The emerging interface of mass spectrometry with materials

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Abstract
Mass spectrometry (MS), a hundred-year-old subject, has been a technique of profound importance to molecular science. Its impact in solid-state materials science has not been evident, although many materials of modern science, such as fullerenes, have their origins in MS. Of late, mass spectrometric interface with materials is increasingly strengthened with advances in atomically precise clusters of noble metals. Advances in instrumentation along with recent developments in synthetic approaches have expanded the chemistry of clusters, and new insights into matter at the nanoscale are emerging. High-resolution MS coupled with soft ionization techniques enable efficient characterization of atomically precise clusters. Apart from that, techniques such as ion mobility, tandem MS, etc. reveal structural details of these systems. Growth, nucleation, and reactivity of clusters are also probed by MS. Some of the recent advancements in this field include the development of new hyphenated techniques. Finer structural details may be obtained by coupling MS with spectroscopic tools, such as photoelectron spectroscopy, vacuum ultraviolet spectroscopy, etc. With such advancements in instrumentation, MS can evolve into a universal tool for the characterization of materials. The present review captures highlights of this area.

Introduction
Mass spectrometry (MS), a century-old discipline concerning the investigation of matter using ions, is undergoing revolutionary changes. While the systems being examined went through systematic changes from atomic and molecular species to proteins and macromolecules in the course of evolution of MS, the perception of matter itself underwent a drastic transformation in this period. Materials science is becoming increasingly molecular today, and constituents of molecular matter are acquiring new properties leading to novel applications. Investigations require newer tools, and MS has evidently met the needs in this area. This has happened due to efficient methods of ionization of large molecular systems1,2. The first use of MS dates back to a century ago when Sir J.J. Thomson measured the m/z values of gaseous ionized molecules3,4. He also found the first evidence of isotopes of an element5. Later in 1922, Aston received a Nobel Prize in Chemistry for his discovery of isotopes in several nonradioactive elements5. Initially, MS gained importance in the analysis of organic molecules, and ionization techniques like electric discharge and electron impact (EI) were used in such studies. Slowly, scientists started using MS for the analysis of sugars, alkaloids, and peptides6. The development of hyphenated techniques like gas chromatography–mass spectrometry (GC–MS)7,8 further strengthened the use of MS as an analytical tool. The use of tandem MS (MS/MS) techniques, where mass spectrum of a mass-selected species is analyzed, became a popular tool for understanding the structures of molecules. For extending MS/MS studies to larger molecules like proteins and peptides, Todd, McGilvery, and Baldwin constructed a high-resolution double-focussing mass spectrometer9. But still, MS/MS studies for large molecules were possible only with harsh ionization techniques like fast atom bombardment. For the study of large molecules like proteins, there was a need for the development of softer ionization techniques. Such needs led to

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the development of electrospray ionization (ESI)\textsuperscript{1}, and for this breakthrough development, a Nobel Prize was awarded to John Fenn in 2002. Koichi Tanaka was also awarded a Nobel Prize in the same year for his development of soft laser desorption (SLD) and its applications for ionization of macromolecules\textsuperscript{10}. Moreover, for the analysis of complex mixtures, high-resolving power (m/\textDelta m) is desired\textsuperscript{11}. The use of time-of-flight (TOF) mass analyzers came into use in the year 1948\textsuperscript{12}. By using dual-stage reflectrons, the flight path of the ions could be extended by multiple reflections, and at present TOF analyzers can reach a resolving power of about 50,000 or more at m/z 20–16,000. In 1974, fourier-transform ion cyclotron resonance (FTICR) analyzers were introduced\textsuperscript{13}, which exhibited higher-resolving power compared with the TOF analyzers\textsuperscript{14}. The orbitrap was invented in 1999\textsuperscript{14}, and at present, they can reach a resolution of 6,00,000 at m/z 195\textsuperscript{15}. The gas-phase ions generated inside the mass spectrometer can also be confined for a significant amount of time in “ion traps”, and properties of the trapped ions have been studied in the literature\textsuperscript{16}. Though MS is mainly used for proteomics these days, it also became popular for studying materials. In this review, we have captured how MS has enriched the field of materials science.

Extended solids have been the materials of recent past. They have unique tools for structural characterization, principally revolving around diffraction techniques of various forms\textsuperscript{17}. The molecular systems on the other extreme had MS as their integral or most essential tool for compositional (to a lesser degree structural as well) analysis. As extended solids became molecular in their building blocks, as evident from the recent advances in nanoscale matter, analytical requirements to understand composition reached newer scales. Molecular materials of the past were composed of smaller constituents weighing a few hundred mass units. Many of them were stable under the harsh conditions of electron impact MS, and therefore were investigated extensively using sector-based instruments. Coupled with methods of ion activation, fragmentation gave a wealth of information on molecular structure\textsuperscript{18}. These studies were complemented by nuclear magnetic resonance (NMR) spectroscopy, and structural details of molecules with NMR active nuclei could be understood with precision\textsuperscript{19,20}. This was expanded to even solution-state structure determination of macromolecules. The other extreme of structural insight came from electron diffraction, which was instrumental in understanding structures of simple molecules at the early part of the last century\textsuperscript{21}. Soon, structural details of small molecules in the gas phase were understood mostly by spectroscopy, particularly for those molecules in the atmosphere as well as in interstellar space. Electron diffraction of another kind became a prominent analytical tool with the advent of electron microscopy (EM). With cryo-EM in low-dose diffraction, structures were being solved at Angstrom (Å) resolution in conjunction with high-quality modeling. In addition to single-crystal diffraction, NMR, electron diffraction, and spectroscopy, there are a number of scattering and analytical tools involving X-rays, electrons, positrons, neutrons, photons, and ions to unravel the structure and properties of materials. While this review does not intend to cover comprehensively any of these techniques, we wish to note that the evolution of materials demands new kinds of techniques for compositional and structural analysis. This has happened because constituent units in advanced materials became more and more discrete while increasing in complexity. Along with this change, constituents of matter expanded from diatomics to polyatomics to macromolecules to nanoparticles. While the need to study all of them in isolation became intense, experimental methods of MS in ionization and ion analysis also got evolved.

