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Krista Vikse & J. Scott McIndoe

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Ionization methods for the mass spectrometry of organometallic compounds

Krista Vikse*^a and J. Scott McIndoe*^{b,c}

Addresses

- a. *Department of Chemistry and Biochemistry, San Francisco State University, 1600 Holloway Ave., San Francisco, CA 94132, USA. Tel: +1 (415) 338-2212; E-mail: kristak@sfsu.edu*
- b. *Department of Chemistry, University of Victoria, PO Box 1700 STN CSC, Victoria, BC V8W 2Y2, Canada. Fax: +1 (250) 721-7147; Tel: +1 (250) 721-7181; E-mail: mcindoe@uvic.ca*
- c. *2018 Erskine Fellow, College of Science, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand.*

Abstract

The rapid development of new ionization methods has greatly expanded the ability of mass spectrometry to target diverse areas of chemistry. Synthetic organometallic and inorganic chemists often find themselves with interesting characterization problems that mass spectrometry could potentially find the answer for, but without a guide for choosing the appropriate method of analysis. This tutorial review seeks to provide that guidance via a simple flow chart followed by a brief description of how each common ionization method works. It covers all of the commonly-used ionization techniques as well as promising variants, and aims to be a resource of first resort for organometallic chemists and analysts tackling a new problem.

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Introduction

Organometallic¹ and coordination chemists tend to approach mass spectrometry with a healthy degree of caution, primarily due to the fact that most instruments are tasked to the analysis of organic and biological molecules, and are rarely set up to handle other types of sample. As a result, when their samples are submitted to a facility and prepared and analyzed under standard conditions, the data obtained can be sub-optimal. It is also sometimes the case that the wrong ionization technique is chosen for a sample, and this tutorial review aims to equip organometallic chemists with enough background knowledge to make informed decisions about what method should be employed.

Which ionization technique should I use for my sample?

To simplify the selection of an ionization technique, a flow chart is presented in Scheme 1 that is based on the physical properties of the sample. Most chemists are aware of these parameters before conducting analyses of a new compound, and while the chart is a blunt tool it nonetheless provides a helpful starting point for consideration. It is of course unusual that chemists will find themselves with ready access to all of the ionization techniques listed in the flow chart, in which case we suggest highlighting just the ones that are available and/or deleting the ones that are not.

Once you have an idea from the flowchart as to what ionization techniques are likely to be helpful, more details follow to further assist decision-making.

Methods

Mass spectrometric ionization methods come in a bewildering variety, and new ones are reported every year. However, most are subtle variations on a few core themes, few make their way into commercial instruments and most organometallic chemists will have access to a limited selection of the most popular methods rather than to a full smorgasbord of options. Here, the various methods have been arranged roughly in the order they are encountered in the flow chart.

¹ The term “organometallic” is used in a loose sense here, to include not just organometallic but coordination complexes. We’ve avoided using “inorganic” because “inorganic mass spectrometry” most often is applied to ICP-MS analysis, which provides compositional but not structural information.

Electron ionization (EI) (a.k.a. electron impact ionization) uses high energy electrons that interact with gas-phase molecules to generate radical cations. This process removes an electron and imparts considerable internal energy to the ion, and as a result it frequently undergoes unimolecular decomposition (Figure 1).^[1-3]

Volatile metal-containing compounds generally provide good EI spectra that are quite comprehensible. They are usually relatively easy to ionize and fragment in predictable ways. The principal problem is getting the species of interest into the gas phase intact in the first place, because the majority of metal-containing compounds decompose on a hot surface long before they develop an appreciable vapor pressure, even under high vacuum conditions. Classes of neutral compound that do provide decent EI-MS include metal carbonyls, main group organometallics and metallocenes, provided their masses are less than 1000 Da.^[4]

EI produces extensive fragmentation, but more often than not in an organometallic context provides acceptable quantities of molecular ion (see Figure 2 – good intensity for the molecular ions of $W(CO)_6$ and $Fe(C_5H_5)_2$, but not for Me_2SnBu_2). That, of course, is the most sought-after datum, but some additional information on the structural identity can be gleaned from the observed fragments.

Considering a neutral metal complex of the general formula ML_yX_z , where L = neutral ligand and X = formally anionic ligand (or combinations thereof), fragments tend to consist of loss of L or loss of X where in both cases the positive charge remains on the metal-containing fragment. So, for example, $W(CO)_6$ will lose 1-6 CO ligands and Bu_2SnMe_2 will lose either the butyl or methyl radical. A resulting feature of EI spectra of organometallic complexes is the retention of the characteristic isotope pattern of the metal in nearly all the fragment ions.

Summary: *EI best for volatile, neutral compounds with molecular weight <500 Da.*

There are variants of EI that exist (*vide supra*), nearly all of which were developed with the intent of making the molecular ion more prominent in cases where it is difficult to observe. They may be worth trying in the event that molecular ions are not detected, but such cases are often a function of the analyte decomposing on the sample stage rather than a result of the ionization process itself.

Chemical ionization (CI) involves the generation of highly reactive gas-phase species such as CH_5^+ , which, upon encountering a molecule, M, will transfer a proton to generate a protonated molecular ion $[M + H]^+$ (Figure 3).^[6]

CI is most commonly used when a compound does not provide a detectable molecular ion under EI conditions, and there is a considerable literature on this topic from the period before the development of other soft ionization methods.

Developed with similar motivations to CI but considerably more recently, **Cold EI** supersonically cools the ions in a helium expansion immediately after formation, reducing their internal energy fast enough that unimolecular decomposition is greatly slowed.^[7,8] As a result, it is good at preserving the molecular ion intact for analysis. As a relatively new technique, it has not yet been widely applied in an organometallic context.

