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TECHNICAL NOTE

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Optical Detection of the Anesthetic Agent Propofol in the Gas Phase

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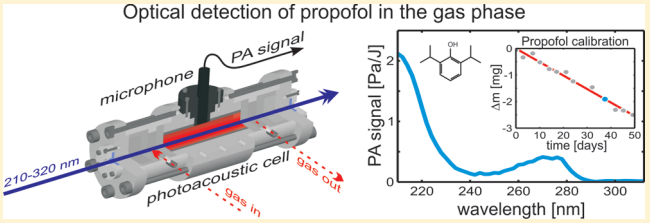
Supporting Information

ABSTRACT: The anesthetic agent propofol (2,6-diisopropylphenol) is the most widely used intravenously administered drug in general anesthesia. However, a viable online capability to monitor metabolized levels of propofol in patients does not currently exist. Here we show for the first time that optical spectroscopy has good potential to detect metabolized propofol from patients' exhaled breath. We present quantitative absorption measurements of gas phase propofol both in the ultraviolet and middle-infrared spectral regions. We demonstrate that a detection limit in the subparts-per-billion concentration range can be reached with photoacoustic spectroscopy in the UV spectral region, paving the way for the development of future optical monitors.



Every year over 100 million people undergo surgery, mostly performed under general anesthesia.[1] In the vast majority of cases, anesthesia is induced with an intravenous anesthetic drug and then maintained with gaseous anesthetic agents, which are inhaled as vapors. This situation is changing however, as it is becoming increasingly popular to use intravenous drugs, such as propofol, for both induction and maintenance of anesthesia and so dispense with vapors—known as the "total intravenous anesthesia" (TIVA) technique. The clinical advantages of doing so, although not clear-cut, include a perception of reduced postoperative nausea and vomiting and improved recovery times.[2] Another factor influencing the increased use of TIVA with propofol is a concern that inhalational anesthetics adversely affect cognitive abilities in the short term and possibly permanently.[3,4] Furthermore, recent studies have linked inhalational anesthetics to an increased propensity for amyloidal plaque formation in the brain, which might accelerate the onset of neurodegenerative disease, such as Alzheimer's.[5,6] In contrast, there is little or no evidence that such problems are associated with propofol.[5]

One major disadvantage of a TIVA technique is the difficulty that physicians have in judging the depth of anesthesia: because the inhalational anesthetics are administered at high concentrations (several percent by volume) their uptake by the patient is easily measured using standard infrared absorption spectroscopy[7] and the depth of anesthesia can be estimated from the exhaled vapor concentration.[8,9] This is not the case with TIVA: clinicians use mathematical algorithms validated in studies of healthy volunteers to estimate serum and brain propofol concentrations of the drug rather than direct measurement, or brain function monitors based upon the electroencephalogram whose accuracy is under active debate.[10−12] There are several models and a great deal of discussion about which is most effective; that none is entirely accurate is reflected in the fact that patients undergoing TIVA may be at increased risk of awareness during surgery.[13−15] Propofol is also one of the most commonly used drugs for sedating patients in intensive care units, where vapors are not used.[16] In the absence of algorithms to estimate serum or brain concentrations in the critically ill, clinicians rely on blunt end points such as numeric descriptive scales to estimate depth of sedation.[17] Inadequate sedation can result in recall of events and post-traumatic stress disorder, and oversedation can cause low blood pressure, reduced cardiac output, and immune suppression: all of which are highly undesirable for patients and reduce their chance of survival and subsequent quality of life.[18]

The ability to monitor metabolized drug levels would be strongly desirable to assess the depth of anesthesia and permit the optimal tailoring of drug dosage to a patient's individual

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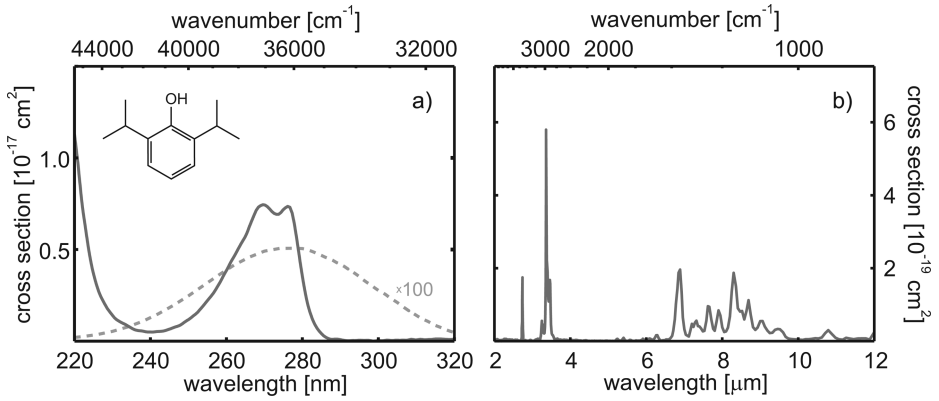

