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Article

Sniffing with mass spectrometry

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ABSTRACT

Gaseous compounds are usually on-line detectable on sensors. The limitations of conventional sensors are suffering from incapability for exactly identifying multiple components as well as incompatibility to possible toxicants in every odor sample. Herein, we discuss an inlet modification to the laboratory standard mass spectrometer, inspired by the sensitive olfactory systems of animals, for direct sniffing, established by connecting a mini pump to the nebulizer gas tubing. The modified mass spectrometry method—sniffing-mass spectrometry (sniffing-MS)—can acquire detailed fingerprint spectra of mixed odors and shows high tolerance to toxicants. Furthermore, the method has a low limit of detection in the order of parts per trillion and is a 'sampling-free' technique for analyzing various gaseous compounds simultaneously, thus offering versatility for smelling daily commodities, tracking diffusion, and locating position of odors. Sniffing-MS can mimic or even surpass the olfaction of animals and is applicable for analyzing gaseous/volatile compounds, especially those polar compounds, in a simple manner depending on the intrinsic molecular mass-to-charge ratio.

1. Introduction

Gaseous compounds can be measured based on light, electric, or magnetic signals by devices known as chemical sensors or "electronic noses" [1–3]. Currently available devices, however, suffer from ineffectual quantification in the simultaneous analysis of mixtures of multiple gaseous compounds [4]. The olfaction of sniffer animals (e.g., patrol dogs), on the other hand, is sensitive to various odor molecules and is invaluable for judicial expertise, but animals are vulnerable to poisoning with toxic substances such as viruses and chemical warfare agents (e.g., nerve agents) [5,6]. Therefore, an alternative approach with multiple detection channels and tolerance to poison is highly desired for efficient detection of multiple gaseous/volatile molecules in ambient conditions [4,7,8].

Mass spectrometry (MS), based on measurement of the intrinsic molecular mass-to-charge ratio (m/z), is a versatile technique that can determine the chemical composition of almost all molecules [9]. MS has shown its significantly wide applications in, for example, detecting environmental contaminants [10,11], tracking chemical reactions [12–14], studying chemical bond energies [15–17], analyzing bioactive compounds [18,19] and inorganic species [20–22]. About four decades ago [23], MS techniques were developed for the analysis of volatile molecules by means of atmospheric ionization. Atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI) have been designed to interface gas chromatography and mass spectrometry (GC–MS) for the ionization of gaseous compounds from GC in the ambient environment [24,25]. Fenn et al. [26] also reported an electrospray method for ionization of gaseous compounds. In the last twenty years, proton transfer reaction mass spectrometry [27,28], selected ion flow tube mass spectrometry [29], extractive electrospray ionization [30], and secondary electrospray ionization [31] have also been used for real-time analysis of volatile organic compounds. Specifically, "sampling-free" mass spectrometric techniques, such as desorption electrospray ionization [32] and direct analysis in real time [33] featuring ionization in the ambient environment, have recently been increasingly studied. These pioneering works involving ambient ionization facilitate advances in the direct detection of gaseous/volatile compounds in air.

Here, we show that a mass spectrometer with a modified inlet can perform extremely well in directly detecting various compounds in the air, mimicking the olfaction of animals. This kind of analytical technique with an aspirating inlet is appropriately

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named sniffing-mass spectrometry (sniffing-MS). Superior to traditional sensors that usually detect individual target compounds, sniffing-MS can probe even mixtures of gaseous/volatile molecules in a full-scan fashion, regardless of their toxicity.

To exemplify the merit of the sniffing-MS, we coupled a six-port valve with a mini pump and added a quantitative loop to the nebulizer gas tubing for aspirating and detecting the exact volume of the gaseous sample. With the help of such a modification, we extend the application of sniffing-MS to track the dynamic diffusion of gaseous compounds and locate odor source(s).

