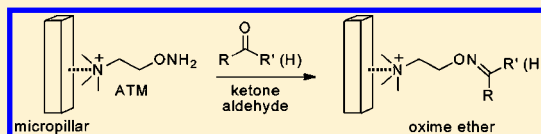


Preconcentration and Analysis of Trace Volatile Carbonyl Compounds

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ABSTRACT: We describe a preconcentration device that may be suitable for quantitative analysis of trace volatile ketones and aldehydes in ambient air as well as in human breath. The approach is based on microreactor chips fabricated from silicon wafers. The microreactors have thousands of micropillars in microfluidic channels for uniformly distributing a gaseous sample flowing through the chips. The surfaces of the micropillars are functionalized with a quaternary ammonium aminoxy salt, [2-(aminoxy)ethyl]-*N,N,N*-trimethylammonium iodide (ATM), for trapping trace ketones and aldehydes by means of oximation reactions. ATM adducts and unreacted ATM are eluted from the microreactor with less than 40 μL of methanol and directly analyzed by nanospray Fourier transform ion cyclotron resonance (FTICR) mass spectrometry (MS). Ketones and aldehydes at levels of 1 ppbv have been detected using this microreactor and FTICR-MS system.



Detection of volatile organic compounds (VOCs) at trace level (ppbv to pptv) has become an important research area because of demanding applications in homeland security, environmental monitoring, and noninvasive health diagnosis.^{1,2} The analysis of trace VOCs challenges existing analytical methods because their concentrations are beyond instrument limits of detection. This problem is further exacerbated by other interfering gases that are mixed in large concentration with the VOCs. Gas chromatography coupled with a mass spectrometer detector (GC/MS) is currently a dominant technique for analysis of trace VOCs in air.^{3–6} A complex preconcentration process consisting of cryogenic adsorption and thermal desorption typically is required before trace VOC samples can enter into a GC column.^{7–12} In recent years, microfabricated gas preconcentrators and gas chromatography columns have demonstrated the potential for real-time, low-power, and hand-held gas detection.^{1,2} Preconcentrators fabricated from silicon wafers using microelectromechanical system (MEMS) technology typically consist of a microhot plate and an adsorption material placed adjacent to the heating element.^{13,14} These MEMS preconcentrators have common issues of inefficient physical adsorption and thermal desorption.^{12–14}

The analysis of carbonyl compounds in air has been studied for air quality monitoring.^{8–10,15–18} A particle or fiber-packed cartridge impregnated with 2,4-dinitrophenylhydrazine (DNPH) has been used for trapping carbonyl compounds. DNPH was also used for preconcentration and derivatization of volatile carbonyl compounds in exhaled breath.^{19,20} Ketones and aldehydes in exhaled breath can also be detected by proton transfer reaction mass spectrometry (PTR-MS)^{21,22} and selected ion flow tube mass spectrometry (SIFT-MS) without any preconcentration process.^{23–25} PTR-MS and SIFT-MS have been used for in situ monitoring VOCs in ambient air and exhaled breath.^{26–29} Most recently, solid-phase microextraction (SPME) with adsorbed *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA) has been used for analysis of aldehydes

in exhaled breath.^{30,31} SPME is a popular preconcentration method introduced a decade ago as a rapid extraction technique for analysis of volatile organic compounds from a variety of matrixes.³² However, SPME is only a semiquantitative method due to competitive adsorption on the SPME fiber. It is also difficult to determine the actual volume of air that is sampled by the SPME fiber.

In recent years, several investigators have suggested that certain ketones and aldehydes in exhaled breath could be used as metabolic markers of lung cancer for noninvasive diagnosis of lung cancer in its early stages^{30,31,33,34} and chronic obstructive pulmonary disease (COPD).²⁰ The reported concentrations of these ketones and aldehydes in breath are in the ppbv to pptv range. Ketones and aldehydes are produced in biochemical pathways as intermediates, and many are unique to a given pathway. Ketones and aldehydes are also generated from oxidative reactions, such as lipid peroxidation.^{35,36} Therefore, development of a fast and reliable protocol for quantitative analysis of all trace ketones and aldehydes in exhaled breath is a crucial step to fulfill breath analysis as a noninvasive diagnosis method.

