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Time-correlated Single Ion Counting Mass Spectrometer with Long and Short Time-of-Flight Tubes and an Evaluation of Its Performance for Use in Trace Analysis of Allergenic Substances

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An analyte molecule was ionized using a femtosecond laser as the ionization source and was measured by a twin-type time-of-flight mass spectrometer with long (42 cm) and short (6.4 cm) flight tubes. The signal was measured using an analog signal digitizer and a time-correlated single ion counting system, and performance was evaluated by comparing data obtained from both instruments. The short mass spectrometer had a mass resolution of 450 and was used in the trace analysis of allergenic substances in a fragrance.

Keywords Laser spectrometry, multiphoton ionization, mass spectrometry, allergenic substance

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Introduction

Mass spectrometry is currently used in various fields of basic research and industrial applications as well. It has become an essential tool for trace analysis in the material, environmental, and forensic sciences. A miniaturized mass spectrometer is particularly useful, since it is more convenient to use and has been utilized in a micro-scale lab-on-a-chip system.[1,2] A variety of miniaturized mass spectrometers have been developed to date. For example, because it is compact, an ion trap mass spectrometer is frequently employed as a portable type device.[3-6] A time-of-flight mass spectrometer is simple and has better mass resolution. This type of mass spectrometer has excellent sensitivity and has an advantage over other techniques based on field-swept detection since a complete mass spectrum can be obtained using a single-shot ionization source over a wide mass range.[7] A miniaturized time-of-flight mass spectrometer based on laser desorption ionization (LDI) and matrix-assisted laser desorption ionization (MALDI) was developed in 1995 – 2010.[8-18] The size of a mass spectrometer, which consists of a reflectron-type, was reduced to 7.5 cm, and a number of biological substances including peptides and digestion products have been analyzed. Another type of miniaturized time-of-flight mass spectrometer was designed for use in space missions.[19,20] The mass spectrometer is estimated to have a weight of 280 g (including the laser and all electronics), a volume of 84 cm^3, and an electric consumption of 3 W. A different type of miniaturized mass spectrometer was developed for the field-portable analysis of chemical warfare agents, which requires compactness, fast response, and high sensitivity.[21-23] A photoionization source combined with a quadrupole ion trap and a time-of-flight mass spectrometer (flight length, 22 cm) was developed for measuring chemical weapons-related compounds. Such a mass spectrometer can be used for on-line gas monitoring, and could also be used as a detector for a gas chromatograph. More recently, a miniaturized orthogonal time-of-flight mass spectrometer (flight length, 20 cm) was developed in an attempt to improve mass resolution, in which an electron ionization source was used for general purpose and a vacuum ultraviolet lamp for observing a molecular ion based on single photon/photoelectron ionization.[24-26] The mass resolution was significantly improved by increasing the flight time of the ion (flight distance, 17 m) using pulse oscillation, multi-turn, and spiral obit configurations.[27-30]

Laser ionization mass spectrometry has excellent sensitivity and allows subfemtogram detection when a picosecond/femtosecond laser is used for ionization.[31] However, the expense and high cost of maintenance of the laser, *e.g.*, a Ti:sapphire laser, were obstacles to practical use. A reliable, low-cost laser (*e.g.*, a fiber laser) is commercially available and has high average power. However, the repetition rate of the laser is *ca.* 1 MHz, which is faster than the maximum recording rate of the digitizer (*ca.* 20 kHz) used to obtain a mass spectrum. To overcome this problem, a time-correlated single "ion" counting technique can be used, which requires a laser with a high repetition rate and a short pulse width and is useful for improving time resolution. To date, a nanosecond nitrogen laser (30 Hz, 3 ns) has been used as the ionization source in MALDI mass

