Sonic spray ionization mass spectrometry: a powerful tool used to characterize fragile metal-assembled cages

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Sonic spray ionization mass spectrometry (SSI MS) is shown to be effective in characterizing metal-assembled cage structures that are not observed using conventional electrospray ionization mass spectrometry (ESI MS) techniques. A palladium-assembled resorcinarene-based cage containing nitrile ligands and a palladium(II) triazine cage were characterized and their +1 molecular ion peaks were observed using this method. An *N*,*N*-bis(pyridylmethyl)amine resorcinarene cavitand–metal ion complex was observed to yield peaks corresponding to open tetranuclear complexes and closed cage complexes depending on the metal ion. Molecular ion peaks for these complexes were not detected when ESI MS was used. The soft ionization inherent in SSI MS coupled with its relatively simple design provides a powerful tool to characterize such supramolecular assemblies, which are of current interest.

Introduction

It is difficult to analyze supramolecular assemblies and labile metal complexes that contain non-covalent bonds using conventional mass spectral analysis methods such as fast atom bombardment (FAB) and matrix-assisted laser desorption/ionization (MALDI) mass spectroscopy, because these ionization methods impart sufficient energy to the analyte molecule to cause dissociation, preventing observation of the molecular ion. Electrospray ionization (ESI) is commonly used as an alternative "colder" ionization source less likely to cause dissociation of the molecular ion. However, even ESI causes significant fragmentation of labile supramolecular assemblies where the structure relies on weak bonding interactions. Fragmentation is assumed to result from the elevated temperatures used during desolvation from the electric fields involved in generating the spray, and/or from energetic collisions between ions and neutrals as ions are transferred into the vacuum system of the mass spectrometer. In the last decade, cold-spray ionization (CSI) MS has been introduced as a gentler alternative to ESI. However, CSI MS requires the use of a fairly complex apparatus to cool the sample as it is being sprayed using liquid nitrogen and dry ice baths, and requires the use of an applied voltage to charge the compounds.

Even with its limitations, ESI has become an important technique to analyze metal-assembled structures. In fact, very large metal-assembled structures have been detected using ESI. ESI of resorcinarene compounds has been used successful to identify dimer formation around alkali metal centers,[1] alkyl ammonium cations,[2] and guest molecules.[3] Also, clustered resorcinarene ions of masses up to 6000 amu have been detected.[4] The association of resorcinarenes with chiral molecules has also been investigated using ESI MS.[5] Mass spectrometry has also been used to look at other host–guest interactions of resorcinarenes,[6] including the equilibrium between metal-assembled capsules.[7] However, even ESI is too harsh for detection of some metal-assembled structures due to the weakness of the metal–ligand bonds, desolvation problems or the voltages required to ionize the compounds. Such complexes are not ionized or are fragmented in the electrospray ionization process, so that molecular ions are not observed.

Like ESI, sonic spray ionization is an external ion source for mass spectrometry.[8] The fundamental differences between ESI and SSI are the means of forming solvent droplets, the solution concentrations and flow rates required, the magnitude of the applied voltage, and (presumably) the method of ion production. The SSI source involves two capillaries, one nested inside the other. The inner capillary introduces a solution of analyte while the outer capillary provides a coaxial nitrogen gas flow to facilitate droplet nebulization. SSI is typically operated at atmospheric pressure and without applying an electric potential to the source. These features make SSI a very soft ionization method, reducing fragmentation of non-covalent assemblies, fragile analytes, and (thermally) labile compounds. Hirabayashi and coworkers[9] initially reported SSI as a novel ion source for capillary electrophoresis/mass spectrometry and for liquid chromatography/mass spectrometry in a series of publications in the 1990s. They reported that the maximum number of ions was produced by this

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method when the nebulization gas was flowing at sonic velocity (gas velocity of Mach 1)—hence the term sonic spray.

Ion and charged droplet production in SSI is not completely understood.[2b,10,11] Nonetheless, we can compare the performance of SSI and ESI. For example, unlike ESI (which typically produces multiply-charged ions), low charge states of the analyte molecules are usually observed with SSI. Furthermore, the SSI source has little or no applied voltage compared to ESI and exhibits no observable Taylor cone when no voltage is applied. A voltage can be applied to increase the ion production and to provide higher charge states similar to those observed with ESI; this technique is termed "electrosonic spray ionization," or ESSI.[2c] Also, SSI requires higher pressure gas flow, higher sample flow rates, and higher concentration of the analyte solution compared to ESI. In SSI, some cooling of the sample occurs during the spray process due to adiabatic expansion of the spray gas at the ion source.

