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Review

Analysis of low molecular weight compounds by MALDI-FTICR-MS☆

Hao-Yang Wang*, Xu Chu, Zhi-Xiong Zhao, Xiao-Shuang He, Yin-Long Guo*

Shanghai Mass Spectrometry Center, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, PR China

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ABSTRACT

This review focuses on recent applications of matrix-assisted laser desorption ionization-Fourier-transform ion cyclotron resonance mass spectrometry (MALDI-FTICR-MS) in qualitative and quantitative analysis of low molecular weight compounds. The scope of the work includes amino acids, small peptides, mono and oligosaccharides, lipids, metabolic compounds, small molecule phytochemicals from medicinal herbs and even the volatile organic compounds from tobacco. We discuss both direct analysis and analysis following derivatization. In addition we review sample preparation strategies to reduce interferences in the low *m*/*z* range and to improve sensitivities by derivatization with charge tags. We also present coupling of head space techniques with MALDI-FTICR-MS. Furthermore, omics analyses based on MALDI-FTICR-MS were also discussed, including proteomics, metabolomics and lipidomics, as well as the relative MS imaging for bio-active low molecular weight compounds. Finally, we discussed the investigations on dissociation/rearrangement processes of low molecular weight compounds by MALDI-FTICR-MS.

Contents

Abbreviations: MS, mass spectrometry; MS/MS, tandem mass spectrometry; CID, collision-induced dissociation; SORI-CID, sustained off-resonance irradiation collision-induced dissociation; IRMPD, infrared multiphoton dissociation; *m*/*z*, mass-to-charge ratio; $[M+H]^+$, singly protonated molecule; $[M-H]^-$, singly deprotonated molecule; LC, liquid chromatography; TLC, thin layer chromatography; CE, capillary electrophoresis; GPC, gel-permeation chromatography; ESI, electrospray ionization; MALDI, matrix assisted laser desorption ionization; DIOS, desorption/ionization on silicon; SALDI, surface-assisted laser desorption/ionization; NALDI, nano-assisted laser desorption-ionization; TOF-MS, time-of-flight mass spectrometry; FTICR-MS, Fourier transform ion cyclotron resonance mass spectrometry.

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* Corresponding authors. Tel.: +86 21 54925300; fax: +86 21 54925314.
E-mail addresses: haoyangwang@mail.sioc.ac.cn (H.-Y. Wang), ylguo@mail.sioc.ac.cn (Y.-L. Guo).

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1. Introduction

Mass spectrometric methods measure m/z of molecular and fragment ions of compounds with high accuracy and precision. Tandem mass spectrometry (MS/MS) identifies the origins of the fragment ions [1,2]. Taken together these data can assist in determining the structure of molecules. Sample preparation [3], analytical derivatization [4,5], preparative chromatography preconcentrate and fractionate the isolate to increase sensitivity [6,7] and reduce interferences particularly matrix effects in suppressing ionization [8].

In this article we present an overview of the past applications of matrix-assisted laser desorption ionization (MALDI) [9,10] Fourier-transform ion cyclotron resonance mass spectrometry (FTICR-MS) [11] for low molecular weight compounds analysis directly or with analytical derivatization. During the recent five years, there have been significant progresses in the field. However, to our best knowledge, no review has discussed the issue that good chemical methods can enhance the determination of small molecules by FTICR-MS, which is one of the most sophisticated instrumentations available to the analytical chemist. In this review we discuss the sample preparation and analytical derivatization techniques suitable for determination of small molecules by MALDI-FTICR-MS. Meanwhile, some other important reports about time-of-flight mass spectrometry (MALDI TOF-MS) [12] concerning the similar topics were also discussed due to the fact that these technologies have also been applied in MALDI-FTICR-MS experiments.

1.1. MALDI-MS: vacuum MALDI and AP-MALDI

MALDI and ESI [13] are both soft ionization techniques for the determination of biological and synthetic macromolecules. However, ESI produces multiply charged ions which complicate interpretation. Nowadays, MALDI is coming to be a widely used soft ionization technique in mass spectrometry, allowing the analysis of biomolecules (biopolymers [14]: such as proteins [15,16], peptides [17] and saccharides [18]) and large organic molecules (such as polymers [19] dendrimers [20] and other macromolecules [21]). In traditional MALDI analysis, the sample is dispersed in a solid matrix (normally a compound that efficiently absorbs the laser radiation) and achieves rapid desorption/ionization into positively or negatively charged ions by using a pulse of radiation from an ultraviolet or infrared laser.

AP-MALDI [22] generates ions at atmospheric pressure whereas the cluster ions of matrix and analyte could be clearly observed due to reduced fragmentation caused by the collisional cooling of the expanding plume. Dissociation of these clusters can be achieved by applying higher laser frequency or adapting the parameters of the atmospheric pressure interface [23]. This technique has a large tolerance for laser frequency variations. AP-MALDI has been combined with FTMS to obtain the unambiguous characterization of RNA samples modified by solvent accessibility reagents for structural studies of RNA and protein–RNA complexes and providing high-resolution spectra for analytes with little or no evidence of metastable decomposition [24]. The high resolution advantage of FTICR-MS enables the application of a data-reduction algorithm capable of discarding the signal devoid of plausible isotopic distribution, thus facilitating the analysis of complex analyte mixtures produced by nuclease treatment of RNA substrates [25].

1.2. The practical considerations in MALDI analysis for low molecular weight compounds

Table 1 summarized some recent reviews for the important and interesting applications of MALDI-MS. From Table 1, we could see that MALDI is also a powerful technique to provide both qualitative and quantitative determination of low molecular weight compounds, as well as on coupling of MALDI to liquid and planar chromatographic techniques to extend its range of applicability [35,36].

