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The study of electrochemistry with ambient mass spectrometry

Pengyuan Liu ^a, Qiuling Zheng ^a, Howard D. Dewald ^a, Rebecca Zhou ^a, Hao Chen ^{a,b,*}^a Center for Intelligent Chemical Instrumentation, Department of Chemistry and Biochemistry, Ohio University, Athens, OH 45701, USA^b Edison Biotechnology Institute, Ohio University, Athens, OH 45701, USA

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ABSTRACT

Ambient ionization methods, which can be used to ionize samples directly with no or little preparation under ambient conditions, are a new generation of ionization technologies for mass spectrometry (MS). In this article, we review the coupling of electrochemistry (EC) and MS using ambient ionization methods, such as liquid-sample desorption electrospray ionization (DESI), nanospray DESI and flowing atmospheric pressure afterglow (FAPA). With these novel coupling interfaces, unique applications could be realized, such as online reduction and analysis of disulfide bond-containing proteins and peptides, and investigation of electrochemical reactions on electrode surfaces.

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1. Introduction

Both electrochemistry (EC) and mass spectrometry (MS) are powerful analytical techniques. The combination of these two techniques strengthens their power by complementing one with the other. In the coupled EC-MS, MS serves as a sensitive detector to provide structural information of the products or intermediates of electrochemical reactions [1,2]. Meanwhile, electrochemical conversion can also be used to enhance the ionization efficiency of analyte for MS analysis [3,4]. The first EC-MS coupling was introduced by Bruckenstein in 1971 by using MS equipped with an electron-impact (EI) ionization source to detect volatile redox products generated from a porous electrode [5]. Following this seminal work, different ionization methods were developed to combine EC with MS, including

thermospray (TS) [6], fast-atom bombardment (FAB) [7], chemical ionization (CI) [8], atmospheric pressure chemical ionization (APCI) [9], atmospheric pressure photoionization (APPI) [10] and electrospray ionization (ESI) [2]. The advantages of the combined EC-MS methods have been the subject of a number of reviews [11–17].

Ambient ionization methods [18–22] introduced by Cooks are a family of the latest means that can be used to ionize samples directly with no or little preparation under ambient conditions. EC-MS has been interfaced with ambient ionization methods, such as liquid-sample desorption electrospray ionization (DESI) [23–30], nanospray DESI [31] and flowing atmospheric pressure afterglow (FAPA) ionization [32], because ambient ionization methods have the capability of direct sampling (i.e., the electrolyzed sample from an electrochemical cell can be directly ionized) and have high tolerance to the selection of electrolytes and solvents, providing the advantages of fast response and simplified instrumentation. This review surveys the results of these new interfaces, including the instrument configurations and applications.

* Corresponding author. Tel.: +1 (740) 593 0719; Fax: +1 (740) 597 3157.
 E-mail address: chenh2@ohio.edu (H. Chen).

2. Discussion

2.1. Coupling of EC-MS with liquid-sample DESI

In DESI, which was originally developed by Cooks in 2004 [33], a charged droplet spray aims analyte on a surface for desorption and ionization under ambient conditions. The resulting ions are collected and detected by a nearby mass spectrometer. Typically, DESI focuses on the ionization of solid samples on surface. For a liquid sample, it could be blown away before ionization due to the use of nitrogen as nebulization gas for the DESI spray. To overcome this problem, the liquid sample can be dried on the surface [18,34,35] or added onto a piece of filter paper [36,37], prior to DESI analysis.

In our laboratory, to enable direct analysis of liquid sample, a fused silica capillary is employed to introduce liquid samples continuously for ionization, which is termed as liquid-sample DESI [23]. In this variant of DESI, a spray solvent, such as methanol, water or acetic acid is used to generate charged microdroplets with the assistance of a high-voltage spray (~5 kV) and nebulizing N₂ gas (~170 psi). The sample solution is infused via a piece of capillary and subject to DESI ionization once it exits from the tip of the capillary. The ionization of liquid sample occurs as a result of the interaction of infused sample and the charged microdroplets generated from the DESI spray. Due to the capability of the direct sampling of liquids, liquid-sample DESI is also used to combine EC with MS, simply by pointing the DESI spray probe onto the tip of an electrochemical cell outlet capillary (Fig. 1a) [24].

So far, ESI is the dominant interface used for coupling EC with MS because ESI is a soft ionization method and suitable for the ionization of heavy, polar and labile compounds. There are many successful examples of EC-ESI-MS that have been reported in the literature [2,38,39]. However, there are some limitations of ESI-MS for EC studies. First, EC is often conducted in aqueous solution, which is not the optimal solvent for ESI-MS. Addition of organic solvents, such as alcohol, usually resolves this drawback [11]. Second, in the previously reported studies for the combination of EC with ESI [1,2], the EC system usually needed to be floated or decoupled from the ESI source (using a grounded transfer line to connect the electrochemical cell and ESI source), since ESI operates at a high voltage whereas electrochemical cells are operated at a low potential. The grounding of the transfer line in the electrochemical cell provides safety for operators using the electrochemical cell but could lead to electrode cross-talk, as the potential difference between the grounding point and the electrospray probe or the electrochemical

cell would lead to additional redox conversions [11]. The situation is somewhat simpler for Agilent or Bruker MS instruments, which have their spray needles grounded [11]. In contrast, in the case of EC-DESI-MS coupling, the high voltage used for DESI spray and the low potential used for electrolysis are physically separated, so avoiding electrode cross-talk or inherent redox reactions from the spray source. The polarity of the DESI probe or the electrochemical cell could be freely switched, enhancing the applications of EC-MS.