Direct analysis in real time (DART) is an ambient technique that uses Penning ionization (high energy metastable He* atoms and molecules e.g. N₂*) to confer charge to gas-phase analytes. Like EI, CI and Cold EI, it requires volatile samples to function, but unlike them the samples do not need to be placed under vacuum to be studied, they simply need to be brought near the source of the mass spectrometer in open air. Developed in 2004 by Cody,^[9] its ease of use is enormously appealing but it has been infrequently applied to organometallic applications, probably because of two main restrictions: the requirement for volatility, and the very ambience that makes it appealing for other applications makes it problematic for air- and moisture-sensitive samples.^[10]

Summary: *CI/Cold EI/ DART best for volatile neutral compounds with molecular weight <500 Da that do not provide molecular ions with EI.*

Field ionization (FI)

A molecule encountering a sufficiently high potential gradient (such as at the tip of a very sharp electrode) can have its molecular orbitals distorted to the point that quantum tunneling of an electron to an anode can occur, and form a positive ion (Figure 4). This process is called field ionization when the molecule is in the gas phase; if the sample is adsorbed on the surface of the anode (“emitter”), it is called **field desorption (FD)**. The emitter is made by decomposing a carbon-rich molecule near a heated wire such that carbon “whiskers” are grown on the surface.^[11,12]

Both FI and FD are relatively “soft” ionization techniques compared to EI (less fragmentation) and an abundant [M]⁺ ion is usually generated. In both cases, careful preparation of the emitter (a tedious process requiring a separate apparatus) is crucial to the success of the experiment. It is this limitation that renders FI/FD a specialist technique in the face of more recently developed, convenient means of ionization (FAB and then ESI). FD has the ability to analyze compounds that are somewhat less volatile and/or thermally robust than required for EI, and a wider range of compounds is therefore accessible. The general inconvenience of FI and FD has meant it has been largely rendered obsolete by later methods,

but the development of **liquid injection field desorption ionization (LIFDI)**^[13], in which the sample is supplied to the emitter in solution from a sealed vial via a capillary, has enhanced the utility of the technique for organometallic chemists and the approach has enjoyed a mini-renaissance.^[14,15] Fragmentation still occurs (see Figure 5), but there are distinct advantages in the extension of the mass range and convenience of handling the sample inside a vial and keeping it free from oxygen and moisture.^[16]

Summary: *FI/FD/LIFDI best for neutral compounds less than <1000 Da without labile ligands. LIFDI is compatible with air-sensitive samples.*

Fast atom bombardment (FAB) and liquid secondary ion mass spectrometry (LSIMS)

FAB and LSIMS both involve bombarding a sample dissolved in a liquid matrix with fast-moving particles: atoms such as Xe for FAB and ions such as Cs⁺ for LSIMS.^[17,18] The energy of the particles is sufficient to blast matrix and sample alike into the gas phase for analysis (Figure 6).

Various liquids with properties of low volatility, chemical inertness, low viscosity, ability to dissolve the sample, and ability to assist in ionization have been utilized as matrices. Popular choices include glycerol, 3-nitrobenzyl alcohol (3-NBA) or 2-nitrophenyloctylether (NPOE; for non-polar samples). Continual bombardment of the matrix leads to complex solution reactivity and a relatively strong chemical background signal over a wide m/z range (known as “grass”). FAB can be complicated by redox, fragmentation and clustering processes in the study of metal complexes, but nonetheless has been widely used for mass spectrometric analysis of organometallic and coordination compounds, whether charged or neutral.^[19] Ions from FAB/LSIMS can result from charge exchange between the incident particles and sample to produce $[M]^{+/-}$, or frequently protonation to provide $[M + H]^+$ ions, sodiation to produce $[M + Na]^+$, etc. Acidic compounds may provide an $[M - H]^-$ ion through deprotonation. Singly charged ions are typically transferred to the gas phase uneventfully; doubly charged ions often undergo reduction or oxidation to the ± 1 state, or can associate with a singly charged counterion to provide a singly charged ion. FAB and LSIMS are relatively soft ionization techniques, though harder than either ESI or FD insofar as a fragment ion is often the most intense peak in the spectrum. Common fragment ions are due to loss of a neutral monodentate donor ligand such as CO or PR₃. Figure 7 shows the LSIMS spectrum of $[Ru(\text{bipyridine})_3]Cl_2$,^[20] which shows some of the features that complicate spectra of compounds ionized using this technique: chemical noise at low m/z , loss of neutral ligands, charge reduction, and association with a counterion.

Summary: LSIMS/FAB best for polar and singly charged compounds of mass 500-1500 Da.

Matrix-assisted laser desorption ionization (MALDI)

The development of ionization methods involving fast-moving particles desorbing analytes from a surface (FAB/LSIMS and before that, plasma desorption, which used alpha particles) inspired work on laser desorption methods. However, the laser tended to decompose samples while ablating them from the surface, and it took the development of suitable matrices for the technique to achieve its potential. The first was a cobalt powder, which Tanaka showed to be effective in enabling the analysis of high molecular weight biomolecules (and for which he won a share of the 2002 Nobel Prize), and it was rapidly followed by Karas and Hillenkamp with organic matrices, for the most part aromatic acids.^[21,22] The matrix acts to absorb most of the incident light, and its resultant ablation into the gas phase carries the analyte with it. A complex series of events ensue in the gas phase, from which singly positively charged ions emerge as the lucky charged survivors of the energetic plume of cations, excited molecules and electrons generated by the laser pulse (Figure 8).