1.2.1. Signal suppression and quantification of MALDI-MS

MALDI-FTICR MS analysis provides specificity, sensitivity and speed, due to its ability to monitor selected mass ions to enhance signal-to-noise ratio, avoid the need for intensive sample cleanup and long analysis times, and even achieve the quantification of target compounds. The presence of signal suppression in MALDI-FTICR MS experiments shares some common aspects with other MS analysis strategies, which compromise qualities of the MS spectra, decrease the response of target compounds and reduce the accuracy and reproducibility of MALDI quantitative analysis. The ion suppression effect [38] is due to the salts and buffers of biomedical samples and in sample preparation including: matrix signals applied in experiments, ion-pairing agents, ionic detergents, endogenous compounds, drugs, metabolites, and proteins. The options for minimizing or correcting ion suppression consist of some specific sample cleaning-up steps, chromatographic separation, reagent modifications, derivatization, modifications to the matrix in MALDI sample preparation and effective internal standardization. Another problem in MALDI-MS analysis is the matrix-suppression effect, which is caused by the consumption of primary matrix ions by neutral analytes via a secondary ion-molecule reaction in the ionization process, therefore the suppression of matrix peaks or signals is observed when sufficient analytes are present to react with all matrix ions. The molar ratio of analyte and matrix in the sample and laser intensity are the important factors to induce MSE for small-molecule analysis. These factors have already been discussed thoroughly by Luider [37].

Quantitative analysis by MALDI-FTICR MS meets the challenge of the poor precision. Many strategies could be applied to minimize such problem, such as increasing homogeneity of the matrix/analyte crystals by incorporating some additional reagents, using ionic liquid matrices, choosing high molecular matrix or applying the matrix-free approaches. Meanwhile, applying internal

Table 1
Recent reviews about the application of MALDI-MS.

Authors	Years	Topics and references
Aubriet	2007	Laser-induced FTICR-MS of organic/inorganic compounds [26]
Fogg	2006	Inert-atmosphere MALDI-MS for metal complexes/catalysts [27]
McIndoe	2000	The characterization of metal clusters [28]
Montaudo	2006	The characterization of synthetic polymers [29]
Schubert	2009	The structural assignment of synthetic polymers [30]
Higashi	2004	Derivatization of neutral steroids to enhance their detection characteristics in mass spectrometry [8]
Schiller	2009	MALDI-MS for lipidomics [31]
Schiller	2009	MALDI matrices for apolar compounds [32]
Schiller	2009	MALDI with liquid and planar chromatographic techniques [33]
Schiller	2010	An update of MALDI-TOF MS in lipid research [34]
Cohen	2002	Low molecular weight compounds [35]
Cohen	2007	Small-molecule desorption/ionization mass analysis [36]
Luider	2011	Biomedical application of MALDI-MS for small-molecule analysis [37]

standards and averaging results within spot and spot-to-spot are also the widely used methods in quantification analysis by MALDI-MS [39].

The characters of FTICR-MS analyzers in quantification for small molecular metabolite compounds have been discussed by Brown [39]. FTICR-MS analyzers have the highest resolving power of all mass analyzers and also have wide mass range, high sensitivity and high dynamic range. Use of a mass selective quadrupole optic lens before detection cell would enhance the performance of small molecule analysis due to selective enhancement of the ion pass ratios when focusing on the interesting mass range of small molecules. All these special advantages make the MALDI-FTICR MS an ideal instrument for small molecule analysis.

1.2.2. The separation technologies prior to MALDI-MS

Although MALDI is used primarily as a stand-alone analytical method, substantial efforts have been directed toward coupling MALDI with various column and planar separation methods [12] (termed hyphenated MALDI techniques). The use of a separation technique prior to MS analysis greatly reduces the signal suppression of low-abundance ions in analysis of complex mixtures, thus enhancing its sensitivity. The accomplished hyphenated MALDI techniques an be classified as two main types: off-line and on-line. Because of the advantages of MALDI like fast, efficient and high tolerance to nonvolatile buffers and impurities [40,41], the samples for MALDI are typically applied to solid supports and fractionated off-line with liquid or gel separations [42]. Investigators have hyphenated MALDI or desorption/ionization on porous silicon (DIOS) analysis with separation techniques such as HPLC [43], GPC [44], CE [45], TLC [46] and polyacrylamide gels [47]. Many measures like exciting samples at atmospheric pressure [48,49] or continuously streaking [50] on the target are implemented to improve the characters of off-line MALDI.

Meanwhile, there have been still numerous attempts to achieve on-line MALDI analysis of flowing liquid samples because of its high speed, high throughput and effective for ultra trace analysis, where fewer sample handling steps would reduce the sample losses. Liquid samples have already been analyzed directly in vacuum using two kinds of mechanical designs of on-line MALDI. In one approach, liquid samples are transported into the mass spectrometer through a capillary and deposited onto a rotating wheel [51] followed by the solvent evaporation forming a thin sample trace on the position which will rotate for laser desorption. A second mechanical approach is a modification of the rotating ball inlet [52,53]. For the rotating ball MALDI analysis, a solution containing matrix and analyte are delivered to the surface of a stainless steel ball that rotates several times each minute [54]. As the ball rotates, the solution is exposed to vacuum where the volatile solvent evaporates leaving the matrix and analyte on the rotating ball [55,56]. When the ball has rotated one-half turn, it is in position for laser desorption and following analysis [57–59]. The combination of separation methods with MALDI-FTICR-MS has been wildly applied in various fields including comparative neuropeptidomic analysis in crustacean model organisms in conjunction with stable isotopic labeling [60], analysis of neuropeptides from individual neuroendocrine organs of crab cancer borealis [61,62], structural characterization of toxin-binding gangliosides [63,64] and the studies of isotope beating effects in the analysis of polymer distributions [65].

1.3. FTICR-MS

1.3.1. The principle of FTICR-MS

The principle of the ion cyclotron resonance (ICR) was developed by Lawrence and coworker [66] and this technique was utilized for mass spectrometry by Sommer around 1950 [67,68]. In 1974 [69,70], the combination of the FT (Fourier transform) technique with ICR by Comisarow and Marshall formally means the naissance of FTICR-MS which has been widely applied as a powerful and versatile analytical tool in chemistry and biochemistry [71,72]. In a FTICR-MS analyzer, ions are trapped in a Penning trap by a strong magnetic field with electric trapping plates and where the ions are excited to a larger cyclotron radius by an oscillating electric field vertical to the magnetic field in a packet. A small image current will be induced and detected in the pair of detection plates when the packet of ions are excited closer to the plates. Each generated current frequency of cyclotron motion will correspond to a certain m/z value, for the ions with different m/z values have different ICR frequencies, and the simplest or idealized relationship between the cyclotron frequency and the mass to charge ratio is given by: $f = q\boldsymbol{B}/2\pi m$, where f = cyclotron frequency, q = ion charge, $\boldsymbol{B}$ = magnetic field strength and m = ion mass [73]. Thus, in practice, the useful signal is extracted from the data by performing a Fourier transform to give a mass spectrum when we sweep all the expected frequencies to excite and detect all the expected ions through the m/z range.

