Mass Spectrometry in Organometallic Chemistry

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There are unique challenges associated with applying mass spectrometry (MS) to the analysis of organometallic compounds. High reactivity, a lack of volatility, and/or sensitivity to heat, oxygen and water all conspire to make the transfer of material into the gas phase without decomposition fraught with difficulty, and low polarity provides the additional complication that ionisation is not always trivial. Various methodological and technological developments over the last decade have improved the situation, but organometallic chemists are still faced with a bewildering array of options and there is yet to emerge a one-size-fits-all solution.

1 Introduction

The choice of ionisation method has the greatest impact on whether or not sensible results are obtained from MS studies, and so much of this review will be spent dealing with the available options. The review also covers the different types of mass analysers and the necessity (or otherwise) for high resolution, looks briefly at the information provided from MS/MS studies and finally samples some of the more sophisticated experiments possible in the gas phase when the mass spectrometer is used as a reaction chamber.

2 Ionization Methods

2.1 Electron ionisation

The first ionization method to find routine use in mass spectrometry was electron ionisation (EI).[1] The ionization source is under vacuum, and the sample is driven into the gas phase by the application of heat (gases are simply allowed to bleed into the source, and volatile liquids require no heating). Electrons are boiled off a metal filament and accelerated across the source, and impinge on the gaseous sample moelcules at at energy of (usually) 70 eV. The interaction of these electrons with the the analyte are sufficiently energetic to remove an electron from a molecular orbital, thus generating a radical cation, $[M]^{\bullet+}$, a positively charged, odd-electron species. Typically, the encounter results in considerable internal energy being imparted in addition to the removal of the electron, so subsequent fragmentation processes are common. Consequently, the ions formed in the source are a mixture of molecular ions, $[M]^{\bullet+}$, and fragment ions, and these are accelerated into the mass spectrometer proper by application of a positive potential, and analyzed conventionally. The mass spectrum is contains both molecular weight (from the molecular ion) and structural information (from the characteristic fragmentation pattern).

EI is ideal for the routine analysis of non-polar, low molecular weight (<1000 Da) compounds. The combination of high vacuum and the ability to heat to several hundred degrees is generally sufficient to drive enough sample into the gas phase

that analysis may proceed. The caveat that the sample must be reasonably thermally stable does of course apply, so fragile complexes are generally not suitable due to decomposition. EI is most powerful in conjunction with gas chromatographic separation in the hyphenated technique of GC-MS. Chemists interested in catalysis often use this as a standard, quantifiable method for the analysis of reactant/product mixtures. Chiral columns can effect separation of enantiomers, hence measurement of enantiomeric excess following asymmetric catalysis is also possible. The MS essentially acts as a sophisticated detector; libraries of EI spectra can be computer searched and spectra of unknowns rapidly matched to known compounds.

2.2 Chemical ionisation

Introduction of a gas such as methane to an electron ionisation source results in ionisation to $[CH_4]^{\bullet+}$, which because of the higher pressure of the source, reacts with more CH_4 to generate $CH_3^{\bullet}$ and $[CH_5]^+$. $[CH_5]^+$ is a strong acid, and an encounter with a polar molecule M will result in protonation to form $[M + H]^+$, a "quasi-molecular ion". This process is not especially energetic and a result is that relatively little internal energy is deposited, and fragmentation is limited. Chemical ionisation [2] is thus a useful method for providing molecular weight information on molecules whose molecular ion is absent in an EI experiment. Volatile, polar molecules are an unusual combination in organometallic chemistry, so CI has found little application in the field.

A modern development in CI is to perform the experiment in a source at atmospheric pressure, hence the technique of APCI. A corona discharge is generated in the source by the application of a potential to a sharp wire, and ionisation of the solvent molecules results in highly efficient protonation of not-especially-basic substrates. APCI does not, as yet, have many adherents in the organometallic community.

2.3 Field ionisation/field desorption

Molecules encountering an extremely steep electric field gradient can have their moelcular orbitals perturbed to the extent that an electron can tunnel to the electrode. Atomically sharp carbon whiskers can be grown on metal wires, and with sufficiently high potential applied to such emitters, molecules nearby may be ionised, and this is the basis of the field ionisation (FI) technique. FI was the first genuinely "soft" ionisation technique, and provides intense molecular ions with limited fragmentation. Field desorption (FD) is the same technique,[3] but the instead of the sample being in the gas phase already, a solution of the analyte is evaporated directly on to the emitter. Unfortunately, the emitters are fragile and tricky to make and analysis is rather slow, and FI/FD nearly died out as a technique. However, it has been revived somewhat with genuine relevance to organometallic chemistry, thanks to a recent methodological development in sample introduction. Liquid introduction FD ionisation (LIFDI) [4] involves the loading of the emitter while in the source by means of a capillary. The capillary is placed very close to but not touching the emitter, and a plug of a solution containing the dissolved analyte is drawn through the capillary by the action of the vacuum, and disperses onto the emitter (Figure 1).

Figure 1. Left: sample in solution form in sealed GC vial. A needle-tipped capillary punctures the septum and sample is drawn into the mass spectrometer. Right: sample is deposited by capillary action onto the emitter (inside the high vacuum source of the instrument). Reproduced with permission of H. B. Linden.

The solvent evaporates, and a voltage is applied to the emitter. This simple idea has some profound advantages; attaching a needle to the capillary allows it to be thrust straight into a septum-sealed vial. For organometallic chemists, this means the sample can be prepared as a solution in the glovebox, sealed, and delivered to the MS without fear of decomposition.[5] Spectra show next to no fragmentation due to the gentle ionisation method (Figure 2).

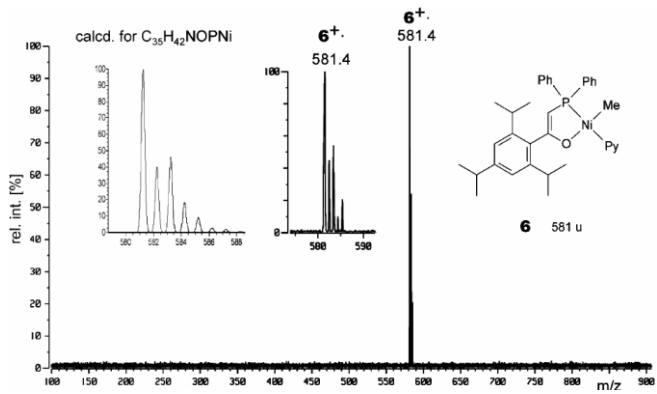


Figure 2. LIFDI mass spectrum of a non-polar, labile organometallic complex from toluene showing no fragmentation. The observed isotopic pattern of $\mathbf{6}^{+\bullet}$ corresponds very well to the calculated isotopic distribution (see insets). Reproduced with permission of H. B. Linden.