The energy of the plume unlocks oxidation events for electron-rich complexes to provide radical cations, or in the case of compounds with basic sites in conjunction with a weakly acidic matrix, protonated molecular ions $[M+H]^+$, and both of these routes to ionization have parallels to FAB (as does of course the use of a matrix).

MALDI would seem to be the technique most likely to take over the MS analysis of neutral compounds that were previously analyzed by FAB/LSIMS; however, the popularity of MALDI is disproportionately low in the organometallic community, more so perhaps than any other popular ionization technique. The lack of success has historically been due to a lack of suitable matrices. But this situation has been remedied by the introduction of matrices suitable for organometallic compounds by Fogg and co-workers, who have shown that unfunctionalized polyarenes such as anthracene and pyrene perform well as matrices for fragile metal complexes.^[23] Fogg also pioneered the fully integrated combination of mass spectrometer and full-size glovebox, which is an essential adjunct for MALDI of highly air- and moisture-sensitive compounds given the necessity of exposure to the atmosphere during sample preparation.^[24] Figure 9 shows the MALDI-TOF mass spectrum of a variety of ruthenium complexes.

Complexes of biomolecules (peptides, sugars, proteins, oligonucleotides), polymers, dendrimers and supramolecular assemblies that provide good MALDI spectra in the uncomplexed form can often be successfully characterized when metals are incorporated. Compounds which themselves strongly absorb UV light often produce intense spectra under laser ablation even in the absence of added matrix (i.e. simple laser desorption ionization, LDI). Examples include porphyrins^[25] and fullerenes^[26]. Transition metal carbonyl cluster compounds also provide rich spectra without the use of matrices in both positive and negative

ion modes, but as the spectra contain only products attributable to extensive fragmentation and aggregation, LDI-MS is not especially useful as a means of identification.^[27–30]

Summary: *MALDI best for polar and electron-rich neutral compounds.*

Electrospray Ionization (ESI)

ESI involves spraying a sample solution from a charged capillary into a chamber (called the source) at atmospheric pressure. Ions in that solution are transferred into the gas phase through desolvation aided by a stream of warm nitrogen gas (Figure 10). Fenn (Nobel Prize 2002) developed the technique in the late 1980s and showed it was capable of obtaining mass spectra of very large biological macromolecules.^[31] This advance revolutionized the field of mass spectrometry, leading to an explosion of applications and variants.

ESI and its many variants have proved popular with organometallic chemists, especially those working with charged complexes. Keeping solutions away from air and moisture is straightforward with gas-tight syringes or pressurized Schlenk flasks as delivery methods,^[32] and cations and anions both provide good ESI response (see Figure 11 for examples).^[33,34] There are also well-developed derivatization strategies that exploit the reactivity or affinity of neutral complexes for charged species.^[35–37] Protic complexes can be deprotonated to form $[M - H]^-$ ions.^[38] Complexes with hard basic sites (not counting those used to bond to the metal center!) can be protonated to form $[M + H]^+$ ions or will associate with alkali metal ions to form e.g. $[M + Na]^+$ ions.^[39] Electron-rich complexes can themselves be oxidized during the ESI process in the positive ion mode (some electrochemistry occurs during electrospray ionization in order to generate the excess of ions of whatever polarity is being studied). Complexes with soft bases often have strong affinity for silver ions, providing $[M + Ag]^+$ ions.^[40] Metal carbonyl complexes react with methoxide ion to generate $[M + OMe]^-$ ions. Metal halide complexes often dissociate a halide ligand to produce $[M - X]^+$ ions.^[29]

Most organometallic compounds are at least reasonably soluble in solvents suitable for ESI-MS, and the most useful solvents are probably dichloromethane and acetonitrile. Frequently, spectra can be collected under conditions very much milder than those required for samples of biological origin, which usually involve water as a component of the solvent. As such, spectra should be run under extremely mild conditions in the first instance: low temperature and desolvation gas flow rates, and especially very gentle settings for collision-induced dissociation. Problems associated with spraying low polarity solvents principally arise because their boiling points are relatively low and so settings that include harsh source conditions are inimical to obtaining good data. **Coldspray ionization** may be useful and involves ESI-MS performed with a source that can be set at temperatures well below ambient. It is popular amongst chemists trying to preserve delicate solution interactions, such as supramolecular assemblies.^[42] Low polarity solvents also make the electrochemistry that generates the excess of ions more difficult, and in extreme cases (e.g. spraying toluene or hexane) a supporting electrolyte may need to be added.^[43]

While ESI is a soft ionization technique, some structural information can be gleaned from energetic collisions between intact ions and gas-phase atoms (or molecules). This process is known as **collision-induced dissociation (CID)**. Most often, mild CID causes organometallic ions to dissociate L-type ligands, but other common unimolecular reactions can also occur, such as beta elimination or reductive elimination. The combination of CID, m/z , isotope pattern, chemical intuition and molecular formula finders are a powerful means of identifying unknown compounds.^[44]

Certain ESI variants have potential in specific applications. The most broadly available is probably **atmospheric pressure chemical ionization (APCI)**, and is a promising method for studying species soluble only in non-polar solvents such as toluene or hexane, where ESI is less effectual.^[45] The hardware for APCI can be included as a minor add-on to ESI instruments and involves passing the solution through a heated (as opposed to charged, as in ESI) capillary, and the resulting plume passes through a corona discharge that acts as a continuous generator of gas-phase ions (such as $[H_3O]^+$) that will react with sample molecules to provide protonated $[M+H]^+$ ions. APCI can be applied to solids with the use of an atmospheric solids analysis probe (**ASAP**), which places a sample in front of an APCI plume.^[46] This treatment is sufficient to vaporize analyte molecules from the surface into the gas phase, and has some advantages in terms of simplicity that lends the technique well to applications that call for the quick determination of a molecular weight.