2. Materials and methods

2.1. Mass spectrometric method

All the experiments were carried out in the positive or negative ion mode on a Bruker Esquire HCT ion trap mass spectrometer (Billerica, MA) coupled with standard ESI and APCI sources. The experiments involving quantitative analysis were conducted with a modified inlet, as shown in Fig. 1. Parameters of the ionization were optimized to enhance the signal intensity. Methanol/H_2O 50:50 (v:v) was used as the spray solvent at a flow rate of 0.24 mL/min. For the standard ion sources, regardless of ESI or APCI, the pressure of the nebulizing nitrogen, the flow rate, and the temperature of de-solvation gas were set at 482 kPa, 2 L/min, and 250 °C, respectively. For the ESI source, the capillary voltage was set at 4 kV. For the APCI source, the capillary voltage and the temperature of vaporizer were set at 1 kV and 350 °C, respectively.

2.2. Bio-macromolecule analysis

Bio-macromolecules (such as insulin and bradykinin) were dissolved in a solvent comprising 50% methanol and 50% water for further MS detection through an assisted sprayer, which facilitated changing the sample state from the solution phase into the gas phase as aerosols. All the other samples were fed into the mass spectrometer directly under ambient conditions unless otherwise stated.

2.3. Preparation of standard concentration of gaseous ethyl acetate and quantification of ethyl acetate with sniffing-MS

A certain volume of ethyl acetate was dropped into a sealable glass bottle, and then the bottle was heated up to 50 °C to vaporize the ethyl acetate. Gaseous ethyl acetate with a certain concentration was thus prepared for further analysis in the mass spectrometric conditions. The relationship between the mass spectrometric signal intensity and concentration was acquired using ESI mass spectrometry to detect ethyl acetate with concentrations in the range of 0–35 $\times 10^{-5}$ mol/L.

2.4. Limit of detections (LODs) for sniffing-MS analysis

As the concentration required for analytes for LOD analysis is as low as of the order of ppt (part per trillion), a method previously reported in literature [34,35] was adopted. To prepare each analyte with a low concentration, 1.0 mL of the liquid sample was placed in a sealed 10-mL volumetric bottle, which was maintained at 25 °C for 1 h to afford saturated headspace vapor of the analyte. To obtain different dilution ratios for the saturated vapor, gas-tight syringes were used to take different volumes of the gaseous samples from the sealed bottles. Then, each of the gaseous samples was injected into another sealed 10-mL volumetric bottle, which was then maintained at 25 °C for 30 min. A T-piece was used for introduction of sample into a flowing nitrogen stream for ionization. The as-obtained gaseous sample taken by another gas-tight syringe was introduced as a sample stream using a syringe pump at a constant speed (flow speed of the sample was set at 60 μL/min) into the T-piece sealed with a rubber stopper. Meanwhile, a flowing nitrogen stream with a constant pressure of 482 kPa (flow rate of ~0.7 L/s, as tested by a rotameter) was also introduced to the T-piece. The concentration of the gaseous sample was calculated by the ratio of the flow speeds of the two streams. The signals of corresponding compounds were selected as those of parent ions in tandem MS conditions, which allowed isolation of the target ion in the ion trap for easier observation. The LODs were evaluated by measuring a series of samples with decreasing concentration and corresponded to a concentration with a signal-to-noise (S/N) ratio of around 3:1.

2.5. Monitoring the diffusion of cigarette smoke in the air

One volunteer smoked at 3 m away from the mass spectrometer for 1 min, and the diffusion of the smoke was monitored by mass spectrometer. The experiments were repeated five times, and the extracted ion chromatograms for nicotine (m/z 163.1) were recorded. In the-performed experiment conditions we detected every target signals in 5 min. The relative standard deviation (RSD) for the time of which the smoke diffused to mass spectrometer from 3 m away was 18.7%. Similarly, the burning matters such as papers or plastics can be sniffed by the mass spectrometer as well.