The importance of MS as a tool for characterization of materials\textsuperscript{22–24} has got strengthened with the advancement in the science of atomically precise nanoclusters (NCs)\textsuperscript{25,26}, which are materials with atomic precision. Such clusters exhibit unique electronic and optical properties, and have precision in its compositional structure in the metal core and the protecting ligand layers. Till date, single-crystal X-ray crystallography has been used to resolve the structures of several clusters like Au\textsubscript{23}L\textsubscript{18}, Au\textsubscript{28}L\textsubscript{20}, Au\textsubscript{38}L\textsubscript{24}, Au\textsubscript{40}L\textsubscript{24}, Au\textsubscript{52}L\textsubscript{32}, Au\textsubscript{62}L\textsubscript{44}, Au\textsubscript{102}L\textsubscript{44}, Au\textsubscript{113}L\textsubscript{52}, Ag\textsubscript{44}L\textsubscript{30}, Ag\textsubscript{25}L\textsubscript{18}, Ag\textsubscript{27}L\textsubscript{12}, etc., where L corresponds to different types of ligands. However, due to their extremely small size, size determination by other techniques like transmission electronic microscopy (TEM) or powder XRD has been less reliable. In contrast, MS can accurately identify precision in their compositions. Techniques such as ion mobility–MS (IM–MS) and tandem MS (MS/MS) are becoming increasingly important for understanding the size, shape, and dynamics of cluster systems. Moreover, advancement in instrumentation has enabled the determination of inherent properties of clusters like electron affinity (EA), ionization energy (IE), electronic transitions, etc., through the development of new hyphenated techniques. In this review, we will discuss the recent advances in those emerging directions, and elucidate how MS is evolving into a promising tool for materials characterization.

This has become possible due to advancements in various areas of ionization, mass analysis, detection, sensitivity, resolution, etc. The landmark developments in these aspects are captured in Table 1.
Role of MS in the discovery and characterization of materials

One of the most popular classes of materials of modern science, fullerenes, was discovered using a mass spectrometer. When a pulsed laser evaporated a solid disk of graphite, cooling of the resulting carbon species by a high-density helium flow resulted in the formation of carbon clusters, which were then detected by a TOF MS. In low density of He gas, even numbered clusters, $C_n$ ($n = 38–120$) were formed, with increase in the He pressure to ~760 torr, the abundances of the peaks due to $C_{60}$ and $C_{70}$ were increased. Later, in 2003, Li et al. observed that $Au_{20}$ cluster which possesses a tetrahedral structure, shows similar atomic packing but largely different properties compared with bulk gold.

Early stages of characterization of noble metal clusters by MS

Gas-phase clusters of noble metals like $Au_n$ or $Ag_n$ were also investigated by MS. Furche et al. assigned the structures of $Au_n$ ($n < 13$) clusters by a combination of mass spectrometric and theoretical studies. Lechtken et al. determined the structures of $Au_{14}$ -- $Au_{19}$ clusters by trapped ion electron diffraction. Later, in 2003, Li et al. observed that $Au_{20}$ cluster which possesses a tetrahedral structure, shows similar atomic packing but largely different properties compared with bulk gold.

Table 1 Landmark events in the history of mass spectrometry and their importance in enabling the characterization of materials

| Progress in instrumentation | Systems studied by MS | Resolution | Mass range |
|-----------------------------|----------------------|------------|------------|
| 1912 Measurement of m/z values by Thomson | Isotopes of elements, Atomic weights using MS | early studies by MS | Aston (130) |
| 1918 Electron ionization | Early studies by MS | TOF (4000-5000 at m/z ~100) | Magnetic sector (~2000) |
| 1936-37 Secondary ion MS | 1940s Organic mass spectrometry, Mixture of organic analytes could be separated by GC–MS | Analysis of organic molecules | FTICR (~29,000) |
| 1946 Time of flight | 1980s high molecular-weight polymers, peptides, proteins, nucleic acids, ESI for macromolecules | Analysis of materials with MS | MALDI TOF (~2,00,000) |
| 1952 Double-focusing instruments | 1996 Analysis of intact live viruses | | |
| 1955 Advanced TOF | 1996 LDI for characterization of thiol-protected clusters | | |
| 1956 GC–MS, high-resolution MS | 2008 MS of intact $Au_{13}(PET)_{18}$ clusters | | |
| 1953-58 Quadrupole analyzers | 2018 MS of $Au_{2000}$ NPs | | |
| 1962 Ion mobility | | | |
| 1966 Chemical ionization | | | |
| 1967 Tandem MS | | | |
| 1968 Electrospray ionization (ESI) | 1985 Discovery of fullerenes by laser-induced vaporization | | |
| 1974 Fourier transform (FT) Ion cyclotron resonance | 1996 LDI for characterization of thiol-protected clusters | | |
| 1975 Surface-induced dissociation | 2008 MS of intact $Au_{13}(PET)_{18}$ clusters | | |
| 1978 Triple quadrupole | 2018 MS of $Au_{2000}$ NPs | | |
| 1981 Fast atom bombardment MS | | | |
| 1987 MALDI | | | |
| 1999 Orbitrap | | | |
| 2004 Desorption electrospray ionization | | | |

*Does not strictly correspond to the time evolution presented in the left column

Chakraborty and Pradeep NPG Asia Materials (2019) 11:48 Page 3 of 22
demonstrated that the EA of Au$_{20}$ cluster was comparable with that of C$_{60}$, as shown in Fig. 2a. Along with such studies on gas-phase bare metal clusters, MS slowly evolved into a powerful tool for the characterization of ligand-protected noble metal NCs also.

