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# Online monitoring of chemical reactions by polarization-induced electrospray ionization

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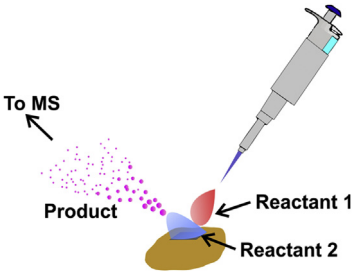
## HIGHLIGHTS

- PI-ESI MS is used to carry out fast reactions and ionization simultaneously.
- Reaction species (~10 μL) can be on-line monitored using PI-ESI MS in real time.
- Intermediates can be detected by PI-ESI MS within 100 ms.
- Selective detection and quantification of acetone in urine samples by PI-ESI MS are demonstrated.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Polarization-induced electrospray ionization (PI-ESI) is a simple technique for instant generation of gas-phase ions directly from a microliter-sized droplet for mass spectrometric analysis. A sample droplet was placed over a dielectric substrate and in proximity (2–3 mm) to the inlet of a mass spectrometer. Owing to the polarization effect induced by the high electric field provided by the mass spectrometer, the droplet was polarized and the electrospray was generated from the apex of the droplet. The polarization-induced electrospray could last for tens of seconds, which was sufficiently long to monitor fast reactions occurring within few seconds. Thus, we demonstrated the feasibility of using the droplet-based PI-ESI MS for the online monitoring of fast reactions by simply mixing two droplets (5–10 μL) containing reactants on a dielectric substrate placed in front of a mass spectrometer applied with a high voltage (−4500 V). Schiff base reactions and oxidation reactions that can generate intermediates/products within a few seconds were selected as the model reactions. The ionic reaction species generated from intermediates and products can be simultaneously monitored by PI-ESI MS in real time. We also used this approach to selectively detect acetone from a urine sample, in which acetone was derivatized in situ. In addition, the possibility of using this approach for quantitative analysis of acetone from urine samples was examined.


## 1. Introduction

Monitoring of chemical reactions in real time can elicit useful information to understand reactions as well as to elucidate the possible reaction mechanisms. Depending on reaction types, chemical reactions can be completed within seconds, hours, or even days [1]. The most challenging part is to monitor ionic reaction species that only have a short lifetime. Furthermore, the sensitivity of analytical tools can also affect the observation of reaction monitoring. Mass spectrometry (MS) is a sensitive analytical technique [2], and it is also a suitable tool for monitoring of chemical reactions in real time [3]. Nevertheless, the ability to use MS for online

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monitoring of chemical reactions is highly dependent on the type of ionization methods. Considering that most chemical reactions are conducted in liquid phase, electrospray ionization (ESI) [4–6], which can be readily used to ionize liquid samples, is a suitable ionization method used in monitoring chemical reactions. If a chemical reaction requires a few hours to complete the reaction, offline monitoring is sufficient to observe the change of ionic reaction species during the reaction. Thus, ESI-MS has been used to monitor chemical reactions since the early 1990s [7–9]. By contrast, fast reactions that can be completed in a few seconds should be monitored online by MS in real time to obtain instant information regarding the generation of intermediates and products.

The rapid growth of the development of open-air ionization techniques [10–22] operated at atmospheric pressure has further promoted the exploration of new approaches to monitor chemical reactions by MS. For example, certain ionization techniques [23–28] allow mixing reactant solutions in proximity to the inlet of a mass spectrometer followed by immediate ionization for MS analysis. Such developments enabled the acquisition of ions generated from reaction intermediates and products [23–26]. It is quite useful for research involving organic synthesis, where reactions are usually monitored by thin layer chromatography after the reaction was completed. These newly developed ionization methods provide the possibility to monitor chemical reactions in real time, and therefore useful chemical structure information can be promptly obtained. An ideal setup should facilitate immediate detection by MS as soon after mixing of reactants. In this pursuit, several interesting setups have been reported for monitoring of chemical reactions. Zare and co-workers performed an approach by fusing two electrospray streams that contained reactants in front of the inlet of mass spectrometer. Given the short fusion time of liquid droplets with diameters of 13 ± 6 μm, they demonstrated that the ions derived from ionic reaction species could be instantly recorded using their approach [23]. Additionally, desorption electrospray ionization (DESI) [12], in which a stream of electrospray is used to desorb and ionize molecules from the sample placed on a substrate close to the inlet of a mass spectrometer, has been demonstrated to be useful for online reaction monitoring [25,26].