Figure 1. (a) UV absorption cross section of gas phase propofol obtained at atmospheric pressure and 45 °C. The molecular structure of propofol is shown in the top left corner. The spectral resolution corresponds to 0.1 nm. The UV cross section of acetone, multiplied by a factor of 100, is also shown for reference (dashed line). (b) Mid-IR absorption cross sections of propofol diluted in nitrogen obtained using FTIR spectroscopy. The sample was contained in a 5 m long cell heated to 150 °C. The spectral resolution corresponds to 7.7 cm $^{-1}$.

needs but is a much more difficult task compared to inhalational anesthetics.[14,15] Techniques such as liquid and gas chromatography and mass spectrometry have been used in hospitals to measure propofol concentration in the blood of patients undergoing surgery or in intensive care. Although displaying excellent sensitivity and selectivity, such instrumentation is too expensive and complex for routine clinical usage. Despite recent advances in the detection of low concentration analytes in liquid samples by optical absorption techniques,[19] a direct measurement of propofol concentrations in the blood is not viable, due to the low prevailing concentrations and substantial interference from multiple background species. Recently, an indirect determination method was demonstrated, which makes use of coloring reagents, a disposable functionalized polymer biochip and an optical absorption measurement at 655 nm.[20] The biosensor was shown to have good sensitivity and specificity for detecting propofol from blood samples but cannot be used in situ during surgery because it requires blood sampling followed by sample pretreatment and features a relatively long response time of 60 s.

Detection of propofol via exhaled breath is an attractive alternative approach and has been accomplished off-line by mass spectrometry,[21−27] but quantification of metabolized propofol is very challenging with estimated concentration levels in the exhaled breath in the parts-per-billion (10^{-9}, ppb) range.[22−26] A sensor for exhaled propofol that is quantitative, fast, economical, and rugged for use in clinical environments does not currently exist. Optical spectroscopy has the potential to make progress toward this goal, and in different contexts, its potential for online monitoring of exhaled breath has already been demonstrated.[28−30] So far, however, there have been no reported studies on the optical detection of propofol in the gas phase. We address this issue in the current work and present the first quantitative measurements of absorption cross sections of gas phase propofol in both the mid-infrared (mid-IR) and near-ultraviolet (UV) spectral regions with a view to establishing optimal detection strategies. While measurements in the mid-infrared spectral region suffer from strong interference by other species present in breath, we show that photoacoustic spectroscopy performed in the UV spectral region is a viable approach for the quantitative detection of propofol at the ppb level. This appears compatible with the requirements for clinical diagnostics of metabolized propofol from patients' breath.

EXPERIMENTAL SECTION

Absorption spectra were quantified both in the UV and mid-IR spectral regions. The photochemistry of liquid propofol in the UV was subject of a previous study,[31] and the IR spectrum of gaseous propofol is available online;[32] however, quantitative absorption cross sections for gas phase propofol are currently not available. Figure 1 shows the wavelength dependent UV and mid-IR absorption cross sections obtained by direct absorption measurements in a temperature stabilized, propofol containing cell. In Figure 1a, the electronic absorption spectrum of propofol is shown for the wavelength range spanning 220−320 nm. The measurement was performed in an air filled absorption cell containing a small amount of propofol held at 45 °C and atmospheric pressure. Under these conditions, the saturated vapor pressure of propofol is 18 Pa, resulting in a mixing ratio of 180 ppm.[33] Two $\pi-\pi^*$ transitions stemming from the aromatic part of the propofol molecule contribute significantly to the observed absorption feature between 250 and 290 nm; the maximum absorption cross sections is ca. 7×10^{-18} cm^2 molecule^{-1} at 270 nm and is in good agreement with the previous absorption studies in the liquid phase.[31] In addition, the absorption cross section of acetone over the same wavelength range is also shown (magnified by a factor of 100) as it represents the dominant interfering species in exhaled breath (see Discussion). The mid-IR spectrum of propofol (see Figure 1b) was measured using a commercial temperature-controlled Fourier transform infrared (FTIR) spectrometer (Gasmet Dx4000, Gasmet Technologies Ltd.). The feature around 3700 cm^{-1} is due to the O−H stretching vibration, and those observed near 3000 cm^{-1} stem from C−H stretching in the isopropyl group (see molecular structure on inset of Figure 1a). There are further contributions in the 1000−1500 cm^{-1} range arising from several C−C and/or C−H stretching and bending modes associated with the isopropyl and aromatic groups.