In this paper, we describe a novel preconcentration approach for analysis of trace ketones and aldehydes. We designed and fabricated a microreactor chip (preconcentrator) using MEMS technology. The benefits of the MEMS approach are advantages in microstructure flexibility and microliter sample size in comparison to conventional DNPH-based packed cartridges.^{15–18} Thousands of micropillars in the microreactors distribute gas flow and provide large surface areas for trapping target gases. The surfaces of the micropillars are functionalized by a quaternary ammonium aminoxy salt, [2-(aminoxy)ethyl]-*N,N,N*-trimethylammonium iodide (ATM), as a “capture

Received: August 17, 2011

Accepted: December 7, 2011

Published: December 7, 2011

phase" via oximation reactions with ketones and aldehydes. This approach is suitable for quantitative analysis of ketones and aldehydes in exhaled breath. For rapid analysis and identification of VOC adducts on a microliter sample size, we use nano-electrospray Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS), which is benefited by the permanent positive charge of ATM. The complete elution of the capture phase and its adducts avoids the current problems of sample transfer from a preconcentrator to analytical equipment. In addition to the aminoxy group for oximation of the carbonyl VOCs, the ATM molecule was designed with a positively charged group (quaternary ammonium ion) for enhancing detection by nano-electrospray FTICR-MS. Combining the strategies of (i) a fabricated microfluidic microreactor, (ii) efficient oximation chemistry for trapping carbonyl compounds, and (iii) analysis by FTICR-MS provides an innovative approach for analysis of trace carbonyl compounds in gas mixtures.

EXPERIMENTAL SECTION

Materials. All reagents and solvents, including deuterated acetone (acetone- d_6) (99.9%), acetone (99%), 2-butanone (99%), 2-pentanone, propanal, *n*-butanal (99%), *n*-hexanal (98%), and methanol (99.9%), were purchased from Sigma-Aldrich. The quaternary ammonium aminoxy compound ATM was synthesized according to a published method.³⁷ The toxic organic gas mixture TO-15 standard was purchased from the Spectra Gases Co., Branchburg, NJ.

Microreactor Fabrication. The design and fabrication process mirrored the procedures of the MEMS device.^{12–14} A brief description of the fabrication is presented here. Detailed design and fabrication procedures will be published elsewhere. Deep reactive ion etching (DRIE) was used to create microfluidic channels and micropillars with a height of roughly 250 μm on a silicon wafer. Then the microreactor channels and micropillars were thermally oxidized to form a 50 nm SiO_2 thin film in an O_2 and H_2O atmosphere. The fabrication was finished by bonding the wafer-supported microreactors with a Pyrex glass wafer using an anodic wafer bonding process. Each wafer was subsequently diced, and the connection ports were opened for connecting fused silica tubes to the microreactors. The surface functionalization of the micropillars by ATM was performed by infusing 3.65×10^{-7} mol of ATM dissolved in 15 μL of methanol into the microreactors through one connection port followed by evaporation of the solvent under vacuum. Finally, fused silica tubes with 190 μm o.d. and 100 μm i.d. were connected to the inlet and outlet ports of the microreactors with a silica-based bonding agent.

Preconcentration of Ketones and Aldehydes. Figure 1 shows a schematic illustration of the setup for preconcentration

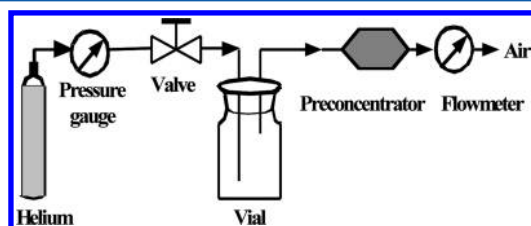


Figure 1. Schematic flow diagram of the preconcentration setup.

of trace ketones and aldehydes in a carrier gas (He). A microreactor is connected to an ultra-high-purity He gas cylinder by the attached fused silica tubes. A mechanical needle valve made

by Hoke Co. is used to adjust the He flow rate, while a flow meter is used to measure the He flow rate. There is no detectable leakage of He in the setup verified by a He gas leakage detector. After the He flow rate is stabilized and the setup is flushed for at least 10 min, a known amount of acetone- d_6 diluted in methanol is injected into the vial with He flowing through the microreactor as indicated in Figure 1. After flowing continuously for 20 min, the flow is then stopped. The flow rate and flow time are recorded after the injection of ketone(s) and/or aldehyde(s), and the microreactor is then disconnected from the setup. The reacted ATM adduct and unreacted ATM are eluted from the microreactor by flowing methanol from one slightly pressurized vial through the microreactor and then into an empty collecting sample vial. The eluted solutions were directly used for FTICR-MS analysis without any further process.