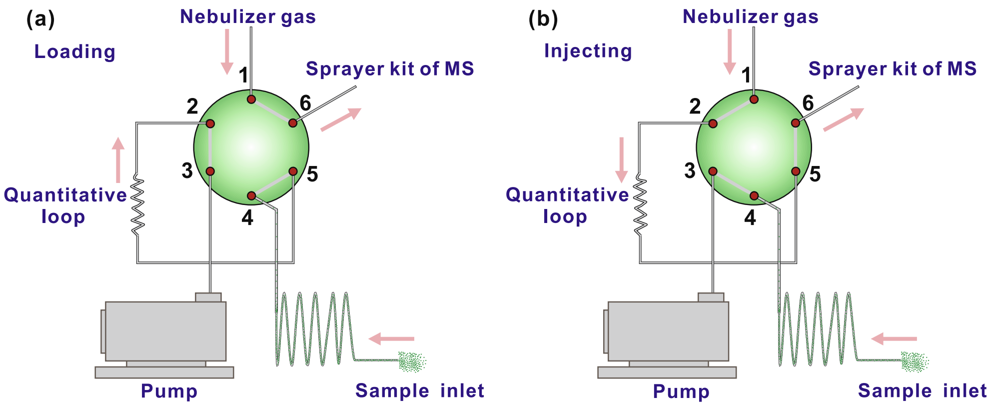

Fig. 1. Schematic setup for quantitative sniffing with mass spectrometry. The setup mainly consists of a pump, a six-port valve, a quantitative loop, and tubings: (a) is the loading mode. (b) is the injection mode.

2.6. Relationship between the mass spectrometric signal intensity and distance from the gaseous source for camphor

The relationship between the signal intensity and distance was acquired by placing a camphor ball (gaseous source) in a random position and measuring the mass spectrometric signal of camphor ball at a horizontal position 140, 80, 50, 30, 20 and 10 cm, away the gaseous source. Five measurements were obtained for each position. As expected, the detected signal decreased with increasing distance from the gaseous source.

2.7. Location of gaseous source

To optimize the experimental conditions for gaseous source location, experiments with different sizes (1.0 and 3.7 cm^3) of camphor ball were conducted. The mass spectrometric signals were reasonably sensitive to the concentration of analytes and were dependent on the size of the camphor ball (gaseous source). The experimental results with different volumes of gaseous source are shown in Fig. S1 (all the experiments were repeated five times, online). The signal intensity was observed to positively correlate with the volume of the gaseous source. In the experimental location, we choose a fixed volume of gas (3.7 cm^3) and a fixed diffusion time (10 min) for the gaseous source location experiment. Camphor ball ($\sim$3.7 cm^3) was used as the gaseous source at the single gaseous source location. First, the camphor ball was placed in a position marked in the three-dimensional space. A random site (tentatively assessed to be close to the gaseous source) was chosen as the origin of coordinates, and a total of 26 sites (corresponding to the inlet of the polytetrafluoroethylene (PTFE) pipe) were set uniformly in the three axes (such as *x*-, *y*- and *z*-axis) of the coordinate system. Mass spectra signals were recorded for each site. The position of the camphor ball could be located at the site with the strongest m/z intensity of camphor along the *x*, y, and *z* axes. The m/z intensity could be normalized if necessary. Pinene was also used as another different gaseous source: the experimental process was similar to that used for camphor ball localization. As pinene is a liquid substance at room temperature, 8.0 g of starch powder was mixed with 2.0 mL pinene to form a ball with a size of $\sim$8.2 cm^3. The strongest signal sites for the two compounds (m/z 137.1 for pinene and m/z 153.1 for camphor) along the *x*-, *y*- and *z*-axis were detected by sniffing-MS with APCI ion source, and sequentially the multiple sources could be located simultaneously. All the experiments were repeated five times.