Before 1980s, the FTICR-MS was restricted in many fields because the ion sources had to be placed inside the detection cell of FTICR-MS under vacuum. Coupling of external sources to FTICR-MS reported by Kofel et al. greatly expanded its applications [74,75], since nearly every widely used ion sources was conveniently located outside the magnet. Several methods have been developed to guide externally generated ions into an ion trap to the detection cell of FTMS inside a high-field magnet [76]. FTICR-MS differs significantly from other mass spectrometry techniques in that the ions are not detected by bombardment on the detector such as an electron multiplier or MCP (microchannel plate) but only by passing near detection plates. Additionally the masses are not resolved in space or time as with other techniques but only by the cyclotron (rotational) frequency that each ion produces as it

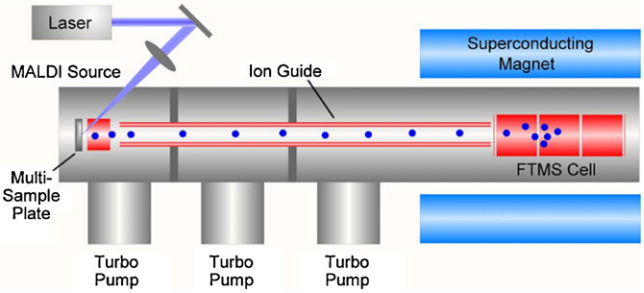

Fig. 1. A working principle of MALDI-FTICR-MS (Ionspec).

rotates in a magnetic field. Thus, the different ions are not detected in different places as with sector instruments or at different times as with time-of-flight instruments but all ions are detected simultaneously over some given period of time in FTICR-MS. The resolution of FTICR-MS can be improved by increasing the strength of the magnet or by increasing the detection duration [77]. The most important attribute of FTICR-MS is the capability for accurate mass measurements [78] with a combination of resolution and accuracy that is higher than any other mass analyzers.

1.3.2. Combination of MALDI with FTICR

MALDI is well suited to be coupled with TOF-MS or FTICR-MS as mass analyzers because the mass spectrum could be generated with an individual shot of the laser rather than working in continuous operation [79]. Nowadays, MALDI has been applied wildly coupled with TOF/TOF-MS (tandem TOF/TOF mass spectrometer) [80], QTOF-MS (quadrupole-time of flight mass spectrometer) [81] and QIT-TOF-MS (quadrupole ion trap time-of-flight mass spectrometer) [82]. The introduction of the CID functions expands the ion structural assignment power of the MALDI-MS technique [83]. Following the demonstrations of using MALDI with TOF-MS techniques, there have been significant efforts in a number of laboratories to adapt the new methodology to associate MALDI with FTICR-MS [84]. The obvious motivation is to achieve reliable identification and high sensitive quantification for target compounds. We selected one example of the MALDI-FTICR-MS (Ionspec, Irvine, CA) and showed its working principle in Fig. 1.

1.3.3. LDI-FTICR-MS

The basic character of MALDI is the introduction of organic matrix. The matrix in MALDI analysis transfers laser energy to the analyte, which reduces the ion fragmentation. However the high background ions of the matrix restricted its application in many fields [85]. Matrix-free laser desorption/ionization (LDI) is an approach in which a sample is placed on a photoactive but non-desorbable support and analyzed without any matrix, which can be considered as a form of MALDI-MS due to the similar principles. Although no matrix is used and some differences exist in the mechanism of ion formation, little or no signals from the modified surfaces are observed in the mass spectrum is the main advantage of matrix-free LDI, as well as the simplified sample preparation without the mixing or co-crystallizing of the analyte with a matrix. Some new matrix-free MALDI techniques including DIOS [86], desorption/ionization on metal films [87,88], desorption/ionization on oxide plates [89] and surface-assisted laser desorption/ionization (SALDI) [90] have emerged and developed rapidly because of the good qualities of simplicity, excellent mass accuracy, high resolution, and sensitivity.

Mass spectrometric imaging of tissue-lipid transfers without matrix is available [91]. Commercially available nanostructured surfaces (nano-assisted laser desorption-ionization or NALDI) are used as substrates for imprinting of tissue sections. Compared with standard MALDI imaging of matrix-coated tissue sections, the NALDI images are of the same quality and no spatial information is lost due to the imprinting process. NALDI imaging is faster due to the absence of the time-consuming matrix deposition step, and the NALDI mass spectra are less complex and easier to interpret than standard MALDI. In this particular application example, NALDI mass spectrometry is able to identify the same lipid species as MALDI mass spectrometry and provides better distinction between kidney and adrenal gland tissues based on the lipid analysis.

Although the performance of MALDI is superior to LDI in the analysis of many groups of compounds, LDI is still the preferred choice in some important applications, including crude oil analysis [92], atmospheric aerosol analysis [93], surface analysis [94], tissue imaging [95] and inorganic compounds analysis [96]. In the last decades, LDI-MS has emerged as one of the most useful methods for analysis of non-volatile organic compounds. The improvements of attainable mass range and resolution for high mass molecules of LDI-FTICR-MS further extend its analytical applications [97], LDI-FTICR-MS has been applied in many fields, such as detection of polycyclic aromatic hydrocarbon (PAH) [98], division of isomers [99], polymer analysis [100], capture of radical ions [101], analysis of biological sample like plasma [102] and studies of some chemical process including gas-phase host–guest effects [103], photo-dissociation [104], and self-assembling complexes [105].

1.3.4. High accuracy and resolution of FTICR-MS

The accurate mass measurement function of FTICR-MS facilitates determination of the composition of molecules based on the mass defect of the elements [106]. Particularly, FTICR-MS is useful to distinguish ions close to each other on the m/z axis but with different elemental compositions [107,108]. During performing the accurate mass measurement of MALDI-FTICR-MS, it was found that collisional damping affected the relationship between ion mass and effective cyclotron frequency. An amended calibration equation has been proposed by us to make the exact mass calibration immune to collisional damping and space-charge effects on mass accuracy with relative errors less than 2×10^{-6} [109]. The MALDI-FTICR-MS method coupling with various chromatographic technologies allows the study of low molecular weight compounds on both qualitative and quantitative level. In low mass range ($m/z < 500$) the higher performance of FTICR-MS instruments can effectively overcome the signal interferences from matrixes and other impurities. This is the most outstanding advantages of MALDI-FTICR-MS in analysis of small molecular compounds.