To study the effect of ATM/ketone and ATM/aldehyde ratios on the capture efficiency, a series of experiments for preconcentrating trace ketones and aldehydes were performed. A constant amount of 3.65×10^{-7} mol of ATM was loaded into each microreactor, while the amount of ketones and aldehydes added to the vial shown in Figure 1 was varied and evaporated into the He flow stream. After preconcentration, unreacted ATM and reacted ATM adduct were eluted from the microreactor. Then a 5 μL solution containing 1.14×10^{-8} mol of acetone- d_6 and 1.17×10^{-7} mol of ATM in methanol was added to each eluted methanol solution as an internal reference for FTICR-MS analysis. The reason for using this ATM/acetone- d_6 molar ratio as the internal reference is to ensure complete reaction of acetone- d_6 with ATM. The amount of captured ketones and aldehydes was determined by comparing the FTICR-MS signal abundance of ATM–acetone- d_6 with that of reacted ATM–ketone and ATM–aldehyde. The capture percentage can be determined by dividing the amount of captured ketones or aldehydes by the added amount of carbonyl compounds in the He flow.

A TO-15 gas mixture standard was also used to determine the capture percentages of ketones and interference of other gases. It was diluted 100-fold with N_2 using an Entech automated dynamic diluter, model 4600, and stored in 6 L SilcoCan canisters (Restek Corp., Bellefonte, PA). The TO-15 used contained 78 organic compounds. After dilution, the TO-15 in the canisters contained 1 ppb acetone, 0.98 ppb methyl ethyl ketone, 1.03 ppb methyl isobutyl ketone, 0.96 ppb methyl butyl ketone, and other volatile organic compounds in N_2 . To preconcentrate ketones from the diluted TO-15, the microreactors were directly connected to the canisters by the silica tube, septa, and stainless steel tubes. The gas pressures inside the canisters were measured before and after the preconcentration process to calculate the amount of ketones flowing into the microreactors.

FTICR-MS Instrumentation. The samples of methanol eluted solutions were analyzed on a hybrid linear ion trap-FTICR-MS instrument (Finnigan LTQ-FT, Thermo Electron, Bremen, Germany) equipped with a TriVersa NanoMate ion source (Advion BioSciences, Ithaca, NY) with an electrospray chip (nozzle inner diameter 5.5 μm). The TriVersa NanoMate was operated in positive ion mode by applying 2.0 kV with no head pressure. Initially, low-resolution MS scans were acquired for 1 min to ensure the stability of ionization, after which high mass accuracy data were collected using the FTICR analyzer where MS scans were acquired for 8.5 min and at the target mass resolution of 100 000 at 800 m/z . The AGC (automatic gain control) maximum ion time was set to 500 ms (but typically utilized <10 ms), and five "microscans" were acquired for each

saved spectrum; thus, the cycle time for each transformed and saved spectrum was about 10 s. The LTQ-FT was tuned and calibrated according to the manufacturer's default standard recommendations, which achieved better than 1 ppm mass accuracy and a 400 000 resolution capability at $m/z = 400$. FTICR mass spectra were exported as exact mass lists into a spreadsheet file using QualBrowser 2.0 (Thermo Electron), typically exporting all of the observed peaks. ATM and ATM derivative species were assigned on the basis of their accurate mass by first applying a small (typically <0.0005) linear correction based on the observed mass of the internal standard.³⁸

RESULTS AND DISCUSSION

To design microreactors for uniform air flow, a computational fluid dynamics (CFD) modulus of CoventorWare software was used to simulate gas flow patterns in the microreactors. The inlet and outlet shapes, micropillar size, and array pattern were optimized on the basis of the simulation results. The micropillar array pattern was designed such that there is no direct short path through the microreactor. The microreactors with optimized microstructures were fabricated on a silicon wafer using standard MEMS microfabrication technology. Figure 2

