas-phase proton addition ionization method, to observe the ionic species that appear as molecule-related ions. Under CI conditions in positive ion mode, compounds **1** and **1**-d_2 appeared as protonated molecules at *m/z* 153 and 155, respectively (Figs. S3a and S3b), and as molecular ions at *m/z* 152 and 154, respectively. Thus, under CI conditions, hydride clearly does not eliminate from the methylene group of the 1-methoxymethyl moiety. The appearance of the molecular ion ($M^{+\cdot}$) could be due to the ejection of an electron from the molecular structure, as in EI, or the elimination of hydrogen from the protonated molecule, $[M+H]^+$. In addition, the molecule-related ion of compounds **1** and **1**-d_2 was observed as a deprotonated molecule $[M–H]^-$ under negative mode CI condition (Figs. S4a and S4b).

3.4 Mass spectral analysis of 4-substituted-1-(methoxymethyl)benzene (2 and 3)

To investigate the contribution of the methoxy group at position 4 to the reaction of formation of $[M–H]^+$, observed in the FAB mass spectrum of compound **1**, the FAB and EI mass spectra of compound **2** (MW: 122) with hydrogen at the position 4, as well as compound **3** (MW: 167) with a nitro group at the position 4, were measured for comparison. In the positive ion mode of the FAB mass spectra of compounds **2** and **3**, peaks corresponding to $[M–H]^+$ (*m/z* 121 and 166, respectively) and $[M+H]^+$ (*m/z* 123 and 168, respectively) were detected (Figs. 4A and 4B). By contrast, molecular ions (*m/z* 122 and 167, respectively) and $[M–H]^+$ (*m/z* 121 and 166, respectively) were observed in the EI mass spectra (Figs. S5a and S5b).

Table 1 shows the relative intensities of the peaks of $[M–H]^+$, $M^{+\cdot}$, and $[M+H]^+$ peaks in the FAB mass spectra of compounds **1**–**3**, whose contributions to the peak intensity were corrected according to the natural isotopic abundance ratio. The relative peak intensities of $[M+H]^+$ with respect to $[M–H]^+$ increased in the order of **1** < **2** < **3**, indicating that the ease of $[M–H]^+$ formation depends on the substituent at position 4. By contrast, in the case of EI, $[M–H]^+$ was not the base peak, and molecular ions were observed as the base peak (Table S1).

3.5 DFT-calculated $[M–H]^+$ formation and fragmentation from compound 1

The $[M–H]^+$ formation by hydride elimination from compound **1** was calculated using DFT. Structural optimization of $[M–H]^+$ (*m/z* 151) provided a stable structure with a