Using an intense UV light source (~ 10 eV) instead of a corona discharge changes the ionization method from APCI to **atmospheric pressure photoionization (APPI)**.^[47] APPI has a similar scope as APCI as far as organometallic compounds are concerned.^[48] Solvent selection is important, because ionization most likely occurs via photoionization of the solvent which then ionizes the sample.^[49-51] Most typically toluene or acetone is used, both of which are effective absorbers of UV light.^[52]

Graham Cooks' group has introduced ESI variants that have found purchase in the organometallic community, notably **desorption electrospray ionization (DESI)** and **direct spray** (a catch-all term for methods where an electrospray is generated from the sample under investigation).^[53,54] DESI involves an electrospray plume which, instead of containing the analyte in solution, is directed at the analyte on a surface. Optimization of the spray geometry in relation to the surface and the mass spectrometer intake results in the gentle desorption of samples from the surface into the gas phase whereupon they can be analyzed conventionally. DESI is an ambient method akin to DART, and so the same sorts of atmospheric exposure issues apply. **Paperspray** uses disposable triangles of paper on to which a solution and a charge is applied. The solution forms an electrospray plume at the sharp point of the paper and analysis can proceed as normal.^[55] Advantages of this approach include elimination of cross-contamination (no shared capillaries for sample introduction) and very low sample consumption (the effective flow rate is on the nanospray level). Zare and others have used paperspray in the study of some very air-sensitive systems, by means of drizzling the analytes onto the paper inside a nitrogen-filled chamber.^[56]

Conclusions

Mass spectrometry of organometallic compounds and coordination complexes requires careful consideration of various experimental parameters, but the most important of these is selection of ionization technique. The most carefully handled sample run under the perfect conditions will not provide meaningful data if the ionization method is ill-suited to its analysis. A basic understanding of the various ionization processes, as described herein, will prepare the organometallic chemist to rationally select the most appropriate approach depending on the characteristics of the sample under consideration.

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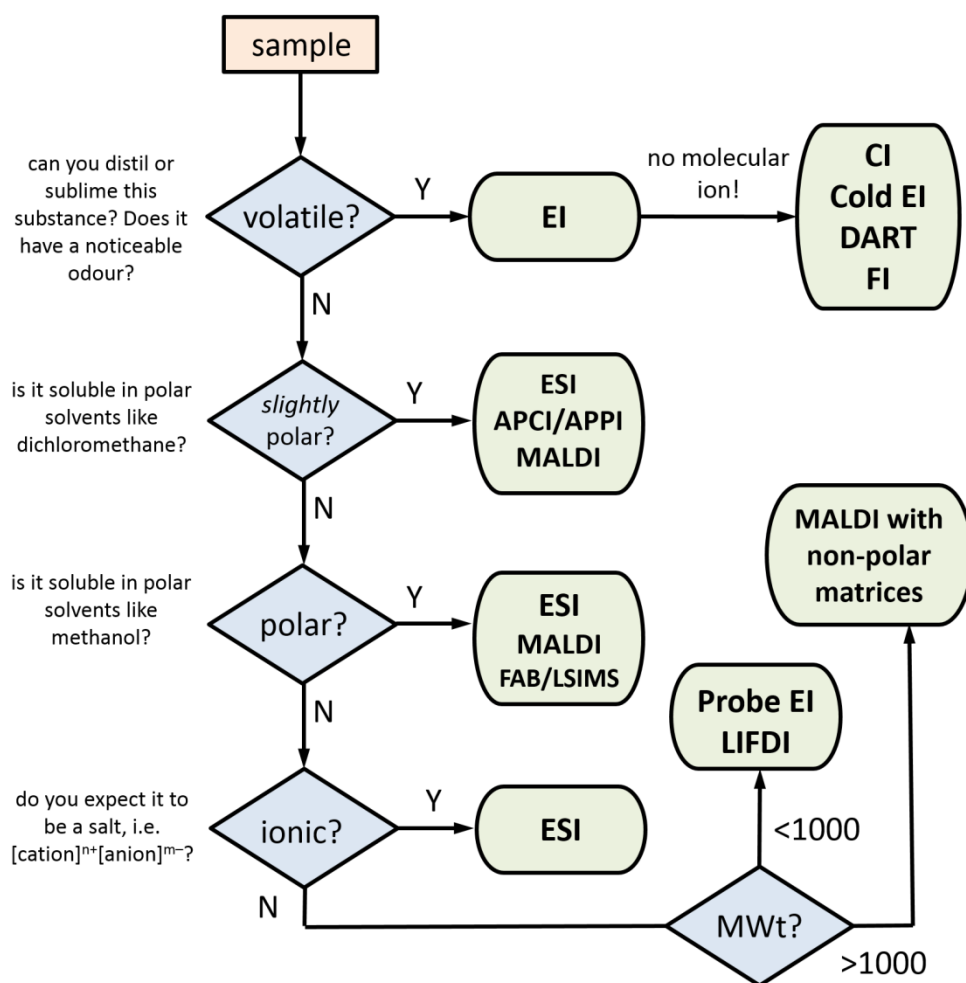
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Scheme 1. Flowchart for the selection of an ionization technique.