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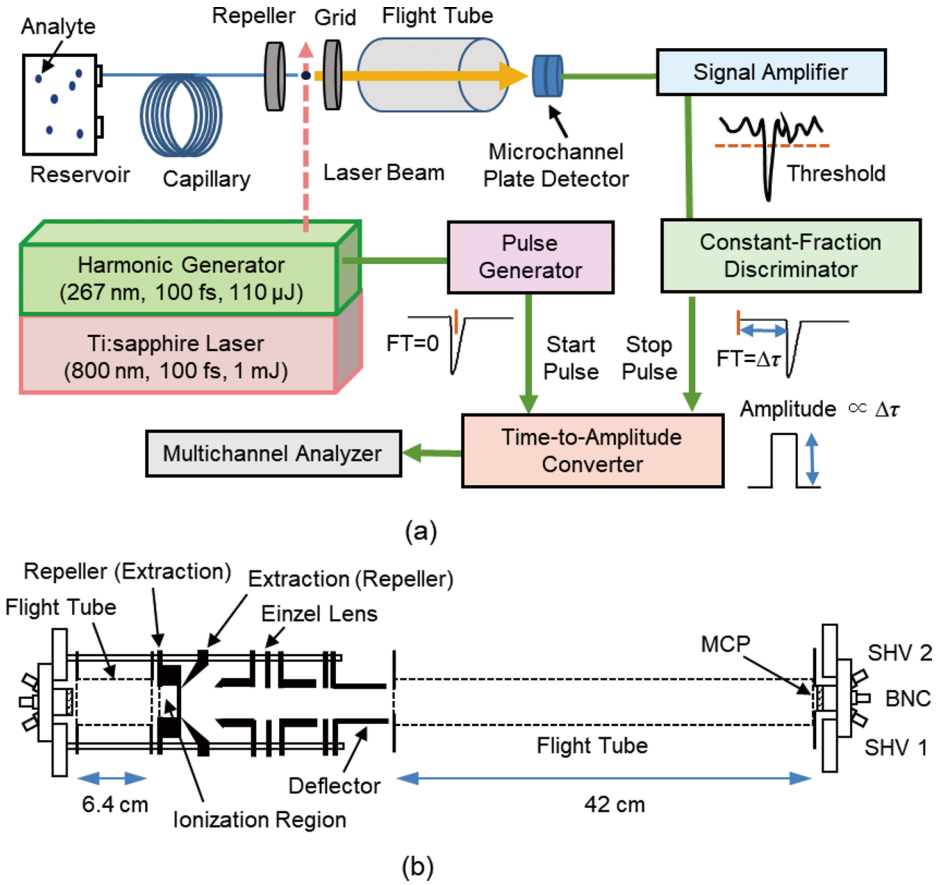

Fig. 1 Schematic diagram of the experimental apparatus. (a) Time-correlated single ion counting system. (b) Time-of-flight mass spectrometer consisting of long and short flight tubes. FT, flight time.

spectrometry (flight time, 20 μs at m/z = 224).[32] A nanosecond tunable laser of an optical parametric oscillator pumped by a Nd:YAG laser (10 Hz, 6 ns) was applied for supersonic jet spectrometry of chlorobenzene (flight tube length 12 cm; flight time, 4 μs).[33,34] Due to the low repetition rate of the laser, it was necessary to increase the accumulation time for recording a mass spectrum with sufficient signal-to-noise ratio. A laser with a repetition rate of *ca.* 1 MHz is now commercially available. It would also be desirable to develop a mass spectrometer that permits the measurement of a mass spectrum within *ca.* 1 μs. If not, the repetitively measured mass spectra are overlapped, and reconstructing the mass spectrum becomes difficult. The flight time can be reduced by decreasing the length of the flight tube and by applying high potentials to the electrodes in order to achieve faster ion acceleration. However, the mass resolution tends to decrease by decreasing flight length, which could partly be compensated for by improving the time resolution of the mass spectrometer using a picosecond/femtosecond laser for ionization and fast detector/electronics for the ion measurement.

In this study, we report on the development of a twin-type time-of-flight mass spectrometer consisting of long (42 cm) and short (6.4 cm) flight tubes for comparison, in which the mass spectrum was collected using a conventional analog signal digitizer and a time-correlated single ion counting system. To evaluate its performance, the mass spectrometer was used in the trace analysis of allergenic substances in a fragrance.