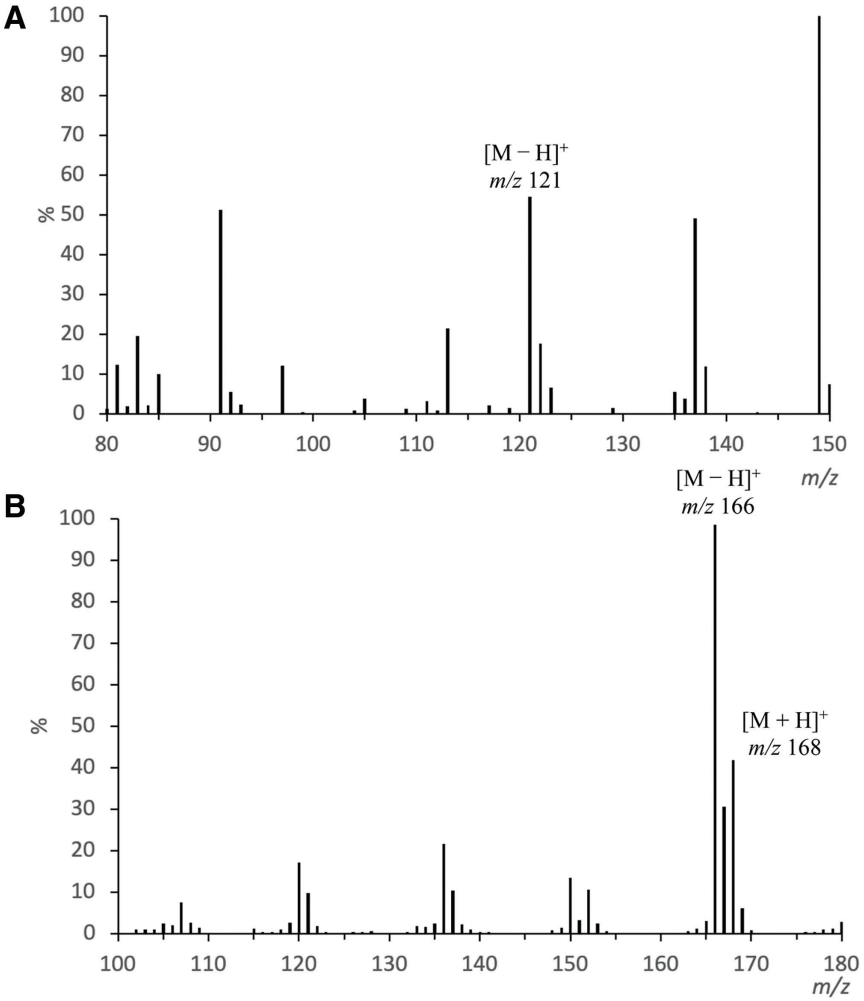

Fig. 4. Positive ion mode FAB mass spectra of (A) compound **2** (*m*-nitrobenzyl alcohol) and (B) compound **3** (glycerol).
FAB, fast atom bombardment.

delocalized positive charge *via* a slightly higher energy transition state (Fig. 5). The $[M–H]^+$ was calculated to be more stable than the protonated molecule $[M+H]^+$ (*m/z* 153). The reactions of the fragment ion $[M–OCH_3]^+$ (*m/z* 121) from compound **1** were also calculated using DFT in cases where the methoxy group was eliminated from position 4 and the methoxymethyl group at position 1. In the result, the fragment ion corresponding to the methoxy group eliminated from the 1-methoxymethyl group (297 kJ/mol) was stable compared with that from the 4-methoxy group (477 kJ/mol) as shown in Fig. 5.

3.6 Mass spectral analysis of 4-methoxy-1-methoxy-d_3-methylbenzene (1-d_3)

Deuterium-labeled compound **1**-d_3 was synthesized by introducing deuterium into the methyl moiety of 1-methoxymethyl in compound **1**, and its FAB mass spectrum was recorded. The peak corresponding to $[M–H]^+$ was detected at *m/z* 154 in positive ion mode, which was 3 u higher than that of compound **1** (*m/z* 151) (Fig. 6). In addition, a fragment ion also appeared at the same mass value (*m/z* 121) as that of the fragment containing the methoxymethyl (O–CH_2–) moiety of compound **1**.

Table 1. Peak intensities of $[M–H]^+$, $M^{+\cdot}$, and $[M+H]^+$ in the FAB mass spectra of compounds **1**, **2**, and **3**.

	Compound **1**		Compound **2**		Compound **3**	
	m/z	%	*m/z*	%	*m/z*	%
$[M–H]^+$	151	100.0	121	100.0	166	100.0
$M^{+\cdot}$	152	4.2	122	23.1	167	21.4
$[M+H]^+$	153	5.3	123	11.2	168	40.9

The relative peak intensities were corrected for their contribution to the peak intensity based on the natural isotope abundance ratio. FAB, fast atom bombardment.

This result indicates that $[M–OCH_3]^+$ appeared by the fragmentation of the methoxy group from the methoxymethyl group at position 1 of compound **1**. The results of the DFT calculations as described in the previous section support the experimental results by MS, indicating that the discussion based on the calculations is valid.