2.4 Fast atom bombardment/Liquid secondary ion mass spectrometry

The development of fast atom bombardment (FAB) [6] and the closely related technique of liquid secondary ion mass spectrometry (LSIMS) enabled the (nearly) routine acquisition of MS data on organometallic complexes.[7] The sample is dissolved in a liquid matrix, typically an involatile, protic substance such as glycerol or *meta*-nitrobenyzlalcohol (mNBA). The viscous solution is introduced to the source of the mass spectrometer, where it is exposed to an energetic beam of atoms (FAB; e.g. Xe) or ions (LSIMS; e.g. Cs^+). The beam blasts matrix and sample into the gas phase, energetically enough that the sample molecules are desolvated and ionised, either by protonation to from a quasi-molecular ion or by removal of an electron to form a radical cation. The liquid surface is rapidly refreshed with new

matrix and sample, so the sample can be analysed continuously for an extended period. Many organometallic complexes are reasonably easily oxidised, so both $[M + H]^+$ and $[M]^{\cdot+}$ ions are frequently observed, and sometimes both for the same sample. Other means of charging the sample are sometimes observed, such as association with a cation such as Na^+ to form $[M + Na]^+$ ions. Both FAB and LSIMS are substantially gentler ionisation techniques than EI, so fragmentation is much reduced in comparison. At low masses, spectra are complicated by matrix ions and aggregates thereof, e.g. $[(matrix)_n + H]^+$. Also characteristic of FAB and LSIMS spectra is the presence of "grass", substantial noise at all values of *m/z* caused by complicated reactivity of energised molecules and ions at the surface of the matrix, and their eventual transmission to the gas phase. Some complications from aggregation phenomena are sometimes observed, e.g. the appearance of $[C_nA_{(n-1)}]^+$ (C = cation, A = anion) ions in the spectra.

FAB and LSIMS were the first ionisation techniques to allow the characterisation of charged organometallic complexes by MS. While harder to desorb from the liquid matrix, ionisation efficiency is of no concern because they already carry a charge, so cations can be observed directly in the positive ion mode (and anions in the negative ion mode). Multiply charged ions are more challenging, and often appear either charge-reduced or accompanied by a singly-charged counterion.

2.5 Matrix-Assisted Laser Desorption Ionization (MALDI)

Laser desorption ionisation had been around for many years when Tanaka showed in 1988 that combining a large amount of a matrix material (in his case, a cobalt metal powder and glycerol) with the analyte of interest enabled the mass measurement of large molecular weight (10,000s Da) biomolecules.[8] This led to an explosion of interest in the technique, and Karas and Hillenkamp's matrix-assisted laser desorption ionisation (MALDI), reported in 1985 [9] but used only for low molecular weight substrates, became the implementation of choice. MALDI uses organic acids with UV chromaphores as the matrix, such as 2,5-dihydroxybenzoic acid (DHB), and samples are prepared by co-crystallising the analyte with a large excess of the matrix. The sample is irradiated with a tightly focused, pulsed UV laser. The high molecular weights are dealt with by using time-of-flight mass analysers, which are perfectly capable of detecting *m/z* ratios well in excess of 100,000. Because the matrix absorbs the great majority of the incident light energy, the sample endures little activation and fragmentation is minimal. Spectra are easy to interpret because only singly-charged species are observed (it is probable that monocations are the principal survivors of the myriad processes that occur in the energetic plume generated from the laser pulse). Ionisation is principally via protonation to form $[M + H]^+$ ions (hence the acidic matrix). MALDI is an popular technique in proteomics and for the analysis of organic macromolecules.

In organometallic chemistry, MALDI has had limited impact, at least partly due to the lack of suitable matrices and the challenges associated with handling air-sensitive solid samples. Molecules that have strong UV chromaphore themselves are prone to unusual reactivity, notably metal carbonyl complexes. $M_n(CO)_m$ clusters do not provide molecular weight information under MALDI conditions,[10] instead undergoing extensive fragmentation and aggregation processes to form a myriad of species (Figure 3).[11]

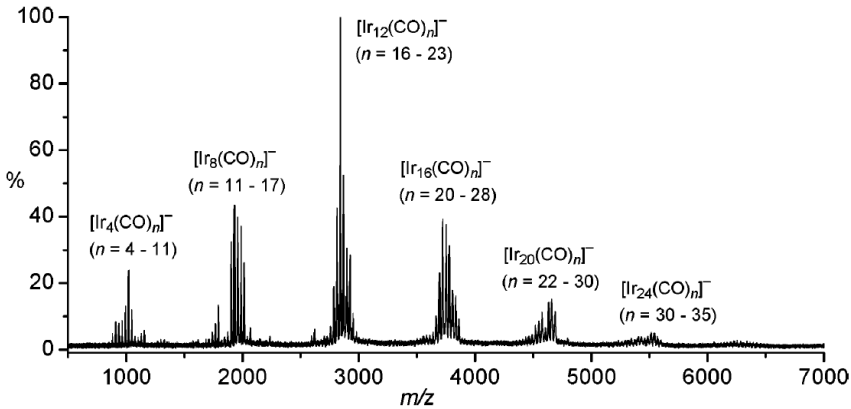


Figure 3. Negative ion LDI mass spectrum of $Ir_4(CO)_{12}$ in the range 500-7000 *m*/*z*. Reproduced with permission of the American Chemical Society from reference 11.

Recent developments in methodology out of the Fogg group in Ottawa may change this unfavourable situation. Direct integration of a MALDI mass spectrometer with an inert atmosphere glovebox removes all issues associated with air- and moisture-sensitivity, as all sample handling is conducted in an atmosphere free of O_2 and H_2O (Figure 4).[12]

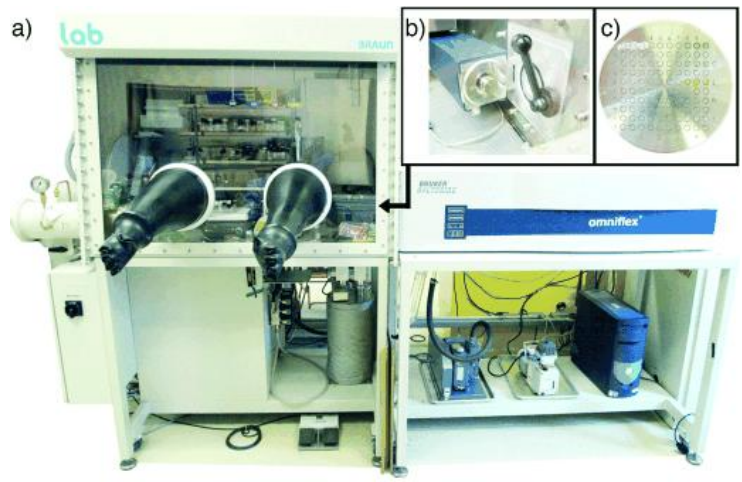


Figure 4. a) Inert-atmosphere MALDI-TOF mass spectrometer; b) open loading chamber projecting into the glovebox; c) target plate. Reproduced with permission of Wiley-VCH from reference 12.

This paper also addressed another issue in MALDI analysis of organometallic compounds: the paucity of suitable matrices. Charge transfer matrices [13] such as pyrene and anthracene were shown to be effective for generating radical cations of neutral organometallic compounds (Figure 5a and 5c) and facilitating the transfer of ionic organometallic compounds to the gas phase (Figure 5b). Addition of paraffin oil to the sample/matrix mixture was used to access samples that were not soluble, thus allowing fast assessment of the composition of solids.

