Sensors and Actuators B 220 (2015) 491–499

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Raman system for sensitive and selective identification of volatile organic compounds

Kelly J. Park[a,1], Constance Wu[a,2], Alison R. Mercer-Smith[a], Ryan A. Dodson[a], Tyler L. Moersch[a,3], Prakash Koonath[b], Andrew C.R. Pipino[b,4], Hsiang-Wei Lu[c], Yongwu Yang[d], Victor S. Sapirstein[d], Charles J. Taylor[a], Angelika Niemz[c,*]

[a] *Chemistry Department, Pomona College, 645 N. College Avenue, Claremont, CA 91711, United States*
[b] *Tanner Research Inc., 825 South Myrtle Ave., Monrovia, CA 91016, United States*
[c] *Keck Graduate Institute of Applied Life Sciences, 535 Watson Drive, Claremont, CA 91711, United States*
[d] *Lambda Solutions Inc., 411 Waverly Oaks Road, Waltham, MA 02452, United States*

ARTICLE INFO

Article history:
Received 8 January 2015
Received in revised form 13 May 2015
Accepted 16 May 2015
Available online 4 June 2015

Keywords:
VOC
Raman
2D correlation analysis
Polymer thin film
Biomarker
Evanescent wave

ABSTRACT

Analysis of volatile organic compounds (VOCs) for medical and industrial applications typically requires complex and expensive mass spectrometric systems to achieve the desired sensitivity and specificity. Raman spectroscopy enables specific compound identification based on distinct spectral fingerprints but traditionally has low sensitivity. We have developed a novel Raman system that provides VOC detection in the low ppm range. VOCs from the gas phase are absorbed and enriched in a thin polymer film coated on the surface of an optical sensor element. The VOC enriched polymer film is probed with evanescent wave excitation and optimized Raman signal collection. The herein described Raman sensor is low-cost, robust, readily manufacturable, and capable of providing high sensitivity without the nanostructured sensors required for surface enhanced Raman spectroscopy. To suppress background noise and interfering spectral features while improving our ability to resolve VOC mixture spectra, we applied two-dimensional (2D) correlation analysis to time series spectra acquired during VOC absorption into the polymer film. We established proof of principle through analysis of known VOC biomarkers for selected bacterial pathogens. The system enabled VOC detection with significantly higher sensitivity than commercial Raman probes. We observed good agreement between spectra of VOCs in the thin film obtained after 2D correlation analysis, and of pure VOCs using a commercial probe. Mixture spectra were further de-convoluted based on the off-diagonal peaks observable in the 2D Raman spectrum in conjunction with segmented data analysis. We anticipate that this system can be applied to a variety of medical, industrial, and biodefense applications.

1. Introduction

Analysis of volatile organic compounds (VOCs) from breath or the headspace of liquid culture, urine, blood, stool, or sputum can be used to identify pathogenic bacteria and fungi, to detect cancer cells, and to diagnose metabolic disorders [1–14]. Even though mass spectrometric techniques are the gold standard for VOC biomarker identification, these systems are complex and expensive and therefore have not emerged for routine clinical use. However, breath analyzers to determine alcohol intoxication levels [15–17], *Helicobacter pylori* infection [16,18], and airway inflammation [19–21] are routinely used in point-of-care or point-of-use diagnostic systems. These devices use electrochemistry [17,19,21] or infrared (IR) spectroscopy [15,16,18,20] to detect simple single volatile compounds, and while these systems have reduced instrumental complexity, they cannot analyze complex VOC mixtures at lower abundance. Electronic noses (eNoses) and colorimetric sensor arrays can analyze VOC mixtures at low abundance using multiple relatively non-specific chemical sensors [10,22–25].

---

[*] Corresponding author. Tel.: +1 909 607 9854; fax: +1 909 607 9826.
E-mail address: aniemz@kgi.edu (A. Niemz).

