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Double-helix micro-channels on microfluidic chips for enhanced continuous on-chip derivatization followed by electrophoretic separation

Xianglu Peng^a, Lei Zhao^a, Jinxiu Guo^a, Shenghong Yang^a, Hui Ding^a, Xiayan Wang^b, Qiaosheng Pu^{a,*}

^a State Key Laboratory of Applied Organic Chemistry, Key Laboratory of Nonferrous Metals Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, Gansu 730000, China

^b Beijing Key Laboratory for Green Catalysis and Separation, Department of Chemistry and Chemical Engineering, Beijing University of Technology, Beijing 100124, China

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ABSTRACT

Micro-channels that contain a special inner structure are critical for efficient mixing and chemical reactions. In this paper, we described the facile fabrication of an integrated microchip with double-helix type micro-channels to improve mixing efficiency and to facilitate multi-step derivatization reactions prior to electrophoretic separation. With a prepared microchip, reagents, samples and reaction products could be driven through micro-channels by siphon, and no other pumping device was necessary. To test its performance, reductive amination of aldehydes with 8-aminonaphthalene-1,3,6-trisulfonate acid disodium (ANTS) was attempted via microchip electrophoresis with laser induced fluorescence (LIF). The effect of the geometry of the reaction micro-channel on the reaction's efficiency was evaluated. Under the selected conditions, successful derivatization of five aldehydes was realized for highly reproducible analysis. The relative standard deviations of the peak areas for 30 consecutive injections were in the range of 0.28–1.61%. The method was applied for the determination of aldehydes in real samples with standard addition recoveries of 87.8–102.8%. Good tolerance of organic solvents was achieved, and the proposed method can potentially be employed for rapid screening of excessively added aldehyde food flavoring.

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1. Introduction

As a common practice for improving detectability, the derivatization of analytes is widely used to obtain higher volatility, thermal stability and sensitivity (Auroux et al. 2002). On-line derivatization is particularly useful because it consumes less reagent and sample, exhibits decreased disturbance from the surrounding environment and achieves high efficiency of the derivatization reaction. These advantages are valuable for sensing analytes associated with precious samples and for system automation (Sun et al., 2008), bedside monitoring (Murakami et al., 2001; Sandlin et al., 2005) and other on-site analysis (Erickson and Li, 2004).

Capillary electrophoresis is an efficient technique for rapid analysis, and on-line derivatization has been widely investigated (Pentoney et al., 1988). However, due to the limitation of single straight capillary structure, the separation efficiency and

repeatability are strongly governed by the difference of sample injection orders and the skill of operators (Taga et al., 1998). Microchip electrophoresis, which involves the same separation mechanism, is more competent as an on-line derivatization method because the reaction unit and the separation channel can be readily fabricated together (Nandi et al., 2013; Pumera, 2007). Both pre-column (Jacobson et al., 1994a; Wang et al., 2000) and post-column (Fluri et al., 1996; Jacobson et al., 1994b) on-line derivatization were achieved at the early stages of lab-on-a-chip systems and were applied as a vital part of many integrated chip systems (Beard et al., 2004; Wu et al., 2013). The integrated systems with a combined separation technique for online monitoring have been widely applied in many biological and chemical disciplines (Chandra et al., 2011), such as on-chip immunoassays (Chiem and Harrison, 1998; Sato et al., 2000), polymerase chain reactions (Khandurina et al., 2000; Wilding et al., 1994), single cell analysis (Gu et al., 2011; Wu et al., 2004; Zare and Kim, 2010) and other chemical analysis (Belder et al., 2006). However, the low Reynolds numbers of the liquid flows in such micro-channels result in inefficient mixing, and special structures need to be adopted in

* Correspondence to: Department of Chemistry, Lanzhou University, 222 Southern Tianshui Road, Lanzhou 730000, China. Fax: +86 931 891 2582.

E-mail address: pucs@lzu.edu.cn (Q. Pu).

order to enhance the mixing process (Reyes et al., 2002; Stroock et al., 2002). Various active and passive microfluidic mixers have been proposed (Benavente-Babace et al., 2014; Jacobson et al., 1999; Lee et al., 2011), but the fabrication of these structures is normally associated with photolithographic (Krishnan et al., 2001) or other micromachining techniques (Qi et al., 2002; Wolff et al., 2003).

Although numerous methods have been reported for attaching certain groups to a molecule, only a small group of reagents that can react directly with analytes in one step, such as *o*-phthalaldehyde (OPA) (Cellar et al., 2005; Pentoney et al., 1988) and naphthalene 2,3-dicarboxaldehyde (NDA) (De Montigny et al., 1987; Wu et al., 2004), are widely used. This is due to the requirement for a rapid reaction for the on-line derivatization. Derivatizations that require multi-step reactions, special organic solvents and other reaction conditions are seldom adopted in the on-line format. Exploring simple and low-cost methods to fabricate efficient microfluidic mixers that improve the reaction efficiency are important for widening the range of reagents and reactions available for on-chip derivatization.