After Brust reported a new method of synthesis of thiol-protected gold NPs in 1994 [46], scientists started the synthesis of monodisperse NPs with molecule-like optical absorption features. In 1996, Whetten et al. used laser desorption ionization (LDI) for the characterization of dodecanethiol protected gold NCs having mass in the range of 27–93 kDa (Fig. 2b) [47]. The LDI measurements suggested that the gold cores consisted of 140–459 atoms, which was also consistent with their TEM measurements.

**Advances in the study of noble metal clusters**

Though LDI was used as the primary characterization tool in the 1990s, softer techniques like matrix-assisted laser desorption ionization (MALDI) and ESI became more popular for the ionization of intact ligand-protected clusters. In 1998, Schaff et al. reported a 10.4 kDa Au-GSH (GSH = glutathione) cluster, Au$_{20}$(SG)$_{18}$ [48]. The composition was proposed from both MALDI MS and ESI MS. Following this, several other reports came on the same cluster until in 2005, it was reassigned as Au$_{25}$(SG)$_{18}$ by Negishi et al. [49]. With advancement in instrumentation, resolution of the mass spectral measurements improved, which enabled successful characterization of the cluster. MS has largely been used in the characterization of gold clusters, particularly due to their high stability under ambient conditions. Though ESI efficiently ionized water-soluble gold clusters, organic-soluble clusters often showed poor ionization efficiency in this technique. In order to overcome this, scientists implemented new approaches like ligand exchange with ionizable ligands [50,51], using Ce(SO$_4$)$_2$ [51], or CsOAc to enhance the ionization [52,53]. In most cases, with the choice of appropriate matrices like sinapinic acid, cinnamic acid, etc., MALDI worked better for the ionization of NCs. In 2008, Dass et al. introduced the use of trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) matrix which proved to be more effective [54], and MALDI MS of intact Au$_{25}$(PET)$_{18}$ clusters was successfully measured (Fig. 3b). Comparison of MALDI MS of Au$_{25}$(PET)$_{18}$ clusters in different matrices showed the superiority of using DCTB (Fig. 3a). Larger NCs like Au$_{102}$(pMBA)$_{44}$ [54] were also characterized using a combination of ESI and MALDI MS. However, due to lesser
stability, mass spectral characterization of silver clusters has always been challenging. As Ag has two isotopes (107 and 109), silver clusters show broader isotope patterns. At the initial stages of research in the field of Ag clusters, mercaptosuccinic acid (H₂MSA) protected Ag₇, Ag₈, Ag₁₁(SG)₇, Ag₁₅(SG)₁₁, Ag₃₁(SG)₁₉, and Ag₃₂(SG)₁₉, etc., clusters were characterized by MS. In 2012, Harkness et al. reported the Ag₄₄(SR)₃₀ NCs which was later crystallized in 2013 by Desireddy et al. and Yang et al. Recently, in 2015, Bakr et al. reported Ag₂₅(SR)₁₈ NCs which exhibits identical structure as that of Au₂₅(SR)₁₈. A luminescent Ag NC, [Ag₂₉(BDT)₁₂(TPP)₄] crystallized in 2013 by Desireddy et al. and Yang et al. were also reported from the same group. High-resolution ESI MS gave the accurate molecular formulae of these clusters, which matched exactly with their composition found in crystal structures. This highlights the importance of using MS as a versatile tool for the characterization of the NCs. Most recently it has been possible to characterize new types of silver

Fig. 2 Early stages of MS of noble metal clusters. a Photoelectron spectra of Au₂₀⁻ cluster compared with C₆₀⁻ at 193 nm and 266 nm. (Copyright© 2003 the American Association for the Advancement of Science) b Mass spectra obtained by laser desorption ionization of dodecanethiol thiol-protected gold clusters, i) crude mixture of clusters and ii–vi) separated fractions. (Copyright© 1996 John Wiley and Sons)
clusters, \([\text{Ag}_{18}\text{H}_{16}(\text{TPP})_{10}]^{2+}\), \([\text{Ag}_{25}\text{H}_{22}(\text{DPPE})_{8}]^{3+}\), and \([\text{Ag}_{26}\text{H}_{22}(\text{TFPP})_{13}]^{2+}\), which are protected by hydrides and phosphines. Hydride-doped gold cluster \([\text{Au}_{9}\text{H}(\text{PPh}_{3})_{8}]^{2+}\) and bimetallic \([\text{H}^{+}\text{PdAu}_{9}(\text{PPh}_{3})_{8}]^{2+}\) clusters were also characterized by ESI MS. The crystal structures of many such clusters are not yet available.

Apart from research in the field of Au and Ag NCs, the applicability of MS has also been extended to the field of clusters of other noble metals, eg., Pt NCs, Pd NCs, Ir NCs, etc. MS has also been proved to be useful in case of non-noble metals; eg. Cu NCs like \([\text{Cu}_{20}\text{H}_{11}(\text{S}_{2}\text{P(OiPr)}_{2})_{9}]^{2+}\), Fe NCs like \([\text{Fe}_{6}\text{H}_{10}(\text{PMe}_{3})_{8}]^{7+}\), Ir NCs like \([\text{Ir}_{9}(\text{PET})_{6}]^{73+}\), etc.

**High-resolution mass spectrometry (HRMS)**

Over the years, there has been a tremendous improvement in instrumentation, which has enabled to obtain HR mass spectra of clusters with minimum fragmentation. A schematic of a HRMS instrument is shown in Fig. 4a. In the TOF analyzer, the trajectory of the ions can be controlled in a shorter “V” or a longer “W” path. With the increase in the path of the ions, the resolution \((m/\Delta m)\) increases from \(~20,000–35,000\) to \(~35,000–50,000\) in the \(m/z\) range of 20–16000. Additional parts like “stepwaves” are used to remove all contaminants before the ions enter the quadrupole of the mass spectrometer. This also increases the sensitivity of the measurement. Precise composition of the core and the ligands and charge states of the cluster can be determined accurately by using HRMS. The compositions are further confirmed from the isotope patterns of the metals (Au, Ag, Pt, Pd, etc.) and that of C, H, and S present in the ligands. HR ESI MS of \([\text{Au}_{25}(\text{PET})_{18}]^{−}\) (PET is phenyl ethane thiol) and \([\text{Ag}_{25}(\text{DMBT})_{18}]^{−}\) (DMBT is 2,4-dimethyl benzene thiol) are presented in Fig. 4b.

