2.30
Electrospray Mass Spectrometry

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Electrospray mass spectrometry (ESMS) was developed primarily by Fenn and co-workers in the mid 1980s, an achievement for which Fenn won the 2002 Nobel Prize for Chemistry.[1] Initially exploited for the analysis of thermally fragile and high-molecular-weight materials including proteins and polymers, recently there has been an exponential increase in applications involving coordination complexes. It is a very gentle ionization process (involving transfer of solution ions to the gas phase), and therefore typically yields molecular ions with little or no fragmentation. The simplicity (and thus ease of interpretation) of spectra obtained by this technique is of great benefit. However, ions generated by the electrospray ionization process can be easily fragmented using established techniques such as collision-induced dissociation (CID).

Reviews covering the basic principles behind electrospray ionization mass spectrometry,[2–6] and applications in inorganic, coordination,[7–11] and organometallic[12,13] chemistry have appeared.

2.30.1 THE IONIZATION PROCESS

In the electrospray process, a dilute solution is sprayed from a metal capillary held at a high voltage (ca. 3,000 V) into a chamber which is at atmospheric pressure. A fine spray of charged solution droplets is produced, from which the solvent is evaporated by a stream of warm gas (usually nitrogen) to give gas-phase ions. The nature of the desolvation process has been the subject of much debate, with the two main theories proposed involving either ion evaporation from the surface of the charged droplet, or a more catastrophic process involving a Coulombic explosion. The gas-phase ions are separated using a variety of techniques. Modern instruments may be found with quadrupole, quadrupole ion trap, Fourier transform ion cyclotron resonance (FTICR), magnetic sector, or time-of-flight (TOF) mass analyzers, with tandem (MS/MS) mass spectrometers becoming increasingly popular. The key features of electrospray ionization are that the sample is introduced as a dilute solution (so direct analysis of reaction mixtures can be easily carried out), the gentle nature of this ionization process, and the ability to couple with liquid chromatographic (LC) separation techniques, giving LC–MS. Sample volatility is not a requirement, unlike ionization techniques such as electron impact. Like all forms of mass spectrometry,

Table 1 Major types of positive ions observed for various types of coordination compounds.*

| Complex	Major positive ion species**
$[L^a nM]$	$[L_n^a M + H]^+$, $[L_n^a M + H + \text{solvent}]^+$, $[2L_n^a M + H]^+$ (and analogous ions from the presence of Na^+, K^+, NH_4^+)
$[L^b nM]$	$[L_n^b M]^{\bullet+}$
$[L^c nM]$	$[L_n^c M + Ag]^+$, $[L_n^c M + \text{solvent} + Ag]^+$ (with added Ag^+)
$[LnMXm]$	$[M-X]^+$, $[M + \text{solvent} - X]^+$
$[LnM]^+$	$[LnM]^+$, $[(LnM)_2 + \text{anion}]^+$
$[LnM]^{2+}$	$[LnM]^{2+}$, $[LnM + \text{anion}]^+$, $[LnM - H]^+$, $[LnM + \text{solvent} - H]^+$
$[LnM]^{3+}$	$[LnM]^{3+}$, $[LnM + \text{anion}]^{2+}$, $[LnM + (\text{anion})_2]^+$, $[LnM - H]^{2+}$, $[LnM + \text{solvent} - H]^{2+}$, $[LnM + (\text{solvent})_2 - 2H]^+$

[a] With basic sites. [b] Electron-donating. [c] With unsaturated groups; X: halide. * At higher fragmentation energies, weakly associated solvent molecules are lost first followed by stripping of neutral monodentate ligands. Formally charged ligands are difficult to remove by CID, as are chelating ligands and those with high hapticity. ** Negative ions of significant intensity are generally seen only for neutral complexes bearing acidic protons, or for anionic complexes. Spectra are typically uncomplicated, consisting of $[L_n M - H]^-$ ions or $[L_n M]^{x-}$, respectively.

ESMS requires very little sample for analysis, picomolar concentrations being easily accessible under ideal conditions. For many types of coordination complex, the electrospray technique can be considered to give a representative picture of the species present in solution. Indeed, in cases where other solution techniques (such as NMR spectroscopy, ESR spectroscopy) have been used to identify solution species present, there is generally good agreement between the various methods.[14]

The isotopic richness of elements present in most coordination complexes means that the use of a simulation program (if not included with the mass spectrometry software, available separately[15] or online (e.g., the "Chemputer" at http://www.shef.ac.uk/chemistry/chemputer/isotopes.html)) is important in ion assignment. Accurate mass determination ($\pm 0.0001\, m/z$) is less commonly employed due to the high likelihood of ambiguity in the ion composition at high mass.

