Direct Determination of Trace Nitrogen Dioxide by Atmospheric Pressure Ionization Mass Spectrometry (APIMS) without Conversion to Nitric Oxide.

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Abstract

The aim of this study was to develop a new method for the determination of NO₂ levels encountered in clinical settings as well as in environmental studies, using a bi-component atmospheric pressure ionization mass spectrometry (APIMS). Hydrogen (1%) diluted in pure argon was ionized by corona discharge in the first ionization component. Fifty ml of the analyte diluted in 250 ml of composite air or carbon dioxide (CO₂) was introduced into the second ionization component and analyzed. When composite air was used as the sample carrier gas, NO in the analyte was oxygenated and there was an increase in the NO₂ content from that in the original analyte. However, when CO₂ was used as the sample carrier gas, the level of NO₂ in the analyte could be determined because CO₂ did not change the NO₂ content from that in the original analyte. A calibration curve with good linearity was obtained using the UG-410 APIMS system, with a regression equation of $Y(\%) = 5.513 \times 10^{-2} X$ (ppb) and a detection limit of 0.9 ppb. Since APIMS detects NO₂ directly within its system, the concentration of NO does not need to be measured. This system may be of great help in the accurate detection and determination of the concentration of low levels of NO₂ during inhaled NO therapy.

Key words: APIMS, nitrogen dioxide (NO₂), nitric oxide (NO), NOx, NO inhaling therapy

Introduction

Nitrogen oxides (NO_x) are well known as air pollutants.¹⁾ Among them, nitric oxide (NO) has been identified as an endothelium-derived relaxing factor (EDRF)²⁻⁴⁾, and inhaled NO therapy has been used clinically to relax the smooth muscle of the airways in various pathological conditions including acute respiratory distress syndrome (ARDS) and primary pulmonary hypertension (PPH)⁵⁻⁷⁾. Since NO in the presence of oxygen (O₂) produces nitrogen dioxide (NO₂), a highly toxic substance⁸⁻¹¹⁾,

the NO₂ level must be carefully monitored during inhaled NO therapy. Several analysis methods have been developed to estimate the NO₂ level. For determination of gaseous NO₂, chemiluminescence analyzers (CL) as well as electrochemical sensors (EC) are widely used. EC sensors have been reported to be less sensitive than CL analyzers.^{12, 13)} A CL analyzer electronically measures photoemission from excited NO₂ produced during the reaction of NO and ozone after converting NO_x to NO. The possibility that CL analyzers produce inaccurate measurements has been raised¹⁴⁻¹⁶⁾. For example, CL readings of NO₂ will be affected by increased fractional inspired O₂ concentrations¹⁷⁻¹⁸⁾ or by nitrogen oxides other than NO and NO₂¹⁹⁾.

The purpose of this study was to investigate whether atmospheric pressure ionization mass spectrometry (APIMS)¹⁹⁾, which is widely used in the semiconductor industry²⁰⁾, can be used for quantitative determination of small amounts of NO₂. APIMS is potentially advantageous in terms of real-time analysis,

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continuous monitoring, sensitivity, and compound specificity²¹⁾. APIMS with one ionization chamber can not measure water impurity in monosilane or disilane, because Si compounds are deposited on the needle of the electrode, and/or blocked the aperture between the ionization chamber and the buffer chamber. To solve this problem, a bi-component ionization chamber APIMS was developed²²⁾, and this system is more widely used in the semiconductor industry. Because APIMS with one ionization chamber, when used in analyzing for NO₂ in an analyte, produced a few of species of nitrogen oxides perhaps in the ionization chamber and they interfered with the analysis (data is not shown), we utilized this bi-component ionization chamber APIMS in this study to measure NO₂ without interference from NO by preventing the formation of NO₂ by the reaction of NO and O₂.

Materials and Methods

Apparatus/Instrumentation.