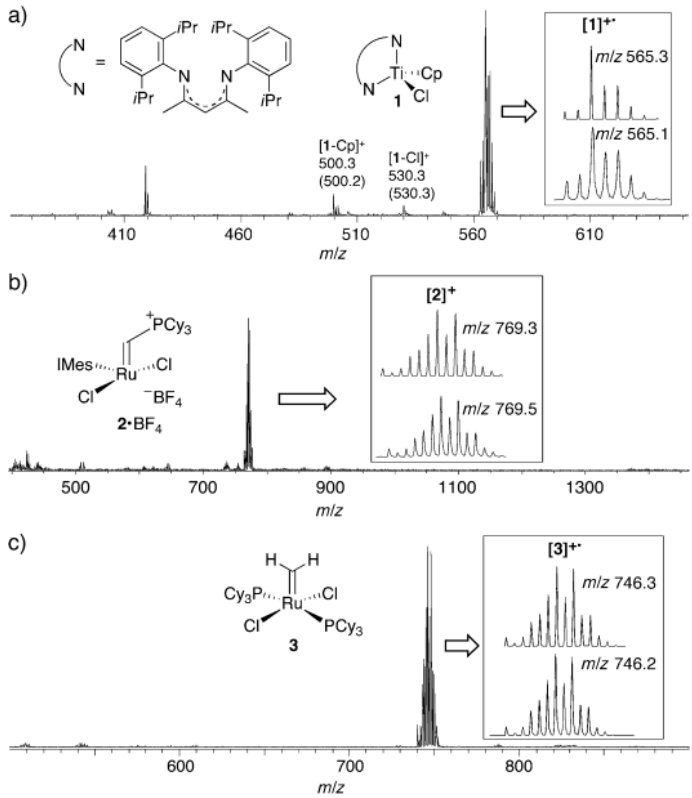


Figure 5. MALDI mass spectra of isolated complexes. a) An oxophilic Ti^{III} complex (pyrene matrix); b) the Piers metathesis catalyst (pyrene); c) a first-generation Grubbs catalyst (anthracene). Labels give found (calculated) *m/z* values. Insets show isotope patterns for the molecular ions (top: simulated, bottom: observed). Cp = C_5H_5, IMes = *N*,*N*-bis(mesityl)imidazol-2-ylidene, Cy = cyclohexyl. Reproduced with permission of Wiley-VCH from reference 12.

2.6 Electrospray Ionization (ESI)

Electrospray is the dispersion of a solution from a charged capillary. When used as an ionization technique, the resulting fine spray of droplets is desolvated by a counter flow of a warm bath gas (usually nitrogen), and the gas phase naked analyte ions eventually produced are transported through a series of differentially pumped chambers into the mass analyser.[14] Fenn demonstrated that electrospray ionisation (ESI) was capable of examining high molecular weight biomolecules [15] on conventional instruments through the phenomenon of multiple charging: if, for example, a protein with mass 25,000 Da acquires 25 protons, a $[M + 25H]^{25+}$ ion will appear at 1001 *m/z* (25,025/25). Independent verification of molecular weight is obtained from the same molecule picking up different numbers of protons (and hence appearing at different values of *m/z*). ESI-MS rapidly became popular for the study of all types of polar molecules and ions (including multiply-charged ions). Polarity is a requirement for two reasons: the ESI process does not confer any charge to molecules (with notable exceptions for especially easily oxidised materials), instead relying on the molecule to associate with a charged species such

as H^+ or Na^+ during the desolvation process, and more prosaically, ESI functions best using polar solvents such as water/acetonitrile and methanol, so analytes should be soluble in these solvents. Conditions for ESI can be set so as to practically eliminate fragmentation, so that only (quasi)molecular ions are observed.

2.6.1 Charging the complex

Organometallic complexes can be routinely analysed using ESI-MS, provided some quite stringent requirements are met. If the complex is cationic or anionic, analysis in the positive or negative ion mode is straightforward, with $[M]^{n+}$ or $[M]^{n-}$ being observed, respectively. However, for neutral complexes the situation is dramatically different: the means by which the complex acquires a charge becomes crucial.

2.6.1.1 Oxidation

ESI is, at its heart, an electrochemical process, because in order for a net excess of positive ions to be generated, the same amount of electrons need to be removed at the charged capillary. This process can involve oxidation of Fe (in the stainless steel capillary) to Fe^{2+}, but in the case of unusually electron-rich neutral metal complexes, they themselves may be oxidised and appear in the spectrum as $[M]^{\bullet+}$. Ferrocene derivatives are particularly prone to this behaviour, as are other low oxidation state metals with electron-donating ligands such as phosphines; for example, $Pd(PPh_3)_2$ appears as $[Pd(PPh_3)_2]^{\bullet+}$ (Figure 6):[16]

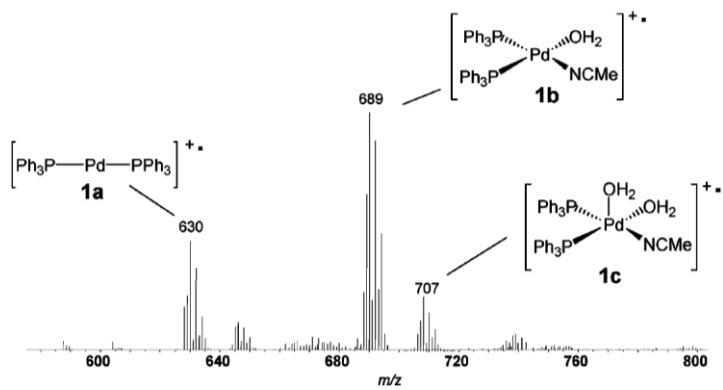


Figure 6. ESI(+)-MS of an acetonitrile solution of $Pd(OAc)_2/PPh_3$. The spectrum is shown across a narrow m/z range in which major Pd species were detected. Reproduced with permission of the American Chemical Society from reference 16.

2.6.1.2 Protonation

Addition of H^+ and/or use of protic solvents is a common protocol in the ESI-MS of polar organic compounds or biomolecules to obtain $[M + nH]^{n+}$ ions. The approach is nowhere near as general for organometallic compounds; they rarely possess suitable basic sites with which to associate with a proton and so their ionisation efficiency is near zero, but even more problematically, many organometallic compounds rapidly decompose in polar solvents even without the addition of acid. Efforts have been made to design ligands for the purpose of being amenable to ESI-MS analysis, which solve the first problem but not the second; these include the "electrospray-friendly" ligands $PPh_{(n-1)}(p\text{-}C_6H_4OMe)_n$ and $PPh_{(n-1)}(p\text{-}C_6H_4NMe_2)_n$ (n = 1-3) [17] and the proton sponge functionalised phosphine ligand shown in Figure 7:[18]

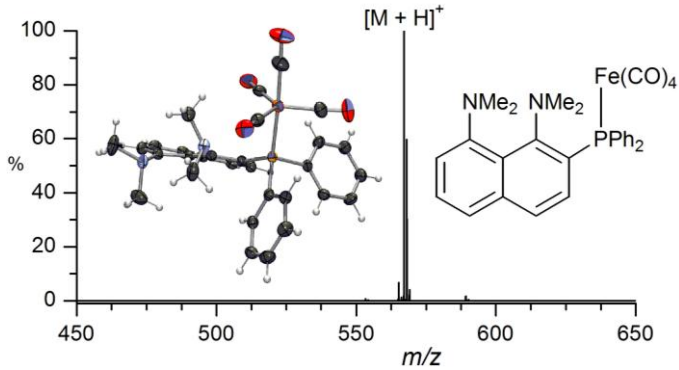


Figure 7. Spectrum and structure of the $Fe(CO)_4$ complex of a proton sponge-functionalised phosphine ligand. Reproduced with permission of the Royal Society of Chemistry from reference 18.