3. Results and discussion

3.1. Modification of laboratory standard mass spectrometers for sniffing-MS

For sniffing-MS technique, as shown in Fig. 1, the setup was simply modified from that of the laboratory standard mass spectrometer by connecting a six-port valve in the nebulizer gas tubing for loading/injection of gaseous samples. A pump was used as the driving force for sniffing the gaseous sample. In the loading process, gaseous sample was aspirated into the quantitative loop of the six-port valve by the sample inlet (No. 4) in ambient environment. During the injection process, the sample was swept into the ion source for detection together with the nebulization gas. To quantitatively analyze the volatile samples, we added a quantitative loop to the six-port valve, which enabled the device to aspirate gaseous compounds with a loading volume of 10.0 mL. Keeping the MS signals intact, the flexible sample inlet for sniffing gaseous sample can be ten meters or more, which facilitates the monitoring of gaseous compounds remotely. As expected, the simple modification is applicable to any mass spectrometer with an ionization source that utilizes nebulizer gas to generate the spray, rendering its wide application to mass spectrometers with disparate ion optics systems and mass analyzers.

3.2. Qualitative analysis of various gaseous compounds

As listed in Table S1 (online) and represented in Figs. S2–S33 (online), similar to the olfaction of animals, the finger-print spectra of multiple molecular ions detected by sniffing-MS are valuable in identifying various mixtures of odor molecules in a full-scan fashion. All the odorous samples are commonly prevalent in our daily life, including those in coffee (e.g., Nestle instant coffee), air pollutants (e.g., tetrahydrofuran and pyridine), liquors (e.g., red wine and beer), daily commodities (e.g., camphor ball and mosquito repellent), perfumes (e.g., the Chanel N°5 and the Adidas perfume), odoriferous plants (e.g., *Plectranthus hadiensis* var. *tomentosus* and narcissus), Chinese herbal medicines (e.g., angelica and cardamom), as well as biomacromolecules (e.g., insulin and peptides). As seen in Fig. 2, the protonated molecule $[M+H]^+$ and the sodium complex $[M+Na]^+$ dominated in the mass spectra for the commercial camphor ball in air. Sniffing-MS achieved by spraying with a methanol-water (1:1, v:v) mixture and ionization by ESI or APCI can generate molecular ions similar to those produced by regular ESI- or APCI-using samples in solution (Fig. 2). When applied to distinguish analogous commodities, for example, in the identification of instant coffee and perfumes produced by different companies, sniffing-MS showed superiority in recording fingerprint spectra. Furthermore, superior to most commercially available GC–MS, in which the quadrupole is usually used as mass analyzer and analytes are generally limited to smaller m/z values than 1,100, the current sniffing-MS technique has shown its applicability for detecting biomacromolecules such as insulin ($C_{256}H_{381}N_{65}O_{76}S_6$) and bradykinin ($C_{50}H_{73}N_{15}O_{11}$) with m/z values of up to 5,000 (Figs. S26 and S27 online), with the implication of the coverage of a wide mass range usually covered by different types of mass analyzers.

3.3. Quantitative analysis and limit of detection (LOD) of reference samples

We added a quantitative loop to a six-port valve. By simple modification, a gaseous sample with an exact volume of 10.0 mL volume can be fed for each loading run and thus allows quantitative analysis. Taking ethyl acetate as an example, as shown in Fig. S34 (online), the vaporized ethyl acetate with increasing concentration correlated well with the increasing intensity of the MS signals ($R = 0.995$). The relationship between the mass spectrometric signal intensity and concentration was acquired using ESI mass spectrometry to detect ethyl acetate with concentrations in the range of 0–35 $\times 10^{-5}$ mol/L.

Some representative chemical compounds such as ethyl acetate, tetrahydrofuran, pyridine and *N*,*N*-dimethyl formamide were quantitatively detected by the sniffing-MS as reference samples (Table S2 online). The latter three compounds are known as environmental pollutants, with implication about the usefulness of sniffing-MS in search for toxic sources. It is worth noting that sniffer animals (e.g., patrol dogs) cannot detect toxic sources such as viruses and chemical warfare agents (e.g., nerve agents).