3.7 DFT-calculated $[M–H]^+$ formation from compounds 1–3

To examine the contribution of electron-donating or electron-withdrawing substituents at position 4 to the

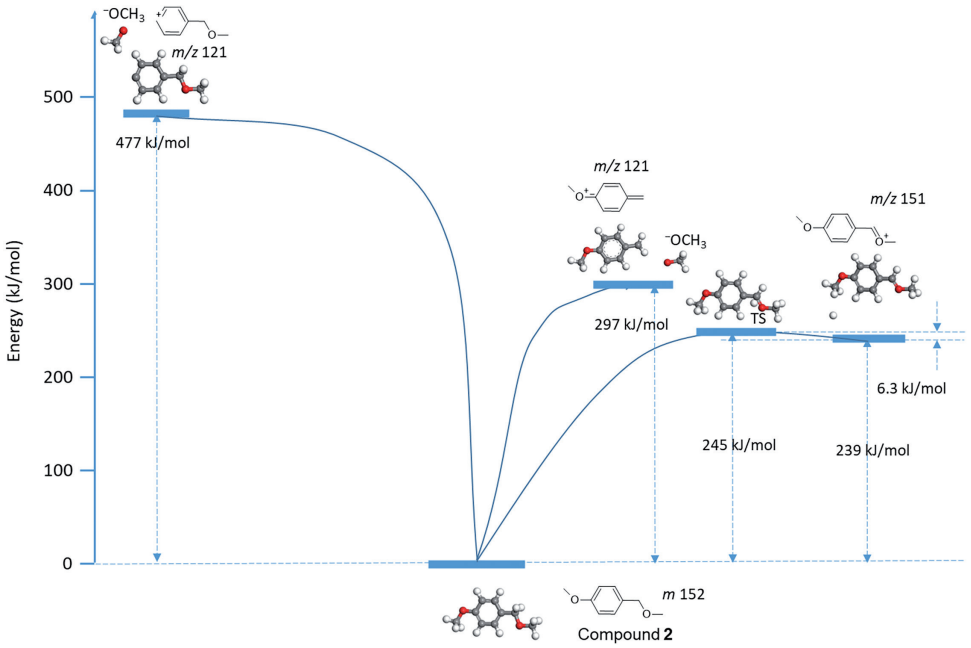

Fig. 5. DFT-calculated energy diagram of dehydrogenation and fragmentation of compound **1**.
Calculated using Material Studio 219 software (BIOVIA); DFT calculation, DMol3 Module; Function: B3LYP; SCF set: DNP; TS search and optimization, complete LST/QST. DFT, density functional theory; LST/QST, linear synchronous transit/quadratic synchronous transit.

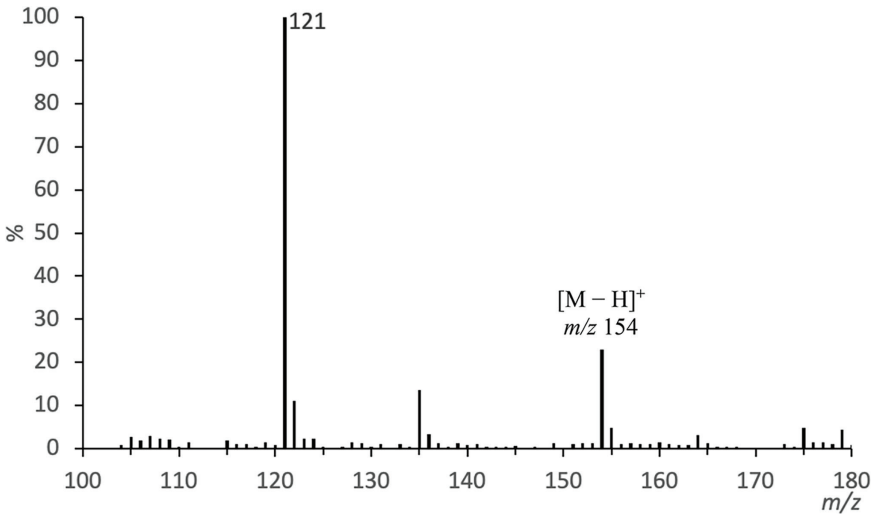

Fig. 6. Positive-ion mode FAB (without matrix) mass spectrum of compound **1**-d_3.
FAB, fast atom bombardment.