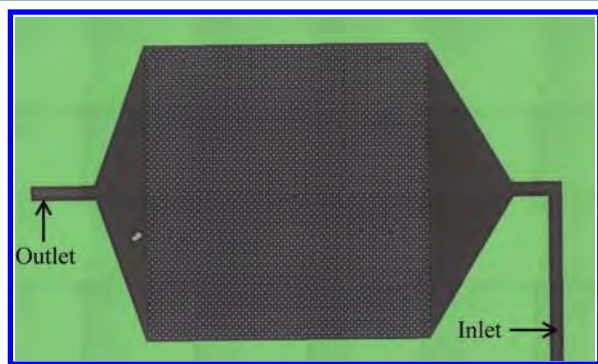


Figure 2. Optical micrograph of a fabricated microreactor before bonding with a glass wafer.

shows an optical micrograph of a fabricated microreactor. The microreactor has a flow channel size of $7 \text{ mm} \times 5 \text{ mm}$. Both the inlet and outlet have a triangular shape for uniform distribution of gas flow. Figure 3a shows a scanning electron microscopy

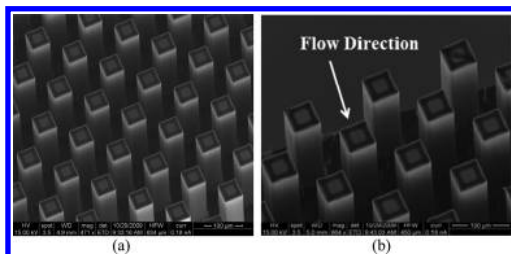


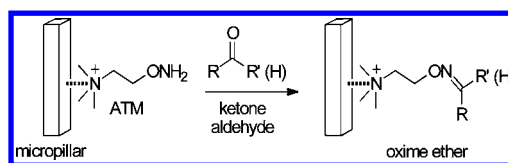
Figure 3. (a) SEM micrograph of the micropillar array. (b) SEM micrograph of the micropillars near the inlet.

(SEM) micrograph of the micropillars created by DRIE. The micropillars have a high aspect ratio with dimensions of $50 \mu\text{m} \times 50 \mu\text{m} \times 250 \mu\text{m}$. Figure 3b shows an SEM micrograph of the micropillar array near the inlet of the microreactor. The pattern of the micropillar array can lead to uniform gas flow as indicated by the CFD simulation. There are more than 5000 square micropillars standing in the microreactor corresponding

to a total micropillar surface area of about 260 mm^2 . The total empty space in the microreactor is about $5 \mu\text{L}$. The micropillar structure of the microreactor and microliter volume are advantages of fabricated microreactors for preconcentration, and these result in microliter-sized samples for direct FTICR-MS analysis.

Scheme 1 shows a schematic illustration of ATM cations adsorbed on SiO_2 surfaces of the micropillars for oximation

Scheme 1. Trapping of Ketones and Aldehydes in the Microreactor via ATM Oximation



reaction with ketones and aldehydes. ATM is adsorbed through electrostatic interactions with negative charges on the micropillar surfaces. To characterize the ATM trapping of carbonyl compounds by the microreactors, acetone- d_6 was first used to distinguish any environmental trace acetone contamination. In these experiments, 2.71×10^{-7} mol of acetone- d_6 in methanol was injected into the vial and evaporated into the He flow stream as shown in Figure 1. The He pressure at the inlet of the microreactor was in the range from 15 to 25 psi. The flow rate of the microreactor was adjusted to 5 mL/min. Figure 4 shows an FTICR-MS spectrum of eluted ATM adducts. The spectral region depicts the oximation product of ATM with acetone- d_6 (165.18688 m/z ion) as well as unreacted ATM (119.11793 m/z ion). Figure 4 also indicates that there was trace acetone contamination (159.20982 m/z ion). To determine whether there was ATM residual in the microreactor, the microreactor was eluted four times with $10 \mu\text{L}$ of methanol each time. A 97.8 mol % of reacted and unreacted ATM was eluted with the first $10 \mu\text{L}$ of methanol. Less than 0.5 mol % ATM was collected in the second and third elutions, and there was no detectable ATM and its adduct in the fourth methanol elution. This result indicates that methanol is very effective for eluting ATM and its adduct from the microreactor. Through this microreactor process, acetone- d_6 is converted to a nonvolatile quaternary ammonium adduct dissolved in methanol that can be directly analyzed by FTICR-MS. To our knowledge, most of the current microfabricated preconcentration devices are based on physical adsorption for preconcentration and thermal desorption for analyte release.^{12–14} Our novel microreactor approach for preconcentration based on chemical reaction and liquid elution for analyte release are fundamentally different from those of previous MEMS-based preconcentrators.^{12–14}