1.3.5. Manipulation of stored ions in FTICR-MS

FTICR-MS allows the extensive manipulation of stored ions to provide additional structural information, including the relative dissociation thresholds of the trapped ions [110]. Tandem-in-time mass spectrometry (MS/MS or MS^n) in MALDI-FTICR-MS enables study gas-phase reactions and ion dissociation by various ion activation techniques: collision-induced dissociation (CID) [111], sustained off-resonance irradiation collision-induced dissociation (SORI-CID) [112], infrared multiphoton dissociation (IRMPD) [113,114], ultraviolet photodissociation (UVPD) [115], blackbody infrared dissociation (BIRD) [116], surface induced dissociation (SID) [117] and electron capture/transfer dissociation (ECD/ETD) [118,119]. Dissociation techniques yield the structural information about precursor ions, which could be used to study the energetics and pathways of fragmentations [120].

Compared with FTICR-MS, post-source decay (PSD), which means that the precursor ions are stable in the ion source and dissociate after exiting the source could be performed in mass spectrometers equipped with TOF mass analyzer to provide the skeleton information for organic molecules, which results are similar or comparable to CID technology. The product ion spectra of

MALDI-PSD for small drug molecules were compared with that of ESI-ion-trap MS^n. PSD gave diverse product ions that were highly indicative of the structure of the drugs. Meanwhile the number of different product ions generated with MALDI-MS was always higher than that with ESI-ion-trap MS^n (with $n \leq 4$) [121]. Both nanoESI and MALDI-FTICR-MS have been used for the identification and structure determination of glycosphingolipids [122]. Fragmentation techniques for lipids such as IRMPD, ECD and electron detachment dissociation (EDD) [123] were used providing observation of additional fragment ions [124].

1.4. Orbitrap

When it comes to FTICR, the discussion about the emergence and development of Orbitrap can not be ignored. Orbitrap, a new analytical tool in which detections occurs by measuring the frequency of the oscillating ions [125]. It is thus similar to FTICR. The instrument of Orbitrap consists of a thin wire central electrode, a coaxial outer electrode, two end-cap electrodes and operates a electrostatic field by only electrostatic devices to confine and analyze injected ion populations [126]. In an Orbitrap, ions from the source rotate around a central electrode and oscillate with a frequency depending on its m/z, following by the data collection and analysis involving the detection of the oscillations and fast Fourier transform [127]. The good sensitivity [128] and high resolution [129] are attractions of Orbitrap, whereas the mass accuracy about 2 ppm [130] and is comparable to the FTICR as well as sector instruments but is better than quadrupoles and TOF instruments.

Orbitrap has been wildly applied in proteomic and metabolomic studies owing to its ability to elucidate the composition of complex samples that contain numerous analytes distributed over wide m/z and concentration ranges [131–133]. Coupling the Orbitrap with different types of ionization sources such as DESI (desorption electrospray ionization) allows direct analysis of untreated samples in their native environment. The accurate mass determination of a target analytes, is a key factor providing utmost confidence in analytical results, promoting the application of Orbitrap with its high resolution and high accuracy to identification of performance enhancing drugs [134,135]. In this report, we emphasize unique aspects regarding the analysis of small molecules by MALDI-FTICR-MS. We organize the topics for discussion as follows:

(1) direct analysis of low molecular weight compounds by MALDI-FTICR-MS;
(2) analysis of low molecular weight compounds using analytical derivatization prior to MALDI-FTICR-MS;
(3) omics analysis and MS imaging via MALDI-FTICR-MS;
(4) study of dissociation/rearrangement processes of low molecular weight compounds with MALDI-FTICR-MS.

2. Direct analysis of low molecular weight compounds by MALDI-FTICR-MS

2.1. Analysis of small biochemical molecules by MALDI-FTICR-MS

The ionization in MALDI is triggered by a laser beam, typically employing UV lasers such as nitrogen lasers (337 nm), frequency-tripled and quadrupled Nd:YAG lasers (355 nm and 266 nm respectively) [136]. Although IR-MALDI is not a frequently used technique it does offer advantages such as softer mode of ionization and greater efficiency in material removal (useful for biological samples), less low-mass interference, and compatibility with other matrix-free laser desorption mass spectrometry methods [137].

MALDI matrices have some common characteristic, such as separating the molecules in the matrix solid solution, protecting the molecules from being destroyed by direct laser beam and facilitating vaporization and ionization [138]. The most widely used matrices are: 3,5-dimethoxy-4-hydroxycinnamic acid (sinapinic acid); α-cyano-4-hydroxycinnamic acid (CHCA); and 2,5-dihydroxybenzoic acid (DHB) [139]. MALDI is capable to create singly charged ions. In the positive ion mode MALDI-MS spectrum, "cationized molecules" such as $[M+H]^+$, $[M+Na]^+$ are the dominant ionic species, and in negative ion mode $[M-H]^-$ dominate. Matrices such as para-nitroaniline (PNA) or 9-aminoacridine (9-AA) produce multiply charged ions $[M+nH]^{n+}$ [140]. Ion signals of radical cations can also be observed in the analysis of organometallic compounds and aromatic compounds [141].

One significant problem for use of MALDI-MS to analyze low molecular weight compounds is the interferences of matrix signals in low m/z range. However, there are still many reports on characterization of low molecular weight compounds by MALDI-MS. Zou reported a novel method of adding the surfactant of cetrimonium bromide (CTAB) to the conventional matrix of CHCA that could substantially or even completely suppress the matrix related background ions and improve the enabling the analysis of small molecules [142].