Apart from the conventional ESI MS analysis, HR mass spectrometers of the present day are also equipped with several other advanced features that enable further studies on the gas-phase cluster ions. Some recent studies are summarized below.

### Ion mobility–mass spectrometry (IM-MS)

MS coupled with IM has proved to be an important tool for structural characterization, and has enhanced research in many areas of biochemical and biophysical studies. In the IM cell, the ions are passed through buffer gases like He, N\(_2\), etc. As a result, species having the same mass but different size and shape exhibit different collision cross-section (CCS), hence show different drift times and get separated. IM–MS is capable of studying the conformational dynamics present in a system, and has largely been used to understand the folding and unfolding mechanism in proteins. In materials science, IM–MS has been used to study the mechanism of formation of fullerenes from polycyclic aromatic hydrocarbons (PAH). Laser desorption of PAHs like \([\text{C}_{60}\text{H}_{21}F_{9}]^{−}\) causes stepwise loss of HF and H\(_2\) (Fig. 5ai), which results in increasing curvature of the remaining PAH fragments and finally closed-cage fullerenes are formed. To understand the mechanism, the extent of curvature in the structure of the products at each step was modeled by comparing the CCS of the computed structures with the experimental CCS observed in IM–MS (Fig. 5aii). IM–MS has also been largely used for understanding the structures of polyoxometallates. Surman et al. showed that Keggin or Dawson type POM clusters (structures are shown in Fig. 5bi) can be used as IM calibrants for high mass negatively charged ions, and using the calibration curves (Fig. 5bii), structures of other POM clusters can be determined.

Recently, IM–MS has also gained importance in the field of protected noble metal NCs. Baksi et al. separated dimers and trimers of \([\text{Au}_{25}(\text{SR})_{18}]^{−}\) using IM–MS. A
schematic of the instrumental setup showing the formation of aggregates of the cluster under increased pressure conditions in the trap, and its subsequent separation in the IM chamber is presented in Fig. 6a. Chakraborty et al. have also shown that alkali metal ions can induce dimerization of $[\text{Ag}_{29}(\text{BDT})_{12}]^{3-}$ NCs in a similar manner. Baksi et al. identified isomerism in $[\text{Ag}_{11}(\text{SG})_{7}]^{3-}$ cluster in the gas phase. However, as the crystal structure of $[\text{Ag}_{11}(\text{SG})_{7}]^{3-}$ is not known, the correlation with the condensed-phase structures could not be established. In another report, the authors showed that $[\text{Ag}_{44}(\text{SR})_{30}]^{4-}$ and $[\text{Ag}_{29}(\text{BDT})_{12}]^{3-}$ clusters also show isomerism in the gas phase, which do not show any isomers in their crystal structure. Four distinct isomeric peaks were
observed in IM–MS of [Ag$_{44}$(FTP)$_{30}$]$^{4-}$ (Fig. 6b). However, two isomers were separated for [Ag$_{44}$(FTP)$_{30}$]$^{3-}$, which indicated that isomerism is charge-state dependent. The influence of the ligand shell in isomerism was studied by using [Ag$_{44}$(SR)$_{30}$] clusters protected by different ligands, which showed different number of isomers. Also, Au$_{25}$(SR)$_{18}$ and Ag$_{25}$(SR)$_{18}$ clusters showed a single peak in IM, suggesting that isomerism is highly selective to the structure and the symmetry of the cluster.

Kappes et al. performed IM studies on Au cluster cations Au$_n^+$. Comparison of experimental CCS with that of theoretical CCS from DFT-optimized structures revealed that Au$_n^+$ have planar structures for $n = 3$–7, while for $n = 8$–10, they show three-dimensional structures. In a recent study, Daly et al. characterized homometallic cluster ions, [Ag$_{14}$(C≡C$\text{Bu}$)$_{12}$Cl]$^+$, [Ag$_{14}$(C≡C$\text{Bu}$)$_{12}$Br]$^+$ and heterometallic clusters ions, [Ag$_8$Cu$_6$(C≡C$\text{Bu}$)$_{12}$Cl]$^+$, [Ag$_8$Cu$_6$(C≡C$\text{Bu}$)$_{12}$Br]$^+$ by IM–MS. These cluster ions showed a single peak in IM, and comparison of the CCS values derived from IM with the CCS values modeled from its X-ray crystal structure suggested that the gas-phase structures of the clusters resembled their condensed-phase structures (Fig. 7a). The shorter arrival time of the heterometallic cluster ions in comparison with that of the homometallic cluster ions was consistent with the observation from their crystal structures and DFT calculations (Fig. 7c). Thus, IM proved to be an effective tool not only for the separation of gas-phase entities but also for structural characterization of the clusters. In another study by Soleilhac et al., the size of GSH-protected clusters were compared in the solid, liquid, and gas phase by using X-ray powder diffraction (XRPD), time-resolved fluorescence anisotropy (TRFA), and IM–MS, respectively. From the CCS values obtained from IM, the radii of the clusters were calculated as 1.22, 1.31, and 1.47 nm for Au$_{15}$(SG)$_{13}$, Au$_{18}$(SG)$_{14}$, and

![Fig. 6 IM–MS studies on gas-phase polymers and isomers of clusters.](image-url)
Au_{25}(SG)_{18}, respectively. Though the absolute values differed, the trends in the size of the above NCs were similar in all the three phases. In comparison with techniques like XRPD and TRFA, IM–MS is expected to become a more convenient technique for determining the size of the clusters due to the ease of sample preparation and lower limit of error (~2%) compared with other techniques.

