FULL TITLE

Analysis of Air-, Moisture- and Solvent-sensitive Chemical Compounds by Mass Spectrometry using an Inert Atmospheric Pressure Solids Analysis Probe

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Abstract

A novel method has been developed that enables chemical compounds to be transferred from an inert atmosphere glove box and into the atmospheric pressure ion source of a mass spectrometer whilst retaining a controlled chemical environment. This innovative method is simple and cheap to implement on some commercially available mass spectrometers. We have termed this approach inert atmospheric pressure solids analysis probe (*i*ASAP) and demonstrate the benefit of this methodology for two air-/moisture-sensitive chemical compounds whose characterization by mass spectrometry is now possible and easily achieved. The simplicity of the design means that moving between *i*ASAP and standard ASAP is straightforward and quick, providing a highly flexible platform with rapid sample turnaround.

Keywords

mass spectrometry, inert ASAP ionization, analysis, moisture- and/or air-sensitive chemicals

Introduction

While the vacuum system of a mass spectrometer makes for an ideal environment to study highly reactive, air-, solvent-, and/or moisture-sensitive compounds, its application is often hampered by suitable methods of sample introduction. This rules out many atmospheric pressure ion sources; even higher vacuum ion sources such as MALDI and EI still have to overcome the time period required to get the sample under vacuum. Although a remote inert environment glove box has previously been used to prepare samples for MALDI MS, the time taken (typically 10s of seconds) to transfer the sample-containing MALDI target from a glove box to the high vacuum of the mass spectrometer, these few seconds of exposure to the atmosphere are often sufficient time for sample degredation to occur[1].

A similar strategy involving use of a glove box situated close to the mass spectrometer, but not surrounding the source housing, has enabled liquid injection field desportion ionisation (LIFDI)[2, 3] and electrospray ionisation (ESI)[4] of analyte solutions from dry non-polar hydrocarbons such as toluene and hexane, transferred from the glove box to the ESI source *via* a capillary tube. The natural extrapolation of this on-line approach is reaction monitoring, an area of general growing interest, as outlined in a recent review by Ray *et al.*[5]. Yan *et al.* demonstrate this using inductive ESI to follow chemical reactions where the reagents are highly susceptible to oxygen and water, monitoring transient reaction intermediates in due course[6]. Vikse *et al.* have also been able to monitor catalytic

reactions under anaerobic conditions by connecting a Schlenk flask to an ESI source[7]. These recent developments highlight speed and sensitivity at which mass spectrometry can deliver analytical answers for such reactive species transferred in a liquid flow of dry solvents. The need to maintain inert liquid transfer lines, syringes and ESI sprayers however is cited as being non-conducive to instrument sharing with applications that use acidic or polar media[8].

In a move to avoid remote sample preparation for mass spectrometry, a number of approaches have been documented whereby construction of a glove bag, purge box, or recirculating glove box around the MS source inlet enable sample preparation and introduction under a controlled inert atmosphere. For transition metal complexes this has enabled field desorption (FD)[9], matrix-assisted laser desorption/ionisation (MALDI)[10], electron ionisation (EI) and laser desorption/ionisation (LDI)[11] MS analyses. Building a sealed glove box around the ion source of a mass spectrometer, or indeed putting the whole analytical instrument inside a glove box[12] is largely impractical, particularly for instruments that are required to remain multifunctional. In response to such difficulties, we have developed a solution in our laboratory that enables solid air-/moisture-/solvent-sensitive samples to be studied by atmospheric pressure ionisation mass spectrometry, and interchangeably with non-sensitive samples[13].

While it is clear that methods for the introduction of analyte samples into EI or FD instruments can be achieved under an inert atmosphere, this type of methodology remains challenging for the 'softer' ionisation techniques such as MALDI and ESI, which are advantageous since the degree of in-source fragmentation is less, a favourable benefit for organometallic and coordination complexes where the ligands are often labile[14]. Atmospheric pressure solids analysis probe (ASAP) MS[15] is a direct analysis approach that sits within the new breed of atmospheric pressure ionisation (API) techniques[16, 17]. Akin to atmospheric pressure chemical ionisation (APCI), samples for ASAP are placed in a melting point tube, which is then introduced into the APCI source housing where a heated gas, such as nitrogen, vapourises the sample. Subsequent application of a corona discharge is used to ionise the neutral gas, producing the radical cation for nitrogen, $N_2^{+\cdot}$. A cascade of ion-molecule reactions then occur, which result in analyte ionisation; detailed ionisation mechanisms have been documented previously[18, 19] and are summarised here:

1) Electron ionization: $N_2 + e \longrightarrow N_2^{+\cdot} + 2e$

2) Reaction: $2N_2^{+\cdot} + N_2 \longrightarrow N_4^{+} + N_2$

3a) Charge transfer: $N_4^{+} + H_2O \longrightarrow H_2O^{+} + 2N_2$

3b) Charge transfer to analyte: $N_4^{+} + \text{analyte} \longrightarrow \text{analyte}^{+} + 2N_2$

4) Proton transfer: $H_2O^{+} + H_2O \longrightarrow H_3O^{+} + OH$

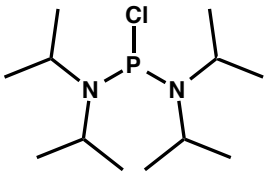
5) Proton transfer to analyte: $H_3O^{+} + \text{analyte} \longrightarrow [\text{analyte} + H]^{+} + H_2O$

6) Hydride abstraction: $X^{+} + \text{analyte} \longrightarrow [\text{analyte} - H]^{+} + XH$

Ultimately, ASAP is well suited to the fast analysis of solids or solutions[20, 21], the former being advantageous to the study of solvent-sensitive compounds. Our development, described herein, is designed to work interchangeably with standard ASAP, providing rapid throughput for samples that include solid air-/moisture-/solvent-sensitive samples, and has been termed inert atmospheric pressure solids analysis probe (*i*ASAP).

Experimental

Compounds **1**[22] and **2**[23] were prepared according to previously reported methods and used as representative air-/moisture-/solvent-sensitive samples with which to test the *i*ASAP methodology.



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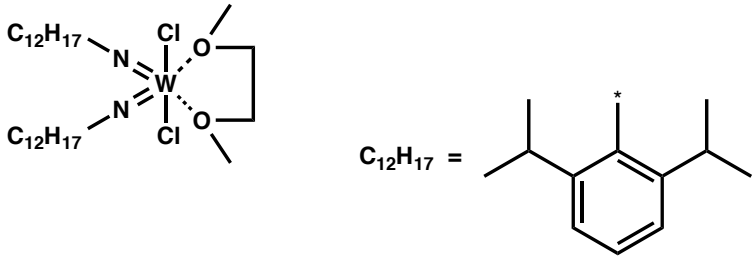

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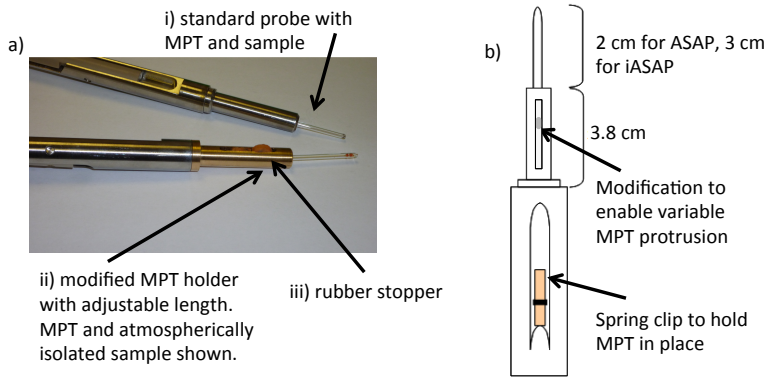
Scheme 1. Representative air-/moisture-sensitive compounds analysed by *i*ASAP MS.

Sample preparation: approximately 1 mg of powdered sample is placed inside a melting point tube (MPT) under an atmosphere of dry nitrogen in a nitrogen-filled glove box (Saffron Scientific). The MPT is then temporarily sealed with plasticine™ whilst still inside the glove box. The atmospherically-isolated sample is then removed from the glove box and the MPT fully sealed with a flame, taking care not to heat the sample. A portion of the MTP, distanced from the sample by about 2-3 cm, is heated and stretched to produce a weak spot that can be controllably broken, as shown in Figure 1. The atmospherically-isolated sample is then placed in an ASAP holder that has been modified to accommodate the shorter and variable length of the sealed MPTs as shown in Figure 1a and b. A slit in this holder accommodates a rubber stopper that physically secures the shortened MPT in place by virtue of pinning it against the main body of the probe holder (Figure 1a). A baffle designed for use with the lock mass spray is used to break the protruding MPT within the inert