2.6.1.3 Ion association

Molecules can be observed as $[M + M']^+$ ions, where M' is usually Li^+, Na^+, K^+ but also NH_4^+, depending on what is present in solution. Such associations require a site somewhere on the molecule which has a partial negative charge δ–. Phosphine oxides R_3PO work well, but even carbonyl ligands on sufficiently electron-rich metal complexes may associate with an alkali metal ion. Frequently there are enough adventitious cations around to observe this process, but small amounts may be added to enhance the effect or to reduce ambiguity (e.g. addition of Na^+ will simplify the MS if adducts are also present from Li^+, K^+, etc.). Silver ions, Ag^+, can be added to organometallic complexes that contain a metal-metal bond to provide an $[M + Ag]^+$ ion via addition across the bond.[19]

2.6.1.4 Deprotonation

Complexes with acidic protons can appear as $[M - H]^-$ ions, and the proton in question does not have to be especially acidic. For example, the methylene protons in bis(diphenylphosphino)methane (dppm) ligands are sufficiently acidic to facilitate analysis,[20] and this property was used to good effect in the examination of the Pauson-Khand reaction (see section 5.2).

2.6.1.5 Charged ligands

Complexes can be made amenable to ESI-MS by appending a ligand that carries a charge remote from the binding site.[21] There are many syntheses that can acheive this end, but as most chemists are unlikely to go to these sorts of lengths without having a very specific purpose for doing so, just one will be mentioned here. Commercial bis- and trisphosphines may be monoalkylated in a single high-yielding step to replace one of the phosphine functional groups with a phosphonium group. The ligands function as mono- or bisphosphines, and the charge makes them readily detected using ESI-MS, both free and when bound to the metal. In the analysis of catalytic systems, which typically involve labile ligands, simply doping in the charged ligand to a system of interest is sufficient (Figure 8).[22]

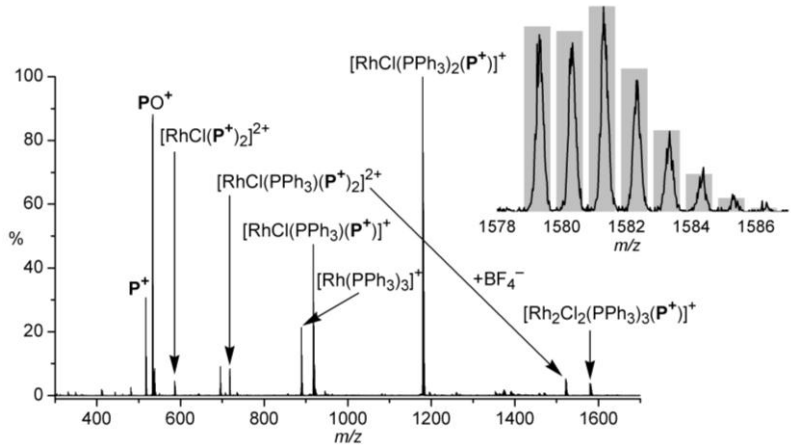


Figure 8. Positive-ion ESI-MS of $RhCl(PPh_3)_3$ and $\mathbf{P}^+$ ($\mathbf{P}^+ = PPh_2C_4H_8PPh_2CH_2Ph$) in chlorobenzene at a cone voltage setting of 10 V. Inset shows the isotope pattern match for $[Rh_2Cl_2(PPh_3)_3(\mathbf{4}^+)]^+$ (calculated pattern in grey bars). Modified with permission of the Royal Society of Chemistry from reference 22.

2.6.1.6 Derivatisation

Metal carbonyl compounds usually provide poor ESI-MS, but can be derivatised by taking advantage of a reaction general to this class of compound: formation of an alkoxy carbonyl ligand through treatment with alkoxide ion, providing a readily detectable $[M + OR]^-$ ion in the negative ion mode.[23] The reaction is fast and selective.

2.6.1.7 Halide loss

Transition metal halide complexes L_nMX may appear in ESI mass spectra as $[M - X]^+$ ions.[24]

2.6.2 Solvents

ESI-MS works well with polar solvents, and tetrahydrofuran, diethylether, dichloromethane etc. all provide acceptable spectra. As a rule of thumb, the more volatile and less polar the solvent, the more the desolvating conditions should be moved to minimum settings. Dichloromethane, for example, can provide good spectra even when there is no heating of source or desolvation gas, and any in-source fragmentation is set as low as possible (energising the ions in the source improves transmission and desolvation at the expense of making the technique somewhat less gentle).[25] The reason non-polar solvents such as toluene or hexane don't work at all in ESI-MS is probably due to the requisite electrochemistry being shut down, so a supporting electrolyte must be added to make it work. This can be in the form of any lipophilic ionic compound, and the ionic liquid $[P(C_6H_{14})_3(C_{14}H_{29})][NTf_2]$ works well for this purpose.[26] Once the ESI-MS process is thus enabled, analysis proceeds in conventional fashion, though of course the lipophilic ions also appear in the spectrum (Figure 9). Provided these signals do not overlap with ions of interest, they do not cause any difficulty.

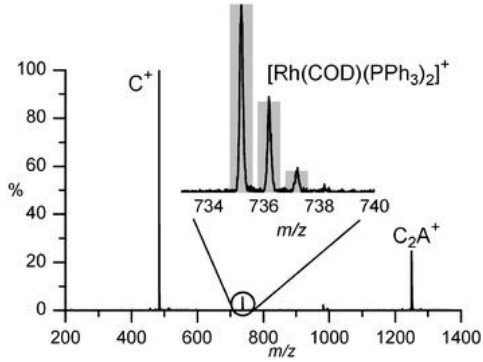


Figure 9. Positive-ion ESI-MS of $[Rh(COD)(PPh_3)_2]^+$ in cyclohexane/$[P(C_6H_{14})_3(C_{14}H_{29})][NTf_2]$. Inset: expansion of isotope pattern match for the analyte. Modified with permission of the Royal Society of Chemistry from reference 26.

