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Nanosensor Device for Breath Acetone Detection

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This paper describes a sensor nanotechnology suitable for non-invasive monitoring of a signaling gas, such as acetone, in exhaled breath. This is a nanomedicine tool comprised of a selective acetone nanoprobe working on the principle of ferroelectric poling sensing, and a microelectronics circuit for comparing the actual sensor signal to a predetermined threshold value, displaying the result using LED signals. This on/off type non-invasive diagnostics platform technology is based on nanotechnology, gives a fast response, it is simple to operate and inexpensive to manufacture, and may truly revolutionize personalized medicine.

Keywords:

1. INTRODUCTION

Hippocrates of Cos in the 5th century B.C. used the smell of a patient's breath as a diagnostic medium, coining terms such as *fetor hepaticus* that survives to this date in the medical nomenclature (describing a condition involving liver failure). It took many centuries and the renowned chemist Linus Pauling in the 1970's to advocate orthomolecular medicine (i.e., relation of contents of human fluids to a healthy state of the body and mind) and to study the content of exhaled human breath in a first attempt to correlate physiological and metabolic processes to the compounds released from one's mouth.[1] The plethora of gaseous components and condensates found in breath are still being characterized nowadays by many workers in science and medicine. Only a few of the gas constituents are already known to be signaling metabolites or disease biomarkers.[2] Among them, nitric oxide, carbon dioxide, ammonia, isoprene are or can be used to monitor conditions from asthma to oxidative stress, from renal failure to blood cholesterol levels, in a non-invasive way. Selective solid-state gas sensing nanoprobes have been prepared and used by our group to detect NO, ammonia, CO_2, etc. at levels in the low ppb range; Breath analyzer prototypes utilizing them have been demonstrated.[3–4]

Our group recently synthesized a novel nanocrystalline polymorph of tungsten trioxide with unique ferroelectric character, by means of scalable rapid solidification processes.[5] This nanophase is stabilized for use at elevated temperatures, and it was employed to detect a polar gas, acetone (a biomarker for type I diabetes) with extreme specificity in simulated breath samples.[5] Acetone detection using chemoresistive sensors was reported before. For example, Ryabtsev et al.'s Fe_2O_3, SnO_2 CdO sensors[6] showed sensitivities less than 5.2 to 10 ppm acetone but no testing for selectivity was reported. The sensitivity of Li et al.'s WO_3 hollow-sphere gas sensors was only 3.53 to 50 ppm acetone.[7] Zhu's et al.'s TiO_2-doped ZnO thick film had cross sensitivity to many other VOCs.[8] Teleki et al.'s TiO_2 nanoparticles showed cross sensitivity to isoprene.[9] Khadayate et al.'s WO_3 thick film showed a 4.5 value of gas sensitivity to 50 ppm acetone (the only gas tested).[9]

Similarly, metal oxide sensors reported in other works[10–13] either lacked satisfying sensitivity to low concentrations of acetone or showed cross sensitivity to other gases. Compared to the literature, the ε-WO_3-based nanosensor that our group has developed offers the advantage of both high sensitivity and good selectivity, which is a breakthrough in acetone detection.[14]

This paper focuses on the use of ε-WO_3 nanoprobes in the development of a breath analysis prototype for the detection of acetone in a single breath sample, i.e., a non-invasive diagnostic tool for the monitoring of diabetes. This is a platform technology (integrated breath collector, gas sensor-breath analyzer unit-display in a single hand-held device) and it may use various selective resistive

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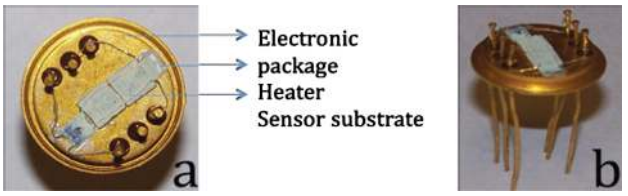

Fig. 1. Key component of the breath analyzer: sensor and heater assembly: (a) top view; (b) side view.

nano-chemosensors for early detection, and monitoring of disease (i.e., it is a nanomedicine tool).

2. EXPERIMENTAL METHOD

The fabrication of Cr-WO_3 nanopowders for use in this study has been reported elsewhere.[5, 14] 10 at% Cr-doped WO_3 nanoparticles, with 80% ε-WO_3 phase content were used to prepare resistive sensors. The sensor materials were deposited onto a home made Pt-electrode coated alumina substrate (3 mm × 3 mm). One sensor or two parallelconnected sensors are adhered to a commercial heater (M1020, Heraeus Sensor Tech.). The heater, whose temperature is controlled by the voltage applied on it, is able to heat the sensor up to 500 °C. This sensor/heater pair is the key component of breath analyzer. It is connected with a transistor outline (TO-8) header (SCHOTT North America Inc.), which is ready to be integrated into the device. Sensing tests were carried out using the gas flow bench facilities of CNSD and the procedure described in Ref. [14].