In this paper, we report the facile fabrication of integrated microchips with double-helix micro-channels that significantly enhance the mixing and reactions before electrophoretic separation on the microchips. Aldehyde flavors were selected as the model analytes to evaluate the performance of the microchips because of two reasons. First, the derivatization of aldehydes through reductive amination is complicated and requires hours with conventional systems; the reaction involves the addition of an amine group to the carbonyl of an aldehyde to produce an imine and a subsequent reduction by NaBH_3CN , which requires higher mixing efficiency than other simple derivatization reactions to yield the final product. Second, rapid sensing of the selected aldehydes is necessary because aldehydes, such as cinnamaldehyde and vanillin, are used as flavoring agents in foods, beverages and pharmaceuticals, while excessive addition of these compounds may be harmful (El-Wahab and Moram, 2012; Lisko et al., 2014). Furthermore, illegal use of other aldehydes in foods to mimic certain flavors is also a large concern. Although the determination of aldehydes can be performed by many other techniques, such as gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry (Pang et al., 2013; Williams et al., 2005), these methods require bulky instruments and are normally not fast enough for on-site analysis. Microchip electrophoresis with on-line derivatization is an ideal method for the rapid screening of these compounds. The goal of this work, therefore, is to prove the applicability of the proposed method with simple fabrication of the integrated microchips for on-line derivatization and electrophoretic separation.

2. Materials and methods

2.1. Fabrication of microfluidic chips

Five types of microchips were used in this work. The microchips with 'Y' type double helix reaction micro-channels, as shown in Fig. 1, were fabricated by the following procedure: A blank plate of cyclic olefin copolymer (COC) (20×70 mm) was sandwiched between two microscope slides with copper wires (80 μm diameter) and a 'Y' shaped wire bundle (made by twisting two copper wires) stretched on one of the slides. The assembly was then fixed with six binder clips and heated in an oven at 127 $^\circ\text{C}$ for 25 min. After cooling, the copper wires were etched away in nitric acid for 15 min. Holes (3 mm in diameter) were drilled at the locations indicated in Fig. 1a at the ends of micro-channels as the access holes. After cleaning with ethanol in an ultrasonic bath, the plate

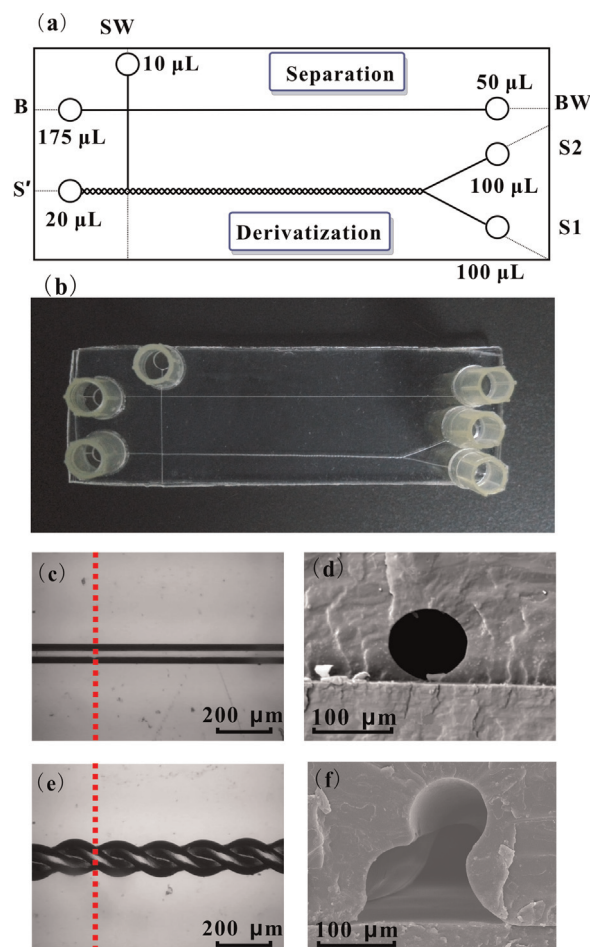


Fig. 1. (a) Schematic diagram of the on-line derivatization microchip; (b) a photo of a COC on-line derivatization microchip; (c) microscopic image of a separation microchannel; (d) SEM image of the cross-section of the separation channel; (e) microscopic image of a double helix reaction channel; (f) SEM image of the cross-section of the double helix reaction channel. Red dash lines in (c) and (e) indicate the approximate locations for SEM images. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with micro-channels was thermally bonded with another blank COC plate of the same size at 117 $^\circ\text{C}$ for 10 min. Small pieces of plastic tube (8 mm long and 6 mm in diameter) were glued at the access holes as the solution reservoirs. The extra channels from the reservoirs to the chip edge were sealed with COC dissolved in toluene (dash lines). The fabrication of the other four types of microchips used in the experiment is described in Supplementary material.

2.2. Chemicals and solutions

Cinnamaldehyde, furfural, glacial acetic acid, ethylether, and sodium tetraborate were purchased from the Tianjin Guangfu Fine Chemical Research Institute (Tianjin, China). 8-Aminonaphthalene-1,3,6-trisulfonic acid disodium (ANTS, 98%) and vanillin were obtained from Sigma-Aldrich. NaBH_3CN was from the Shanghai Jiachen Chemical Regent Factory (Shanghai, China). Benzaldehyde and anisic aldehyde were bought from Chinese National Pharmaceutical Group Corporation (Shanghai, China). Dimethylsulfoxide (DMSO) was purchased from Tianjin Rionlon Chemical Regent Factory (Tianjin, China). Hydroxypropyl cellulose (HPC) was purchased from Bio Basic Inc. (Shanghai, China). All reagents were of analytical grade. Distilled water was used in all experiments.

Stock solutions of cinnamaldehyde, benzaldehyde, anisic

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