nitrogen atmosphere of the API source housing (Figure 1c). For multiple samples analysed sequentially, glass remnants from the MPTs were collected in a small tray placed at the bottom of the source housing. This enabled multiple samples to be analysed without opening the ion source housing between analyses, thus preserving the inert atmosphere inside the source housing for continued periods of operation and facilitating high throughput. To this end, sample turnaround for *i*ASAP is of the order of 30 seconds to 1 minute as with standard ASAP. Despite remains of previous samples collecting in the bottom of the ion source housing, there was no observed memory effect of one sample to the next.



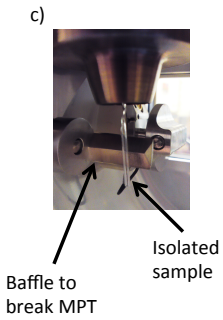


Figure 1. a) Photograph of apparatus used highlighting i) standard MPT holder, ii) modified sample holder and iii) rubber stopper used to further hold shortened MPT in place. b) schematic of modified probe sample holder with dimensions and c) relative sample and baffle positions that facilitate sample release.

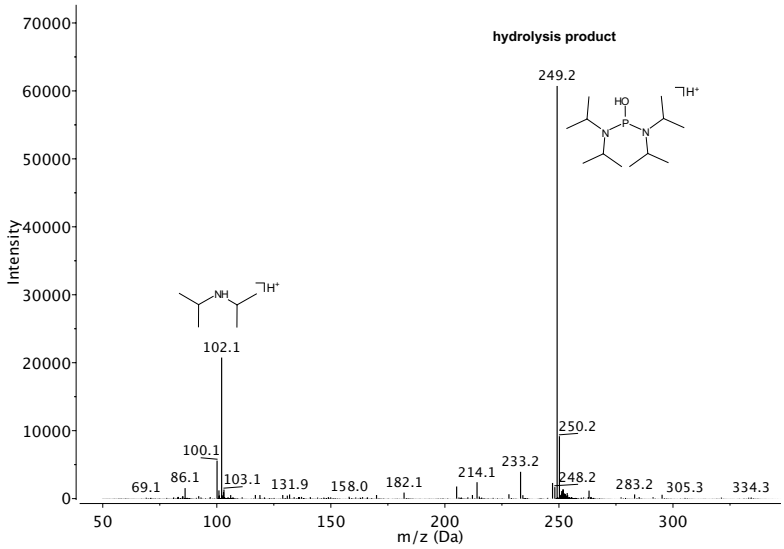
All measurements were made on a Xevo QToF mass spectrometer fitted with an ASAP ion source (Waters Corp., UK). Positive ions were recorded between 50 and 1000 Da. The majority of ion source parameters remained constant throughout the experiments, including capillary voltage (3.00 kV), sampling cone voltage 30 V, corona current (2.5 μA), extraction cone (2 V), source temperature (150 °C), cone gas flow (0 L/h) and desolvation gas flow (800 L/h). Changes were made to desolvation gas temperature which was set to 350 °C for compound **1** and 600 °C for complex **2**.

Data were processed using MassLynx version 4.1 suite of software (Waters Corp., UK).

Results and Discussion

Phosphorus-containing compound **1** is particularly sensitive to the presence of water and protic solvents, hydrolysing rapidly. This can be seen in Figure 2a where the sample, prepared under dry nitrogen in a small round bottom flask and sealed with suba seal, was removed from the glove box and taken for MS analysis. Opened to the MS laboratory atmosphere for the briefest possible time (1-2 seconds), evidence for an intact ion could not be obtained by standard ASAP. It is apparent that the standard ASAP approach: opening the vial, inserting a clean, sealed MPT into the sample and placing this MPT into a holder and into the nitrogen based atmosphere of the ion source is insufficient in this case as the compound entirely decomposes to give the hydrolysis product, liberating diisopropylamine. By sealing the sample inside a MPT under an inert atmosphere and placing the protected sample into the holder and only breaking the MPT under the inert ion source atmosphere (dry nitrogen) a clear signal is observed for the protonated molecule, $[\mathbf{1}+H]^+$, at *m/z* 267 (Figure 2b). Although there is still evidence of some products resulting from hydrolysis, this is likely to have occurred as a result of insufficiently dry nitrogen gas since no special precautions were taken to introduce the gas into the MS instrument housing. The peak at *m/z* 231 corresponds to the loss of the halide and is common for such diamido-substituted P-Cl compounds,

formally giving rise to a well-established phosphenium cation, $\{(i\mathrm{Pr}_2\mathrm{N})_2\mathrm{P}\}^+$[24]. In addition to identifying the target compound, it is now possible to deduce some potential by-products of the chemical synthesis; the peak at *m/z* 281 may be accounted for by isopropyl replaced by tertiary butyl on one ligand.