To test the microreactor for capturing trace levels of acetone, 3.65×10^{-7} to 3.65×10^{-11} mol of acetone in methanol solutions was added to the He flow through the microreactors. A known amount of acetone- d_6 that completely reacted with ATM in methanol was then added to each eluted solution as the internal reference for FTICR-MS analysis. The relationship between the capture percentage and the ATM/acetone molar ratio is shown in Figure 5. As the molar ratio of ATM to acetone increases to 10, more than 99% of acetone in the He flow stream was captured. When the molar ratio of ATM to acetone was higher than 100, $\sim 100\%$ of the acetone was recovered. For the lowest amount of acetone (3.65×10^{-11} mol) evaporated in the He flow stream at a flow rate of 5 mL/min for 20 min, an

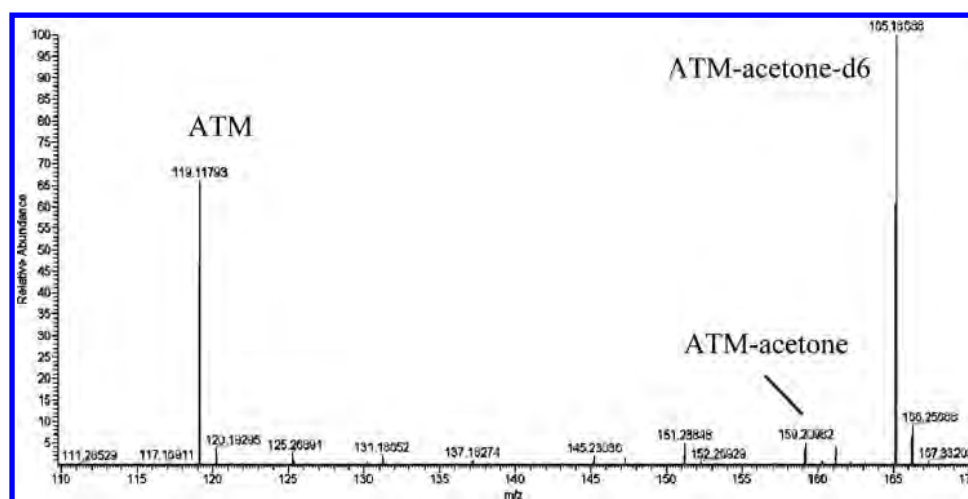


Figure 4. Typical FT-MS spectrum of ATM and ATM-acetone- d_6 eluted from the microreactor.

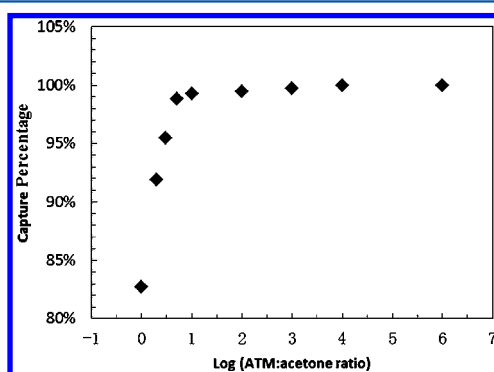


Figure 5. Relationship between capture efficiency and ATM/acetone molar ratio.

equivalent level of 8.9 ppbv was reached. The FTICR-MS signal (abundance) of the ATM-acetone adduct for the sample of 3.65×10^{-11} mol of acetone added into the He flow through the microreactor was still high ($\sim 1\text{E}5$ abundance). The reported acetone level in exhaled breath is in the range of 180–800 ppbv.^{39,40} Therefore, the microreactor approach could be used for analysis of acetone in exhaled breath.