Various matrix components, such as porphyrins, inorganic materials, fullerene, porous silicon, carbon nanotubes, ionic (liquid) matrix [143], and nanoparticles have also been used to eliminate matrix ion interference [144]. The most important advance in this research area is the introducing of the high-mass laser-absorbing materials in MALDI-MS analysis. Ayorinde used meso-tetrakis(pentafluorophenyl)porphyrin (F20TPP) [145] as a matrix in the analysis of some commercial nonylphenol ethoxylates and, with sodium ion dopant. The ethoxymer molecules were sodiated to form $[M+Na]^+$ ions. A comparison of the mass spectrometric data with those obtained when CHCA was used as the matrix indicated that the F20TPP-induced spectra provided comparable data, with less matrix interference in the low m/z range (m/z 100–500). Thus, the use of porphyrins compounds for the analysis of small molecules minimized the interferences from matrix signals. Similarly, Xiong reported a novel strategy to analyze small molecules by using metal-phthalocyanins (MPcs) as matrix [146].

As a pioneer, Buriak reported the use of the pulsed-laser desorption-ionization on a porous silicon surface (DIOS) for analysis of biomolecules [86]. Such method vaporized and ionized the analyte by laser irradiation followed by the trapping of analyte ions deposited on the surface using porous silicon with detection limits at femtomole or attomole level. This technique induces little or no fragmentation, as well as offers good sensitivity and compatibility with silicon-based microfluidics and microchip technologies. DIOS-MS has been wildly applied for quantitative analysis of low molecular weight compounds, organic reaction monitoring, PSD and combining with various chromatographic technologies [147]. Mesoporous silica, SBA-15 was successfully functionalized with quinoline moiety as a matrix in the MALDI-MS analysis of small molecules [148], showing less background interference, high homogeneity and better reproducibility.

Carbon nanotubes (CNTs) [149] proved useful substitutes for conventional organic matrices in the study of low molecular mass analytes by MALDI-MS. The advantages included their large surface area to disperse the analytes sufficiently, preventing the sample aggregation and strong ultraviolet laser absorption allowing easily energy transfer to the analytes. Guo used polyurethane adhesive (NIPPOLAN-DC 205) to attach CNTs on the target efficiently [150] to give longer-lasting signals for post source decay (PSD) analysis. This method has been applied to determination of glucose in urine. Meanwhile, oxidized CNTs were synthesized and used for MALDI-MS analysis of biomolecules [151]. A functionalized car-

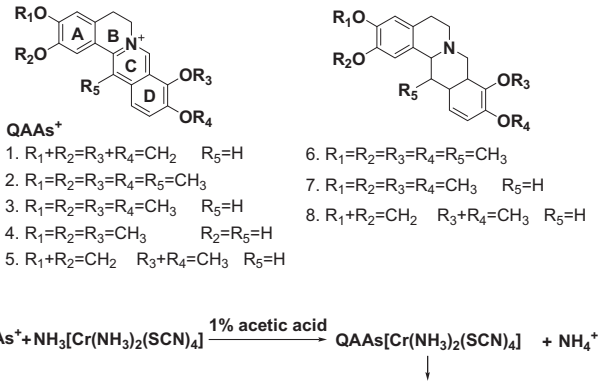

Fig. 2. Some QAAs (1–5) and tertiary alkaloids (6–8) in Rhizoma Corydalis and the precipitation reaction for QAAs with Reinecke salt.

bon nanotubes (CNT 2,5-dihydroxybenzoyl hydrazine derivatives) [152] were synthesized and used as both pH adjustable enriching reagent and matrix in MALDI-MS analysis of trace peptides. Therefore, high efficiency of adsorption and enrichment toward trace peptides can be achieved by adjusting pH value of the functionalized CNTs dispersion.

Carbon nanotubes also served as a matrix for analysis of twenty common amino acids by MALDI-FTICR-MS [153]. The spectra with little or no background interference or fragmentation of the analytes have been obtained. The most intense peaks were corresponding to sodium ion adducts of amino acids with little or no background peaks appears in the low mass region under optimal conditions. Meanwhile, The MALDI-FTICR-MS could be used to analyze small neutral carbohydrates (xylose, glucose, maltose and sucrose) and amino acids with high sensitivities (10 fmol for oligosaccharides) as alkali cation adduct ions by using oxidized short and open-end CNTs [154]. In addition, reliable quantitative analyses for glucose in urine and leucine or isoleucine in corn root were also achieved successfully. Therefore, oxidized CNTs could be expected to be a universal and effective matrix in MALDI-FTICR-MS research for small molecule.

2.2. Analysis of small molecule phytochemicals by MALDI-FTICR-MS

When coupled with suitable extraction technique, MALDI-FTICR-MS can be used to detect and identify small molecule phytochemicals from medical herbs in the qualification and quantification manner. The accurate mass measurements and MS/MS capabilities of the FTICR-MS provide valuable information direct analysis of small molecule phytochemicals from medicinal herbs. For example, high-resolution MALDI-FTICR-MS, could offer the elementary compositions information of major peaks for quaternary ammonium alkaloids (QAAs) of Rluzoma Corydalis [155]. Five QAAs, including coptisine, dehydrocorydaline, palmatine, columbamine and berberine, were determined from the tubers of Corydalis yanhusuo. For further analyzing quarternary ammonium alkaloids, a method of electrophoretic ion migration directly to probe method was developed, which can concentrate charged analyte species for MALDI-MS [156].

A problem hampering the use of MALDI-MS for quantitative measurements is the inhomogeneous distribution of analytes and matrices in sample preparations. An aerospray method was utilized for sample preparation to improve the homogeneity across stainless steel targets for quantitative analysis of QAAs [157] (shown in Fig. 2) by MALDI-FTICR-MS. A selective precipitation reaction with Reinecke salt known to selectively trap QAAs. This method was used to facilitate the separation and purification of QAAs from the complex crude plant extracts. The accurate-mass measurements for the phytochemicals offered additional selectivity for this analysis method. Palmatine and berberine as the representative QAAs in commercial Rhizoma Corydalis were successfully quantified by introducing an internal standard with similar molecular properties as analytes. The LODs were found to be 0.07 fmol for palmatine and 0.24 fmol for berberine respectively. Furthermore, IRMPD experiments permitted sufficient structural elucidation to distinguish QAAs from tertiary alkaloids.