SSI MS was of particular interest to us because it provides a new method to analyze complexes involving weak bonds such as resorcinarene metal-assembled cages. Metal-assembled complexes with weak metal–ligand bonds are frequently difficult to analyze using techniques such as NMR or X-ray methods, or even using conventional ESI.[12] In this paper we show that SSI-MS provides a particularly soft ionization, even when compared with ESI. Evidently, some cooling of the sample occurs during the spray process due to adiabatic expansion of the spray gas at the ion source. By contrast, when using ESI, many of the resorcinarene metal-assembled cages appeared to be electrochemically or thermally labile. When the SSI source was used, cage peaks were enhanced and low charge states (1+ and 2+ ions) were usually observed. Signal for cage complexes was increased over ESI by reducing the decomposition which may have been occurring in the ESI source and by decreasing the number of different charge states being formed. However, the lower charge states generated higher m/z and some signal loss occurred because of detector limitations.

Experimental

General methods

All reagents were purchased from commercial vendors and used as received unless noted. The bpa-resorcinarene cavitand (bpa = bis(pyridylmethyl)amine) was prepared in the manner described previously.[13] The Pd–resorcinarene cage was synthesized following literature procedures and characterized by ^{1}H NMR.[13] ^{1}H-NMR studies were performed on Varian INOVA 300 MHz Multinuclear FT-NMR or VXR 500 MHz Multinuclear FT-NMR spectrometers. NMR chemical shifts are reported in ppm and NMR studies were performed at 22.8 ± 0.5 °C.

Syntheses

2,4,6-Tri-4-pyridyl-*s*-triazine. The literature procedures were used in the synthesis.[14,15] Sublimed 4-cyanopyridine (10.0 g, 96 mmol), 18-crown-6 (1.00 g, 3.8 mmol), potassium hydroxide (225 mg, 4.0 mmol) and decalin (10 mL) were stirred at 200 °C under argon for 5 h. The reaction was allowed to cool to room temperature and the mixture was filtered followed by several washes of hot pyridine (5 × 50 mL) leaving a light yellow to white powder. The solid was dissolved in 50 mL of dilute HCl and reprecipitated with aqueous ammonia. The precipitate was filtered and washed with deionized water until neutral. ^{1}H NMR δ (D_2O–DCl): 8.56 (6H, d) and 8.94 (6H, d); m/z 312 (M^+).

$Pd(en)(NO_3)_2$. The $Pd(en)Cl_2$ was suspended in 3 mL of deionized water and then a 2 mL solution containing 2 equivalents of $AgNO_3$ was added dropwise while stirring under argon. The suspension was stirred in the dark under argon at 35 °C for 3 h providing a yellow solution of $Pd(en)(NO_3)_2$ and a white precipitate of AgCl. The solution was centrifuged and filtered to remove the AgCl and the water was removed by evaporation. The resulting yellow powder was stored under argon and in the dark.

Pd-assembled triazine cage. Literature procedures were used to synthesize the cage.[14] The $Pd(en)(NO_3)_2$ was dissolved in 1.0 mL of 0.03 M HNO_3. 2,4,6-Tri-4-pyridyl-*s*-triazine was dissolved in 4.0 mL of 0.03 M HNO_3 and stirred under argon at 25 °C while the $Pd(en)(NO_3)_2$ solution was dripped in slowly. This solution was allowed to continue stirring for 24 h under argon at 25 °C. The product was stored under argon, in the dark and the solution was used to analyze for cage.

bpa-resorcinarene metal complexes. A 1.0 mL methanol solution of resorcinarene (5.0 mg, 0.071 mmol) was mixed with a 1.0 mL methanol solution of 2.0 or 4.0 equivalents of metal salt to prepare the dinuclear or tetranuclear resorcinarene complexes. The solution was heated at 45 °C with stirring for 48 h under an argon atmosphere. The optimum time for reactions was determined by using MS methods. Product was isolated by allowing the solution to cool and then removing the solvent under a gentle flow of nitrogen.