Experimental

Apparatus

The analytical instrument developed in this study is shown in Fig. 1(a). The analyte prepared in a sampling bag (Tedlar Bag with a mini-valve, PVF, 2L, 3008-93302, cck-2, GL Science) was passed through a restrictor made of a narrow capillary (30 m long, 0.25 mm i.d., Agilent Technologies) to reduce the pressure for introduction into the mass spectrometer, which consists of long (42 cm) and short (6.4 cm) flight tubes, as shown in Fig. 1(b). The long mass spectrometer is made of a repeller electrode (mesh, 0 kV), a skimmer-type extraction electrode (–0.55 kV), a set of einzel lens electrodes (–1.74 kV), a pair of deflector electrodes (–1.73 kV), a flight tube (–1.25 kV), and an assembly of microchannel plates (–2.3 and –0.227 kV, F4655-11, Hamamatsu Photonics). The short mass spectrometer is made of a repeller electrode (the extraction electrode in the long mass spectrometer, +5.26 kV), an extraction electrode (the repeller electrode in the long mass spectrometer, +0.24 kV), a flight tube (–3.11 kV), and an assembly of microchannel plates (–2.3 and –0.227 kV, F4655-11): the short mass spectrometer contains no einzel lens and no deflector electrodes. The third harmonic emission (267 nm, 110 μJ) of a Ti:sapphire laser (800 nm, 100 fs, 1 kHz, 1 mJ, Libra, Coherent) was used as the ionization source. The pulse energy was adjusted using a neutral density filter. The analog signal of the ion was measured using a digitizer (AP240, 1 GHz, 1 GS/s, Acqiris, Agilent Technologies) and was analyzed using software

programmed by LabVIEW (National Instruments) and ORIGIN (LightStone). For time-correlated single ion counting, an impulse signal of the ion was amplified by a timing amplifier (×20, 300 MHz, Model 574, Ortec). The signal was introduced into a constant-fraction discriminator (CFD, Model 584, Ortec) to precisely measure the timing of the signal peak (the signal was differentiated and the rising edge was detected to observe the peak position), the threshold value being adjusted to 10 mV. A time-to-amplitude converter (TAC, Model 566, Ortec) was used for the measurement of the time ($\Delta\tau$) between the laser and single ion pulses, the amplitude of which is proportional to the difference in time between the start and stop pulses. The electric signal synchronized to the laser pulse was delayed by a pulse generator (DG535, Stanford Research Systems) and was used as a start pulse, and the output signal from the CFD was used as a stop signal. The output signal of the TAC was accumulated using a multichannel analyzer (MCA8000A, Amptek) to form a histogram that corresponds to the mass spectrum to be measured. A single ion event was confirmed to be less than 10% by monitoring the single ion signal with an oscilloscope and also by monitoring the intensity distribution of the isotopomers (^{35}Cl and ^{37}Cl) for a molecular ion of pentachlorobenzene.

Reagents and chemicals

Pentachlorobenzene was purchased from Tokyo Chemical Industry and was used to optimize the experimental conditions and to evaluate the performance of the mass spectrometer. The 22 allergenic substances among the 26 compounds specified in the Cosmetics Directive by the Scientific Committee for Consumer Safety (SCCS) were purchased from Wako Pure Chemical Industries (1 pinene, 2 limonene, 3 benzyl alcohol, 4 linalool, 5 methyl 2-octynoate, 6 citronellol, 7 citral, 8 geraniol, 9 cinnamaldehyde, 10 hydroxycitronellal, 11 cinnamyl alcohol, 12 eugenol, 13 methyl eugenol, 14 isoeugenol, 15 ionone, 16 lilial, 17 amylcinnamaldehyde, 18 lyral, 19 amylcinnamyl alcohol, 20 farnesol, 21 hexylcinnamaldehyde) and from Tokyo Chemical Industry (22 benzyl salicylate). Specified amounts of allergenic substances were dissolved in acetone and were vaporized with a diluent gas of nitrogen (2 L) in a sampling bag. The total concentration of the analytes was adjusted to 140 ppm. The other 4 allergenic substances (23 anis alcohol, 24 coumarin, 25 benzyl benzoate, 26 benzyl cinnamate) among the 26 compounds were solid and were not used in this study because of their low vapor pressures at room temperature. Note that the name of the ingredients should be listed on the label of the container of such commercial products when the concentration is higher than 0.001% for leave-on products and 0.01% for rinse-off products. A perfume (Lancôme hypnôse Eau de Parfum) was purchased from a tax free shop and was used as an actual sample. The ingredients listed on the label of the container were as follows: alcohol, parfum, fragrance, aqua, water, linalool, geraniol, limonene, hydroxycitronellal, citral, citronellol, ethylhexyl methoxycinnamate, ethylhexyl salicylate, butyl methoxydibenzoylmethane, benzophenone-3, benzyl benzoate, benzyl alcohol, butylated hydroxytoluene, Cl 17200/RED 33, Cl 42090/Blue 1, Cl 60730/Ext violet 2. This sample was measured without any pretreatment.