2.3. Profiling volatile toxic compounds from tobacco and smoke by MALDI-FTICR-MS

When specific sample preparation technologies were applied, MALDI-FTICR-MS could be used for the quantification of small volatile compounds without chromatographic separation. A method incorporating headspace liquid-phase micro extraction (HS-LPME) coupled to MALDI-FTICR-MS was established to analyze volatile basic components in tobacco [158]. The pH and the polarity of the solvent for HS-LPME were adjusted by the choice of MALDI matrix and additives. Based on the elemental composition and MS/MS information, 25 volatile nitrogenous compounds in tobacco were detected and identified (shown in Fig. 3). The method coupling liquid-phase micro extraction (LPME) with MALDI-FTICR-MS was further developed to measure the content of nicotine in main stream smoke at the single puff level [159]. Glycerol was utilized as a matrix additive in the sample preparation to improve the homogeneity of analyte distribution in a sample spot, which achieved good repeatability of the MALDI-MS signal (RSD < 9%). Selective LPME facilitated the separation and purification of basic components from cigarette smoke. The LPME device was coupled to a smoking machine, and each puff of one cigarette could be gathered by this modified machine. The amount of nicotine in the main stream smoke was measured at the single puff level by LPME/MALDI-FTICR-MS. This method was simple, selective and was sufficiently sensitive to detect nicotine in each puff of one cigarette.

3. Analysis of low molecular weight compounds by MALDI-MS with analytical derivatization

The main objects of analytical derivatization in MALDI-MS were: (1) making the small molecules bigger from low *m*/*z* range with the interferences of the matrix signals to higher *m*/*z* range, which would significantly increase the sensitivity, resolution and S/N ratio; (2) selectively attaching the neutral small molecules with "charge tags" or "easily ionized tags", which would significantly increase the sensitivity; (3) introducing "an isotopic tag" into the analytes as internal standards to complete the quantification of target compounds. Major advantages of MALDI-MS are high sensitivity, high tolerance against impurities such as salts and buffers and the possibility of automating the measurement. Thus when MALDI-MS combined with suitable analytical derivatization strategies, the whole analytical methods will be more powerful to solve the analytical problems for the small molecules compounds.

3.1. Analysis of small amines by MALDI-MS with derivatization

Heinzle investigated the application of well-known and straightforward one-pot derivatization procedures for the measurement of small alcohols, aldehydes, ketones, carboxylic acids, ketocarboxylic acids and amines (shown in Fig. 4a–g) [160]. A pair of isotopically coded light/heavy reagents, tris(2,4,6-trimethoxyphenyl)phosphonium acetic acid N-hydroxysuccinimide esters (shown in Fig. 4h), were synthesized and used to derive low molecular weight molecules containing

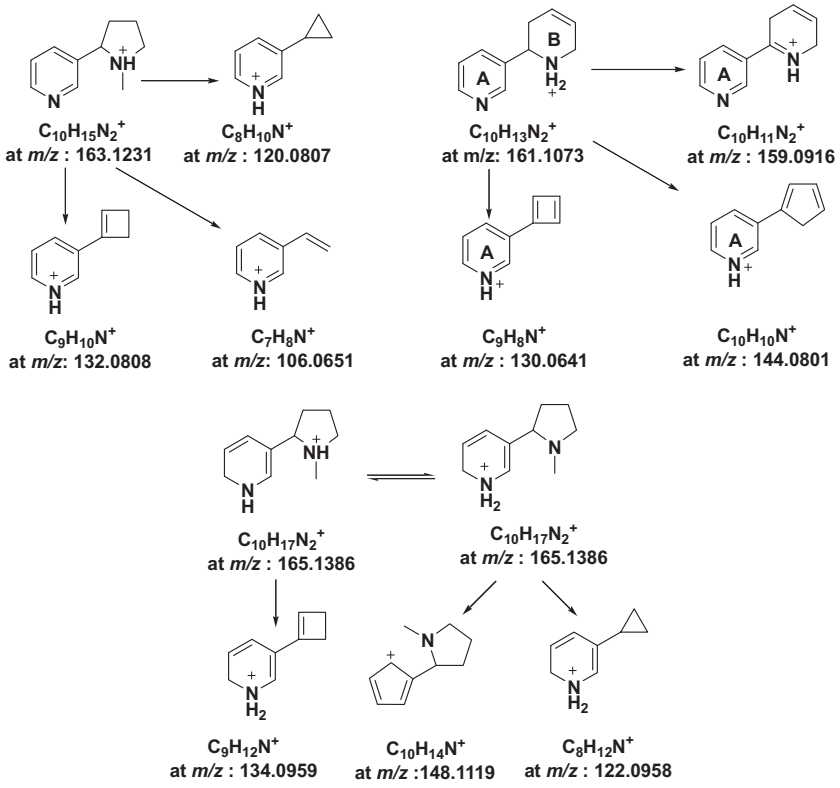

Fig. 3. Proposed fragmentations of the protonated nicotine at *m*/*z* 163 and other related protonated compounds at *m*/*z* 161 and 165 respectively.

primary or secondary amine functional groups for MALDI-MS analysis [161,162]. Such derivatization greatly facilitated MALDI analysis of small molecules and significantly improved the sensitivity of analysis to femtomole range. This method allowed the quantification of small molecules without sample cleanup. Recently, Denekamp reported that primary and secondary alkyl amines substitute readily one of the para-methoxy substituents of tris(2,4,6-trimethoxyphenyl)methyl carbenium ion (shown in Fig. 4i). With this rapid process, the preparation of permanently charged positive derivatives of amines, amino acids and small C-protected peptides is obtained for MALDI-MS analysis of these compounds [163].

3.2. Analytical derivatization strategy for analysis of oligosaccharides by MALDI-MS

The main purposes of analytical derivatization on native oligosaccharides were to add the chromophore groups and cationic (protonable) positions for the improvement of sensitivity in MALDI-MS with hundreds/thousands fold. In a number of publications, incorporating a derivatization step prior to MS experiments have been tried with the aim to increasing analytical performance and aiding detection for the studies of oligosaccharides (Fig. 5) [164]. Oligosaccharides could be derivatized into hydrazones with Girard's T reagent to introduce a cationic site for detection by MS [165] (Fig. 5a). The derivative products were prepared in high yield and did not require extensive clean-up prior to mass spectrometric examination, unlike the products of the commonly used reductive amination derivatization. The detection sensitivity could be increased ten-fold by the derivatization over those afforded by the underivatized oligosaccharides and intense spectra in positive-ion electrospray mode could be obtained dispensing with adding other cations into the solvent. In addition, the use of these derivatives effectively removed the ambiguities of $[M+K]^+$ ions and $[M+Na]^+$ ions from the underivatized sugars in MALDI, furthermore, Girard's T derivatization overcame problems associated with the presence of reducing-terminal and N-acetylamino groups that were often introduced when the oligosaccharides were prepared by cleavage from glycoproteins with hydrazine. By the combination of MALDI-MS detection and PSD of 2-aminopyridine-derivatized oligosaccharides [166] (Shown in Fig. 5b). Another derivatization procedure was shown in Fig. 5c, including the reductive amination of oligosaccharides by benzylamine and the N,N-dimethylation by methyl iodide [167].