3. RESULTS

Table I below tabulates all the data from the cross-sensitivity studies of the nanostructured sensor to a variety of gases (acetone, ethanol, methanol, NO, NO_2, ammonia, CO, ethane, isoprene, and isopentane, all being relevant to the signaling metabolites found in exhaled breath) in three different concentrations: 200 ppb, 500 ppb and 1 ppm.

Table I. Dipole moments and sensitivities of 10 at% Cr-doped WO_3-based resistive sensors to different vapors.[14]

		Sensitivity		
Gas	Dipole moment	0.2 ppm	0.5 ppm	1 ppm
Acetone	2.88D	1.55	2.05	2.90
Ethanol	1.69D	1.08	1.15	1.32
Methanol	1.70D	1.03	1.10	1.23
NO	0.159D	1	1.05	1.09
NO_2	0.316D	1	1.04	1.07
NH_3	1.471D	1.02	1.03	1.05
CO	0.112D	1	1	1
Ethane	0	1	1	1
Isoprene	0.25D	0.26	1.53	1.84
Isopentane	0.105D	1.04	1.16	1.33

The sensing mechanism that enables the selective acetone detection is discussed in the next section and it appears to involve a type of ferroelectric poling mechanism. The nanostructuctured sensor is linear in the detection range of interest to diabetes monitoring (see Fig. 2: relationship between acetone concentration and ε-WO_3 from 0.2 ppm to 2.0 ppm). The concentration of acetone in exhaled human breath normally falls within this range.[15] In particular, at 1.8 ppm, which is set as diabetes diagnosis threshold, the sensitivity is 4.3. This value is used in the breath analyzer design.

There is an approximately linear relationship between gas concentration C and sensor sensitivity S in Figure 2, which can be expressed as:

$$S = 1.1.9 + 1.68C \quad (1)$$

The unit of C is ppm and S is normalized sensitivity (R_0/R_g). This equation could be used to estimate the concentration of acetone according to the resistance change of the sensor. However, it is only an empirical formula and could only be used within the range of 0.2 ppm to 2 ppm.

The basic concept of the sensing device is to compare the resistance of the sensor material to a comparative resistor. The resistance of this comparator is determined by a pre-assumed biomarker concentration threshold in the human breath for certain disease diagnosis as well as the behavior of the sensing material. The sensing material's resistance is determined by the actual biomarker concentration. Assuming the biomarker is a reducing gas, if this resistance is lower than that of the resistor, the actual concentration of the biomarker is then higher than the threshold, which implies that the subject/patient has a high probability to be afflicted with a given disease/suffer metabolic malfunction. The comparison result is manifested by the LED indication.

Figure 3 shows the photograph of the manufactured prototype. The dimension of the prototype is

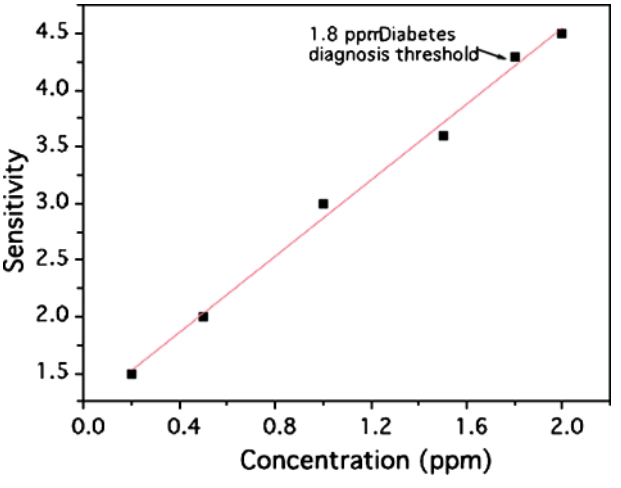

Fig. 2. Relationship between acetone concentration and sensitivity.

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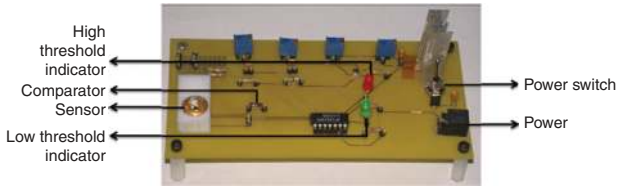

Fig. 3. Designed portable device for disease diagnosis.

15 cm (L) × 7.5 cm (W) which meets the requirement for "portability." The bottom-left part is the sensor. It is isolated from the environment by a specially designed chamber made out of Teflon. A channel with a mouthpiece allows the human breath or controlled gas flow to go through the chamber and interact with the sensor (not shown).