The LODs were determined by measuring molecular ion signals of the hydrogen complex $[M+H]^+$ with decreasing concentrations of samples. The concentration corresponding to a signal-to-noise (S/N) ratio of 3:1 was set as the LOD. As shown in Table S2 (online), the LODs varied with different analytes and could be as low as ppt levels (For example, 35.29 ppt for *N*,*N*-dimethyl formamide). Such

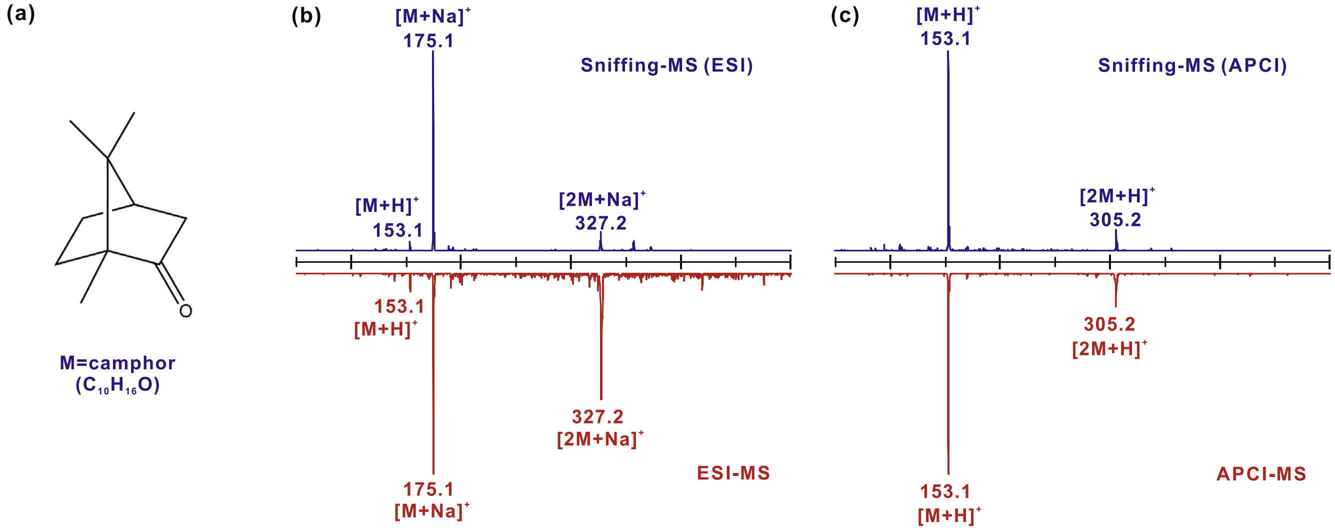

Fig. 2. Mass spectra of a camphor ball analyzed with different ionization sources in sniffing-MS and regular MS. (a) Structural formula of camphor. (b) Mass spectra of a camphor ball ionized by ESI in sniffing-MS and regular MS. (c) Mass spectra of camphor ball ionized by APCI in sniffing-MS and regular MS. The peaks at mass-to-charge ratios (*m*/*z*) 153.1 and 175.1 could be assigned to the protonated ions and sodium complexes of camphor, respectively, whereas those at 305.2 and 327.2 could be assigned to the protonated ions and sodium complexes of the camphor dimer, respectively.

a high sensitivity is comparable with that of currently prevalent electron noses or sensors [2,7].

3.4. Real-time monitoring of gaseous compounds

The simple modification to standard ion source, which facilitates it with the ability of sniffing directly and high sensitivity, promises to render the ordinary mass spectrometer useful for monitoring gaseous compounds in real-time processes. We recruited a volunteer to smoke 3 m away from the mass spectrometer for 1 min, and the diffusion of the smoke was monitored by the mass spectrometer. To eliminate signal fluctuations affected by any unexpected airflow, the experiment was conducted in a room having a space of $\sim(4 \times 5 \times 3)\ \text{m}^3$ with silent ventilation. The experiments were repeated five times, and the extracted ion chromatograms for nicotine (*m*/*z* 163.1) are shown in Fig. S35 (online). As shown, the time for the smoke to diffuse to the mass spectrometer (from 3 m away from the mass spectrometer) was around 0.7–1.0 min. In addition, different kinds of smoke could be evaluated based on the chemical specificity of the sniffing-MS technique (Figs. S13, S32 and S33 online), allowing timely forecasting and distinguishing between fire/smoke sources if combination with chemometrics methods

Additionally, the dynamic concentration change of plant volatile metabolites can be followed on-line by sniffing-MS. As a supplemental material, a movie (Movie S1 online) depicting the in situ detection of *Plectranthus hadiensis* var. *tomentosus* is demonstrated, where the experimenter tapped the *Plectranthus hadiensis* var. *tomentosus* and then tested the evolving volatile metabolites. The movie clearly shows that sniffing-MS can respond to the dynamic concentration changing with molecular information quickly, which could make it a powerful tool for volatile metabolite analysis.