Ligare et al. used ESI IM–MS to study the structural changes upon systematic ligand exchange of \([\text{Au}_{14}(\text{C≡CtBu})_{12}\text{Cl}]^{2+}\) and \([\text{Au}_{11}(\text{PPh}_{3})_{9}\text{H}]^{2+}\) with methyldiphenylphosphine (MePPh_{2})^{85}. Studies revealed that \([\text{Au}_{14}(\text{PPh}_{3})_{7}]^{2+}\) cluster showed two isomers, and on increasing ligand exchange with MePPh_{2}, these isomers underwent a change in relative population from a more compact structure showing lower arrival time to a more extended structure showing larger arrival time, as shown in Fig. 7d. In contrast, \([\text{Au}_{11}(\text{PPh}_{3})_{9}\text{H}]^{2+}\) cluster showed only one isomer. Recently, Hirata et al. showed that phosphine-protected gold clusters like \([\text{Au}_{9}(\text{PPh}_{3})_{6}]^{3+}\) and \([\text{PdAu}_{6}(\text{PPh}_{3})_{3}]^{2+}\) undergo conversion to more compact isomers upon collisional excitation (Fig. 7e)^{86}. Such studies help to understand the fluxionality in the structures of the NCs.

**Gas-phase dissociation studies of noble metal nanoclusters**

While IM-MS reveals enormous information regarding the shape, size, and conformations of the cluster ions, more information regarding their structure and bonding can be obtained from dissociation studies. In collision-induced dissociation (CID), mass-selected ions are subjected to dissociation by collision with gases like Ar, N_{2}, He, etc. Fields-Zinna et al. reported CID studies on ligand-protected Au_{25} NCs and showed that the dissociation involved the Au_{2L3} semirings, which are the staples motifs present in its crystal structure^{87}. The authors used Au_{25}(SC_{2}H_{4}Ph)_{18} cluster, and ligand-exchanged it with \(-\text{S(CH}_{2}\text{CH}_{2}\text{O})_{5}\text{CH}_{3}\) (–SPEG) to facilitate ionization and studied CID on these mixed ligand-protected Na_{x}Au_{25}(SC_{2}H_{4}Ph)_{18-\gamma}(SC_{2}H_{2}O)_{5}\text{CH}_{3}\) clusters using ESI TOF and ESI FTICR MS. CID produced...
fragments such as [Na\textsubscript{2}Au\textsubscript{2}L\textsubscript{3}]\textsuperscript{1+} representing the loss of a single semiring and fragments such as [NaAu\textsubscript{3}L\textsubscript{3}]\textsuperscript{1+} and [NaAu\textsubscript{4}L\textsubscript{4}]\textsuperscript{1+} representing the loss of multiple semirings. Later, Angel et al. studied the fragmentation of Au\textsubscript{25}L\textsubscript{18}\textsuperscript{−} NCs using HR ESI MS. The predominant fragmentation pathway involved the loss of Au\textsubscript{4}L\textsubscript{4} leading to the formation of fragment ions, such as Au\textsubscript{21}L\textsubscript{14}\textsuperscript{−} and Au\textsubscript{17}L\textsubscript{10}\textsuperscript{−}. They also introduced the use of IM–MS/MS, a technique where IM is coupled to CID, which could differentiate between fragmentation from the outer staples, fragmentation from the icosahedral core and the smaller ionic fragments, by separating them into distinct bands (Fig. 8). Black et al. carried out CID on larger Au NCs like Au\textsubscript{144}(SR)\textsubscript{60} and Au\textsubscript{130}(SR)\textsubscript{50} and also showed that the extent of fragmentation is specific to the charge state of the cluster ions. CID of mixed-ligand-protected cluster, [Au\textsubscript{11}(PPh\textsubscript{3})\textsubscript{8}X\textsubscript{2}]\textsuperscript{+} (X = Cl, C≡CPh), showed competing fragmentation channels involving sequential loss of PPh\textsubscript{3} and AuX(PPh\textsubscript{3})\textsuperscript{90}.

The extent of fragmentation also depends on the internal energy distribution of the ions, and hence CID studies were used to understand the stabilities of the cluster ions. Taking Ag\textsubscript{29}(SR)\textsubscript{12}, Ag\textsubscript{25}(SR)\textsubscript{18}, and Ag\textsubscript{44}(SR)\textsubscript{30} NCs as examples, Chakraborty et al. demonstrated that the predominant fragmentation pathways of these NCs involved the loss of Ag\textsubscript{6}(SR)\textsubscript{6}, Ag(SR)\textsuperscript{−}, or Ag\textsubscript{3}(SR)\textsubscript{3}− fragments. By using survival yield analysis and comparing the values of \( F_{\text{com50}} \) (\( F_{\text{com50}} \) is center-of-mass energy corresponding to 50% dissociation of the cluster), the stabilities of these clusters were compared (Fig. 9a), and the order of gas-phase stability [Ag\textsubscript{29}(SR)\textsubscript{12}]\textsuperscript{−} > [Ag\textsubscript{25}(SR)\textsubscript{18}]− > [Ag\textsubscript{44}(SR)\textsubscript{30}]\textsuperscript{3−} was similar to that observed in the solution phase.

Another technique that can be effectively used to study the energetics and kinetics of the fragmentation process is surface-induced dissociation (SID). In this process, mass-selected ions are collided with a surface (usually Au surfaces protected by monolayers of alkanethiols) and impact induced activation leads to dissociation. In comparison with CID, SID is a more convenient technique to extract thermodynamic parameters of the cluster ions, as here the applied CE can be varied through a large range to observe a small change in the threshold internal energies of large ions. Using SID, Johnson et al. quantified the stability and ligand-binding energies of small TPP-protected Au clusters, Au\textsubscript{7}L\textsubscript{6}\textsuperscript{2+}, Au\textsubscript{8}L\textsubscript{6}\textsuperscript{2+}, Au\textsubscript{8}L\textsubscript{7}\textsuperscript{2+}, and Au\textsubscript{9}L\textsubscript{7}\textsuperscript{2+}. Collision energy-resolved fragmentation curves revealed that Au\textsubscript{7}L\textsubscript{6}\textsuperscript{2+} cluster was more stable toward dissociation (Fig. 9b). SID enabled the quantitative estimation of the threshold energies and activation entropies of fragmentation. It also enabled to understand the kinetics of fragmentation by determining the microcanonical rate constants for the different fragmentation pathways (Fig. 9bii) and hence determining the kinetically and thermodynamically favored pathways. Moreover, taking Ag\textsubscript{11}(SG)\textsuperscript{7−} clusters as an example, Baksi et al. showed that CID and SID of the clusters occurred through different pathways. SID produced more fragments compared with CID, and charge stripping from 3- to 2- and 1-charge states of the cluster ions occurred.