Results and Discussion

Long mass spectrometer

Figure 2 shows mass spectra for pentachlorobenzene measured using a long mass spectrometer based on analog signal detection and time-correlated single ion counting. For both methods, the intensity distribution of the isotopomers for a molecular ion was identical to that expected from the abundance of ^{35}Cl and ^{37}Cl (3:1), suggesting there was no signal saturation in analog signal detection and time-correlated single ion counting. A series of fragment ions is more distinctive for a mass spectrum measured by the analog signal digitizer, as shown in Fig. 2(a), which can be explained by the subsequent photon absorption of a molecular ion at a larger pulse energy (30 μJ > 0.8 μJ) for the analog signal detection.[35,36] The observed mass resolution ($m/\Delta m$) was 900 and 910 for analog and ion counting detections, respectively, which corresponds to a pulse width (time resolution, Δt) of 20 ns for one of the isotopomers of the molecular ion. The absence of a significant difference in mass resolution suggests that signal saturation by a space charge effect in analog signal detection and pile-up error in time-correlated single ion counting is negligible.

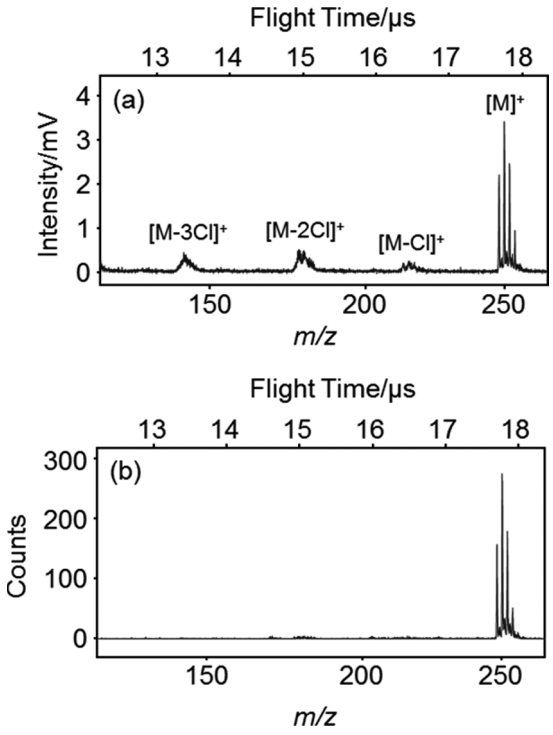

Fig. 2 Mass spectra of pentachlorobenzene. Long flight tube: (a) Analog signal digitizer; pulse energy 30 μJ, averaging time 0.4 s, mass resolution 900. (b) Time-correlated single ion counting system; pulse energy 0.8 μJ, accumulation time 600 s, mass resolution 910.

Short mass spectrometer

Figure 3 shows mass spectra obtained using the short mass spectrometer based on analog signal detection and time-correlated single ion counting. The spectral patterns are very similar to those obtained using the long flight tube. It should be noted that the flight time of $\Delta\tau$ was decreased to a few μs. The mass resolution was 490 and 450 for the analog and ion counting detections, respectively, which corresponds to a pulse width of 2.2 and 2.4 ns for one of the isotopomers of a molecular ion. Thus, the mass resolution would not be determined by the time resolution (Δt) of the signal measurement system (*e.g.*, detector, amplifier, and electronics). The mass resolution is degraded from 900 to 450 when the flight tube length is decreased from 42 to 6.4 cm (flight time, 17.5 → 2.23 μs). The initial velocity distribution (Δv) of the analyte molecule was identical in both experiments, since the same device was used for sample