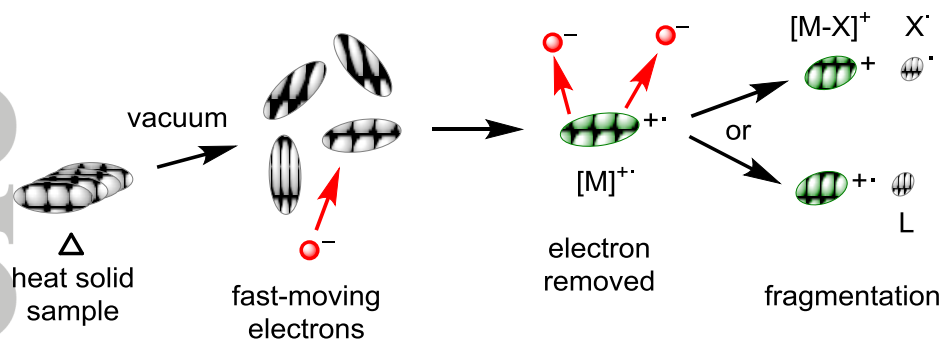


Figure 1. Cartoon showing the EI process. The neutral sample is heated under vacuum, driven into the gas phase and ionized with electrons accelerated to 70 eV. The electrons ionize and fragment the target molecule.

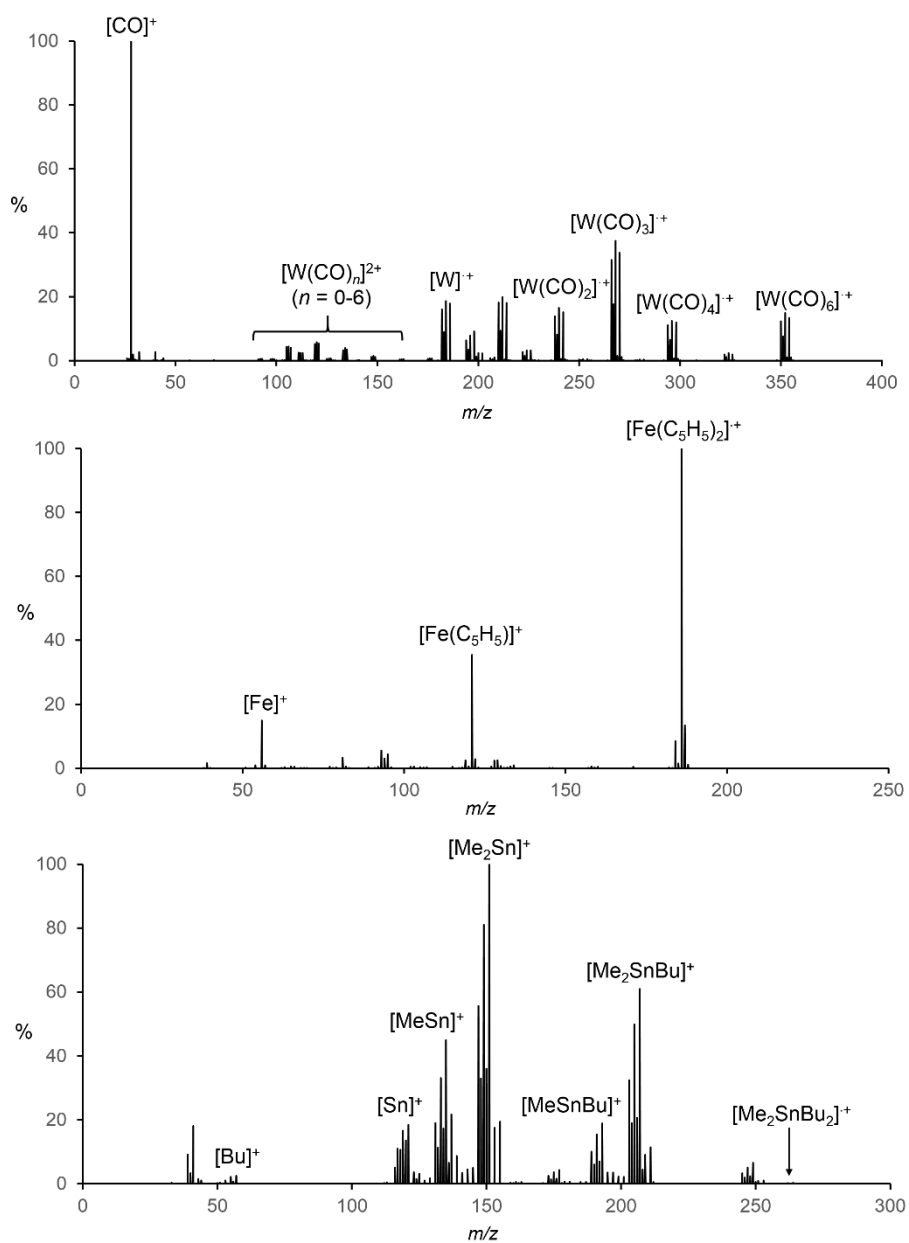


Figure 2. EI mass spectra of (top) $W(CO)_6$, (middle) $Fe(C_5H_5)_2$, and (bottom) Me_2SnBu_2 . Reproduced from the NIST mass spectral library.^[5]