For sensitive measurements of trace concentrations of propofol, we used photoacoustic spectroscopy (PAS) exploiting the 260−280 nm UV absorption band (cf. Figure 1a). PAS is based on the detection of sound waves generated through the absorption of modulated light by the sample.[34] Radial pressure waves were excited in this way in a photoacoustic (PA) cell with 24 mm inner diameter using the frequency-doubled and tunable output from an optical parametric oscillator laser (OPO; NT342/1/UVE,

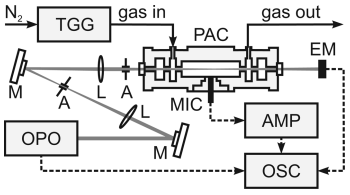

Figure 2. Schematic of the photoacoustic setup for the measurement of propofol at trace concentrations, comprising trace gas generator (TGG), mirror (M), lens (L), aperture (A), photoacoustic cell (PAC), microphone (MIC), meter for laser pulse energy (EM), excitation laser (OPO), microphone amplifier (AMP), and oscilloscope (OSC).

Ekspla Ltd.) which was pulsed at 10 Hz. The setup is depicted in Figure 2. The PA cell was equipped with acoustic filters to minimize the coupling of acoustic background noise into the resonant modes of the cell, thus improving the achievable signal-to-noise ratio. The PA signal was detected with a condenser microphone (BK Type 4192, Brüel & Kjær) and preamplified and filtered (2670, Brüel & Kjær, and SR650, Stanford Research System Inc.). The PA spectrum of propofol was measured by scanning the laser wavelength in 2 nm steps from 210 to 310 nm. At each wavelength position a total of 1000 PA pulses were averaged and recorded on an oscilloscope (Waverunner6100A, LeCroy Co.). Following every laser pulse, the PA signal was sampled for 20 ms resulting in a total sampling time of 20 s per wavelength step.

RESULTS AND DISCUSSION

For clinical relevance a propofol detection limit of 50 ppb or better must be reached by any online diagnostic method. In principle this could be achieved in the mid-IR spectral region shown in Figure 1b by using multipass absorption spectroscopy[35] or cavity enhanced spectroscopy,[36,37] which routinely reach sensitivities in the range 10^{-8}–10^{-9} cm^{-1}. However, we performed both FTIR measurements and simulations of spectra from potentially interfering species present in the exhaled breath gas matrix and found significant overlap with spectra from water, acetone, isoprene, and CO_2 (see Supporting Information Figure S1). For example, an H_2O concentration of 5% will lead to absorptions several orders of magnitude larger than those from propofol in the breath matrix, such that H_2O interference could pose problems even in ultradry samples. Acetone, present at 0.3 to 1 ppm mixing ratio in the breath of both healthy subjects and patients suffering diabetes, is also a major problem in this region, as its spectrum overlaps almost completely with that of propofol and the absorption cross sections are comparable. In contrast, we found that only acetone appears to be significantly interfering with propofol signatures in the UV spectral region (see Figure 1a) where its absorption cross section is around one-hundredth that of propofol.[38] No significant interference was found from CO_2, isoprene,[39] and H_2O in the 260–280 nm region at concentrations relevant for clinical diagnostics. The relative spectral signatures of 10 ppb propofol and 1 ppm of acetone would scale in the ratio as displayed in Figure 1a, meeting the requirements for an online diagnostic, if spectral unmixing methods are employed and/or independent measurements of acetone concentrations are performed, e.g., at 300 nm where there is no significant absorption by propofol, see Figure 1a. We therefore pursued this option further and performed high

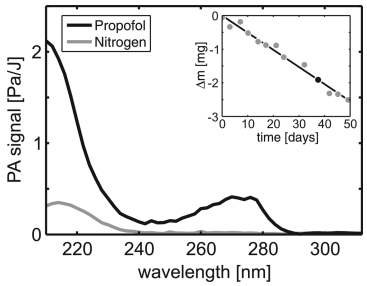

Figure 3. Photoacoustic spectrum of propofol present at 50 ± 5 ppb mixing ratio (black line). The gray line shows the background spectrum acquired from a nitrogen filled PA cell. The spectra contain 52 wavelength data points. The signal-to-noise ratio of 420 at 270 nm yields a detection limit (SNR = 1) estimate of 0.12 ± 0.02 ppb. (inset) Relative mass loss of the permeation tube as a function of time. The black dot indicates the time point corresponding to the PA measurement shown.

sensitivity measurements of propofol in the near UV spectral region with photoacoustic spectroscopy (PAS).