2.6.3 Air- and moisture sensitive organometallics

Many organometallic chemists handle their compounds exclusively under inert atmosphere due to air and moisture sensitivity, and rarely have success with ESI-MS due to the inescapable fact that parts of the instrument are shared by all users. The liklihood of acquiring good data on a highly reactive organometallic complex a few minutes after someone has run an acidic water/acetonitrile solution through the same capillary minutes before is near-zero. However, there are precautions that may be taken that improve the situation. All users should have their own infusion system: a gas-tight syringe and the appropriate chromatography fittings to connect to the MS. Not sharing this with other users limits cross-cotamination to that caused by sharing of the capillary alone. Flushing the system with dry, oxygen-free solvent and simultaneously baking the source and desolvation gas at high temperature is an important first step. A high desolvation gas flow also minimises the extent to which air leaks into the system. Finally, running a relatively high concentration of sample for a very short period is better than a low concentration for an extended period, though of course care has to be taken to minimize contamination for other users. The highest concentrations should still be 20-400× lower than that used for ^{1}H NMR (this represents a dilution of 1 drop in 1 ml for 20×, repeated for 400×), depending on the ionization efficiency of the sample. The ultimate precaution is to mount a glovebox at the front end of the instrument (Figure 10).[27]

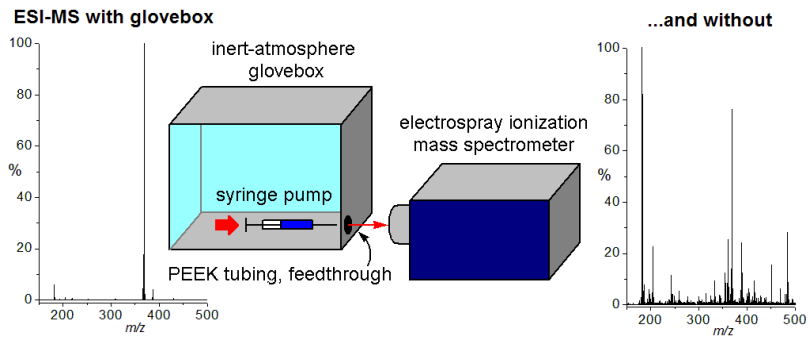


Figure 10. Cartoon of glovebox/ESI-MS combination, and the effect on the MS obtained with and without the glovebox in place. Reproduced with permission of the American Chemical Society from reference 27.

2.7 Recently developed ionisation methods

Two promising ionisation methods have been developed in the last few years, Direct Analysis in Real Time (DART) [28] and Desorption Electrospray Ionisation (DESI).[29] Both involve energetic species impinging on a surface (electronically excited atoms or vibrationally excited molecules in the case of DART, charged droplets in the case of DESI), desorbing and ionising surface analytes without requiring any sample preparation. Both are designed for open-lab use, and so have not found use in organometallic chemistry as yet. However, the ease of analysis means that applications will no doubt arise, especially if means of protecting the sample from decomposition are devised.

2.8 Summary of ionisation techniques

What ionisation technique to choose? Few organometallic chemists have the luxury of the full range of options, but given a choice, the following table gives the method that is most likely to provide good data provided the appropriate precautions are taken to avoid decomposition through exposure to air.

Multiply charged ions:	ESI
Singly charged ions:	ESI, MALDI, FAB/LSIMS
Highly polar molecules:	ESI, MALDI, FAB/LSIMS, (LI)FDI,
Slightly polar molecules:	MALDI, (LI)FDI, FAB/LSIMS, (AP)CI, ESI
Non-polar molecules:	EI, (LI)FDI

3 Compositional information from MS

3.1 Resolution

Resolution is the ability of an instrument to discriminate between ions of similar *m/z* value. It is most commonly defined in modern instrument by $m/\Delta m$, where m is the mass of the ion and Δm is the **f**ull peak **w**idth at **h**alf **m**aximum intensity (FWHM definition), so a peak at 500 *m/z* with a width of 0.1 *m/z* represents a resolution of 500/0.1 = 5000. The higher the number, the better, but for reasons that will be outlined below, there are other issues that should occupy the organometallic chemist before fretting over resolving power.

3.2 Mass analysers

There are a host of different mass analysers: all do the job of separating ions by their mass-to-charge ratio, and there is a fairly close relationship between cost and maximum resolution. A brief summary, in order of increasing performance:

1. **Quadrupole (Q)**. Small, robust, inexpensive scanning mass analysers. Four parallel rods in a square array transmit ions of a particular *m/z* depending on the exact combination and frequency of applied electric field. Typical resolution of ~1000 under normal operating conditions, may be improved by a factor of 2-3× by trading off sensitivity for resolution.
2. **Ion trap**. Also small and robust; mass analysis is performed by

sequentially ejecting ions by their *m/z* ratio from a complicated orbit inside a cell partially filled with He and defined by various curved electrodes. The primary advantage of ion traps is the ability to perform multiple steps of MS/MS in time (that is, in the same mass analyser, but sequentially = MS^n). Resolution is similar to quadrupoles.

3. **Time-of-flight (TOF)**. The group of ions is accelerated down a drift tube by application of an electric field, and as all are given the same amount of kinetic energy their velocities differ according to their mass ($E = mv^2$). Timing how long each ion takes to reach the detector enables a mass spectrum to be collected. The use of reflectrons, ion mirrors that effectively double the length of the drift tube and focus ions, greatly improve the resolution of TOF instruments. Particularly well suited to pulsed ionisation techniques such as MALDI, orthogonal TOFs are also common where a section of a continuous ion beam is pulsed down the flight tube at 90° to the original direction of the beam. Resolution is of the order of 10,000 in a modern instrument, though varies with the length of the drift tube, number of reflectrons, etc.
4. **Sector**. Curved magnets (B) and electrostatic analysers (E) combine to focus a beam of ions by their momentum and kinetic energy, respectively. Sector instruments are bulky and expensive but capable of excellent resolution, >20,000.
5. **Orbitrap**. The orbitrap is the most recently devised mass analysis method, and is a type of ion trap in which the electrodes are an inner spindle and an outer barrel. The ions orbit around the inner spindle, and move back and forth along the central axis at a frequency that is characteristic of their *m/z* ratio. The resolving power is improved with acquisition time, and can reach values as high as 200,000, the best resolution achievable with electric fields alone.
6. **Fourier transform ion cyclotron resonance**. Ions are trapped in circular orbit by a very strong magnetic field, achieved inside a large, superconducting electromagnet. Ions orbit with a frequency related to their *m/z* value, and their passage is recorded by the image current they generate in the walls of the trapping cell. Ions can be trapped indefinitely, and the mass resolution of FTICR instruments is unmatched, with values in excess of 1,000,000 having been achieved. MS^n may be performed. They are large and very expensive to buy and maintain.

Analysers that trap ions in a volume are inherently capable of multiple stages of MS (MS^n) "in time"; that is, the trap is used to select a particular ion, and the remainder are ejected from the cell. The remaining ions are energised and fragmented through collision with atoms (e.g. He, Xe). The product ions may either be scanned to generate an MS/MS spectrum or the process of selection and fragmentation repeated.

Many modern instruments include tandem mass analysers, with a collision cell separating the two. "Triple quads" (QqQ) are the most common of these, though the collision cell is not always a quadrupole (hexapoles, h, are often used) and even if it is, only the first and last quadrupoles are used for mass analysis. Hybrid instruments are those that couple two different types of mass analyser: the quadrupole/time-of-flight (QqTOF) being the most frequently encountered hybrid instrument. FTICRs are often coupled to an ion trap, which collects, stores and selects ions prior to

injection into the FTICR cell.

3.3 Accurate mass

The elements of most interest to the organic chemist are primarily monoisotopic: H, C, N, O, etc., so compounds like $C_{12}H_{16}O_6$ (256.0942 Da) can be distinguished from $C_{16}H_{16}O_3$ (256.1094 Da) despite having the same nominal mass, because their exact mass differs by 0.0152. Organic chemists routinely use exact masses as proof of composition; agreement of theoretical and calculated values to within 5 ppm is a typical standard for low mass organic compounds (mass accuracy in parts per million = $10^6 \times \Delta m/m_{observed}$). The reverse also works: given an accurate mass, a composition can be calculated. For organometallic chemists, the situation is rather different. The majority of metals are polyisotopic, as are many non-carbon based ligands. The number of different elements in play are usually much higher. Even with an accurate mass, the number of possible hits within 5 ppm is liable to be large, and so assignment of composition by this method can be fraught with ambiguity.