Polarization induced electrospray ionization (PI-ESI), which is capable of generating electrospray directly from a microliter-sized droplet, has been demonstrated lately [29]. In PI-ESI, the sample droplet (~5 μL) is placed over a dielectric substrate, which is put in proximity (2–3 mm) to the inlet of a mass spectrometer applied with high voltage (−4500 V). Electrospray can be readily generated from the apex of the droplet because of polarization induced by the electric field provided by the mass spectrometer. Moreover, the ion signals generated from the electrospray can last for tens of seconds. PI-ESI MS has been demonstrated to be useful for the analysis of analytes from small organics to large proteins [29]. Given the simplicity of the setup, PI-ESI MS should be suitable for use in monitoring fast reactions. Furthermore, the sample consumption is extremely low because a microliter-sized droplet is sufficient to be analyzed by PI-ESI MS for tens of seconds. That is, the reacting species derived from fast reactions can be readily monitored by PI-ESI MS by simply mixing two droplets on a dielectric substrate in front of the inlet of mass spectrometer.

Online chemical reactions can also be exploited for online sample pretreatment for complex samples when using MS as the detection method. For example, ketone bodies containing acetoacetate, acetone, and β-hydroxybutyrate have been recognized as biomarkers for diseases such as diabetic ketoacidosis [30], organic academia [31], and bipolar disorder [32]. The level of ketone bodies in patients is in the range of 5 mg/dL–160 mg/dL [33]. Detecting acetone from complex urine samples through in-situ chemical derivatization in front of a mass spectrometer can improve the limit of detection and eliminate the steps of tedious sample pretreatment. Thus, we also demonstrated the feasibility of using the droplet-based PI-ESI to selectively detect trace acetone derivatives from a urine sample reacted in situ with a droplet of derivatizing agents in proximity to the inlet of mass spectrometer.

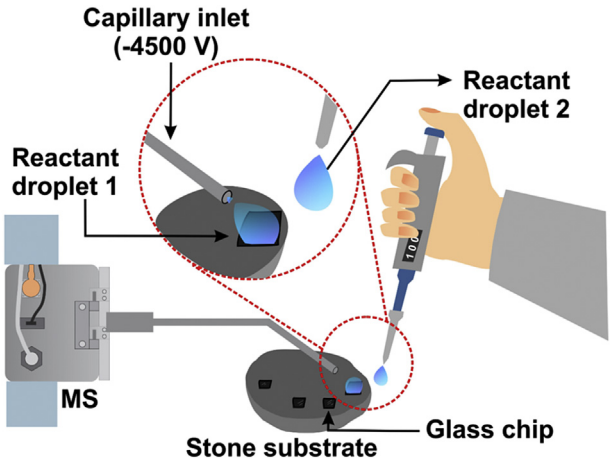
## 2. Experimental

### 2.1. Materials and reagents

Glass slides were obtained from Matsunami Glass Ind. Ltd. (Kishiwada City, Osaka, Japan). Carbon tape was purchased from Ted Pella Inc. (Redding, CA, USA). Stone was collected from the National Chiao Tung University campus. Methanol was purchased from Macron Fine Chemicals (Center Valley, PA, USA). Hydrogen peroxide was obtained from Showa Chemical Co. Ltd. (Japan). Acetone was purchased from Echo Chemical Co. Ltd. (Miaoli, Taiwan). Cysteine, phenylboronic acid, dopamine, glutaraldehyde, aniline, phenylhydrazine, and phenethylamine were purchased from Sigma (St. Louis, MO, USA).

### 2.2. PI-ESI setup for online monitoring of chemical reactions

Scheme 1 Shows the PI-ESI setup for online monitoring of chemical reactions by MS. A glass chip (3 mm × 3 mm) was adhered on a stone (~3 cm × ~0.5 cm) using a double-sided carbon tape, and the stone was placed close (2–3 mm) to the inlet of a micrOTOF Q II mass spectrometer (Bruker Daltonics, Bremen, Germany) or an amaZon SL ion trap mass spectrometer (Bruker Daltonics, Bremen, Germany). Fig. S1 shows the actual photograph of the setup. A metal tube with a bent angle of 135° was used to deliver the ions generated from sample droplet to the mass spectrometer. When using the ion trap mass spectrometer to monitor reactions, the mode of fast chromatography along with ultrascan was used. The acquisition time was set at 10 ms with a speed of 32,500 amu per second. When positive ion mode was operated, the voltage set at the orifice of the mass spectrometer was −4500 V. The temperature of the capillary for ion transfer was set at 220 °C. The length of the metal extension tube adapted to the orifice of the mass spectrometer was ~10 cm with an inner diameter of ~1 mm. A droplet (10 μL) containing reactants was placed over the glass slide. The mass spectrometer was then switched on. The other droplet that contained the other reactant (5 μL) was subsequently coalesced carefully with the droplet on the glass slide. The ions generated




**Scheme 1.** Cartoon illustration of the setup for on-line monitoring of chemical reactions using droplet-based PI-ESI-MS as the detection tool.