Sonic Spray Ionization (SSI)

The sonic spray emitter was constructed based on designs reported in the literature.[11] This emitter was used in place of an electrospray emitter in an otherwise unmodified electrospray interface to the mass spectrometer. This electrospray source has been described previously;[16] it involves spray at atmospheric pressure, followed by a heated stainless steel capillary drying tube to assist in solvent evaporation, a differentially-pumped skimmer, and a differentially-pumped hexapole ion accumulation/focusing device that gates the introduction of ions into the mass spectrometer, a Bruker APEX 47e Fourier transform ion cyclotron resonance mass spectrometer (FTICR MS) equipped with a MIDAS data acquisition system.[17]

The samples were introduced at a flow rate of 800–1200 μL h^{-1} and the analyte solutions usually had between 1 to 2.5 mg dissolved solids per mL. The source gas pressure was 1000 psi. Initial tuning was performed on the protonated +1 molecular ion of the bpa-cavitand (m/z = 1438) in methanol, 10 : 90 v : v water : methanol or dichloromethane. The solvent choice used for tuning was matched to the solvent used to dissolve and spray the desired sample for analysis. ES tuning mix for

LC/MSD ion trap G2431A in acetonitrile, purchased from Agilent, was used as an alternative sample for tuning due to the number of peaks in the standard ranging up to a mass of 2721.89 *m*/*z* in the positive ion mode. A drying tube temperature of 45 °C was used for methanol and acetonitrile solvents while a temperature of 80 °C was used for the water–methanol solutions.

Hexapole collection times were set to optimize ion accumulation (typically about 0.6 s). After ion accumulation, a voltage on a plate downstream from the hexapole is applied to extract ions from the hexapole and inject them into the ion transfer optics of the mass spectrometer, which deliver the ions to the trapping cell of the FTICR MS. Ions are trapped in the FTICR MS for subsequent analysis. The hexapole is used primarily to improve the duty cycle of the instrument. We have also observed that increasing the hexapole accumulation time results in loss of solvent from the analyte–solvent cluster ions that are often observed in SSI; however, increasing the hexapole accumulation time can also increase fragmentation of fragile analytes. Presumably both the breaking up of solvent clusters and fragmentation occur due to collisions in the hexapole.

Results and discussion

We have formed metal-assembled cages by adding Co(II) or Fe(II) to resorcinarenes substituted on the upper rim with iminodiacetic acid ligands.[18] These cages have been characterized by NMR and X-ray analysis. More recently, we have attempted to prepare a new series of cages with metal ions and resorcinarenes substituted with bis(pyridylmethyl)amine (bpa) ligands (**bpa-res**, Fig. 1). These metal complexes have been difficult to characterize by NMR and X-ray due to the presence of paramagnetic metal ions and the lack of single crystal formation. Therefore, we turned to mass spectrometry to help characterize cage formation. Since SSI MS has not been applied to metal-assembled cages, we first carried out baseline studies using metal-assembled cages that have been previously well characterized using ESI MS.

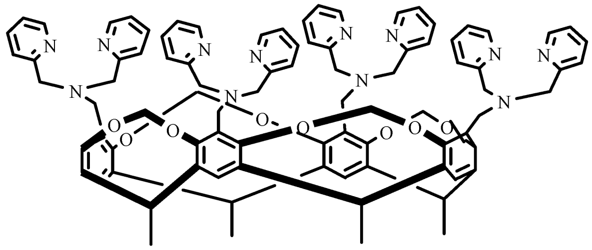


Fig. 1 Bpa-resorcinarene.

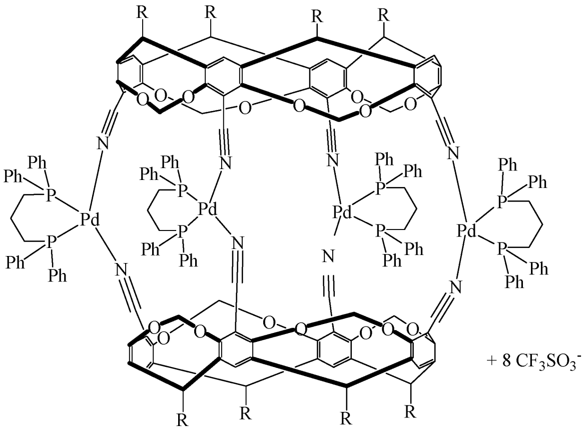


Fig. 2 Palladium-assembled resorcinarene cage, $[(Pd(dppp))_4res_2](CF_3SO_3)_8$, (R = $C_{11}H_{23}$).