For coordination complexes, observed ions can be generated by a range of processes, one or more of which may operate for a given complex. The principal types of ions commonly observed are summarized in Table 1.

(i) Charged complexes may give the parent ions (if the charge density of the ion is relatively low) or less-highly charged fragment ions derived from the parent, if the charge density is high. Electrospray ionization is equally amenable to the analysis of cations or anions, by reversal of the appropriate potentials in the instrument.

(ii) Neutral complexes M can ionize by aggregation with a solution cation (X^+) to give detectable $[M + X]^+$ positive ions, providing that a suitable "basic" site (e.g., ether, amine, ketone, alcohol) is present in the complex. In the case of protic solvents or mixtures thereof (e.g., alcohols, alcohol–water or acetonitrile–water mixtures, in which most complexes, even "sparingly soluble" ones, are sufficiently soluble) the cation is typically a proton, or an adventitious (or deliberately added) alkali metal[16] or ammonium cation present in the solvent. An example, that of $Cr(acac)_3$, (Figure 1) illustrates the observation of dominant $[M + H]^+$ and $[2M + NH_4]^+$ ions, together with several low-intensity ancillary ions. Alternatively, non-protic solvents (e.g., tetrahydrofuran) in combination with a suitable cation source such as potassium iodide[17] can be used for compounds susceptible to protonolysis.

(iii) Coordination complexes which contain a relatively labile anionic ligand can ionize by loss of this ligand to give a detectable cation, which can be solvated, depending on the fragmentation conditions chosen. A wide range of transition metal halide complexes have been found to ionize via this pathway.[18]

(iv) In some special cases, the charged probe tip can act as an electrochemical cell, giving oxidized ions in the electrospray spectrum.[19] Thus, electron-rich substrates such as alkyl-substituted metalloporphyrins can be oxidized to give $[M]^{\bullet+}$ ions rather than, e.g., protonated $[M + H]^+$ ions.[20,21] Alternatively, electrochemical ionization can be carried out prior to analysis.[22]

[M + H]⁺

[2M + NH₄]⁺

[2M – acac]⁺

[M + NH₄]⁺

Relative Intensity (%)

m/z
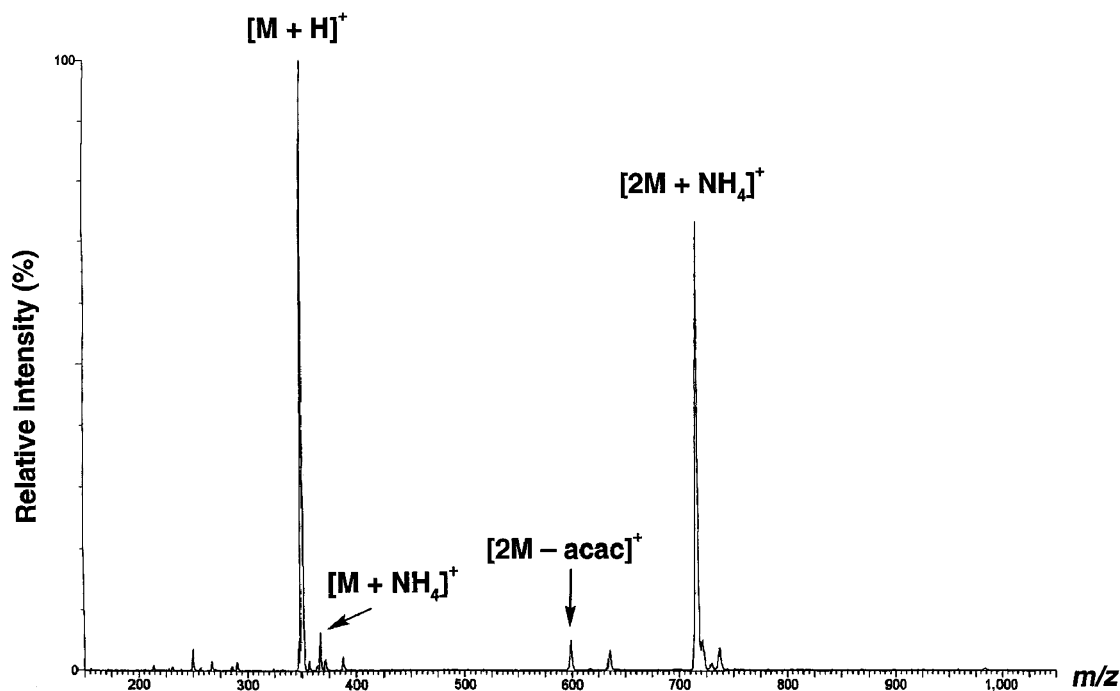
Figure 1 Positive ion electrospray mass spectrum of $Cr(acac)_3$ in MeCN–H$_2$O solvent, using a cone voltage of 25 V. acac = $CH_3COCHCOCH_3$.