An Atmospheric Pressure Ionization Mass Spectrometer (APIMS) System (UG-240-PN; Hitachi Tokyo Electronics Co., Ltd., Tokyo, Japan) was utilized in this study. An APIMS UG-410 system (Hitachi Tokyo Electronics Co., Ltd.) was also used to obtain a calibration curve. Diagrams of the APIMS UG-240-PN system are shown in Figures 1a and 1b. It consists of a gas introduction unit, an ionization chamber, a buffer chamber, an analysis chamber, and an evacuation. The ionization chamber is divided into two rooms, the primary ionization room and the secondary ionization room²³⁾. In the primary ionization room, hydrogen molecules are ionized by corona discharge into anions (hydride ions: H⁻), and these anions are sent to the secondary ionization room, where the sample gas had been drawn by a diaphragm pump in the sample gas control unit and introduced through the gas introduction unit. Each inlet of gas is controlled by a mass flow controller. The mixing ratio is monitored with flow meters. From the known concentration of each introduced gas, the concentration of each gas in the mixture was calculated. In the secondary ionization room where the pressure was maintained at 85% of atmospheric pressure, impurities in the sample gas were amplified through collisions with the primary ions (H⁻) which had been produced in the first ionization room by corona discharge (ion-molecule reaction). The ions enter the buffer chamber through the first slit, and then the analysis chamber through the second slit. The ions were then focused into a Q pole (quadrupole) mass spectrometer (mass range: m/Z 3-360). The buffer chamber and analysis chamber were each equipped with a turbo molecular pump and a rotary vacuum pump in the evacuation unit, and the pressure of the two chambers was maintained at approximately 50 Pa and 10⁻³ Pa, respectively. To increase the rate of mass scanning, we set the Q pole mass range to m/Z 3-100 after confirming that the APIMS spectrogram of background room air did not contain particular major peaks over m/Z=100. The APIMS system has two modes of operation, positive or negative, depending on the potential of the glow corona discharge electrode. We chose the negative mode of operation in this study because NO₂ has higher electron affinity (2.275 eV) than NO (0.024 eV) and H₂ (0.754 eV)²³⁾. The operating conditions of UG-240-PN in the negative mode are shown in Table 1. In accordance with the laws and regulations by the Japanese government, the cylinders were treated and the exhaust gases were vented out of the room and

diluted in the atmosphere, as some of the gases used in this experiment are toxic.

Materials.

All gases used in the experiment were contained in cylinders and purchased from Nihon Sanso Co. Ltd., Tokyo, Japan. The purity of each gas was as follows: oxygen (O₂; >99.99%), nitrogen (N₂; >99.9998%), carbon dioxide (CO₂; >99.99%), composite air (air; CO<0.5ppm, CO₂<0.5ppm, NO_x<0.5ppm, SO₂<0.05ppm), nitric oxide (NO; 110 ppb in N₂), nitrogen dioxide (standard NO₂; 4.58 ppm in air), hydrogen [Ar+H₂; 1% H₂ in pure Ar (purity 99.9995%)].

Procedures/Sample Preparation.

Hydrogen (H₂) diluted in Ar gas was introduced into the corona discharge ionization room at a rate of 1000 ml/min under an atmospheric pressure of approximately 10⁵ Pa. The temperature of the room was 120 degrees Celsius. The current of the corona discharge electrode was -6.0--30 micro A, and the hydrogen molecules were converted to H⁻ ions. Fifty ml/min of the sample gas was mixed with 250 ml/min of the sample carrier gas, and this mixture was introduced into the second ionization room by a diaphragm pump. Composite air and CO₂ were selected as the sample carrier gases. APIMS spectrograms were obtained for the combinations of sample gas and sample carrier gas listed in Table 2, and were examined qualitatively.

Since the UG-240-PN system was a prototype, a calibration curve for quantitative analysis was obtained using various concentrations of the standard NO₂ and CO₂ as the sample carrier gas on the improved APIMS Model UG-410, under conditions similar to those used with the UG-240-PN model. Standard NO₂ and CO₂ gases at various flow ratios were mixed giving the concentrations of NO₂.

Data analysis.