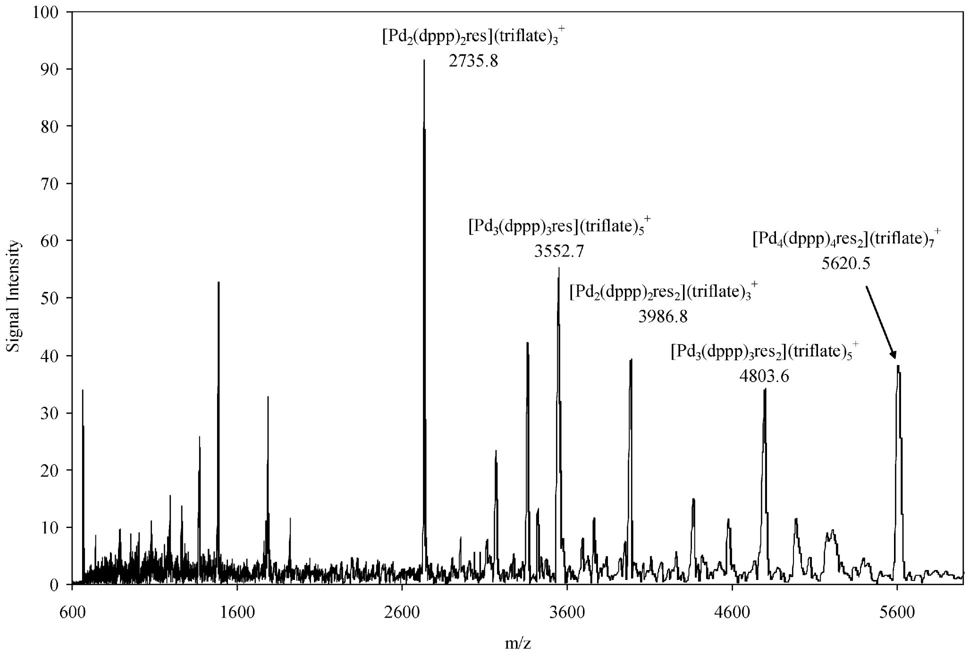


Fig. 3 SSI MS of the palladium-assembled resorcinarene cage, $[(Pd(dppp))_4res_2](CF_3SO_3)_8$. Plus one charge states are most prevalent and arise from the loss of Pd(dppp) units.

One metal-assembled cage based on a resorcinarene framework has been synthesized and characterized by Dalcanale and coworkers.[19] It contains nitrile ligands that coordinate to palladium ions (Fig. 2). NMR and ESI MS were used to show that cages exist in solution. However, ESI MS yielded only the 2+ species, which can be difficult to distinguish from a 1+ half-cage species composed of resorcinarene and two Pd(II) ions. Since the 2+ and 1+ species have the same *m*/*z*, isotopic resolution is vital to distinguish between the two species (cage and half-cage). When we attempted to observe the same cage by SSI MS, we found a strong 1+ species at 5621 *m*/*z*, which corresponds unambiguously to the cage (Fig. 3). The ability to observe strong high *m*/*z* signals is significant, because FTICR performance decreases as *m*/*z* increases. We also observed fragment species resulting from loss of triflate ions and resorcinarene.

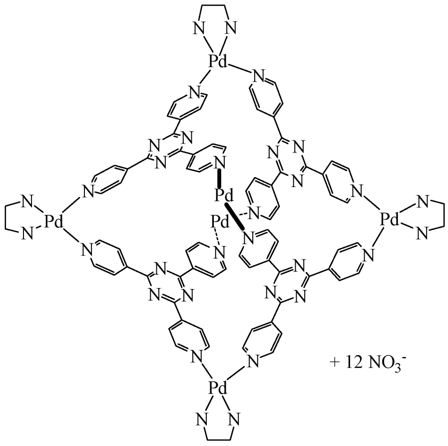


Fig. 4 Palladium–triazine cage, $[(Pd(en))_6(triazine)_4](NO_3)_{12}$. (The ethylenediamines have been left off of the two central palladiums for clarity.)