While both CID and SID produces a lesser number of fragments, extensive fragmentation can be observed by ultraviolet photodissociation (UVPD) as observed in the case of Au\textsubscript{25}(pMBA)\textsubscript{18} and Au\textsubscript{36}(pMBA)\textsubscript{24} NCs. UVPD on these clusters using \( \lambda = 193 \) nm involved high-energy fragmentation pathways and cleavage of Au–S and C–S bonds.
bonds. When the cluster ions were exposed to multiple laser pulses, a series of bare Au cluster ions were formed by sequential evaporation of neutral Au atoms (Fig. 10). Recently, Ghosh et al. showed that the bare cluster ion, Ag$_{17}^+$, can be produced selectively by CID of [Ag$_{18}$(TPP)$_{10}$H$_{16}$]$^{2+}$ clusters and by further increasing the
collision energy, a series of Ag\(_n^+\) (n = 1–17) clusters may be produced\(^6\)\(^3\),\(^9\)\(^4\). In a similar manner, [Ag\(_{25}\)(DPPE)\(_8\)H\(_{22}\)]\(^{3+}\) and [Ag\(_{22}\)(DPPE)\(_9\)H\(_{19}\)]\(^{3+}\) were also used as precursors for bare Ag clusters\(^9\)\(^4\). In a recent study by Jash et al., electrosprayed [Ag\(_{18}\)(TPP)\(_{10}\)H\(_{16}\)]\(^{2+}\) clusters were passed through a heated tube, whereby all the ligand layers were desorbed leading to the formation of Ag\(_{17}^+\) under ambient conditions, and the product ions were subsequently detected by MS (Fig. 11)\(^9\)\(^5\).

**Spectroscopy on the mass-selected gas-phase cluster ions**

The electronic properties of the NCs are probed experimentally by optical and electrochemical studies in solution. However, these experimental results are influenced by the solvents and the counter ions present in solution. So, there is a need to directly probe the energy levels of the isolated cluster ions in vacuum. Anion PES is usually used to determine HOMO–LUMO gaps and EAs. Such studies have been done for bare Au\(_n^-\) clusters\(^9\)\(^6\). Recently, Hirata et al. performed PES on isolated [Au\(_{25}\)(SC\(_{12}\)H\(_{25}\))\(_{18}\)]\(^-\) ions by coupling a magnetic bottle-type photoelectron spectrometer with a TOF mass spectrometer\(^9\)\(^7\). Schematic of the instrumental setup used for the study is presented in Fig. 12a. The photoelectron spectrum of [Au\(_{25}\)(SC\(_{12}\)H\(_{25}\))\(_{18}\)]\(^-\) showed two bands, A and B (Fig. 12b), corresponding to electron detachment from 1 P superatomic and Au 5d orbitals localized on the core Au atoms. The vertical detachment energy (VDE) and adiabatic electron affinity (AEA) of [Au\(_{25}\)(SC\(_{12}\)H\(_{25}\))\(_{18}\)]\(^-\) was determined to be 2.5 eV and 2.2 eV, which corresponds to the values of \(E_{\text{top}}\) and \(E_{\text{th}}\) in the photoelectron spectrum (Fig. 12b), respectively. Hamouda et al. studied photoexcitation of [Au\(_{25}\)(SG)\(_{18}\)-6H]\(^7\), where the yield of electron detachment as a function of the laser wavelength gave the gas-phase optical action spectra, which was found to be similar to the solution-phase spectrum\(^9\)\(^8\). Daly et al. studied the photofragmentation and VUV photoionization of [Au\(_{10}\)D\(_8\)L\(_6\)]\(^2+\) NCs in the gas phase by coupling a linear ion trap mass spectrometer with a beamline of synchrotron, capable of producing high flux of photons that could be tuned in the entire VUV range\(^9\)\(^9\). Upon photoexcitation of [Au\(_{10}\)D\(_8\)L\(_6\)]\(^2+\), a number of photofragments were produced, such as [Au\(_{10}\)D\(_8\)L\(_6\)]\(^{2+}\), [Au\(_{10}\)D\(_4\)L\(_5\)]\(^{2+}\), [Au\(_{10}\)D\(_4\)L\(_3\)]\(^{2+}\), [Au\(_{10}\)D\(_2\)L\(_4\)]\(^{2+}\), and [AuL\(_2\)]\(^+\). The ionization onset of [Au\(_{10}\)D\(_8\)L\(_6\)]\(^2+\) was determined from the onsets in the yield of [Au\(_{10}\)D\(_8\)L\(_6\)]\(^3+\) as a function of photon energy. Two ionization onsets were determined as ~9.3 eV and ~10.6 eV, which might be due to removal of electrons from orbitals of different energy levels. In another study, authors from the same group performed VUV and UV spectroscopy on [Ag\(_{14}\) _\(_\text{Cu}_n\)(C\(_{6}\)tBu)\(_{12}\) X]\(^+\) (X = Cl and Br) cluster ions\(^8\)\(^3\). The ionization onsets of the cluster ions were determined to be ~8.8 eV, and this was similar for all the ions, irrespective of the nature of halides or the extent of Cu doping (Fig. 12c). Photofragmentation of the same
clusters were studied in the wavelength range of 235–291 nm by coupling a laser with the ion trap. The plot of photofragmentation yield as a function of the wavelength of the radiation gave the UV spectra of the cluster ions in the gas phase (Fig. 12d). The experimental optical absorption spectra were also in accordance with TDDFT calculations (Fig. 12d).