3.5. Locating gaseous source by sniffing-MS

To track gaseous sources in three-dimensional space, commercially available camphor balls were used as the stable gaseous source because of its stable sublimation that could steadily release gaseous camphor molecules in ambient conditions. The orientation-dependent relationship between the MS signals and the distance of the camphor source from the inlet of the MS instrument (i.e., the distance between the camphor and the end of the PTFE pipe connected to the No. 4 joint of the six-port valve, as indicated in Fig. 1) is shown in Fig. 3a. To eliminate unstable signals affected by unexpected airflow, the experiment for locating the

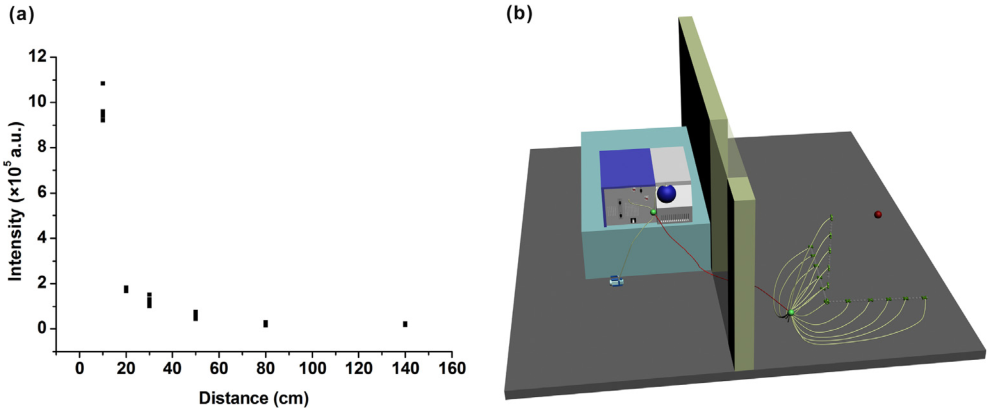

Fig. 3. Relation between mass spectrometry signal intensities and the distance from gas source. (a) Mass spectrometric signal intensity against the distance from the gaseous source of camphor. (b) 3D schematic diagram for locating the gaseous source in room. The gaseous source and the multiple-port valve are indicated as green and red balls, respectively.