3.4 Isotope patterns

Organometallic chemists can use the combination of nominal mass and isotope pattern to provide convincing compositional information. The majority of metals of interest to organometallic chemists are polyisotopic, and only a few are monoisotopic (cobalt, rhodium and gold are notable examples). For example, the cationic tin compound $[Br_2Sn(C_4H_8Br)(C_4H_8MC_5H_5)]^+$ provides a rich isotopic signature characteristic predominantly of the combination of one tin (10 isotopes) and three bromine (two isotopes) atoms (Figure 11).[30]

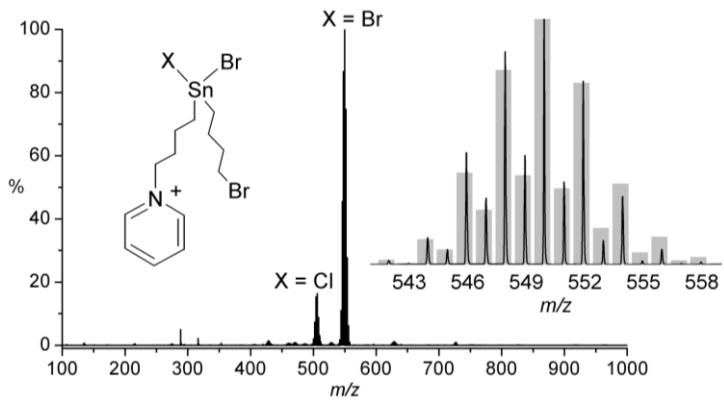


Figure 11. The match between theoretical (grey bars) and experimental (black line) in the inset gives compelling evidence for the identity of the ion as $[Br_2Sn(C_4H_8Br)(C_4H_8MC_5H_5)]^+$. Reproduced with permission of the Royal Society of Chemistry from reference 30.

4 MS/MS

Many modern instruments that employ soft ionisation methods have the capability for MS/MS analysis. For the purposes of structural characterisation, this means the generation of product ions from a precursor ion selected by the first stage of MS, the

so-called "product ion scan". The other types of scan are the precursor ion scan, in which the second analyser is set and the first analyser scanned; the neutral loss scan, in which both analysers are scanned, but the second offset by a fixed amount from the first; and selected reaction monitoring, where both analysers are set at fixed values. These last three are primarily analytical techniques designed to boost sensitivity limits for a given class of compounds, and are usually run in conjunction with chromatographic techniques (GC or LC). They also only work with MS/MS "in space", that is, two mass analysers. MS^n-capable instruments (MS/MS "in time") cannot do these experiments.

Because product ion scan MS/MS is applied primarily to soft ionisation techniques in which even-electron quasimolecular ions are produced, the discussion here will focus on these examples.

4.1 Collision-induced dissociation

There are a number of ways to activate an ion to induce it to fragment, including activation by surface impact or irradiation, but the most common method is collision induced dissociation (CID). The selected ion is accelerated in the presence of noble gas atoms (He in ion traps, but usually Ar or sometimes Xe in other types of MS) or nitrogen, and collisions result in the conversion of translation energy into internal energy. Sufficient energy results in fragmentation of the precursor ion to make product ions, and this process happens in a rational enough way so as to provide basic structural information. CID is usually performed in a collision cell located between two mass analysers ("in space") or in the trapping cell of an MS^n instrument ("in time"), but can also be executed in the source. In-source CID occurs between the atmospheric pressure of the source and the vacuum of the mass spectrometer; a voltage is applied across the skimmer cones (hence the term "cone voltage") that separate the differentially pumped volumes in this region, and this accelerates the ions in just the same way as in a collision cell.

A traditional way to think about ligands in organometallic complexes is to divide them into X and L types.[31] X-type ligands (e.g. halides, hydrides, alkyls) are anions in their free form, whereas L-type ligands are neutral (e.g. carbonyls, phosphines). Other ligands can be represented as combinations of these types (e.g. cyclopentadienyl ligands would be L_2X). CID generally results in loss of L-type ligands first, because L-type ligands are generally stable as free entities. Removal of X-type ligands require bond homolysis and formation of a radical, $X^{\bullet}$, a higher energy process. For example, the complex $[RhCl(PPh_3)(PPh_2C_4H_8PPh_2CH_2Ph)(\eta^4$-cyclohexadiene$)]^+$, which carries a charged phosphine/phosphonium ligand, fragments in a predictable way under CID. Loss of a chlorine radical is not observed; instead, the complex decomposes predominantly by phosphine ligand dissociation (Figure 12).

Note that the MS/MS data allows clear identification of three of the four ligands, and the remaining component (RhCl) can be easily assigned through combination of mass and isotopic data. The fragmentation pathway that leads to loss of C_6H_8 is a minor one, and this feature is common to all chelating ligands: they are much harder to remove by CID than the corresponding monodentate ligands.

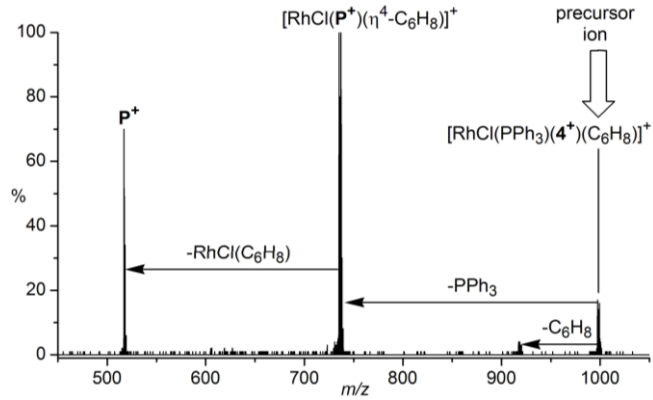


Figure 12. MS/MS of $[RhCl(PPh_3)(\mathbf{P}^+)(\eta^4\text{-}C_6H_8)]^+$. Only a small proportion of the product ions involve loss of C_6H_8; the predominant fragmentation pathway is loss of PPh_3 then $\mathbf{4}^+$. Reproduced with permission of the Royal Society of Chemistry from reference 22.

Multiply-charged organometallic complexes fragment following the same rules, but the resulting spectra can be complicated by the fact that dissociation can yield two charged product ions rather than a product ion and a neutral molecule. For example, $[Rh(PPh_3)(PPh_2C_4H_8PPh_2CH_2Ph)_2Cl]^{2+}$, an analogue of Wilkinson's catalyst, carries two charged ligands, so loss of one generates two cationic fragments. This process is unambiguously detected by the appearance of two monocations equally spaced away from the precursor ion at lower and higher *m/z* values (Figure 13).