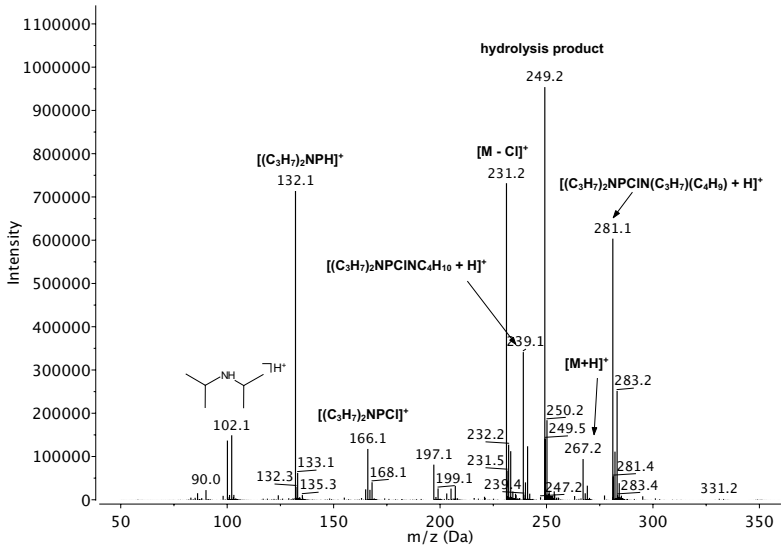
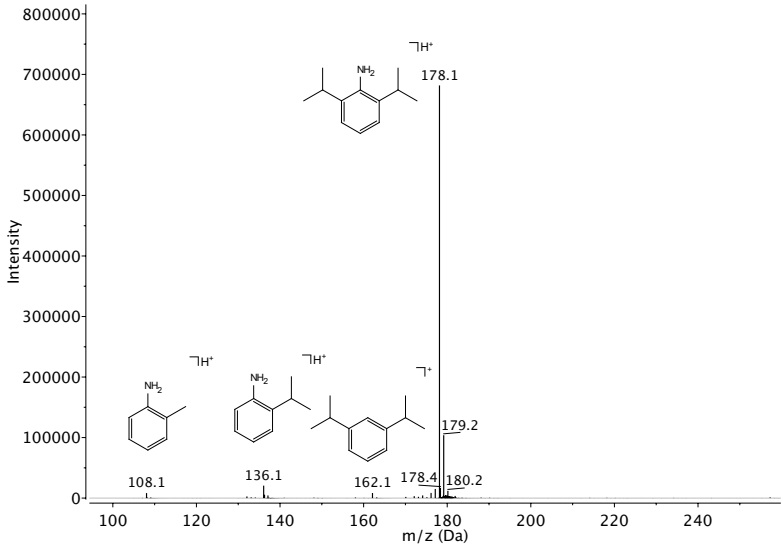


Figure 2. a) ASAP and b) *i*ASAP analysis of Compound 1.

When complex **2** is analysed by mass spectrometry as quickly as possible from a sample vial on an open bench as opposed to being maintained under an inert atmosphere throughout the analysis, decomposition is rapid. Figure 3a shows the presence of the 2,6-diisopropylanilinium (*m/z* 178), 1,3-diisopropylbenzene (*m/z* 162), 2-isopropylanilinium (*m/z* 136) and 2-methylanilinium (*m/z* 108) from analysis of the products that result from the decomposition of **2** under air. In contrast, using our *i*ASAP method there is clear evidence for the hydride abstracted species for the complex **2** at *m/z* 691, [**2**-H]$^+$ (Figure 3b). Such hydride abstraction is known to occur during ionisation of some compounds, most recently reported for *N*-(1,3-diphenylallyl)benzenamines by Fang *et al*.[25].