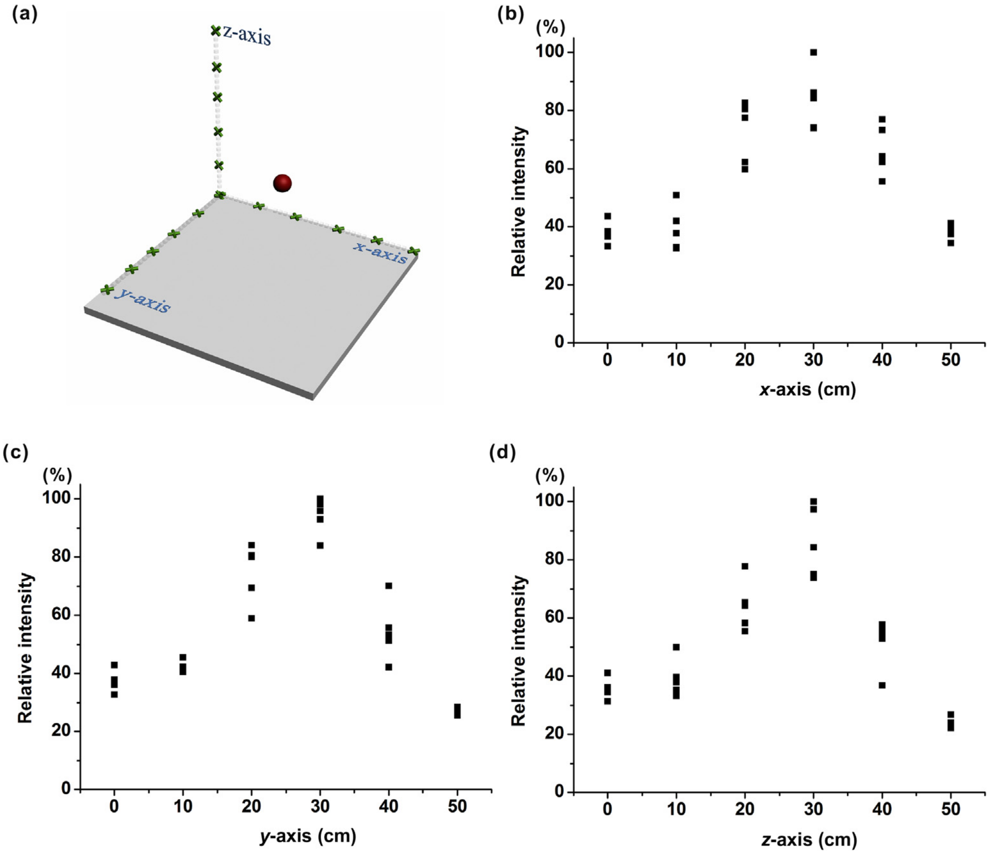

Fig. 4. Relative intensities of camphor ball acquired by mass spectrometry. (a) Schematic diagram representing process for locating the gaseous source in the three-dimensional space. The red ball is the gaseous source of camphor. The green crosses in the axis of Cartesian coordinates are the sites where the gaseous compounds are collected for sniffing-MS detection. (b)–(d) Relative intensities (repeated five times) of camphor acquired in *x*-, *y*- and *z*-axes, respectively.

gaseous source was conducted in a cleanroom where a space of ~$(6 \times 5 \times 3)$ m^3 with silent ventilation facilitated mimicking the open ambient environment, and the PTFE pipe inlet was modified by equipping it with a multiple-port valve that facilitated steady feeding of the gaseous species with minimum airflow disturbance (Fig. 3b).

For the experiment in the cleanroom, where a camphor ball (with a size of ~3.7 cm^3) was located, a random spot close to the gaseous source (the camphor ball) was chosen as the origin of Cartesian coordinates in three-dimensional space, and the sample inlets of PTFE pipe for feeding camphor-containing air were set at five sites for each of the rectangular axes (*x*-, *y*- and *z*-axis) in the orthogonal coordinate system (as shown in Fig. 4). Absolute *m*/*z* intensities of camphor molecular ions ($[M+H]^+$ *m*/*z* 153.1) were recorded for locating the gaseous source. For a total of 26 feeding sites, stronger signal spots could be identified along the *x*-, *y*- and *z*-axes, respectively, reasonably reflecting the closer distance toward the gaseous source. From the characteristic *m*/*z* signals of camphor (standardized to relative intensity) along the *x*-, *y*- and *z*-axes, therefore, the gaseous source could be roughly located (30, 30, 30 cm) in the corresponding coordinate system (Figs. 4, S1, and S36 (online)). Depending on the chemical specificity of sniffing-MS, in principle, the location of the gaseous source could be doubly checked by another camphor ion such as $[2M+H]^+$ (*m*/*z* 305.2) for accuracy.

When camphor and pinene were used as two different gaseous sources located separately in the cleanroom, as shown in Figs. 5 and S37 (online), the strongest signal intensities for pinene (*m*/*z* 137.1) were averaged at (20, 20, 30 cm) and camphor ball (*m*/*z* 153.1) at (30, 30, 30 cm). Obviously, the present sniffing-MS method is suitable for sniffing multiple gaseous sources at the same time and is more straightforward and versatile than currently prevalent sensor technologies by which usually only a single odor source is detectable.