The APIMS system was run on a DELL computer (Optiplex XM590) with Microsoft Corp. Windows Vers. 3.1 on which Microcal Software Inc. Origin Vers. 3.65 and APIMS Vers. 2.02 (Hitachi Tokyo Electronics Co. Ltd.) were installed. The

Table 1 Operation conditions of APIMS Model UG-240-PN in the negative mode for ion formation and detection.

Glow discharge source pressure	10 ⁵ Pa
Source gas composition	Ar+1%H ₂
Vacuum system pressure	10 ⁻³ Pa
Source sampling rate	300ml/min
Discharge voltage	-720V
Discharge current	-6.0--30microA
Temperature	120 °C

Table 2 Sample carrier gas and sample gas used for APIMS. An APIMS spectrogram was obtained for the sample gas and sample carrier gas noted in each row. The purity of each gas is described in the Materials and Method Section.

Sample Carrier Gas (250 ml/min)	Sample Gas (50 ml/min)
Composite Air	Room Air
Composite Air	NO/N ₂ : O ₂ =1:4
CO ₂	Room Air
CO ₂	NO/N ₂ : O ₂ =1:4
CO ₂	NO ₂ /Air

Fig. 1a A diagram of APIMS Model UG-240-PN in the negative mode of operation.

When used in the positive mode of operation, a moisture remover region (a molecular sieve trap is usually used, not shown in the diagram) is needed.

APIMS: Atmospheric Pressure Ionization Mass Spectrometry

MFC: Mass Flow Controller

MFM: Mass Flow Meter

APC: Automatic Pressure Controller

⧻: valve

Fig. 1b Detailed schematic of APIMS

amounts of ions detected by the system were simultaneously displayed on the CRT.

Results

The APIMS spectrogram of background room air with composite air as the sample carrier gas is shown in Figure 2. The ion peak at m/z 46, which represents NO₂⁻, was slightly higher than the peaks that represent noise. The concentration of NO₂ in the background room air, which was simultaneously analyzed with a widely used chemiluminescence analyzer (CLD 700 AL, ECO Physics Co. Ltd., Duernten, Switzerland) that was considered accurate for the present purpose, varied between 10

Fig. 2 Spectrogram of APIMS (mass numbers 3-100) of background room air with composite air as the sample carrier gas.

First ionizing gas: Ar + 1% H₂, 1000 ml/min

Sample carrier gas: Composite air, 250 ml/min

Sample gas: Background room air, 50 ml/min

Fig. 3 Spectrogram of APIMS (mass numbers 3-100) of NO diluted in N₂ and 80% O₂ with composite air as the sample carrier gas.

First ionizing gas: Ar + 1% H₂, 1000 ml/min

Sample carrier gas: Composite air, 250 ml/min

Sample gas: 22 ppb NO / N₂ + 80% O₂, 50 ml/min

and 30 ppb. When 110 ppb NO diluted in pure O₂ at a ratio of one to four, resulting in 22 ppb NO, was introduced into APIMS, the resulting ion peak at m/z 46 (Figure 3) was higher than that on the APIMS spectrogram of background room air (Figure 2). The mass number of NO is 30, but in the negative mode of operation NO was not detectable because it does not have strong electron affinity (0.024 eV).

Carbon dioxide (CO₂) gas was adopted as a sample carrier gas, because of its strong electron affinity and of its fairly low price. When the same sample gas of NO diluted in O₂ was introduced with CO₂ as the sample carrier gas, NO failed to increase the height of the peak at m/z 46 (Figure 4). The height of the peak is nearly identical to that of the m/z 46 peak when

background room air was analyzed with CO₂ as the sample carrier gas (Figure 5). In order to confirm that NO₂ produces a peak at m/z 46 with CO₂ as the sample carrier gas, standard NO₂ gas at a concentration of 4.58 ppm diluted in air with CO₂ as the sample carrier gas was introduced into the system, and analyzed. A high peak at m/z 46 was observed, while an increase in the height of the peak at m/z 62 was not seen (Figure 6).