2-Butanone and 2-pentanone were also used to characterize the capture percentage of the microreactors. In these experiments, a constant amount of 3.65×10^{-7} mol of ATM was loaded into each microreactor while varying the added amount of individual ketone into the He flow through the microreactors. After pre-concentration, unreacted ATM and reacted ATM adduct were eluted from the microreactor by methanol. Figure 6 shows that, as the ATM/ketone molar ratio increases, the capture percentage also increases. For an ATM/ketone molar ratio larger than 10, more than 92% of the added ketones were captured in the microreactors. The capture percentage of acetone was higher than those of 2-butanone and 2-pentanone at the same ATM/ketone molar ratio. The result may imply the difference in reaction kinetics of ketones with ATM.

The obvious different capture efficiencies for different ketones have led us to design a series of experiments to test the effect of the ATM/aldehyde ratio on the capture percentages of propanal, *n*-butanal, and *n*-pentanal. Again, a constant amount of ATM (3.65×10^{-7} mol) was loaded into each microreactor while correspondingly decreasing the added amount of aldehydes in the He flow stream to change the ATM/aldehyde

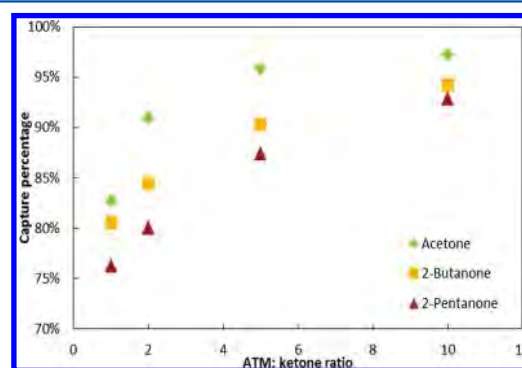


Figure 6. Relationship between capture efficiency and ATM/ketone molar ratio.

ratio. Figure 7 shows that, as the ATM/aldehyde molar ratio increases, the capture percentage also increases. For an ATM/

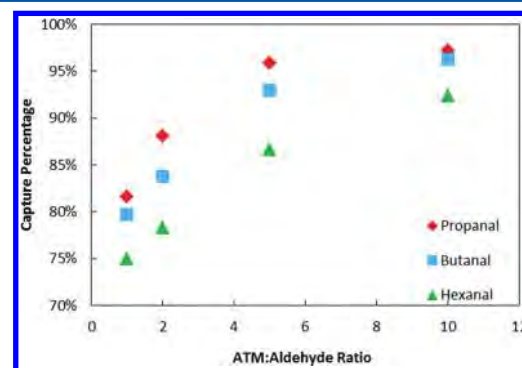


Figure 7. Relationship between capture efficiency and ATM/aldehyde molar ratio.

aldehyde molar ratio greater than 10, the capture percentages are above 92%. The reason is that, for higher ATM/aldehyde molar ratios, more ATM molecules relative to aldehydes provide higher reaction probability for capturing aldehydes. The capture percentage of propanal was higher than those of *n*-butanal and *n*-hexanal at the same molar ratios. These results also imply that the ATM reaction rate with low molecular weight aldehydes may be greater than that of high molecular weight aldehydes. A detailed study on the reaction kinetics between ATM and