In MALDI analysis of oligosaccharides, a large sensitivity increasing (by a factor of 1000) could be obtained by introducing a quaternary ammonium center ('quaternization'). Such a quaternary ammonium center could be introduced into the saccharide molecular by reacting with commercially available glycidyltrimethylammonium chloride (GTMA) [168] (shown in Fig. 5d) or Girard's reagent T. Reducing saccharides can be derivatized by GTMA specific to alcohol functionalities and Girard's reagent T targeted on aldehyde and keto groups, whereas non-reducing saccharides, as well as sugar alcohols, can be derivatized using GTMA. Although sucrose, raffinose and sorbitol do not react with Girard's reagent T, they all produce intense signals after derivatization with GTMA. An example of the application of these derivatization reactions is provided by the analysis of oligosaccharides in beer.

9-Aminofluorene (9AmFL) was investigated as an "easily ionized tags/label" of oligosaccharide for MALDI-FTICR-MS characterization and it was highly sensitive to UV detector and had no interference with MS analysis. The 9AmFL tag/label has high molar absorptivity with chemical stability, and could easily introduce reductive amination into the aldehyde terminus of oligosaccharides [18] (Fig. 5e). Various linear and branched oligosaccharides were labeled by 9AmFL in the presence of sodium dopant. Series of Y- and B-fragments were observed in mass spectra. Protonation of the labeled compounds prior to mass spectrometric analysis resulted

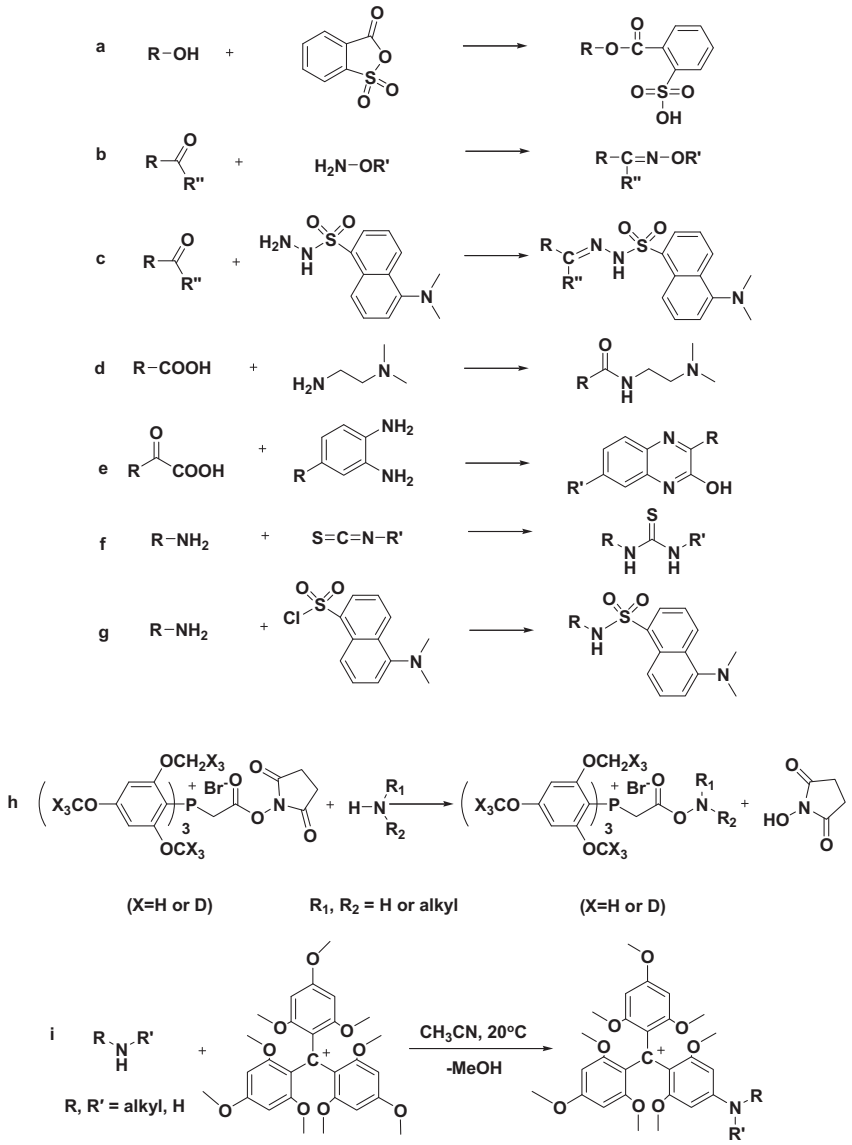

Fig. 4. Reaction schemes for the derivatization procedures of small amine compounds: (a) esterification of alcohols with 2-sulfobenzoic acid anhydride; (b) formation of oximes from aldehydes (R″ = H) or ketones (R″ = alkyl by reaction with hydroxylamines; (c) formation of dansylhydrazones by reaction of aldehydes (R″ = H) or ketones (R″ = alkyl) with dansylhydrazine; (d) amidation of carboxylic acids with asymmetric dimethylethylenediamine; (e) formation of quinoxalinoles by reaction of α-ketocarboxylic acids with o-phenylenediamine (R′ = H, Cl); (f) formation of thioureas by reaction of amines with isothiocyanates; (g) formation of sulfonamides by reaction of amines with dansyl chloride; (h) amines charge derivatization by the H/D tagged TMPP-Ac-OSu ([tris(trimethoxyphenyl)phosphonium] acetic acid N-hydroxysuccinimide ester); (i) amines and amino acids charge derivatization by. tris(2,4,6-trimethoxyphenyl)methyl carbenium ion.

in simplified spectra (Y-fragments only) and allowed for complete sequence analysis.