The response time of the device is 20 seconds. At 1.8 ppm acetone exposure, the resistance lowers down to around 3.5 MΩ which was set as the lower threshold value of the analyzer. The upper threshold was set to 20 MΩ a little higher than the sensor's baseline value. Then we introduced increasing concentrations of acetone into the chamber by adjusting the gas flow coming from each gas cylinder. From, 500 ppb to 1 ppm, then 1.5 ppm, no change on the device was observed. The green light turned on when the concentration was further raised to 1.8 ppm. This means that this device only responds to 1.8 ppm or higher concentrations of acetone gas, as required for diabetes diagnosis.

In order to validate the selectivity of the gas analyzer, several types of other gases were introduced which are common in human breath, including NO, NH_3, CO, ethanol, methanol, and ethane. The sensor did not show any response to NO, NH_3, CO, ethane up to 10 ppm, which is much higher than the respective gas concentrations found in exhaled human breath. The device did not show any response to ethanol and methanol up to 3 ppm. However, higher concentrations turned the green LED on. As elevated levels of ethanol and methanol levels are usually associated with alcohol ingestion and fruit consumption[16] the subject should avoid consuming alcohol or eating fruits prior to testing.

4. DISCUSSION

Acetone is a reducing gas (that is when a *n*-type semiconducting oxide is used as a sensing element, the presence of acetone will result in lowering it's electrical resistance).

The sensing mechanism os acetone by semiconducting metal oxides typically involves physisorption, chemisorption, and electron transfer processes. Since W^{6+} and Cr^{6+} ions are strong Lewis acids, they tend to easily adsorb acetone molecules which is a Lewis base:[17–19]

$$(CH_3)2C{=}O(g) + W^{6+}(s) \rightarrow (CH_3)2C{=}O \rightarrow W^{6+}(a) \quad (2)$$

In this and the following equations, g means gas molecules; s means surface state; a means adsorbate species.

Surface acetone reversibly transfers to its isomer, enolate, which can react further with another acetone molecule to yield mesityl oxide:[17–18]

$$(CH_3)2C = O \rightarrow W^{6+}(a) \leftrightarrow CH_2{=}C(CH_3)OH \rightarrow W^{6+}(a) \quad (3)$$

$$CH_2 = C(CH_3)OH \rightarrow W^{6+}(a) + (CH_3)2C{=}O(g) \rightarrow (CH_3)2C{=}CH{-}C(CH_3){=}O \rightarrow W^{6+} + H_2O \quad (4)$$

Chemisorption and accompanying electron transfer occur afterwards, as described in Ref. [19]:

$$(CH_3)2C = O \rightarrow W^{6+} + W{-}O{-}(s) \rightarrow (CH_3)2C \downarrow O - W \uparrow O{-}W(a) + e^- \quad (5)$$

$$CH_2{=}C(CH_3)OH \rightarrow W^{6+} + W{-}O{-}(s) \rightarrow CH_2{=}C(CH_3){-}OW(a) + HO{-}W(a) + e^- \quad (6)$$

The above reaction processes still cannot explain the selectivity to acetone. Recently, attention has been paid on the surface chemistry of ferroelectric materials. Research based on $LiNbO_3$ and some other materials has shown strong evidence that the dipole moment of a polar molecule may interact with the electric polarization of some ferroelectric domains on the surface.[20–22] This interaction would then increase the strength of molecular adsorption on the material surface. Here, it is suggested that the acentric structure of ε-WO_3 plays an important role on the selective detection of acetone. The ε-WO_3 is a type of ferroelectric material that has a spontaneous electric dipole moment. The polarity comes from the displacement of tungsten atoms from the center of each [WO_6] octahedra. On the other hand, acetone has a much larger dipole moment than any other gas (see Table I). As a consequence, the interaction between the ε-WO_3 surface dipole and acetone molecules could be much stronger than any other gas, leading to the observed selectivity to acetone detection.

Ethanol and methanol gases have lesser dipole moments than acetone and the sensitivities to these two gases are lower than acetone but higher than most other gases. NO, NO_2, CO and ethane have very small dipole moments and ε-WO_3 is inert with these gases. Exceptions are NH_3, isoprene and isopentane gases. The dipole moment of NH_3 is comparable to ethanol and methanol, but ε-WO_3 is not sensitive to this gas at all. In contrast, isoprene and isopentane exhibit rather weak dipole moments, but ε-WO_3 has some interaction with these two gases, esp. isoprene. Further studies are needed to elucidate the actual sensing mechanism involved. Overall, the extremely low cost, the

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rapid response of the oxide detector, the reversibility of it's response, the ease of integration with microelectronics circuitry, and the device stability are unique features of this nanosensor technology. Moreover, it's most important feature is that it simply involves a single breath exhaling into a mouthpiece; a reading of the sensor resistance change being translated to gas concentration (which can also be displayed either on the breathanalyzer unit or wirelessly transmitted for remote monitoring). There is no need for complex signal processing or pattern recognition This is a true nanomedicine application.

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