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Development of a colorimetric sensor Array for the discrimination of aldehydes

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ABSTRACT

A brand-new colorimetric sensor array was developed based on cross-reactive mechanism to discriminate 9 kinds of aldehydes and 16 volatile organic lung cancer biomarker candidates in low concentration. Sixteen out of twenty-seven dyes were selected to mix with 2,4-dinitrophenylhydrazine (DNPH) in optimized concentration to serve as specific sensing elements, and polyethylene glycol-1000 was chosen from four kinds polyethylene glycols to act as stabilizer. Resultant sensor array shows improved response (about tenfold higher) to aldehydes than former study, and exhibited very good selectivity in low concentration ranging from 40 ppb to 10 ppm with the presence of interfering counterparts. Data analysis was performed by both hierarchical cluster analysis (HCA) and discriminant analysis (DA), which demonstrates the excellent discrimination ability of the sensor to structurally similar aldehydes related to lung cancer. Besides, formaldehyde-spiked air samples were analyzed with developed sensor array, suggesting promising utilization potentiality to monitor such toxic gas. Theoretical detection limit was down to 8.2 ppb with a liner range from 10 ppb to 150 ppm. The sensor array can be further developed for early diagnosis of lung cancer as well as monitoring of domestic and industrial formaldehyde pollution.

1. Introduction

Volatile aldehydes are among the most common source of pollution in daily life due to their widespread presence in a plenty of chemical additives, industrial processes and incomplete combustions [1]. Acknowledged as an important components of toxic substances, aldehydes can be widely found in environmental atmospheres [2], industrial materials [3], alcoholic beverage [4], as well as human metabolites [5–7], which testify their significance in environmental, industrial and biological applications. In the area of environmental monitoring, formaldehyde poses a great threat to human health. It can lead to intensive irritant reactions of eyes and mucous membranes, and probable human carcinogen [8,9]. In view of its widespread use, toxicity and volatility, it is therefore highly problematic as an indoor pollutant. Related organizations thus banned it from use in certain applications (such as processing systems, preservatives for liquid-cooling, and antifouling products), and set the maximum allowed concentrations. The safe-exposure standard set by the World Health Organization is 80 ppb averaged over 30 min. While the permissible exposure limit (PEL) set by Occupational Safety and Health Administration (OSHA) is 750 ppb and the immediately dangerous to life or health (IDLH) limit is 20 ppm [10].

Besides, there is an increasing interest concerning the role of volatile aldehydes as biomarker in biomedical field. According to previously studies, there is a significant difference in the composition of volatile organic compounds in human breath and other metabolites. Discrimination of those volatile biomarkers would undoubtedly provide a non-invasive alternative for the diagnosis of lung cancer. Despite controversial debate in accurate VOCs biomarkers, partially due to exogenous interferences and individual difference, it is highly convinced that volatile aldehydes are very likely to be among lung cancer biomarkers [11]. For example, solid-phase micro-extraction–gas chromatography–mass spectrometry method had been utilized for the determination of endogenous hexanal and heptanal in urine samples [12]. The results demonstrated that hexanal urinary concentrations in cancer patients were slightly higher than those found in control group ones. Hexanal and heptanal have also been measure in serum samples, which suggested that their concentration levels in the samples of lung cancer patients were sharply higher than those in healthy people [6]. In addition, it was also found that the levels of C3–C9 aldehydes in exhaled breath were increased in the non-small cell lung cancer (NSCLC) patients without slight effect of smoking habits and age

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[7]. So that straight aldehydes might be better biomarkers associated with NSCLC than other VOC patterns. Since the concentration of volatile aldehydes as toxic pollutant and cancer biomarkers are extremely low, normally several ppb to a hundred ppm, detection of aldehyde at very low concentration level is of great importance for both environmental surveillance and biomedical diagnosis.

A plenty of techniques and methods have been devised for the detection and measurement of gaseous aldehyde. Traditionally, aldehydes can be analyzed by standard techniques such as liquid chromatograph [4,13], gas chromatograph [3,12], and electrochemical techniques [1,14]. Based on large instrumentation, those methods do offer very good choices and fine results to analyze this group of compounds. However, despite high sensitivity and good reproducibility, above-mention method all involves unavoidable drawbacks like expensive and cumbersome operations and also time-consuming procedures, which is adverse for real-time and field use. There are also inexpensive techniques including colorimetric or fluorometric methods with the application of pigments, and so forth [2,15,16]. But lack of sensitivity greatly hinders those methods from wide application. Moreover, they also need a relatively long detection time and boring steps to get final results. Thus, there still remains a pressing need for the development of a sensitive, rapid, inexpensive and facile method for aldehyde detection.