Using the UG-410 APIMS system, a calibration curve was obtained by plotting relative ion intensity versus the calculated concentration of NO₂ (Figure 7), where relative ion intensity was calculated according to the following equation.

(Relative Ion Intensity)=(Absolute Ion Intensity)/(Total Absolute Ion Intensity)

Fig. 4 Spectrogram of APIMS (mass numbers 3-100) of NO diluted in N₂ and 80% O₂ with CO₂ as the sample carrier gas.

First ionizing gas: Ar + 1%H₂, 1000 ml/min

Sample carrier gas: CO₂, 250 ml/min

Sample gas: 22 ppb NO/N₂ + 80%O₂, 50 ml/min

Fig. 6 Spectrogram of APIMS (mass numbers 3-100) of NO₂ diluted in air with CO₂ as the sample carrier gas.

First ionizing gas: Ar + 1%H₂, 1000 ml/min

Sample carrier gas: CO₂, 250 ml/min

Sample gas: 4.58 ppm NO₂ diluted in air, 50 ml/min

Fig. 5 Spectrogram of APIMS (mass numbers 3-100) of background room air with CO₂ as the sample carrier gas.

First ionizing gas: Ar + 1%H₂, 1000 ml/min

Sample carrier gas: CO₂, 250 ml/min

Sample gas: Background Room Air, 50 ml/min

Fig. 7 A calibration curve obtained on UG-410 in the negative mode of operation.

Standard NO₂ and CO₂ gases were mixed at various flow ratios giving the indicated concentrations of NO₂.

Regression equation: $Y(\%) = 5.5153 \times 10^{-2} X$ (ppb), $r=0.9999$

Detection Limit: 0.9ppb

peaks at *m/z* 62 and 63. The peak at *m/z* 62 is slightly higher than noise level in both experiments, but this does not appear to be NO₃⁻ or (NO₂-O⁻) for the following reason: although the NO₂ content was higher when NO diluted with pure O₂ (1:4) was used as the sample gas than when background room air was used as the sample gas, the height of the peak at *m/z* 62 in the two APIMS spectrograms did not differ. This fact leads to the assumption that most of the NO₂ was made not in the ionization room, but mainly in the gas introduction unit through the reaction of NO with O₂. Thus, in Figure 2, the peak at *m/z* 46 represents not only NO₂, but also NO in the background room air, although the concentration of NO in background air is usually very low (several ppb). It remains to be clarified whether the oxygen that reacts with NO to form NO₂ is derived from the sample gas itself or from the sample carrier gas. As is often the case of any analytical method for nitric oxides, the length of introduction unit should be as short as possible.

If the sample or sample carrier gas contained oxygen and NO reacted with O₂, the Gibbs standard free energy change was calculated to be -34.80kcal/mole as shown in the next equation.

Therefore the sample carrier gas was changed to CO₂, which does not react with NO, has strong electron affinity, and can serve as a main electron reservoir. The reaction in the following equation cannot occur because the change in Gibbs standard free energy, which was calculated to be +53.12 kcal/mole, is very high.

In Figures 4-6, it was confirmed that NO₂ produced a peak at *m/z* 46 where the sample carrier gas was CO₂, without a clear change of NO to NO₂. In Figure 6, it also appears that in this negative mode of operation, O₂ in the sample (the sample contained some oxygen because it is balanced with air) and O⁻ in the ionization chamber do not react with NO₂ molecules to produce nitrate ions (NO₃⁻) either in the gas introduction unit or in the ionization or the buffer chambers. As is often the case with APIMS (or Q-pole detection of ions), it is very natural to have a slight increase or decrease in the height of the peaks which are not derived from the analyte on the APIMS spectrogram where NO₂ is used as the sample gas (Figure 6), from those on the APIMS spectrogram where background room air is the sample gas (Figure 5), because a large amount of NO₂ interferes with the ion distribution or maybe induces some change in the electrical environment of the devices inside. For example, when CO₂ was used as the sample carrier gas, the CO₃⁻ peak was the main peak in the mass spectrogram, which represents ions at 60 daltons. When 4.58 ppm NO₂ was introduced into the APIMS, the height of the peak at *m/z* 60 decreased because it provided electrons to NO₂, although CO₃⁻ still produced a major peak and remained as a large reservoir of electrons. Therefore, even though there were slight changes in absolute ion intensity, the concentration of each ion in the sample was calculated as relative ion intensity.