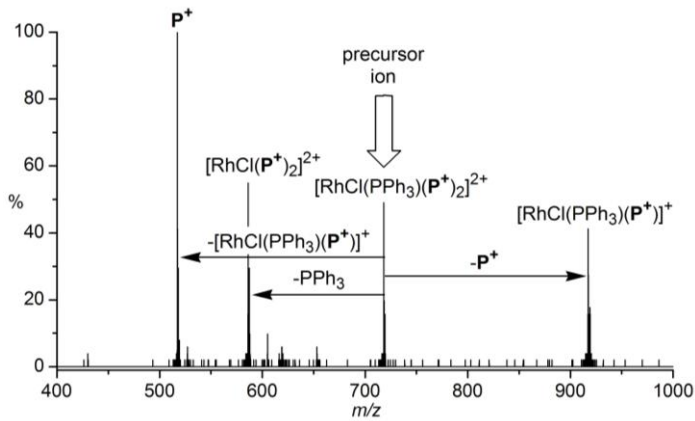


Figure 13. MS/MS of $[RhCl(PPh_3)(\mathbf{P}^+)_2]^+$ ($\mathbf{P}^+ = PPh_2C_4H_8PPh_2CH_2Ph$). Loss of PPh_3 (586 *m/z*) and loss of $\mathbf{P}^+$ (generating two charged fragments, $\mathbf{P}^+$ at 517 *m/z* and $[RhCl(PPh_3)(\mathbf{P}^+)]^+$ at 917 *m/z*) are competitive; while $\mathbf{P}^+$ is a better ligand, it experiences Coulombic repulsion from the other charged ligand and is therefore eliminated more easily). Reproduced with permission of the Royal Society of Chemistry from reference X.

The complex $[Rh_2(\mu\text{-}Cl)_2(PPh_3)_3(PPh_2C_4H_8PPh_2CH_2Ph)]^+$, a charged version of Wilkinson's dimer, fragments under CID by splitting in half rather than by loss of a phosphine ligand (Figure 14). This process is analogous to this compound's solution chemistry: the phosphine ligands are inert, and the complex dissociates in the same

fashion as observed in the gas phase.

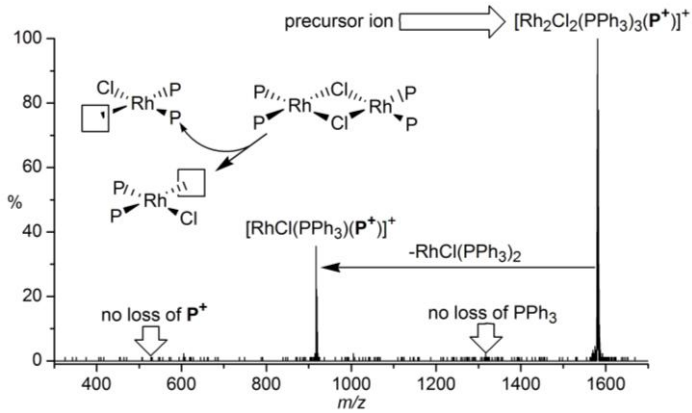


Figure 14. MS/MS of $[Rh_2Cl_2(PPh_3)_3(\mathbf{4}^+)]^+$. Neither loss of PPh_3 or loss of 4^+ ($PPh_2C_4H_8PPh_2CH_2Ph$) is observed; instead, the dimer cleaves in two symmetrically. Reproduced with permission of the Royal Society of Chemistry from reference 22.

Apart from homolytic cleavage of a bond, another way in which X-type ligands are lost from organometallic complexes is in a pair, by reductive elimination. The normal rules for reductive elimination apply – there needs to be a stable oxidation state two lower than in the original complex and the X ligands need to be adjacent. This process can also follow intramolecular oxidative addition, so if a complex undergoes gas-phase *ortho*metallation of a triphenylphosphine ligand, it may subsequently reductively eliminate HX.

As a general rule, the first few fragmentations are reasonably easy to assign, the remainder less so, especially if X-type ligands are all that remain on the metal.

4.2 Energy-dependent ESI-MS

One of the issues with interpreting data generated by CID, whether in the source or in the collision cell, is that establishing a default setting to provide just the right amount of fragmentation for all compounds is not plausible. At some CID settings, one complex might have undergone numerous fragmentations, while others are entirely intact. For example, at a cone voltage of 15 V, the aforementioned $[Rh(PPh_3)_2(PPh_2C_4H_8PPh_2CH_2Ph)Cl]^+$ exists only as the $[M - PPh_3]^+$ ion, whereas the dimeric $[Rh_2(\mu\text{-}Cl)_2(PPh_3)_3(PPh_2C_4H_8PPh_2CH_2Ph)]^+$ is entirely unaffected. Accordingly, there is a need to collect data at a range of values so as to ensure that all fragmentation processes of interest are observed. A brute force approach is to collect data at all values of CID energies, and display the entire collection of spectra (as many as 200) in the form of a contour map, where ion intensity at a given value of *m/z* vs. CID energy provides the topological information. Such a presentation of data is known as "energy dependent",[32] and Figure 15 shows an example for an anionic transition metal carbonyl cluster, $[H_3Ru_4(CO)_{12}]^-$.[33]

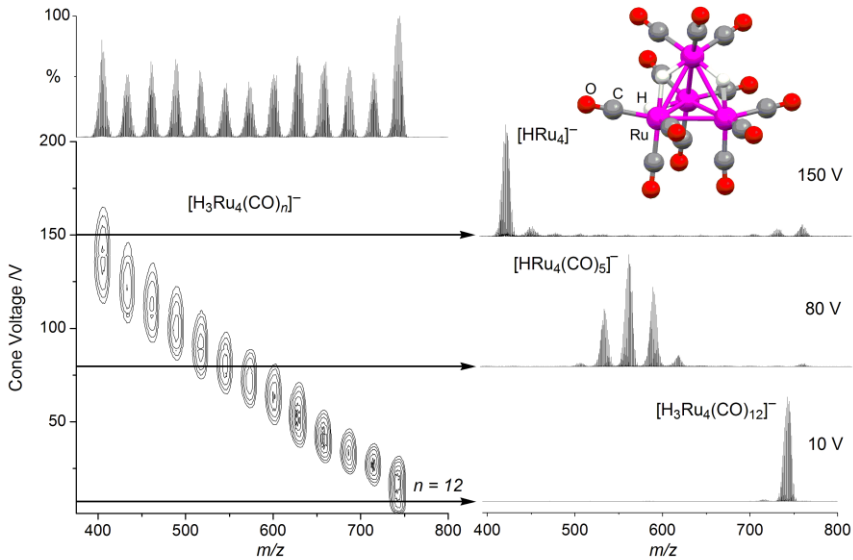


Figure 15. The left-hand contour plot of $[H_3Ru_4(CO)_{12}]^-$ clearly shows the loss of twelve CO ligands as the cone voltage is increased. The three conventional mass spectra at the right provide snapshots of the ligand stripping process, at 10, 80, and 150 V; note the number of product ions missing from this portrayal. Inset: structure of the anionic ruthenium carbonyl cluster $[H_3Ru_4(CO)_{12}]^-$. The Ru atoms describe a tetrahedron; each Ru atom has three terminally-bound CO ligands and hydride ligands bridge three of the six Ru–Ru bonds. Reproduced with permission of the American Society for Mass Spectrometry from reference 33.