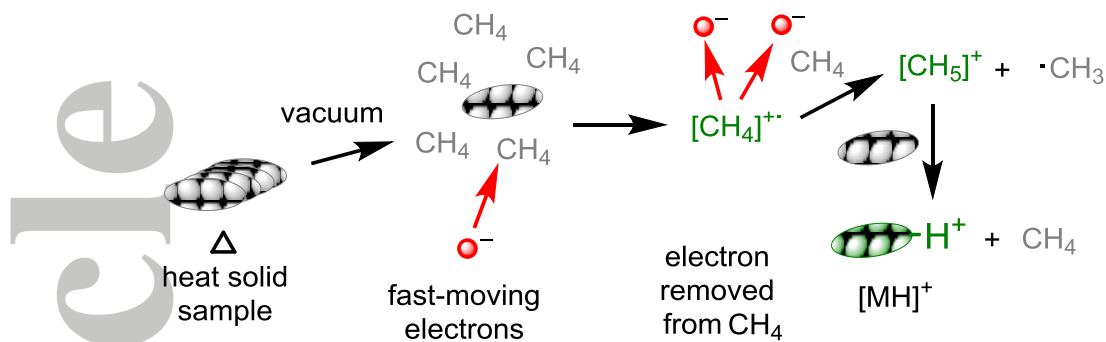


Figure 3. Cartoon showing the CI process. The neutral sample is heated under vacuum, driven into the gas phase in the presence of a reagent gas (typically methane) and the reagent gas is ionized with electrons accelerated to 70 eV. The resulting [CH₄]⁺ ions react with CH₄ to make •CH₃ radicals and [CH₅]⁺, and the latter protonates gas phase sample molecules to make [MH]⁺ ions.

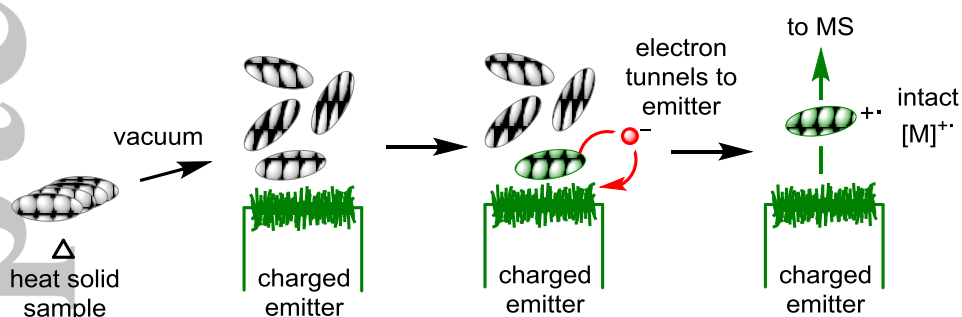


Figure 4. Cartoon showing the FI process. The neutral sample is heated under vacuum, driven into the gas phase near a high surface area emitter. If the molecule gets sufficiently close, an electron tunnels to the anode and the molecule is repelled and drawn into the mass spectrometer. In FD, the sample is coated on the surface of the emitter prior to evacuation.

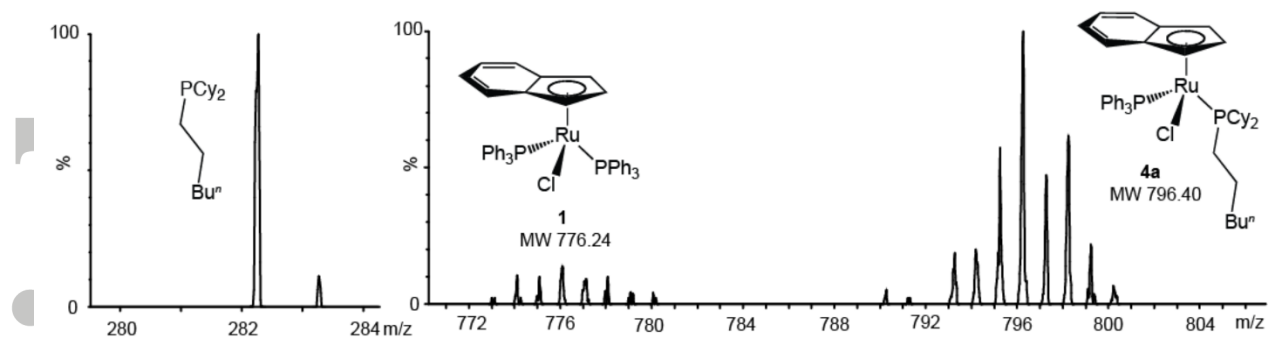


Figure 5. LIFDI spectrum of a mixture of Ru complexes, showing both intact $[M]^{++}$ complexes (right) and free ligand (left). Spectra provided courtesy of Lisa Rosenberg.

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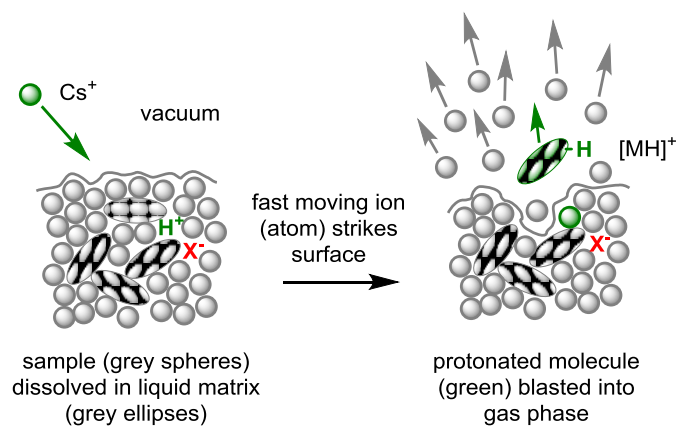


Figure 6. Cartoon showing the **FAB/LSIMS** process. The neutral sample is dissolved in a liquid matrix, placed under vacuum and exposed to a beam of energetic atoms or ions (as shown here). The energy transferred to the solution propels matrix and sample into the gas phase, and ions can be analyzed.