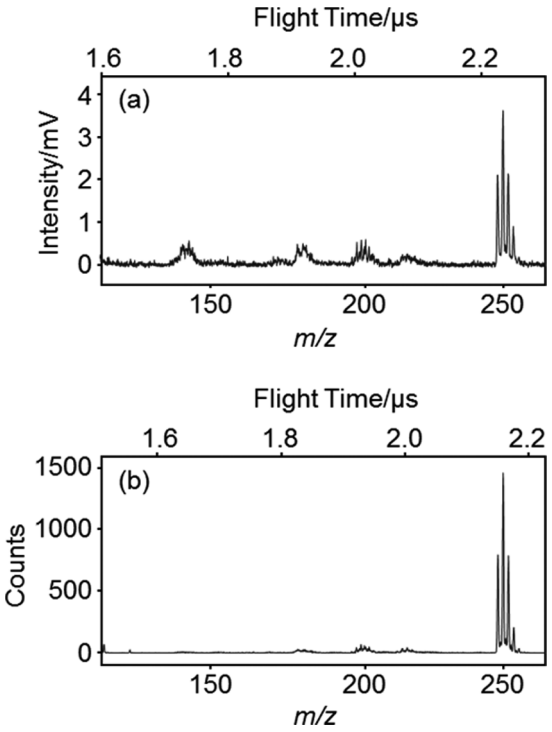

Fig. 3 Mass spectra for pentachlorobenzene. Short flight tube: (a) Analog signal digitizer; pulse energy 30 μJ, averaging time 0.5 s, mass resolution 490. (b) Time-correlated single ion counting system; pulse energy 3 μJ, accumulation time 600 s, mass resolution 450.

introduction/ionization (see Fig. 1). The mass resolution determined by Δv remains unchanged for a linear-type time-of-flight mass spectrometer, even when the flight time is reduced by decreasing the length of the flight tube and by increasing the potentials applied to the electrodes for ion acceleration. Accordingly, the degradation in mass resolution can be attributed to a local distribution (Δx) of the analyte molecule in the ionization region. It should be noted that this effect can be reduced by increasing the flight tube length and by tightly focusing the laser beam on the ionization region. Applying a higher potential to the electrodes for faster ion acceleration will be useful for reducing the flight time, thus permitting the use of a low-cost, high-repetition-rate laser. As demonstrated, the mass resolution of the short mass spectrometer would be sufficient for measuring low-molecular-weight hazardous organic compounds ($M_w < 500$) in the environment.

Analysis of allergenic substances

A standard sample mixture containing the 22 allergenic substances was measured using the short mass spectrometer equipped with a time-correlated single ion counting system to demonstrated the potential advantage of such an instrument for use in practical trace analysis. As shown in Fig. 4, a mass spectrum could be measured for a sample containing 6.63 ppm of each allergenic compound even at a pulse energy of 0.6 μJ: the pulse energy was decreased in this experiment to demonstrate the advantage of this technique for multiphoton ionization using a laser with low pulse energy, high repetition rate, and high average power (*e.g.*, 1 μJ × 1 MHz = 1 W). Seven signal peaks can be assigned to allergenic substances, and the other unassigned peaks represent impurities in the chemical reagents and/or from the material in the sampling bag. In a previous study using a gas chromatograph, all of the standard chemicals

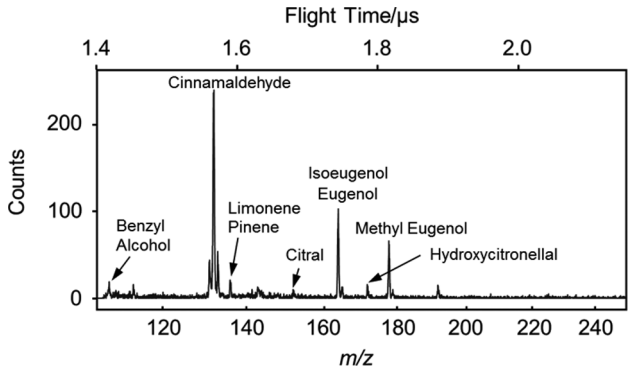

Fig. 4 Mass spectrum measured for a sample mixture containing 22 allergenic substances prepared at a concentration of 6.63 ppm for each component. Pulse energy 0.6 μJ, accumulation time 600 s. Names of the compounds assigned in this study are written in the figure.