**Resolving the solution-phase growth and nucleation of clusters**

Apart from such studies on gas-phase cluster ions, MS also proved to be powerful in unraveling complex solution-phase phenomena. Understanding the mechanism of nucleation and growth of clusters in solution has always remained challenging. In 2012, Yu et al. reported the size controlled growth of Au$_{25}$ NCs where they slowed down the reduction rate by using CO as a mild reducing agent\(^{100}\). By using MALDI MS, the authors demonstrated that a mixture of Au$_{10-15}$ NCs was produced within 5 min of reaction, followed by the formation of Au$_{16-25}$ NCs over a period of 40 min, which finally size focussed to Au$_{25}$ NCs after 24 h. However, due to fragmentation, only the core masses could be identified, and no information was obtained about the ligand shell of the intermediate.
products. More recently, in 2014, in another report from the same group, ESI MS was used to trace all the stable intermediates involved in the formation of Au25 clusters starting from Au thiolates. This study showed that the formation of Au NCs occurred by a 2e hopping process, which involved a fast reduction step followed by slow interconversion and size focussing steps. All the intermediates involved in the process were detected by ESI MS, and the changes in the solution composition with gradual growth of the NCs were also in accordance with the changes in the optical absorption features (Fig. 13). Similar studies have been reported by the same group where ESI MS was used to understand the steps involved in the process of conversion of Au25 to Au44 NCs. Isoelectronic conversion from [Au23(SR)16]− to [Au25(SR)18]− NCs was also studied by ESI MS. Careful mass spectrometric analysis of the system revealed the size-conversion reaction as [Au23(SR)16]− + 2 [Au25(SR)3]− → [Au25(SR)18]− + 2 [Au(SR)]2−. Based on HRMS measurements, Chen et al. have recently formulated a balanced equation for the stoichiometric synthesis of Au25(SR)18 NCs as, 32/x [Au(SR)]x + 8e− = [Au25(SR)18]− + 7 [Au(SR)]2−. Similar studies have also been done to understand the growth of silver clusters like [Ag27(SPh−tBu)12]3− and [Ag30(SPh−tBu)30]4−, and step-by-step mechanism of ligand exchange induced cluster conversion reactions, e.g., the conversion from Ag44 to Ag25 clusters and vice versa.

Reactions between nanoparticles

Inter-cluster reactions are an emerging area in the field of NCs. Krishnadas et al. demonstrated the reaction between Au25(FTP)18 and Ag44(FTP)30 NCs, which produces a mixture of alloy clusters in solution. Exchange of Au–Ag atoms between the clusters were observed by using MALDI and ESI MS (Fig. 14a, b). In case of reaction between clusters protected by different ligands like Au25(PET)18 and Ag44(FTP)30, ligand exchanges were also observed in MS. In another report from the same group, the authors demonstrated reaction between Au25(SR)18 and Ag44(SR)18 clusters leading to the formation of alloy clusters Ag44Au44(SR)18 (n = 1–24) (Fig. 14c). The authors also detected a dianionic intermediate, [Ag25Au25(SR)30]2− (Fig. 14d) at the early stages of the reaction, which provided better insights into the mechanism of such reactions. Salassa et al. used MALDI MS and NMR spectroscopy to show that monolayers of clusters are dynamic in nature, and inter-cluster ligand exchanges can occur during collision between the NCs. Using isotopically pure silver clusters made of 107Ag and 109Ag, Chakraborty et al. studied rapid isotopic exchange in silver clusters by HR ESI MS and found that the solution-state exchange dynamics of the clusters is similar to that occurring in water (H2O + D2O = 2HDO).

Supramolecular chemistry of monolayer-protected noble metal NCs

MS has also been used for exploring supramolecular chemistry of clusters. Chakraborty et al. studied supramolecular functionalization of [Ag29(BDT)12]3− clusters with fullerenes (C60 and C70) by HR ESI MS (Fig. 15a). The authors also used CID studies to gain further insights into the nature of the interaction and IM–MS (Fig. 15b) to study the structure of the adducts. Mathew et al. studied supramolecular functionalization of [Au25(SBB)18]− clusters with cyclodextrins (CD), the adducts [Au25(SBB)18−CDn]− (n = 1–4) were characterized by using MALDI and ESI MS (Fig. 15c). Recently, Nag et al. separated isomers of the inclusion complexes [Ag29(BDT)12−CDn]3− (n = 1–6) (Fig. 15d) by using IM–MS. Two isomers were observed for n = 2, 3, and 4 while no isomerism was observed in the case of n = 1, 5, and 6 complexes, suggesting similar behavior to that observed in octahedral transition metal co-ordination complexes.

Liquid chromatography (LC) - MS

Characterization, analysis, and separation of mixtures of clusters by chromatography have been pursued for long. Some of the recent developments include directly coupling chromatographic techniques to MS. Black et al. coupled reversed-phase chromatography with mass spectrometry to MS. In another report, isomers of Ag29(LA)12 (LA = (R)-a-lipoic acid) clusters were separated using LC–MS (Fig. 16b).

Toward nanoparticles

Though the atomically precise NCs have been extensively characterized by MS, plasmonic NPs are not atomically precise, and determination of their exact composition still remains challenging. Recently, with the tremendous advancement in instrumentation and using a combination of ESI, LDI, and MALDI MS, it has been possible to assign approximate composition to some such plasmonic NPs, e.g., Au333(SR)39, Au500(SR)−129, Au-940(SR)−160, etc. NPs. Recently in 2017, the crystal structure of a plasmonic NP, Au279(SPh−Bu)44 was reported. MS measurements also revealed the composition in accordance with the crystal structure. Even larger NPs, Au−1400 121 with a mass of ~300 kDa (Fig. 17a) and Au−2000 124 with a mass of ~400 kDa (Fig. 17b) were recently characterized by MALDI MS.