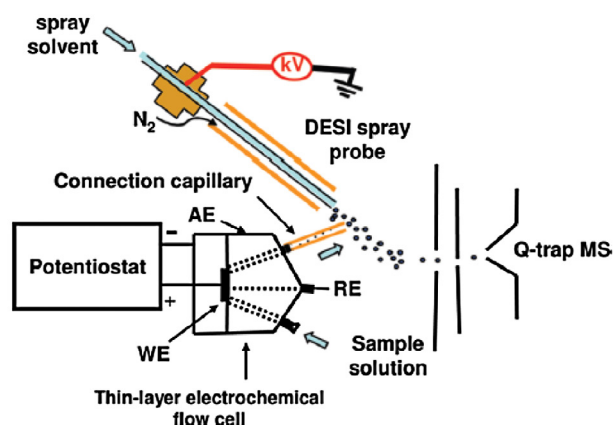
Direct analysis of electrolyzed samples in aqueous phase without organic additives was also demonstrated using DESI-MS [24]. In addition, it is noted that non-volatile salts, such as 10 mM NaCl can be used as electrolyte [24]. These results show the high tolerance of DESI towards electrolyte and solvent compositions. Due to the direct sampling capability of DESI above, electrolyzed solution can also be directly ionized from the electrode without using the connection conduit. For example, DESI ionization can occur to the electrolyzed solution on the end surface of the anode (Fig. 1b) as it flows out of a tubular electrochemical flow cell [23]. This alternative configuration greatly shortens the sample-transfer time. Some interesting utilities of the coupled EC-DESI-MS include investigating the redox conversion of protein or peptide-disulfide bonds [25–30] and elucidating the mechanisms of electrochemical reactions of small molecules (e.g., electroreduction of nitroaromatics) [28].

The redox-active disulfide bond is a common protein post-translational modification (PTM), which provides reversible covalent cross-linkages in proteins to maintain protein three-dimensional structures and biological functions [40,41]. However, the presence of disulfide bonds always makes the MS analysis of protein structures complicated because these extra linkages could hold the protein together even after breaking the protein/peptide-ion backbones. Thus, cleavage of disulfide bonds to facilitate protein/peptide structural elucidation becomes necessary.

The traditional protocol for disulfide-bond reduction involves use of an excess amount of chemical reductants, such as dithiothreitol (DTT) [42] or tris(2-chloroethyl)phosphate (TCEP) [43]. But the chemical reduction increases the labor and the time of the experiment, because the reduction process usually takes 30 min or more with an additional desalting step required, and protection of the resulting free thiol groups is also necessary to avoid thiol re-oxidation or disulfide-bond scrambling prior to MS analysis.

Several different tandem MS techniques have been reported to be able to break disulfide bonds in the gas phase. Electron-based ion dissociations, such as electron-capture dissociation (ECD) [44] and electron-transfer dissociation (ETD) [45], are able to cleave

(a) Online coupling of a thin-layer flow cell with DESI-MS



(b) Online coupling of a tubular EC cell with DESI-MS

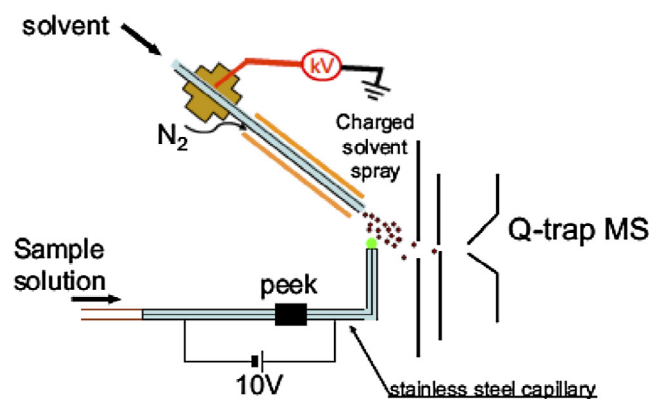


Fig. 1. On-line coupling of (a) a thin-layer electrochemical flow cell with DESI-MS. WE, Working electrode; AE, Auxiliary electrode; RE, Reference electrode (Reproduced from [24], with permission from ACS, ©2009); and, (b) a tubular electrode cell with DESI-MS (Reproduced from [23], with permission from Elsevier, ©2009).

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