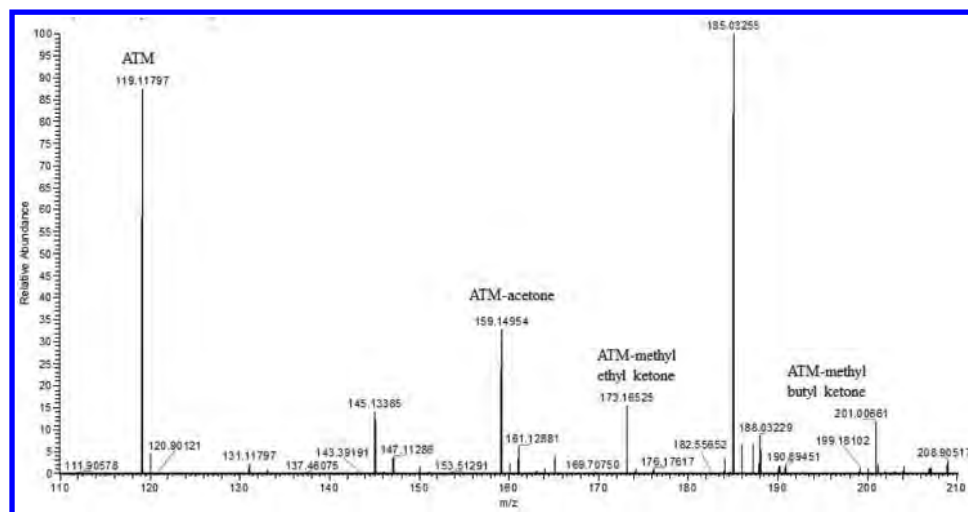


Figure 8. FTICR-MS spectrum of a preconcentrated TO-15 gas mixture with 1 ppb acetone, 0.98 ppb methyl ethyl ketone, and 1.03 ppb methyl butyl ketone.

carbonyl compounds is currently in progress to understand this process.

To understand the effect of a large number of polar and nonpolar VOCs on ATM selective capture of aldehydes and ketones at trace concentrations, a standard TO-15 VOC was diluted to 1 ppbv acetone, 0.98 ppbv methyl ethyl ketone, and 1.03 ppbv methyl butyl ketone with N_2 and stored in a 6 L canister. The initial pressure of the canister was 30 psi. The gas mixture flowed through the microreactor at a flow rate of 5 mL/min until the pressure of the canister reached 15 psi, and then the flow was stopped. Figure 8 shows the FTICR-MS spectrum of the preconcentrated VOCs. This result indicates that the microreactor is capable of preconcentrating ketones at the 1 ppbv level in a large number of VOCs. The calculation indicates that 97% of the acetone was captured and detected by FTICR-MS while 87% of the methyl ethyl ketone and 81% of the methyl butyl ketone were captured. The molar ratio of ATM to acetone for the amount of acetone flowing through the microreactor from the canister was larger than 100. Figure 5 indicates that 100% capture was achieved for acetone added into the He flow at an ATM/acetone molar ratio greater than 100. The difference between the capture percentages of acetone in the He flow and in the TO-15 indicates slight interference of other VOCs on the capture percentage of acetone. The capture percentages for methyl ethyl ketone and methyl butyl ketone in TO-15 were lower than that of acetone. This experiment demonstrates that the microreactor with ATM coating is promising for analysis of trace ketones and aldehydes in VOC mixtures. We have used the microreactors for preconcentration and analysis of ketones and aldehydes in exhaled breath. Ketones and aldehydes with alkyl chain length from C1 to C12 in exhaled breath were captured and detected.⁴¹ Since ATM molecules selectively react with ketones and aldehydes by the oximation reactions, the interference of other compounds in exhaled breath, including O_2 , CO_2 , H_2O , and a large number of VOCs, on the capture of carbonyl compounds can be calibrated. The FTICR-MS analysis can identify all ATM adducts.

CONCLUSIONS

A novel microreactor preconcentration approach has been developed for the analysis of trace ketones and aldehydes in gaseous mixtures. The microreactor is functionalized with the

quaternary ammonium aminoxy compound ATM for oximation reactions with ketones and aldehydes. By design, thousands of micropillars in the microreactor not only increase the contact area, but also uniformly distribute gas flow to maximize the collision probability of ATM with ketones and aldehydes in the gas phase flowing through the microreactor. Since ATM and its oxime ether adducts are positively charged, analysis by FTICR-MS is greatly improved. The preconcentration efficiency varies with the molecular weight of ketones and aldehydes and is related to the ATM/ketone and ATM/aldehyde ratios. A total of 97% of the acetone at a level of 1 ppbv in TO-15 has been captured by the microreactor. The microreactor with ATM coating may provide a new approach for analysis of trace ketones and aldehydes in ambient air and in exhaled breath.

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ACKNOWLEDGMENTS

Financial support of this research project by the University of Louisville through its Clinical and Translational Science Pilot Grant program is gratefully acknowledged. We also thank Mr. John Metaxas at the Air Quality Monitoring Laboratory of the University of Louisville for helpful discussion and for providing the TO-15 samples.

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