Another well characterized cage was used to confirm the new SSI MS technique. This complex was originally synthesized by Fujita and coworkers (Fig. 4).[20] It is based on four triazine groups brought together by six Pd(II) ions. NMR characterization as well as X-ray analysis showed the existence of the cage.[14] MS was also used to characterize this cage, but cold spray ionization (CSI) was needed to observe the cage. Analysis of the Pt(II)–triazine cage by MS was achieved by adding DMF, DMSO and/or guanidine to provide an ionizing matrix that allowed the molecular ion peak to be observed. However, under these conditions the Pd(II) complex showed only fragmentation peaks.[21] Addition of an additive molecule to the spray solution matrix to provide π-stacking interactions stabilized the Pd(II) cage so that it could be analyzed by ESI when sprayed from a solution of H_2O–MeCN–DMF in a 2 : 1 : 0.15 ratio.[22] When we analyzed the Pd–triazine cage by SSI MS, we found that, as with the Pd–resorcinarene cage, a +1 species (2926 *m*/*z*) corresponding to the cage was observed (Fig. 5). The mass resolution in this spectrum was sufficient to isotopically resolve the 1+ species. Along with the parent peak, species corresponding to the loss of triazine were also observed. With the softer SSI technique, the complicated source setup needed for CSI and additional ionization or stabilization agents were not required. For these experiments, the Pd(II)–triazine cage was sprayed from a solvent consisting of water–methanol 1 : 2 v : v and sprayed with a drying tube temperature of 80 °C, a lower temperature than the 100–200 °C temperatures used in a number of the ESI MS methods.

The successful observation of two well characterized cages led us to conclude that the SSI method is reliable for these

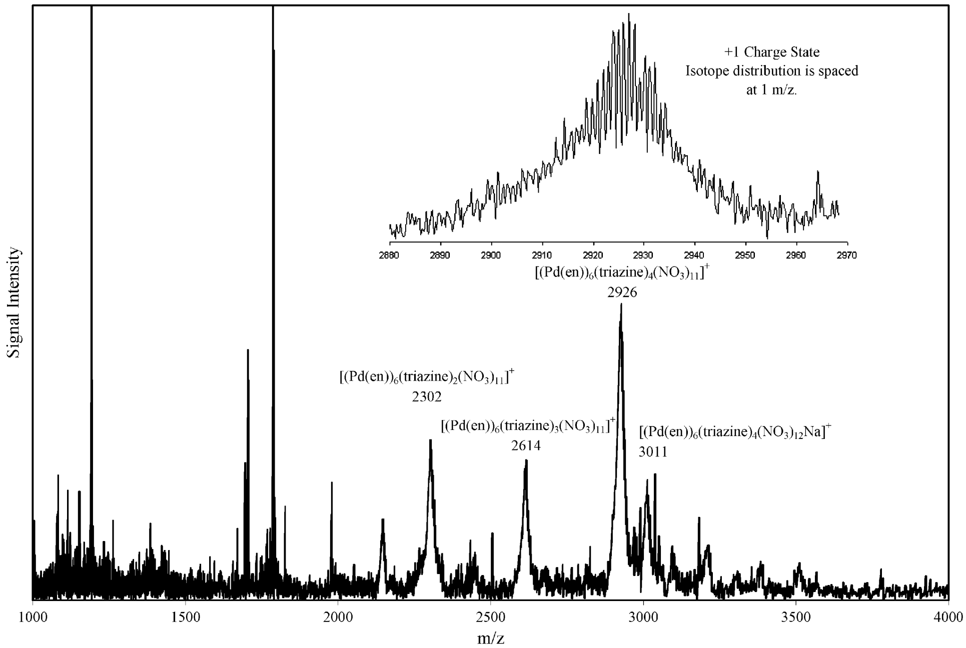


Fig. 5 SSI MS of the palladium–triazine cage, $[(Pd(en))_6(triazine)_4](NO_3)_{12}$. Plus one charge states are observed that show the loss of triazines. The parent peak is expanded, showing the isotope distribution and the plus one nature of the state.

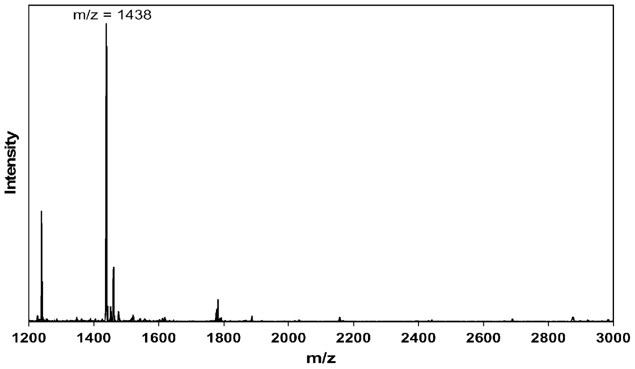


Fig. 6 SSI MS of bpa-resorcinarene (1437 g mol^{-1}). The bpa-resorcinarene without metal ions gives a strong MH^+ signal.

systems. Therefore, we proceeded to study metal complexes of our bpa-resorcinarene by SSI MS. For comparison, we first analyzed the bpa-resorcinarene by ESI. We found significant fragmentation and loss of bpa subunits. However, analysis by SSI under slightly acid conditions produced a strong parent peak (Fig. 6). Fragmentation of the molecule during ionization was minimal using SSI. Indeed, with such a strong signal, we now use this molecule to tune the instrument.