4. Conclusion

To summarize, with the versatility to sensitively detect the otherwise transparent gaseous compounds, the standard mass spectrometric method with a regular ionization source can be a versatile nose to directly sniff or smell various gaseous compounds with concentrations as low as the order of ppt in ambient conditions. Extending the application to gas source location, single or multiple compound(s) sources can be detected spatially, rendering the mass spectrometry technique technologically comparable with or superior to chemical or biological sensors currently available for direct sniffing various volatile molecules free from sampling. Depending on technological innovation toward portable and high-resolution mass spectrometers as well as robotic systems such as the unmanned aerial vehicle flight, sniffing-MS promises a bright future for analyzing various odorous matters (e.g., coffee, perfume, medicine or plant) in our daily life, monitoring pollutants, and explosives or chemical warfare agents for public security.

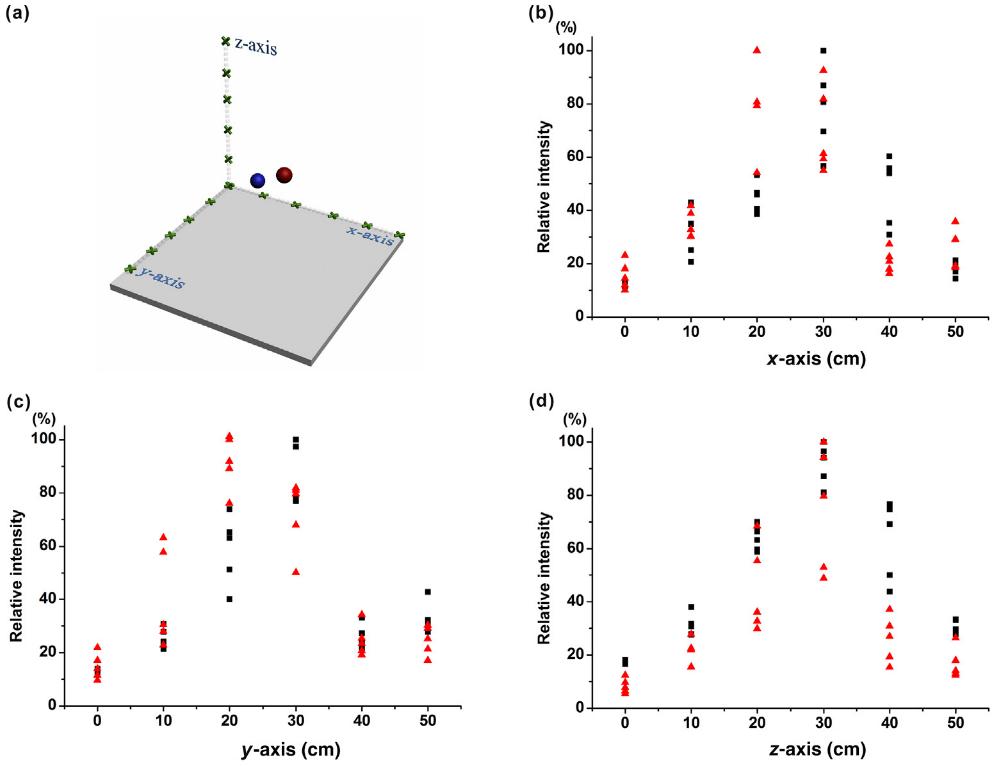

Fig. 5. Relative intensities of pinene and camphor acquired by mass spectrometry. (a) Schematic diagram representing process for locating double gaseous sources in three-dimensional space. The red ball represents the gaseous source of pinene and the blue ball the gaseous source of camphor. The green crosses in the axis are the sites where the gaseous compounds are collected for sniffing-MS detection. (b)–(d) Relative intensities (repeated five times) of pinene and camphor acquired in the *x*-, *y*- and *z*-axes, respectively. The red triangles and blue squares indicate the relative intensities of pinene and camphor signals, respectively.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.scib.2018.06.020.

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