In the past decades, there is an ever-growing interest in the study on the diagnosis of lung cancer by analysis of VOCs in human breath for that it is non-invasive, easy to handle and time-saving [17]. MS techniques (whether or not coupled to chromatographic equipment) provide a reliable method for the determination of mixtures of VOCs and semi-VOCs in different human metabolites [18]. But high-cost and expert interpretation greatly hinders them from wide application and also prolongs the research period. Therefore, many researchers prefer to techniques involving smaller, less expensive equipment, which is simple to handle and able to be miniaturized, particularly sensors or sensor arrays [19,20]. Outstanding studies include polymer-coated surface acoustic wave sensors [21], coated quartz crystal microbalance sensors [22], gold nanoparticles sensor array [23], and also colorimetric sensor array [24]. Selective of semi-selective electrochemical sensors have been proved to be a good choice for breath analysis [25], and after signal compensation it can largely reduce the influence resulted from humidity fluctuation [26]. Yet there are still challenges to develop such sensor systems to deal with various confounding factors in real-world analysis [27,28]. Since VOCs can be influenced by various internal and external factors such as individual physical conditions (age, respiration rate, nutritional status and so on), smoking circadian rhythm, and composition of environmental air, definition of normal composition and ranges of single VOCs in human breath gas remains a tricky problem [29]. Therefore, sensor systems mentioned before all involve the same limitations, that is, they are focused on the overall composition of the VOCs in the metabolites thus lose the specificity of each VOCs marker, which would definitely restrict the selectivity of the sensor and result in false positive/negative discrimination. Accordingly, by comparing the presence/absence of each experimentally validated VOCs in the LC states relative to the control states, most of possible VOC lung cancer biomarker candidates can be divided into seven compound families: hydrocarbons, alcohols, aldehydes, ketones, esters, nitriles and aromatic compounds [11,30]. A feasible strategy to solve above-mentioned problem is to develop specialized sensors for each biomarker family members and then integrate separated sensors to a sensor system. In view of this thought, we employed colorimetric sensor array as detection technique, and firstly chose aldehydes and then other VOC family as biomarkers to design the sensor, which might lead to breakthrough in this research area.

Accordingly, since colorimetric sensor array systems are broad-spectrum sensors, overfitting, which is mainly resulted from sensor dots that are widely responsive, of the training data set poses a big problem [27]. In view of this problem, a feasible way is to improve the selectivity of each sensor dot in the array to selected volatile biomarker. Given that most aldehyde can be easily derivatized with many colorimetric reagents, it is possible choose aldehydes as target biomarker to carry out visual colorimetry, and allows easy measurements [15]. A good case in study is an early report of a highly sensitive colorimetric method for fast formaldehyde detection [10]. Using amine-terminated PEGs as specific agent to create a reactive matrix, a simple pH indicator array was applied to detect the change in basicity upon the reaction of a non-volatile primary amine with formaldehyde. It eventually gave a detection limit down to 50 ppb within 10 min. Nevertheless, apart from its great success in formaldehyde detection, the sensor array cannot response to aldehydes with longer carbon chain or molecular weight. Therefore, it can be hardly utilized for longer-carbon-chain aldehydes detection in biomedical application. Herein, we fabricated a more sensitive sensor array using DNPH as aldehyde-specific sensing elements and polyethylene glycol-1000 as stabilizer. The sensor showed very good selectivity and sensitivity towards aldehydes among other VOCs lung cancer biomarker candidates. It can also discriminate nine kinds of C1–C7 aldehydes in low concentration ranging from ppm level to ppb level, using Hierarchical Cluster Analysis (HCA) and Linear Discriminant Analysis (LDA). Besides, formaldehyde-spiked air samples were also analyzed with as-prepared sensor array, exhibiting very low detection limit and good linear range. The sensor array would provide an efficient tool for early diagnosis of lung cancer, and monitoring of domestic and industrial formaldehyde pollution.

2. Material and methods

2.1. Chemicals and preparation of stock solutions

Four porphyrins were obtained from Frontier Scientific (Logan, UT, USA), and the other indicator dyes (listed in table S1) were supplied by Sigma–Aldrich (St. Louis, MO, USA). Porous hydrophobic membrane used for dye staining was bought from Milli-pore Co. Ltd. (Bedford, MA, USA). 2, 4-dinitrophenylhydrazine (DNPH), polyethylene glycol-400 (PEG-400), polyethylene glycol-800 (PEG-800), polyethylene glycol-1000 (PEG-1000), polyethylene glycol-4000 (PEG-4000), aldehyde solutions, and other gas solutions were purchased from Jinchun Industry Co., Ltd. (Shanghai, China). All the other chemicals are of analytical pure and used without further purification. Ultra-pure water was generated by a Millipore Direct-Q Water system (Molsheim, France).

Accordingly, the reaction between aldehyde and DNPH is catalyzed by acid [31]. At high acid concentrations the carbonyl group of aldehyde is activated by the acid but at lower acid concentrations, or in basic solutions, the carbonyl group becomes less reactive, which hinder aldehyde from dehydration to the hydrazones. Although $HClO_4$ has been frequently used as catalyst to derivatize aldehydes, we use H_2SO_4 instead for the sake of stability of resultant solution. Typically, 0.4 g DNPH was added to a mixed solution of 3 mL water and 10 mL ethanol, and then 2 mL concentrated sulfuric acid was added dropwise. The solution was stirred for 10 min and then went through filter paper to obtain a yellow DNPH store solution. For prophyrin solution, 10 mg dye was added into 3 mL DMF solution and stored in dark place before use. Water solutions were used instead for alizarin and nitrazine yellow while all the other dye solutions were prepared using ethanol solution with the same concentration. Gas samples were prepared by a self-made gas distribution device. Briefly, saturated vapor of each aldehyde was produced by dilution with dry and wet nitrogen to