We next attempted to observe metal complexes of the bpa-resorcinarene and possible cage formation (Fig. 7). Initially, four equivalents of metal ions per resorcinarene were combined to promote the formation of open (non-cage) complexes. When ESI was used to observe the complexes, we again observed fragmentation with loss of bpa and metal ions (Fig. 8). The multiply charged 2+ and 3+ signals were dominant. This result contrasts sharply with what we obtained with SSI. With SSI, the 1+ parent species were observed when metal ions (Co^{2+} and Cu^{2+}) were added to the resorcinarene (Fig. 9). Seven chloride anions were observed to be associated with the complexes and, in the case of the copper complex, signals were observed for a normal successive loss of copper ions. The identification of the metal complexes was straight forward since 1+ charge states were observed.

Finally, we focused on observing the formation of metal-assembled cages by SSI MS. Knowing that Fe(III) coordinates

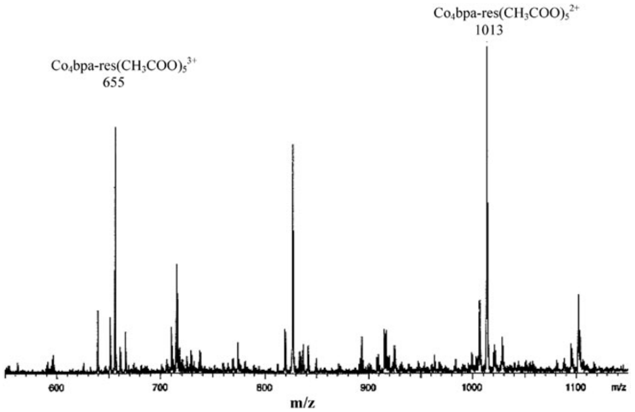
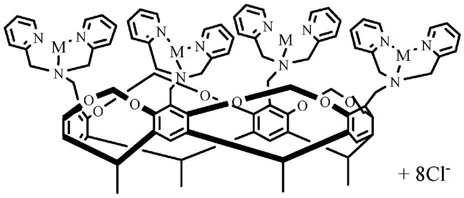
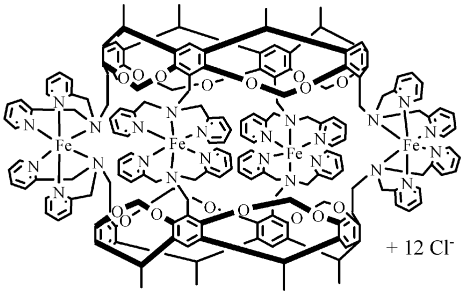


Fig. 8 Cobalt bpa-resorcinarene complex analyzed by ESI. The lowest observed charged state is the plus two.



M_4(bpa-res)Cl_8
M = Co^{2+}, Cu^{2+}



Fe_4(bpa-res)$_2Cl_{12}$

Fig. 7 Bpa-resorcinarene metal complexes. In the case of Cu^{2+} and Co^{2+}, one bpa-resorcinarene binds to four metal ions. With Fe^{3+}, two bpa-resorcinarenes bind to four metal ions.

