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Review

Beyond the flask: Reactions on the fly in ambient mass spectrometry

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ABSTRACT

Ionic reactions in bulk solution generally occur relatively slowly, and the course of reaction can be followed by on-line monitoring using, for example, electrospray ionization mass spectrometry (MS). In another approach, ionic reactions occurring in confined volumes can be studied with a focus on increasing reaction rates upon reduction in solution volume (e.g., by solvent evaporation from small droplets). Such a situation is encountered in ambient ionization MS, which involves the ionization of samples in their native state without significant sample preparation. Reagents can be included in the spray solvents used in ambient ionization and rapid derivatization reactions can accompany ionization. These latter experiments form the topic of this review. Emphasis is on their value in chemical analysis, but the products of these reactions can also be collected easily and form the basis for small-scale synthesis.

Contents

1. Introduction

Historically, there has been a disconnection between reactions occurring in the mass spectrometer and those in the solution

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phase. The gas phase is the traditional medium for studying the kinetics, the thermochemistry and the mechanisms of ion/molecule reactions [1–4]. However, solvents play an important role in ionic reactions in solution [5,6] and their study in the gas phase is limited to the use of minimally-solvated ions [7]. Now, with the development of spray-based ionization methods, reactions in solution have begun to be studied with the aid of mass spectrometry (MS) in three separate types of investigations:

1. on-line monitoring of the course and the mechanisms of solution-based reactions [8–11];
2. preparative MS, in which macroscopic amounts of products of ionic reactions occurring in solution are collected [12]; and,
3. chemical derivatization of analytes occurring simultaneously with spray ionization to produce products with favorable properties for subsequent MS analysis.

The use of electrospray ionization to follow reactions in solution, including identification of intermediates, has been studied by several investigators for some years [10,13]. Within the past 10 years, ambient ionization MS has been developed as an analytical method to enable direct analysis of samples in their native environment without any sample preparation or pre-separation [14–19]. Ambient ionization can be performed with addition of reactants to the spray, providing all-in-one derivatization, ionization, and analysis. In reactive desorption electrospray ionization (DESI) [20], a target analyte on a substrate is interrogated using small droplets containing a reagent. Through a process of thin-film solution-phase extraction and transport in the form of secondary droplets splashed from the surface [21,22], reaction products formed on the millisecond timescale are transferred to the atmospheric inlet of a mass spectrometer.

The several forms of ambient spray-based ionization have potential analogies with bulk solution-phase chemistry. Reactive ambient techniques have previously been reviewed with emphasis on the fundamental phenomena [23,24], but this article seeks to outline the organic reactions that have been performed to improve analytical MS. The focus of effort has been on category (3) above – simultaneous derivatization and ionization to improve chemical analysis by MS. For this reason, the experiments to be discussed focus on enhanced ionization, with elucidation of reaction mechanisms and intermediates by reaction monitoring and preparative chemistry being minor themes. The overview of reactions in ambient MS presented here also provides insights for future work in this field.

2. Ambient reactions in mass spectrometry

This review covers only ambient spray-based techniques, so reactions associated with plasma, laser, and thermal-based ambient ion sources are not included. Methodology is noted but the focus is the chemistry. Outlined below are qualifications for inclusion in the review and experimental considerations. Following this, the ambient reactions covered are organized by functional group.

2.1. Reaction types

Our goal in this review is to describe the organic reactions that often occur on an accelerated timescale in ambient MS. Reactions occurring in the bulk-solution phase can be monitored by spray-ionization methods but there is a sharp distinction between on-line reaction monitoring [8] and the study of solution-phase reactions by spray-ionization methods (i.e. reaction monitoring by MS attempts to utilize the ionization source for analytical purposes and to achieve a representation in the mass spectrum of the chemical species in the reactor). By contrast, studies of reactions occurring in the course of spray ionization seek to characterize these reactions and their accelerated rates in evaporating droplets, utilizing the products to assist in chemical analysis. We focus on reactions that occur between the ionization source and the vacuum inlet of the mass spectrometer, so we address off-line experiments as reference examples only.

2.2. Reaction conditions

Most reactions studied in ambient MS have been bimolecular, although termolecular and unimolecular examples are also known. The reactions covered are often homogeneous, but reactions following drop casting of reagents [25] might be heterogeneous. Many of the reactions are pH sensitive and it is known that the pH changes as the droplets evaporate [26,27]. It is often unknown whether observed rate accelerations take place in the condensed phase, liquid-gas interface, gas phase, or in the micro-solvated environment (see Fig. 1). The reaction conditions portrayed in Fig. 1 represent each of these scenarios. Fig. 1 (top) represents what is sought in reaction monitoring: reaction in bulk solution but no confounding reaction in the course of analysis. Fig. 1 (middle) is the classic case of reactive ambient ionization, in which reagent B is added to analyte A and they react to generate product C (often pre-charged or easily ionized to overcome charge suppression and/or matrix suppression). Fig. 1 (bottom) represents the same situation, but in the extreme (and probably unlikely) case that the product is formed via gas-phase ion/molecule reactions.

2.3. Reaction products and reaction intermediates

Reaction yields in on-line MS are not easily accessed; factors, such as ionization efficiency and ion transport, make peak intensities only rough indicators of product amounts. Off-line methods, such as UV–Vis, IR, and Raman, can be useful in determining reaction yields. There may also be reaction side-products that cannot be measured by MS (typically due to poor ionization efficiency). Conversely, because of the short flight time to the mass spectrometer (of the order of 20 µs to 20 ms), short-lived and unstable intermediates may be accessible, and this is a significant driving force for mechanistic studies using reaction monitoring [28].

The degree to which an observed reaction intermediate is the product of the special conditions of the analysis (small evaporating droplets) or is an accurate representation of an intermediate that

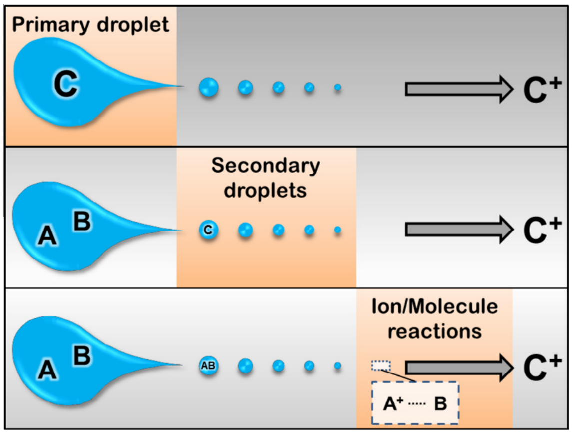

Fig. 1. Types of bimolecular reactions in ambient charged microdroplets. (Top) Reaction occurs in bulk solution before the primary droplet is formed. (Middle) Reaction occurs in smaller secondary microdroplets after coulombic fission of the primary droplet. (Bottom) Reaction occurs as an ion/molecule reaction after solvent has evaporated.