Note that at any particular value of cone voltage, the spectrum contains only about 3-4 product ions, of 12 in total. The fragmentation involves sequential stripping of all 12 carbonyl ligands and two of the hydrides (as H_2) to ultimately generate $[HRu_4]^-$. EDESI-MS is most useful when applied to ions that generate many product ions or when the order in which product ions are formed is important. If only a few ions are of interest, breakdown graphs may be more appropriate.

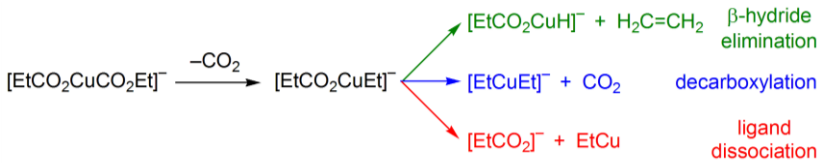
5 Gas phase reactivity

There have been an enormous number of studies on the gas phase reactions of metal cations with molecules to generate organometallic complexes.[34-36] However, because the reacting metal cations are generally unligated or with a single ligand only, the chemistry observed has no solution counterpart. Instances in which the *reacting* metal complex is organometallic and generated from a low-energy process do have relevance to the synthetic chemist and the handful of examples here will be drawn from this second approach.

Gas phase species are inherently reactive, as no solvent needs to be displaced. Encounters between an ion and a molecule are sufficiently long-lived that all possible orientations are sampled. The result is that despite the low pressure and short reaction time, favorable reactions proceed quite readily and the analogy between solution and gas phase reactivity is often quite strong. Experimentally, the primary requirement is simply to introduce the molecule of interest to the same region of space as the ion to be analyzed, and allow them to collide. In order for reactions to be registered as such, they must of course involve a change in mass.

5.1 Organometallics via gas phase decarboxylation

The O'Hair research group has demonstrated that a modified 3D quadrupole ion trap can be used as a "chemical laboratory" in which organomatallic complexes can be synthesised, purified and reacted with small molecules in the gas phase.[37] For example, the anionic copper dicarboxylate, $[Cu(CO_2Et)_2]^-$, readily undergoes decarboxylation under CID conditions followed by one of three fundamental reactions: β-hydride elimination, further decarboxylation or ligand dissociation:[38]



The innate reactivity of the organometallic products generated from various metal carboxylates can be probed in detail by allowing them to react with water and other simple molecules.[39-41]

5.2 Pauson-Khand reaction

Norbornene was introduced to the collision cell of a modified triple quadrupole and allowed to react with mass-selected $[Co_2(CO)_3(Ph_2PCHPPh_2)(\mu\text{-HCCPh})]^-$, a putative intermediate in the Pauson-Khand reaction (formation of a cyclopentenone from an alkyne, and alkene and carbon monoxide).[42] The gas phase reaction showed clearly the formation of $[Co_2(CO)_3(Ph_2PCHPPh_2)(\mu\text{-HCCPh})(\text{norbornene})]^-$, in which the norbonene occupies the vacant coordination site (Figure 16). Remarkably, this represented the first identification of an intermediate in what is doubtless a mechanistically complex reaction.

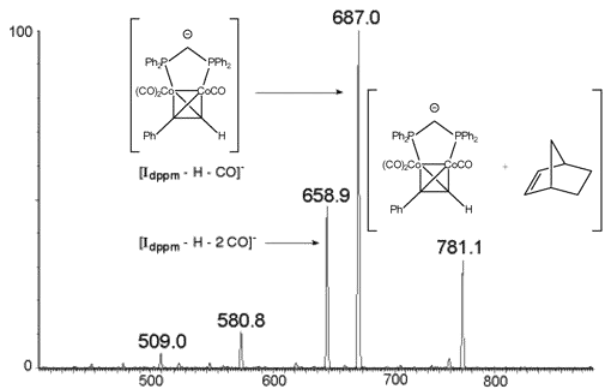


Figure 16. ESI-MS of $[Co_2(CO)_3(Ph_2PCHPPh_2)(\mu\text{-HCCPh})]^-$, *m/z* 687 (and its reaction with norbornene). Reproduced with permission of the American Chemical Society from reference 42.

5.3 Catalyst screening

The Chen group has demonstrated the utility of ESI-MS in screening of catalysts,[43] and a key component of their approach is the use of gas-phase reactions to probe the

activity of known or suspected catalysts. Triple quadrupole mass spectrometers are modified by the replacement of the collision cell and ion guides with "high pressure" multipole (octopole or even 24-pole) reaction cells, thus enabling a great increase in the number of collisions the ions undergo before exiting. This strategy has enabled the detailed examination of a wide range of classic reactions in organometallic chemistry, including hydrogenation,[44] olefin polymerisation,[45] olefin metathesis,[46] aldehyde olefination [47] and C-H activation.[48] The example in Figure 17 shows the gas-phase reaction between a cationic Hofmann carbene and a vinyl ether to probe basic metathesis activity. If the vinyl ether was substituted for norbornene, multiple additions of the substrate could be observed, hence accessing gas-phase polymerisation.

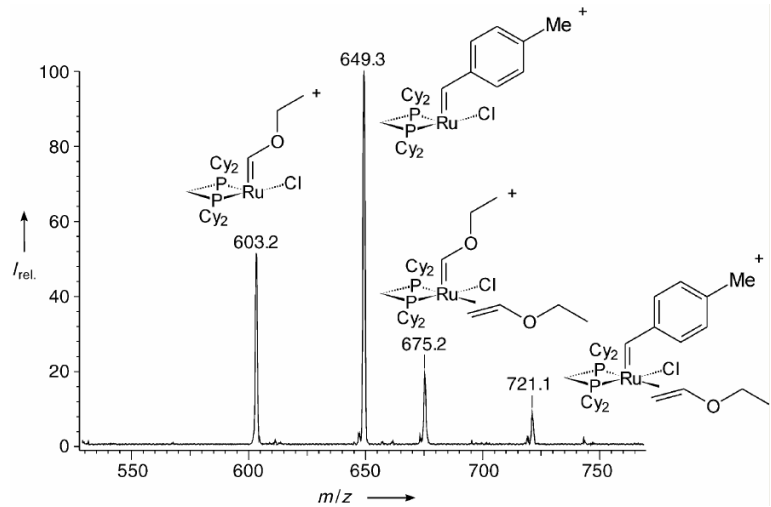


Figure 17. Representative mass spectrum from the reaction of a Hofmann carbene complex with ethyl vinyl ether in the gas phase. One isotopomer of the starting complex, preselected by mass, appears at *m/z* 649. The adduct mass at *m*/z 721 is assigned as the π complex; the signal at *m/z* 603 is the metathesis product. Coordination of another substrate gives *m/z* 675. Reproduced by permission of Wiley VCH from reference 43.

6 Conclusions

Mass spectrometry is a powerful and fast analytical tool, and diverse methods have been developed capable of delivering samples into the gas phase and ionising them to facilitate separation. It has few peers in its ability to rapidly analyse complex mixtures. Many of the methodological and technological challenges preventing routine analysis of organometallic compounds have been met, but it remains true that there is no standard approach that will successfully meet all the needs of the organometallic chemist. A sound understanding of the various options available and their strengths and weaknesses is key to providing the correct mass spectrometric answer to a characterisation problem, and this review only skims briefly over what is a large, dynamic and constantly growing area of research and development.

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