PAS is an ultrasensitive, "zero baseline" absorption technique, that has potential for use in operating theater using compact and rugged devices. A PAS spectrum of 50 ppb gaseous propofol is shown in Figure 3. Mixing ratios of propofol in the ppb range were generated with a trace gas generator (OVG-4, Owlstone Ltd.). For this purpose, liquid-phase propofol (97% purity, Alfa Aesar) was sealed inside a Teflon tube. Gas phase propofol subsequently diffuses through the Teflon tube wall into the pure nitrogen carrier gas (N_2, 99.999% purity, AGA Ltd.), flowing at 0.11 standard L min^{-1} through the trace gas generator and PA measurement cell. The mixing ratio of propofol in N_2 was determined by monitoring the mass loss of the Teflon permeation tube upon escape of propofol. The permeation tube was temperature stabilized at 80 °C and weighed regularly over a period of two months (see the inset of Figure 3). For the background measurement, the PA cell was flushed with pure N_2.

The resonance frequency of the first radial acoustic resonance of the PA cell and the corresponding quality factor were 18.7 kHz and 370, respectively. The temporal width of the laser pulses are short (10 ns) allowing the excitation of a broad range of acoustic resonance frequencies up to about 100 kHz. The spectral width of the laser is 5 cm^{-1} corresponding to 0.04 nm at 270 nm. Any variations in the quality factor and resonance frequency as well as laser pulse energy were accounted for by using previously reported normalization methods.[40] Due to the relatively high acoustic resonance frequency, the background noise level (6 μV rms) was dominated by electronic noise. With a laser pulse energy of 0.6 mJ at 270 nm and an acquisition time of 20 s, a signal-to-noise ratio (SNR) of 420 was obtained. Taking the uncertainty in the propofol mixing ratio into account, we estimate a detection limit of 0.12 ± 0.02 ppb for propofol in an N_2 matrix, well within the required sensitivities of a few tens of ppb.

We note however that the gas matrix can affect the PA signal by changing the nonradiative decay pathways and the gas matrix effects in breath samples are subject of future investigation. We verified that PA experiments on propofol are not adversely affected by the presence of water vapor and CO_2 at concentrations up to 5%. Acetone is a potential interfering species in this particular spectral range; however, as shown in Figure 1a, the absorption cross-section of acetone is just over one hundred times weaker than that of propofol and the spectral overlap is not

complete—the acetone spectrum has significant absorption toward the long wavelength edge of the propofol spectrum. Therefore, it can be envisaged that acetone could be measured independently by using UV laser excitation in the 290−320 nm region where propofol shows no absorption. Furthermore, it has been shown that the phase information within a PA signal can be used to separate chemical species even in the case of overlapping absorption spectra if their respective nonradiative decay times differ.[41] Finally, in clinic a baseline can be established from an exhaled breath sample from the patient prior to drug administration, which contains no propofol but only acetone; we emphasize however that acetone levels, which will show large interindividual variation, will also have to be monitored during any clinical procedure as they may change over the period of an operation.[42] To minimize possible artifacts arising from condensation of propofol onto the walls of the gas inlet line and inside the PA cell, both the inlet line and cell were heated and maintained at 60 and 50 °C, respectively. To check for such artifacts, the PA signal was measured as a function of inlet line and PA cell temperature, while keeping the sample concentration constant. Over a range from 25 to 60 °C, the amplitude of the PA signal remained constant to within ±5%, suggesting that condensation effects had a minimal influence on the measurements. Moreover, at the used mixing ratio of 50 ppb, the partial pressure of propofol was well below saturation levels, such that major sample condensation could not occur.

The noise equivalent absorption coefficient of the PA setup was 2×10^{-8} cm^{-1} which could be further improved, e.g. through use of a more powerful laser for excitation. On the other hand, UV microchip lasers would offer the additional advantage of higher repetition rates for sampling, reducing the dead time between signal sampling intervals. This technical note demonstrates that optical detection of gas phase propofol is feasible at concentrations in the ppb range. Absorption cross sections of the molecule were quantified in the UV and mid-IR spectral regions, and photoacoustic spectroscopy used to detect propofol in an N_2 carrier gas at ppb level concentrations. The results show that concentration levels corresponding to metabolized propofol in the exhaled breath can be detected by optical means, paving the way for the development of clinical breath sensors.

■ ASSOCIATED CONTENT

Supporting Information. Supplementary Figure 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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