[1] Current address: Food and Drug Administration, 1 World Trade Center, Ste 300, Long Beach, CA 90831, United States.

[2] Current address: Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Old Addenbrooke's Site, Cambridge CB2 1QW, UK.

[3] Current address: Tru Vue, Inc., 2150 Airport Drive, Faribault, MN 55021, United States.

[4] Current address: Office of Naval Research, 875 N. Randolph St, Arlington, VA 22203, United States.

http://dx.doi.org/10.1016/j.snb.2015.05.093
0925-4005/© 2015 Elsevier B.V. All rights reserved.

However, eNoses measure an aggregate response to VOC mixtures, and not the mixture composition. Furthermore, eNose sensor arrays typically require elaborate calibration and cannot be readily adapted to new or revised VOC signatures.

Raman spectroscopy can identify chemical compounds with high selectivity because a unique spectral fingerprint exists for each molecule. Compared to IR spectra, Raman spectra have sharper features, enabling higher selectivity, and are more resistant to water interference. However, conventional Raman spectroscopy is not very sensitive. Sensitivity can be enhanced by many orders of magnitude using surface-enhanced Raman spectroscopy (SERS) [26–28], but SERS requires nano-structured substrates, which are fragile and difficult to manufacture in a manner that ensures reproducible results. On the other hand, evanescent wave Raman excitation can be used to analyze compounds at or near a surface with increased sensitivity by exploiting the two-photon character of normal Raman scattering, together with the surface electric field enhancement. Robust solid immersion lenses (SIL), fabricated from high refractive index sapphire or ZnSe, enable exceptionally high evanescent excitation and collection efficiency [29,30]. Compared to IR absorption, evanescent-wave Raman derives a stronger signal enhancement from total internal reflection (TIR) because the TIR electric field enhancement is approximately squared in the Raman cross-section, as both the excitation and Raman-shifted photons experience a comparable enhancement [31]. Evanescent wave TIR Raman has been employed to probe thin polymer films [30,32,33] and the structure of water near Langmuir–Blodgett films [34].

Attenuated total reflection (ATR)-IR sensors have been used to measure traces of organic compounds in water, mainly for environmental applications [35–43]. These systems employ a thin polymer film [38,40–42] or sol gel layer [39,43] to absorb organic compounds, concentrating the analyte in the evanescence sensing region, and enabling limits of detection in the low ppm and in some cases ppb range. However, these types of sensors have not yet been applied to measuring VOCs in air. Furthermore, resolving multi-component mixtures with overlapping bands in a spectrum is challenging and limits the specificity of the sensor.

Two-dimensional (2D) correlational spectroscopy is a powerful technique used to extract information about spectral bands changed by a perturbation from a plethora of spectral features insensitive to change [44,45]. It is routinely used in nuclear magnetic resonance (NMR) spectroscopy and has also been extensively applied to vibrational spectroscopy [44–48]. The correlation transform provides one dimensional (1D) spectra from which background features are effectively removed. Overlapping spectral features can be spread out in the 2D plane, permitting analysis of complex mixtures [45,46,49]. 2D-correlation Raman spectroscopy involves the collection of a set of 1D Raman spectra from a system in response to a perturbation. The collected spectra are then subjected to 2-D correlation analysis, resulting in the so-called synchronous and asynchronous spectra [45]. Sets of peaks that change during time series data acquisition with identical time constants either perfectly in phase or 90° out of phase will only have cross-peaks in the synchronous or asynchronous 2D spectrum, respectively. Most practical cases are in-between these two extremes, and thus will give rise to cross-peaks in both spectra, but with different relative intensities. In 2D spectroscopy, any spectral feature that does not change with the perturbation vanishes from the final result. 2D-correlation IR spectroscopy has been applied to study water absorption into polymer films [50,51], adsorption of small molecules at interfaces [52], and diffusion of small molecules inside polymers [53,54], but has not been applied to the types of ATR-IR sensors mentioned above. 2D-correlation Raman analysis has been used to study a wide range of compounds including small molecules, polymers, proteins, lipids, and DNA [48,55–59]. However, to the best of our knowledge, there have been no previous demonstrations of evanescent wave Raman spectroscopy on polymer films enriched with organic compounds from aqueous solution or the gas phase, and of the analysis of their spectra via 2-D correlation analysis.