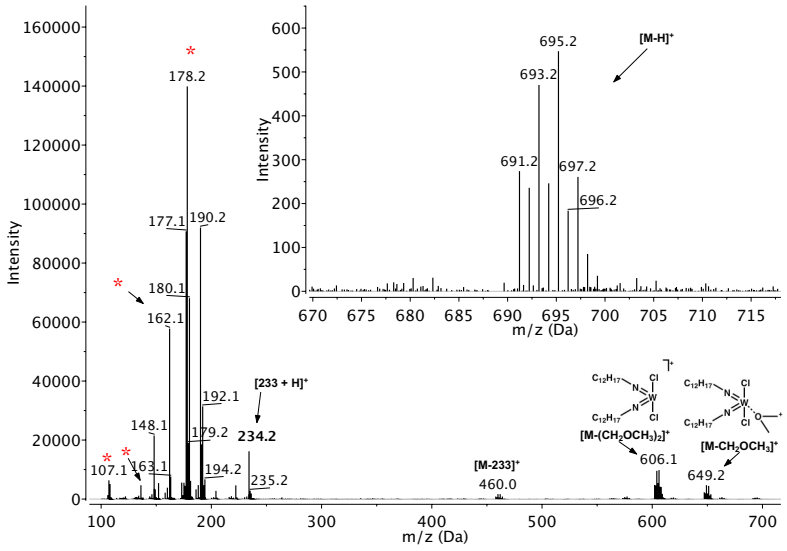


Figure 3. a) ASAP and b) *i*ASAP analysis of Compound 2. Starred peaks indicate ions common to both ASAP and *i*ASAP; structures are given for both in Figure 3a.

In addition to the target complex **2**, there is also evidence in the *i*ASAP analysis of this sample for in-source dissociation. Cleavage across the 1,2-dimethoxyethane ligand correlates to the loss of CH_2OCH_3 giving rise to *m/z* 647, and also the loss of the whole 1,2-dimethoxyethane ligand to give *m/z* 602 as shown by the proposed structures in Figure 3b. These product ions are easy to track owing to a distinct pattern arising from the WCl_2 isotopologues (see supplementary information). The same profile for these isotopologues is also observed at *m/z* 458 and corresponds to neutral loss of 233 u from the target compound. This is proposed to arise from the gas-phase rearrangement of the ligands. The peak at *m/z* 234, tentatively supports this proposal as the neutral loss could be conceivably protonated in a subsequent step. It should be noted that contribution

by thermal degradation cannot be ruled out. In our experience the analysis of metal-ligand complexes by ASAP are more successful at higher desolvation gas temperatures and prolonged exposure at such temperatures (600 °C in this case) is known to lead to thermal decomposition of synthetic polymers[20].

As with compound **1**, again there is again some degree of degradation of the sample of **2** as identified by *i*ASAP, something attributed to the presence of residual water vapour or air in the nitrogen or API source housing. This is evidenced by peaks corresponding to *m/z* 108 for 2-methylanilinium ions, *m/z* 136 for 2-isopropylanilinium, *m/z* 162 for 1,3-diisopropylbenzene and *m/z* 178 for 2,6-diisopropylanilinium (starred peaks in Figure 3b).

For both compound **1** and complex **2**, it is clear that preventing exposure to a hostile environment with the *i*ASAP methodology described herein delivered success. This new analytical approach to mass spectrometry of air-/moisture- or solvent- sensitive chemicals clearly enables such ions to be observed intact. This, therefore, paves the way for rapid detection from crude mixtures and thereby monitor reactions, or for further characterisation by tandem mass spectrometry and accurate mass measurement.

Conclusion

This *i*ASAP protocol provides a simple, versatile way to introduce highly reactive compounds to a mass spectrometer, as demonstrated by mass spectrometric analysis of the air-/moisture-sensitive samples **1** and **2**. More over, requiring no exposed component parts that need be shared with non-sensitive applications, a single instrument can perform all analyses required, and interchangeably, making this an ideal solution for laboratories sharing instruments or providing a service where sample throughput is crucial.

The modification is simple, cost efficient and can be made easily to existing Waters Corp. time-of-flight instrumentation with lock mass capability. As far as we are aware this, our original work[13] is the first example where a sample in a sealed vessel is opened inside the inert gas atmosphere of the ion source of a mass spectrometer. A similar approach has now been commercialized[26], building on our name *i*ASAP.

Acknowledgements

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