Mass spectrometry as a tool for materials synthesis

Electrospray as a method of ionization has also been used for organic synthesis. While synthesis of new molecules...
Fig. 13 ESI MS showing stepwise growth of Au\textsubscript{25}(SR)\textsubscript{18} clusters. a Reaction scheme showing the formation of Au\textsubscript{25}(SR)\textsubscript{18} clusters from Au thiolates under the mild reducing environment of CO. b Time-dependent UV–vis spectra, and c ESI MS during the formation of Au\textsubscript{25}(SR)\textsubscript{18} clusters from Au thiolates. ESI MS shows detection of several intermediate species (numbered 1–27), which are listed in the table presented on the right\textsuperscript{101}. (Copyright\textsuperscript{©} 2014 American Chemical Society)
in sprays was observed before, bulk synthesis of molecules with which characterization is possible was not attempted earlier. Using a home-built nano-electrospray source, Sarkar et al. showed that spraying an aqueous solution of silver acetate (AgOAc) over a TEM grid, resulted in the formation of 1D nanowire structures of Ag NPs (Fig. 18). The precursors for the formation of the nanostructures were ions. Such studies unfold new routes of synthesis of materials using mass spectrometric interfaces.

Conclusions and future perspectives

In conclusion, we have presented how MS has enriched the field of materials science; in particular, the field of monolayer-protected atomically precise NCs. From the discussion presented above, it becomes clear that MS has developed into a powerful tool for materials characterization, and it is expected to expand further in the future. MS as a technique is capable of building new interfaces which connects itself with independent disciplines. This has produced GC–MS, LC–MS, and their variations. New hyphe-nated methodologies and their power to understand structural details would expand further in the coming years. Combined with automation, synthesis of materials of atomic precision is expected to produce greater throughput in precision manufacture. Newer methods, utilizing the properties of molecular solids, and molecular building
blocks such as infrared (IR) absorption will be important to study molecular interactions on such materials. Interfaces such as ion chromatography or PES could be built with the mass spectrometer, which can produce new information related to structural changes and associated electronic structure. As the science of the noble metal clusters is enriched by MS, a thorough study on these systems also reveals their potential to be used as mass spectrometric standards. Due to their high efficiency of ionization, distinct isotope patterns, stable intensities, and high m/z values, they can be used as calibrants for mass spectrometers. This might help in overcoming the limitations of the lack of proper calibrants in the high mass range, and especially in the negative ion mode.

Gas-phase IR in combination with IM–MS has recently gained importance in revealing the structural details of proteins. It has also proved to be powerful in understanding the geometries of other molecules such as the aggregates of protoporphyrin IX where IR spectroscopy confirmed that the pairing of carboxylic groups occurred during the formation of the stacked conformations. Moreover, IM–MS in combination with IR has also been used in understanding the structures of isomers of small molecules like the N-protonated and O-protonated forms of benzocaine, and structures of serine octamers. In a similar manner, such studies may be extended in the case of clusters as well. Gas-phase IR can give more insights into the structure of the isomers or polymers of clusters. It can also be helpful for understanding interactions in the case of supramolecular adducts of clusters.

Spectroscopy and dynamics of trapped clusters ions, produced inside the mass spectrometer, can present new insights into their electronic structure. Trapped ion electron diffraction may be used for determining structures of noble metal NCs. Other possibilities include studies such as trapped ion laser-induced fluorescence. Spectroscopy of isolated cluster ions like electron detachment spectroscopy, PES, and single-particle fluorescence may be explored for a wide range of ligand-protected clusters. Such studies may even be done on...
specific isomers of the clusters to obtain isomer-specific properties. Catalysis of isolated cluster ions may be studied. Ion soft landing may be used to deposit ligand-protected cluster ions on specific substrates.

Extensive studies can also be done with clusters synthesized in macromolecular templates like proteins, DNA, etc., which are of particular interest because of their biocompatibility. Till now, most of the protein-protected clusters are mainly characterized by MS due to the difficulty in their crystallization. Though this aspect has not been discussed in detail in this review, enormous literature exists on the use of MS in understanding their composition, mechanism of growth, etc. MS has always been effective in revealing structural details of proteins. In a similar way such studies can be extended to clusters synthesized in protein templates.

With such enormous possibilities, the proliferation of MS into materials science could make it an indispensable tool in that branch of science as has happened with TEM. This would produce new demands for instrumentation, associated interfaces, calibration standards, and associated needs. Expanding the limits of mass spectrometry in mass range and resolution would push traditional analytical methods further. Depending on the properties of such materials, possibilities to do catalysis, IR spectroscopy, fluorescence spectroscopy, and electron diffraction in mass spectrometers, as discussed above, could expand our understanding of phenomena to even greater detail.

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Conflict of interest
The authors declare that they have no conflict of interest.

Fig. 16 Liquid chromatography (LC) MS on clusters. a Extracted ion chromatograms corresponding to Au104L45, Au130L50, Au137L56, and Au144L60 clusters, respectively, obtained by LC-MS on their mixture. b LC-MS on Ag29(LA)12 clusters showing the separation of the two isomers. Peaks 3 and 4 correspond to dimer- and trimer-like species. (Copyright© 2016 American Chemistry Society)
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Fig. 17 MS of nanoparticles. a MALDI MS of Au<sub>1400</sub> (~300 kDa) nanoparticle. SAXS molecular envelope and STEM images of the nanoparticle are shown in the insets (Copyright © 2018 American Chemistry Society) b MALDI MS of Au<sub>2000</sub>(SC<sub>6</sub>H<sub>13</sub>)<sub>2</sub> (~400 kDa) nanoparticle. UV–vis spectrum of the nanoparticle is presented in the inset (Copyright © 2018 American Chemistry Society)

Fig. 18 Synthesis of materials using mass spectrometric tools. a Optical image of electrospay of AgOAc solution. b Mass spectra of the spray showing the presence of Ag and its hydrated Ag ions. c TEM image and d HRTEM of brush-like structures formed by electrospraying the AgOAc solution on a TEM grid (Copyright 2016 John Wiley and Sons)
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