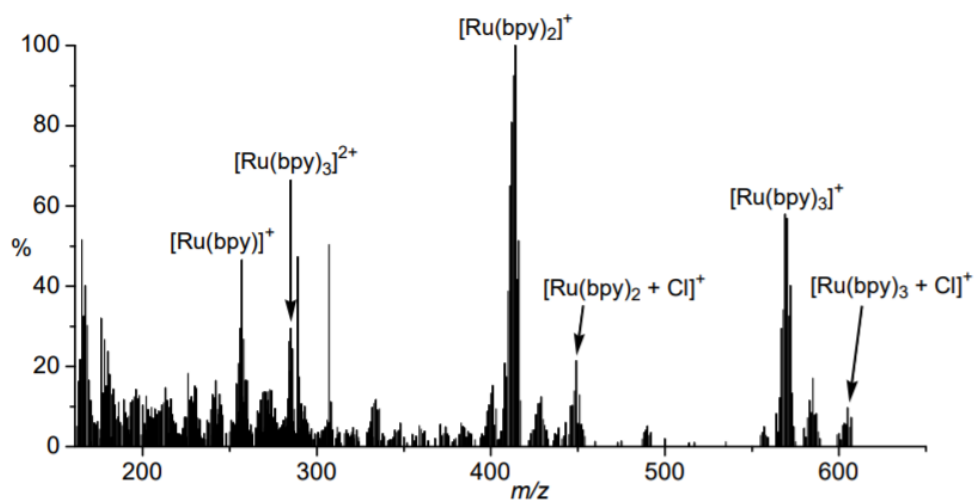


Figure 7. LSIMS spectrum of [Ru(bipyridine)₃]Cl₂ in a 3-nitrobenzyl alcohol matrix. Adopted with permission from reference 20.

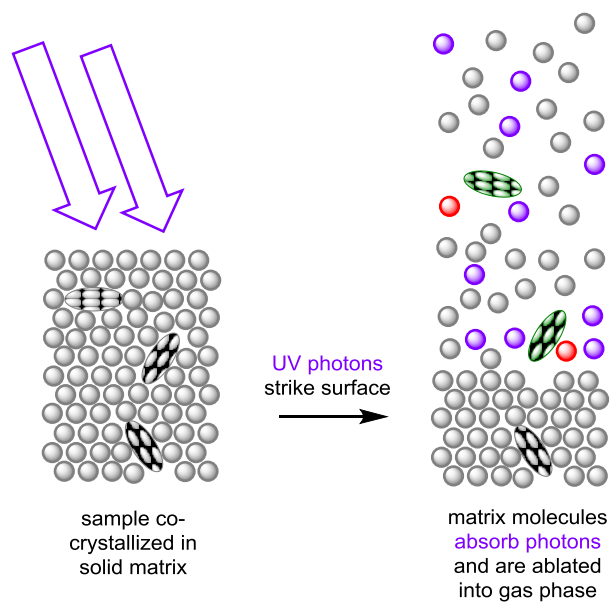


Figure 8. Cartoon showing the MALDI process. The neutral sample (grey ellipses) is co-crystallized in a solid matrix (grey circles), placed under vacuum and exposed to pulsed UV laser. The matrix molecules absorb most of the photons (excited matrix molecules shown in purple), and are ablated into the gas phase, carrying the analyte molecules with them and ionizing them through protonation (green ellipses, red circles are deprotonated matrix molecules) and (if electron-rich) oxidation.

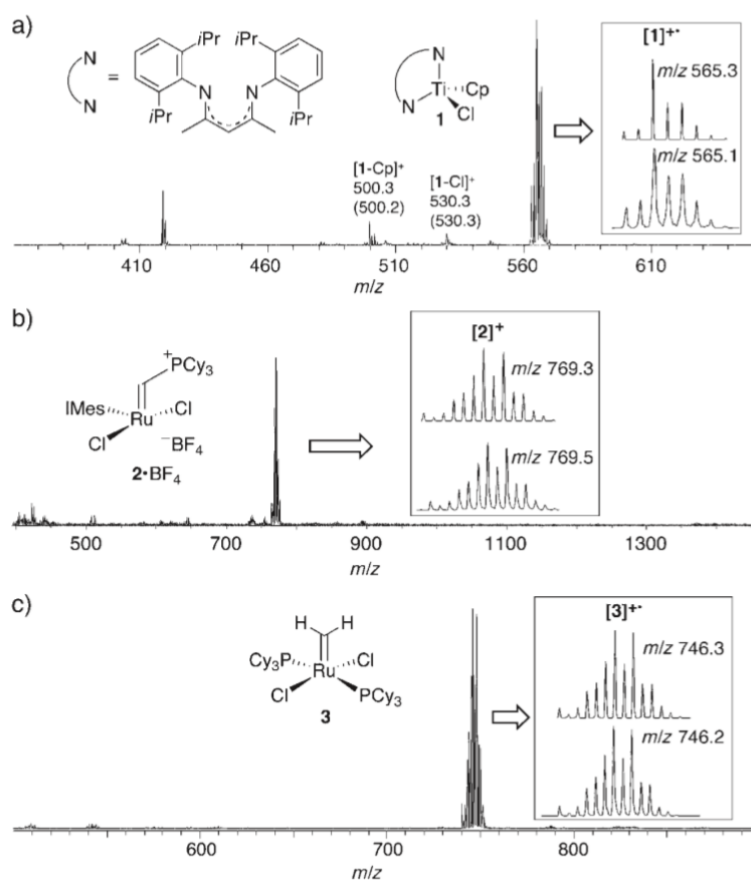


Figure 9. MALDI mass spectra of isolated complexes. (a) An oxophilic Ti^{III} complex (pyrene matrix); (b) the Piers metathesis catalyst (pyrene matrix); (c) a first-generation Grubbs catalyst (anthracene matrix). Labels give found (calculated) m/z values. Insets show isotope patterns for the molecular ions (top: simulated, bottom: observed). Cp = C_5H_5 , IMes = $\text{N,N}'$ -bis(mesityl)imidazol-2-ylidene, Cy = cyclohexyl. Spectra reproduced with permission from reference 23.

