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The Bridge Connecting Gas-Phase and Solution Chemistries

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In memory of John B. Fenn

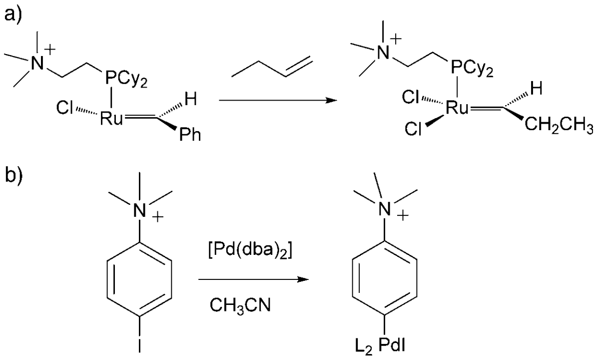
electrospray ionization · ion chemistry · ion/molecule reactions · mass spectrometry · reaction mechanisms

Mass spectrometry (MS) has long served as the gas-phase nursery for exotic ions of ephemeral existence and reactions of ephemeral occurrence in solution.[1] These examples include CH_5^+, the first ever pentavalent form of carbon,[2] which was later formed in a superacid solution by Olah and Schlosberg;[3] and many elusive ionized molecules such as the prototype carbonyl ylide in its "excentric" distonic ion form,[4] ${}^+CH_2{-}O{-}CH_2^{\cdot}$, with an apparently bizarre separation of charge and spin sites. MS has also served as the gas-phase medium in which to form key ions and hence probe reaction mechanisms and establish intrinsic reactivity orders. Gaseous NO_2^+, for instance, was used to settle the mechanism of electrophilic aromatic nitration, a chemical canon that was enthusiastically debated over for decades.[5] Intrinsic physicochemical properties and catalysis, most particularly directed to the activation of inert C–H bonds, have also been extensively investigated in gas-phase reactions of (organo)-metallic ions.[6] MS was born, however, with a "genetic defect", that is, "blindness" to neutral species. But an elegant strategy was elaborated, and distant charge sites (negative or positive) were used as charged tags to allow MS to manipulate otherwise neutral species such as radicals.[7]

However, skepticism obscured the beauty of gas-phase ion chemistry because the high vacuum was considered by many as an eccentric environment with no bridge to the "real world" of solutions. But John Fenn[1] came to the rescue with his Nobel Prize winning electrospray ionization (ESI) technique.[8] To paraphrase Fenn: "ESI made the power and elegance of MS applicable to both gas-phase and solution ions". ESI was revolutionary since it brought MS down to the "real world" of solutions by "fishing" solution ions directly into the gas phase. ESI-MS provides continuous snapshots of the dynamic ionic composition of reaction solutions,[9] and ESI-MS "ion fishing" investigations of reaction mechanisms are therefore free from the gas-phase skepticism; the MS bridge is still being used since ions are transferred to the gas phase for MS analysis but they are fished from the reaction medium exactly at the moment of action, and stay mostly undisturbed in the gas phase during their flight to the MS detector. But ESI is also blind to neutral species. To again overcome this limitation, the elegant concept of charged tags developed in the gas phase[9] was brought into solution to facilitate the "flight to the moon", as Scheme 1 exemplifies.[10] In his Nobel lecture,[11] Fenn summarized ESI as "wings for molecular elephants"; similarly, the combination of ESI and charged tags can be viewed as "charged wings for the flying fish of reaction intermediates" (Figure 1).

The gas phase continued to play a major role since the gaseous intermediates can still be investigated by MS to access intrinsic reactivities and functions in the specific reaction step they were fished from. ESI has also allowed

Figure 1. ESI plus charged tags: "charged wings for the flying fish of reaction intermediates".



Scheme 1. a) A charge-tagged ruthenium complex that was fished into the gas phase to undergo metathesis reactions with an olefin[10a] and b) a charge-tagged Pd complex recently proposed for investigations of Heck and other cross-coupling reactions.[10b] Cy = cyclohexyl, dba = *trans,trans*-dibenzylideneacetone.

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solution ions to be transferred to the ambient gas phase to undergo atmospheric-pressure reactions; classical organic reactions such as the Fischer indole synthesis, the Borsche–Drechsel cyclization, and the pinacol rearrangement have been successfully performed under thermal activation (Figure 2).[12] ESI has also provided access to gaseous ions, such as metal-centered catalytic species, that are otherwise inaccessible by gas-phase ionization techniques. In interesting variants, ESI has been used to fish imidazolium ionic liquid species to the gas phase to form charge-tagged (di)radicals, carbenes, and radical arynes.[13]

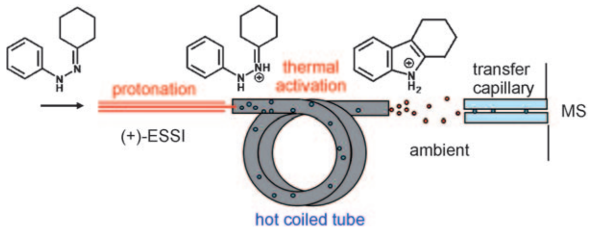


Figure 2. ESSI ion fishing and an example of an ambient thermally activated gas-phase ion/molecule reaction.