were detected.[37] The missing signals for the other standard chemicals can be attributed to their low volatility, since the sampling bag was used at room temperature. An analytical curve was constructed for pinene, which was a straight line in the 0 – 7 ppm range with an R^2 value of 0.96. This finding suggests that this technique can be used for the quantitative analysis of allergenic substances in the air. The detection limit was examined using eugenol, which was 0.84 ppm at 0.4 μJ. At high pulse energies, the signal intensity increased significantly and the sensitivity could be further improved, although a low detection limit was not confirmed experimentally due to the difficulty associated with the preparation of the sample at low concentrations because of adsorption of the analyte at the surface of the sampling bag.

Figure 5(a) shows the mass spectrum measured for an actual sample (perfume). The signal peaks observed at $m/z = 94$ arose from impurities (probably phenol) in the sampling bag and the signal peaks at $m/z = 18$ and 32 from water and oxygen, respectively, in the ambient air. The expanded view of the area, as indicated by a broken line, is shown in Fig. 5(b). Four signal peaks can be assigned to benzyl alcohol, limonene, geraniol/linalool, and butylated hydroxytoluene. Eight allergens were listed in the label of the perfume bottle. The other four components remained unassigned, probably due to the low volatilities of these substances at room temperature.

Conclusions

A twin-type mass spectrometer using both long and short flight tubes was constructed in this study. The mass resolution decreased from *ca.* 900 to *ca.* 450 when the flight tube length was decreased from 42 to 6.4 cm. These values remained unchanged even when the analog signal digitizer was replaced with a time-correlated single ion counting system, suggesting that the mass resolution is not determined by the time resolution (Δt), *i.e.*, the response time of the detector/electronics, but is determined by the local distribution (Δx) of the analyte in the ionization region. The mass spectrometer that was developed was applied to the trace analysis of allergenic substances in the air, suggesting that the instrument has a potential advantage for use in on-line monitoring of hazardous compounds such as chemical warefare agents in the atmosphere.

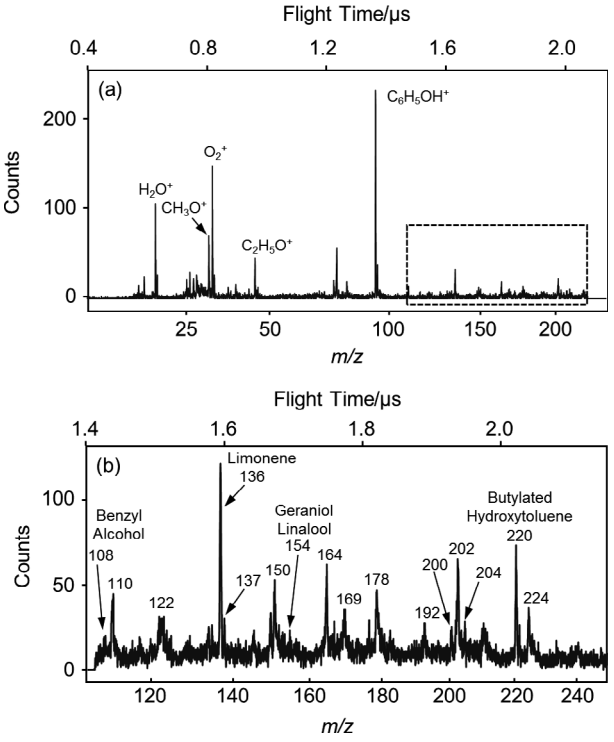

Fig. 5 (a) Mass spectrum of an actual sample (perfume). Pulse energy 9.2 μJ, accumulation time 600 s. (b) Mass spectrum of the part specified by the broken line in (a). Pulse energy 14.2 μJ, accumulation time 600 s. The *m/z* values for the unassigned signals are shown in the figure.

Acknowledgements

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