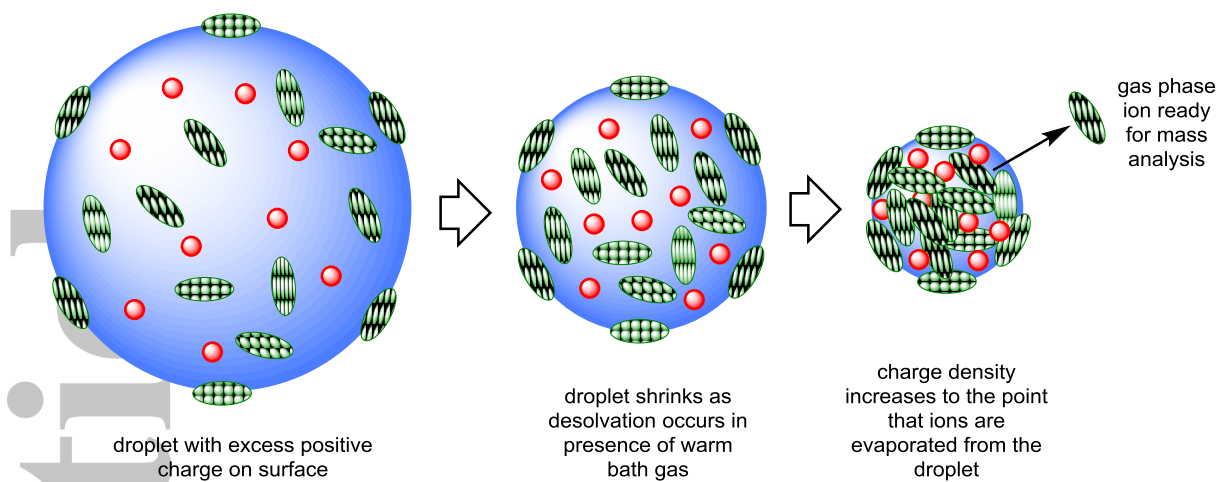


Figure 10. Cartoon showing the ESI process. Solution-phase ions are passed through a charged capillary, and the solution separates into tiny droplets from which the solvent is evaporated. The excess charges arrange themselves on the surface, and as the charge density increases, ions are evaporated into the gas phase.

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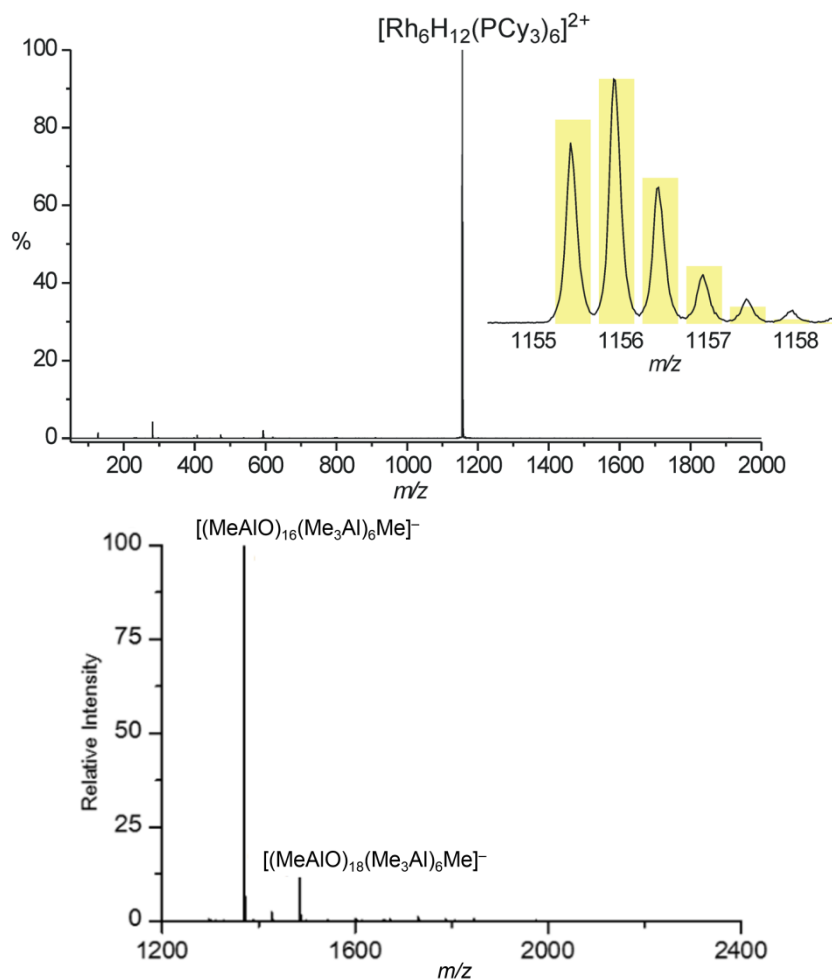


Figure 11. ESI mass spectra of a dicationic rhodium cluster compound (top, with isotope pattern inset) and of an anionic methylalumoxane oligomer (bottom). Note the lack of fragmentation which is characteristic of ESI, and in the dicationic example, preservation of the original charge state, evident from the peaks in the isotope pattern being m/z 0.5 apart. Spectra reproduced with permission from references 33 and 34.