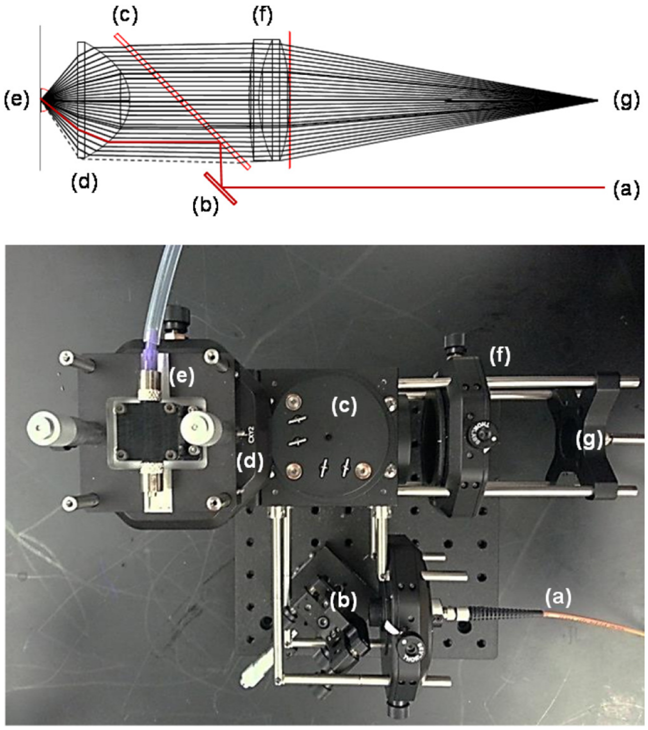

Fig. 1. Sensor optics: ray tracing scheme (top) and actual system (bottom). (a) Filtered laser light is reflected from (b) an adjustable gold mirror, and (c) a dichroic mirror, prior to being focused by (d) an aspheric lens onto (e) a ZnSe hemisphere. Scattered Raman emission is collimated by the aspheric lens, then passed through the dichroic mirror and focused by (f) an achromatic doublet onto (g) the fiber bundle that transmits the output signal onto the CCD detector in the instrument. In the actual system, the orientation of the aspheric lens and ZnSe hemisphere is rotated by 90° by another mirror so that the sensor surface is horizontal. A flow cell is mounted on top of the stage holding the ZnSe hemisphere.

In this study, we present proof of principle for a novel Raman system that enables VOC analysis from the gas phase. This system entails a robust optical sensor design using commercial off-the-shelf components appropriate for mass production. VOC enrichment in a thin polymer film, combined with evanescent wave excitation and optimized signal collection, provides sensitivity much higher than existing commercial Raman probes and comparable to similar ATR-IR sensor designs. Specific identification of individual VOCs and the ability to resolve mixture spectra are facilitated by the inherently sharp features of Raman spectroscopy, coupled with 2D correlation analysis. We anticipate that this system, once suitably refined, can be applied to different medical, industrial, and biodefense applications.

2. Experimental

2.1. Optical design

The optical system used in these studies consists of a Dimension P2 Raman spectrometer (Lambda Solutions Inc., Waltham, MA) in conjunction with a custom designed sensor with evanescent wave excitation, as described in Fig. 1. The sensor surface consists of the flat side of a 10 mm diameter ZnSe hemisphere lens (ISP optics, Irvington, NY), coated with a thin polymer film. This hemisphere was mounted above an aspheric lens (NA = 0.86, 30 mm diameter). As shown in Fig. 1 (top), the excitation laser beam is