Ambient mass spectrometry[14] has recently opened another route in the MS bridge for reaction screening. For instance, low-temperature plasma (LTP) ionization was used in a unique way: in situ monitoring at the naked surface of a reaction solution.[15] Desorption ESI (DESI) was also used to monitor the reaction of a ligand in the spray droplets with a catalyst that was deposited on a surface. The reaction occurred in the microscale volume of the DESI droplet on a very short timescale (milliseconds).[16] Highly charged DESI microdroplets have also been reported to greatly accelerate chemical reactions.[17] An ambient MS technique that combines Venturi self-pumping and voltage-free easy ambient sonic spray ionization (V-EASI) that is able to perform continuous monitoring of reaction solutions (Figure 3) has also been described.[18]

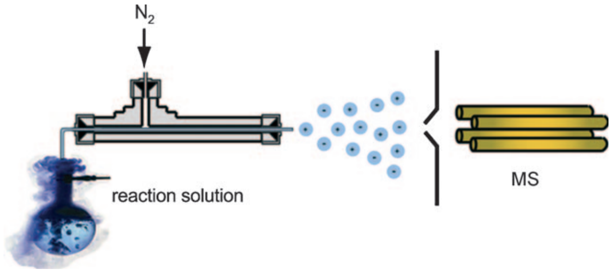


Figure 3. Continuous reaction monitoring by V-EASI.

But despite the appeal of the real world MS investigations of reactions in solution, gas-phase studies have heroically survived, and are still revealing new surprising and promising reactions. The work of Price and co-workers[19] is a prime example. A doubly charged ion, SF$_4^{2+}$, was formed and shown to perform a series of very efficient reactions (Scheme 2) that lead to the fluorination of model neutral molecules, including the activation of CH$_4$ to form C–F bonds. The time-of-flight mass spectrometer used was also unique since it provided an additional dimension for reaction monitoring: for each collision, it measured both the masses and the initial velocities of each pair of product ions, therefore providing a two-dimensional mass spectrum with distinct reaction channels. Theoretical calculations, which are ideally compared to gas-phase-ion chemistry, were also used to rationalize the results.

$$CH_4 \xrightarrow{SF_4^{2+}} CH_2F^+ + SF_3^+ + 2H$$

$$C_2H_4 \xrightarrow{SF_4^{2+}} C_2H_2F^+ + SF_3^+ + 2H$$

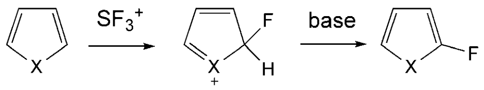
$$C_2H_6 \xrightarrow{SF_4^{2+}} C_2H_4F^+ + SF_3^+ + 2H$$

$$CO \xrightarrow{SF_4^{2+}} FCO^+ + SF_3^+$$

Scheme 2. Reactions of the SF$_4^{2+}$ ion.

Fluorine is a highly electronegative element; hence fluorination dramatically affects molecular properties, thus imparting substantial metabolic stability to bioactive molecules. The stability and inertness of C–F bonds means that their facile synthesis, particularly by C–H activation, still provides a challenge for chemists. The gas phase therefore served, and will continue to offer, a convenient laboratory in which chemists can quickly test many potentially useful fluorination reactions, and other types of reactions with a myriad of conventional or "exotic" ions. The limit is our creativity!

The crucial challenge is, however, to bring these gas-phase reactions down into the solution phase, in which most practical chemistry is carried out. But again, only our creativity is required to cross the bridge: For the SF$_4^{2+}$ ion, it was suggested that solvated SF$_4^{2+}$ could be formed by selective in situ photoionization of SF$_4$ or SF$_6$ or via zwitterions of the form R^{2-}–SF$_4^{2+}$. The authors[19] also noted that the analogous gaseous SF$_3^+$ ion had been reported to promote monofluorination of heterocyclic compounds (Scheme 3).



Scheme 3. Monofluorination of heterocyclic compounds by gaseous SF$_3^+$.

MS currently offers a bridge with a myriad of previously unthinkable routes for chemists to make ions fly from "the earth to the moon" and vice-versa,(Figure 4), and to investigate chemical reactions at the molecular level with unsurpassed speed, selectivity, sensitivity, ease and, now, great flexibility. We can run reactions in solution and go ion fishing with ESI or one of the many ambient MS techniques currently available. To facilitate the flight of the molecular fish to the moon, the reactants (and consequently the intermediates) can be loaded with charged wings (Figure 1). Reactions can be greatly accelerated in highly concentrated and highly charged droplets or very fast reactions can be monitored by droplet fusion during DESI.

Figure 4. Pictorial view of the mass spectrometry bridge between gas phase and solution chemistries.

But as the work of Price and co-workers has nicely reminded us, the gas-phase environment of mass spectrometers continues to a play crucial role in chemical investigations. A reaction intermediate can be fished from solutions to allow the individual investigation of its intrinsic gas-phase reactivity or catalytic role. Its chemical behavior in solution can also be anticipated by making a desirable (perhaps elusive) gaseous ion and by studying its intrinsic reactivity. A great variety of solvated (organo)metallic ions can also be gently fished from solution to the ambient or high-vacuum gas-phase environment for intrinsic reactivity screening.

Indeed, because of continuous and strong revitalization, the long-standing bridge of mass spectrometry that connects gas-phase and solution chemistry is getting stronger and increasingly more useful, and is paved continuously with new routes for chemical investigations at the molecular level. A much brighter future lies ahead!

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