(v) For the characterization of ligands by ESMS, coordination complexes may be generated *in situ* by addition of a suitable metal ion; the use of Ag^+ ions has been used to derivatize a range of phosphine and arsine ligands, allowing mass spectrometric characterization.[23] Complexes with arene ligands can also interact with Ag^+ ions.

2.30.2 STRUCTURAL INFORMATION

Electrospray ionization is a very convenient and successful means of generating gas-phase ions from a variety of substrates. These ions can then be subjected to fragmentation processes in order to yield structural information. CID can be easily achieved in most commercial electrospray mass spectrometers by acceleration of the ions by means of an applied cone voltage (a potential difference applied across two cones which accelerates the ions, causing collisions with gas and residual solvent molecules) or its equivalent. The advantage of this approach is that the degree of fragmentation can be carefully tuned. A singly charged parent ion will often undergo loss of neutral ligand molecules in the initial stages, whereas a multiply charged ion will typically fragment by loss of a charged species or gain of a counterion, to reduce the charge on the parent ion.

Energy-dependent electrospray ionization mass spectrometry (EDESI-MS) uses a map of cone voltage versus *m/z* upon which ion intensity is plotted, which provides a complete picture of the fragmentation pattern particularly suitable for the structural analysis of mixtures.[24,25]

2.30.3 APPLICATIONS

Many types of coordination compounds have been characterized by ESMS; a selection of examples is given in Table 2.

ESMS is particularly useful for the analysis of solutions containing rapidly exchanging,[26] or paramagnetic species, which are less readily accessed by other solution techniques such as NMR spectroscopy. Studies of kinetically labile equilibria have been carried out, and it was concluded that it would only be difficult to quantify species distributions which change during the 5 µs timescale for ion desorption from an evaporating droplet.[27] Metal–ligand binding constants and relative stabilities of metal–ligand combinations can be determined, such as between alkali metal cations and crown ethers,

Table 2 Coordination complexes which have been studied by ESMS.

Class of complex	References
Oxo, nitrido, and imido complexes	42–44
Metal phosphine complexes	18,45,46
Metal halide complexes	18,47
Polyoxometallate anions	48–51
Alkoxide complexes	28–31,52
Thiolate complexes	53,54
Dithiocarbamate complexes	55
Polypyridyl complexes including supramolecular derivatives	56–58
Macrocyclic complexes	59,60
Metallodendrimers	61,62
Diketonate complexes	63
Metal derivatives of peptides and proteins	64,65

cryptands, or other macrocycles.[28–31] Reactive intermediates[32] and complexes formed during catalytic processes can also be detected.[33,34] Electrochemical cells can also be coupled to ES instruments, such that charged species generated electrochemically can then be analyzed directly.[35] ESMS is ideal for the rapid screening of microscale reactions (thus minimizing wastage), and directing subsequent synthetic chemistry on the macroscopic scale. An example is the coordination chemistry of the metalloligands $[Pt_2(\mu\text{-}E)_2(PPh_3)_4]$ (E = S, Se), which form chalcogenide-bridged aggregate cations with a diverse range of metal–halide substrates.[36,37]

2.30.4 COMPLICATIONS

Low-mass, highly charged ions have a limited stability in the gas phase, and anions will either lose electrons or negatively charged fragments, while small, charged cations will often react with the solvent with the formation of, e.g., oxo or hydroxo species.[38–40] Copper(II) complexes often undergo reduction to copper(I).[41] Spectra may be complicated by competing ionization processes, such as addition of H^+, Na^+, K^+, or NH_4^+ ions to a single, pure substrate; spiking the analyte solution with an excess of the authentic cation(s) typically resolves this complication.

2.30.5 REFERENCES

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