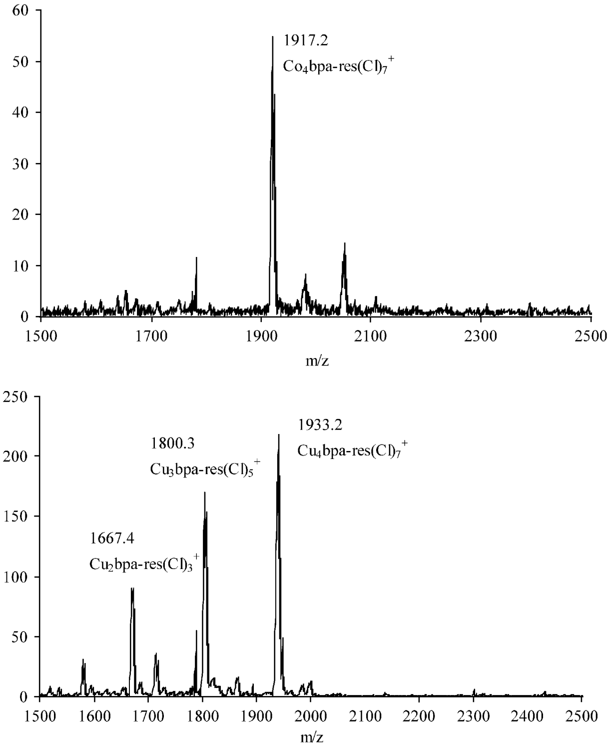


Fig. 9 SSI MS of Co_4bpa-resCl_8 (top) and Cu_4bpa-resCl_8 (bottom). In the top spectrum, the most intense signal is from the Co^{2+} species, but as seen by the 2052 m/z peak arising from Co_4bpa-res$(Cl)_{11}{}^+$, there is a Co^{3+} species. In the bottom spectrum, the Cu_4bpa-res$Cl_7{}^+$ shows successive loss of $CuCl_2$ fragments.

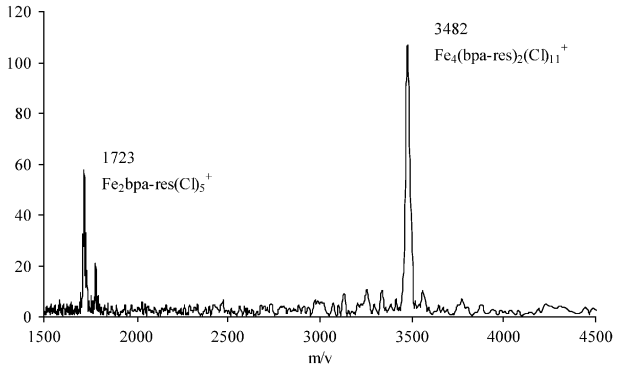


Fig. 10 SSI MS of $Fe_4(bpa\text{-}res)_2Cl_{12}$. The complex loses one chloride and is detected in a plus one charge state.

to bpa forming octahedral complexes, we added two equivalents of $FeCl_3$ to the bpa-resorcinarene in methanol. As Fig. 10 shows, we observed a molecular ion peak that corresponds to the cage, 3482 *m*/*z*. The molecular ion peak has eleven chlorides associated with the cage. The instrument was tuned to enhance the high molecular weight cage signal. The other peak shown in the spectrum corresponds to half of a cage. This observation of the cage species by SSI MS is significant because NMR was not effective in identifying the cage due to broadening of the ^1H signals by the paramagnetic iron ions.

Conclusions

SSI MS is a powerful tool for characterizing metal-assembled cages. The palladium-assembled resorcinarene and triazine cages previously characterized using NMR and ESI MS were clearly identified using SSI MS. A new iron-assembled resorcinarene cage has been identified using SSI MS. Soft ionization by SSI allows fragile compounds to remain unfragmented during ionization and results in singly charged species. SSI can be used with nonpolar and polar solvents such as methylene chloride, methanol, and water. SSI holds promise as a tool to characterize a wide variety of supramolecular complexes.

Acknowledgements

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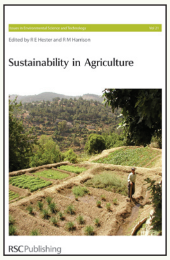

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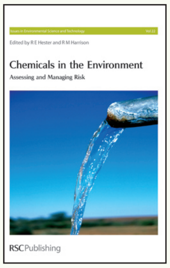

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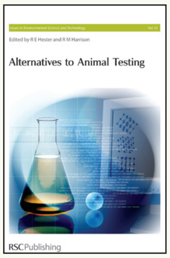

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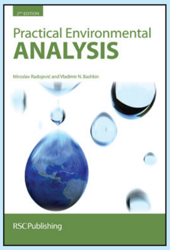

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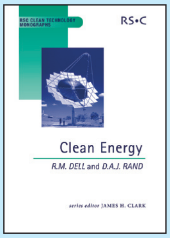

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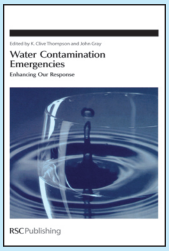

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