$[M–H]^+$ formation, the barrier energies of the $[M–H]^+$ formation reactions of compounds **1**–**3** were calculated by DFT (Table 2). The calculated charges of the carbon and oxygen atoms at the benzylic positions are also shown. The barrier energies increased in the order of **1** < **2** < **3**, indicating that $[M–H]^+$ was preferentially formed when the compound had a methoxy group and an electron-donating group at position 4. The calculated charges on the carbon and oxygen atoms at the benzylic position were positive and negative, respectively. The absolute value of the charge of $[M–H]^+$ of compound **1** was lower than that of compounds **2** and **3**, indicating that the charge was more delocalized, that is, the generated ion was more stable. This is also supported by the MS results. The order of the relative peak intensities of $[M+H]^+$ *vs.* $[M–H]^+$ shown in Table 1 is in good agreement with the order of magnitude of the $[M–H]^+$ formation reaction.

3.8 Contribution of substituent effects to $[M–H]^+$ formation

The studies by Hammett *et al.* on the substituent effects in the reactions of aromatic compounds are well known.[21] Plotting the logarithm of the relative peak intensities of $[M–H]^+$ *vs.* $[M+H]^+$ against the σ values according to the Hammett rule, which indicates the substituent effects, gives a good linear correlation (Fig. S6). The Hammett equation assumes that the stability of the cation owing to the electron donating/withdrawing properties of the substituent depends on the

Table 2. DFT-calculated substituent effect on hydride elimination from methyl 4-substituted benzyl ether.

Reactant	Energy barrier kJ/mol	Before H^--elimination		After H^--elimination	
		Charge on benzyl oxygen	Charge on benzyl carbon	Charge on benzyl oxygen	Charge on benzyl carbon
1	245	−0.482	0.104	−0.018	0.138
2	420	−0.482	0.106	−0.293	0.250
3	448	−0.482	0.102	−0.292	0.259

DFT, density functional theory.

contribution of the inductive effect. The linear correlation shown in Fig. S6 indicates that the reaction mechanisms of the $[M–H]^+$ formation from compounds **1**–**3** are the same and the inductive effect of the substituent is a key factor in the $[M–H]^+$ formation reaction.

4. CONCLUSION

The detailed MS analysis of compound **1** revealed that the peak of $[M–H]^+$ was observed in the positive ion mode FAB mass spectrum of compound **1**. In addition, the mass spectrum of the isotopically labeled compound **1**-d_2, in which the hydrogen at the benzyl position was replaced with deuterium, revealed that the hydride elimination site was the benzyl position of compound **1**. DFT calculations showed that hydride elimination from compound **1** occurred readily and that the generated $[M–H]^+$ was stabilized by delocalization of the positive charge, in agreement with the experimental MS results. The DFT calculations also showed that the methoxy group was more likely to be eliminated from the methoxymethyl group than from position 4, which was in good agreement with the experimental mass spectrum of the isotopically labeled compound **1**-d_3. Therefore, it is reasonable to use DFT calculations to explain the MS results.

In the CI mass spectra of compounds **1** and **1**-d_2, $M^{+\cdot}$ appeared together with $[M+H]^+$, but the $[M–H]^+$ signal was relatively weak. In the EI mass spectrum of compound **1**, the intensity of the peak of $[M–H]^+$ at *m/z* 151 was about 60% of the intensity of $M^{+\cdot}$ (Table 1), which is due to the hydrogen elimination from the benzyl position by simple α-cleavage based on the unpaired electron of $M^{+\cdot}$. In the FAB mass spectrum, the intensity of the $[M–H]^+$ peak was 100%. By comparison, the intensities of the peaks of $[M+H]^+$ and $M^{+\cdot}$ were as low as 5%. As mentioned above, it has been reported that the difference in the signals resulting from gas-phase ionization is due to ionization occurring in the condensed phase under FAB conditions, which is supported by the results of this study. This suggests that the phenomenon occurs in compounds with specific structures. In addition, one of the significant factors contributing to $[M–H]^+$ formation in 4-substituted-methoxymethylbenzenes is the electron-donating substituent at position 4. Finally, the high linear correlation of the Hammett plots indicates that the generated cations are stable due to the inductive effect.

The knowledge gained from this study on $[M–H]^+$ formation in 4-substituted-1-methoxymethylbenzene derivatives will contribute to a better understanding of the ionization process in MS.

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