Although the number of nonspecific ion-molecule reactions in the first room (the corona discharge room) is reduced to almost null in a bi-component APIMS from that in a conventional APIMS system with one component ionization chamber, the reduction in number of reactive ions in the

second room generally raises the limit of detection. However, the UG-410 was ten times more sensitive compared with the prototype UG-240-PN, with a very low detection limit under similar conditions.

The length of time of sample analysis was approximately 45 seconds when the system scanned an ion environment between 3 and 100 daltons. However, when measuring the environmental atmosphere or when analyzing inspired gases during inhaled NO therapy, both of which contain comparatively stationary composite gases, the analysis time can be reduced to about ten seconds (the time that it takes for the analyte to reach the analysis unit from the sample induction unit) by manually setting the ion counting mode within narrow limits, on condition that scanning of 3-100 daltons mass spectra is performed at fixed intervals to confirm that the ion distribution is relatively constant.

This study was performed under dry conditions. If humidified samples were used, the water content would increase the amount of ions in the second ionization room and therefore the calibration curve should be more sensitive as long as appropriate settings are selected. If the water content is removed with an absorber, there is a possibility that a fraction of NO₂ would be lost from the sample. In the negative mode of operation, APIMS does not require water content removal from the sample, which is one of the advantages of APIMS.

Along with the adhesive property of NO₂, the adhesiveness of water to the walls of the tubes in the gas introduction unit which extend from the inlet of the sample to the inlet of the second ionization chamber, needs to be further investigated and solved. In this method, dilution of the sample with a sample carrier gas (CO₂) of 500% sample volume, decreased the rate of reaction of NO with O₂. Miyamoto, et al.²⁴⁾, mentioned that humidity is not a concern in terms of formation of NO₂ from NO but, again, in this APIMS method, dilution of samples with sample carrier gas is favorable because it reduces the humidity of the analyte.

With this apparatus, direct measurement of NO₂ in low-range resolution could be performed. As another advantage of this apparatus, the concentration of NO can be determined by passing the sample gas through a molecular sieve absorber in the positive mode of operation (data not shown). This bi-component APIMS system will be a clinically useful alternative to monitor the NO₂ level during inhaled NO therapy. As mentioned above, in the negative mode of operation, humidity has little effect on the analysis itself. Water in the analyte may be involved in ionization, but under appropriate conditions it does not form clusters with the ions to be analyzed. This system in the negative mode has wide application for sensitive analyses not only in environmental studies, but also in medical and biological studies, where most analytes contain humidity to some extent. In the latter field, since APIMS is a mass spectrometry method, compounds other than nitrogen dioxide which are involved in metabolism could possibly be detected in low-range resolution depending on their electron affinity. In the positive mode of operation, the concentration of ammonia and methane could be determined on the order of ppb or sub-ppb (data not shown). Other candidate compounds may be determined in the positive mode according to a compound's ionization potential. For medical application, the APIMS system with one ionization chamber was utilized as a breath test^{25,26)}, but this system did not prevail probably because of the

non-specific ionization of sample impurities in the (single) ionization chamber and the low demand for medical use. This bi-compartment ionization chamber APIMS has reduced non-specific ionization, and will be commonly used in the future. In environmental studies, this system is also expected to determine trace ingredients of a sample depending upon their molecular electric properties, with an appropriate application of a filter in the introduction unit when the analyte contains airborne particulates, or by dilution with an appropriate sample carrier gas when the analyte is dense. Further studies are needed to find the best combination of sample carrier gas and specific candidate compound.

In conclusion we succeeded in measuring directly trace

impurity of nitrogen dioxide in the analyte, without measuring nitric oxide by APIMS in the negative mode of operation.

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