3.3. *N*-alkylpyridinium isotope quaternization with MALDI-FTICR-MS

A simple reaction based on direct *N*-alkylpyridinium isotope quaternization (NAPIQ) was developed for mild derivatization of cholesterol and fatty alcohols (Fig. 6) [169]. Different from the conventional quaternary reagents with cations on themselves, two simple and charge-neutral reagents: pyridine and d_5-pyridine directly attached *N*-cationic tag onto the target compounds in presence of trifluoromethanesulfonic anhydride (Tf_2O) without tedious sample preparation. The derivatization reactions completed in 5 min and achieved charge labeling of the target compounds, which significantly improved the detection limits of analytes by 10^3-folds in further analysis by MALDI-FTICR-MS. The use of commercially available d_0/d_5-pyridine pairs facilitated isotope-coded chemical derivatization and avoided the use of isotope-labeled internal standards. The excess pyridine did not affect the signals of analytes. Utility of the NAPIQ method was used in the identification of cholesterol and fatty alcohols in small amount of human hair sample (<0.5 mg). This method was further applied in the identification of endogenous steroids containing α, β-unsaturated ketone and alcoholic moieties in urine samples.

3.4. Trapping and analyzing neutral radical species by MALDI-FTICR-MS

As an alternative method, MALDI-FTICR-MS has been successfully used to detect and identify neutral free radicals (hydroxyl radical or 2-cyano-2-propyl radical) by forming their adducts with radical trapping agent, 5,5-dimethylpyrroline N-oxide (DMPO) [170] (Fig. 7). The identification of $[(DMPO + {}^{\bullet}OH - {}^{\bullet}H) + H]^+$ at

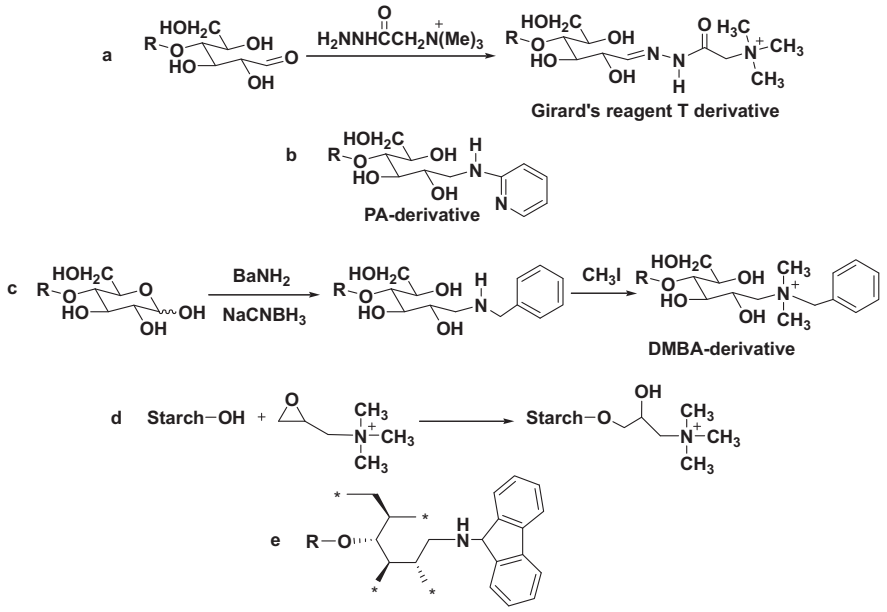

Fig. 5. Derivatization of the reducing terminus of oligosaccharides with Girard's T reagent: (a) Girard's reagent T-derivative; (b) PA-derivative; (c) DMBA-derivative; (d) GTMA-derivative; (e) 9AmFL-derivative.

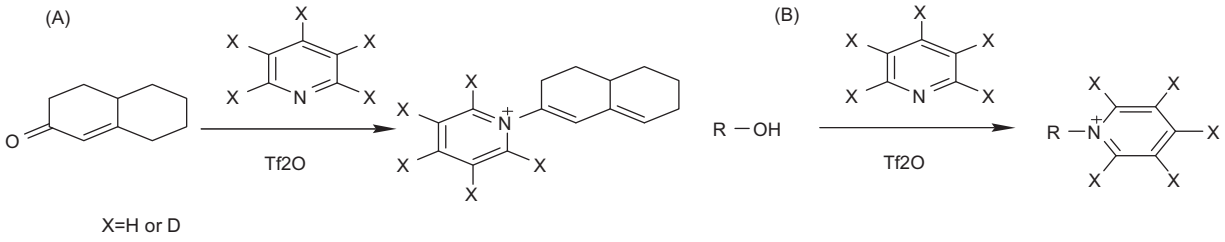

Fig. 6. General scheme for derivatization method: (A) reaction between d_0/d_5-pyridine and alcoholic group; (B) reaction between d_0/d_5-pyridine and α, β-unsaturated ketone group.

m/z 130 and $[DMPO + 2^{\bullet}CH(CH_3)_2CN + H]^+$ at m/z 250 have been achieved by SORI-CID. The results demonstrated that MALDI-FTICR-MS could be an effective tool for the detection and identification of free radical adducts.

3.5. Analysis of volatile toxic aldehydes from tobacco smoke by headspace technology with MALDI-FTICR-MS

In recent years, a micro scale implementation of liquid-liquid extraction, liquid-phase micro extraction (LPME), has become a popular sample pretreatment technique. LPME combines extraction and enrichment together and it is an inexpensive method, easy to operate and nearly solvent-free. Lee reviewed the strategies on chemical reactions in LPME [171], indicating that the chemical reactions during LPME serve to promote the extractability of the analytes, facilitate analytes compatibility with the analytical system and improve detection sensitivity. The reactions during LPME include ion-pair extraction, complexation, chemical derivatization, phase-transfer catalysis and other "special affinity" reactions. This method could naturally be used to spot the "finial droplet" directly on the target for the following MALDI-MS analysis.

Extraction and derivatization in single drop (EDSD) coupled to MALDI-FTICR-MS was utilized to determine small molecular aldehydes (SMAs) in single puff smoke [172] (Fig. 8). A methanol

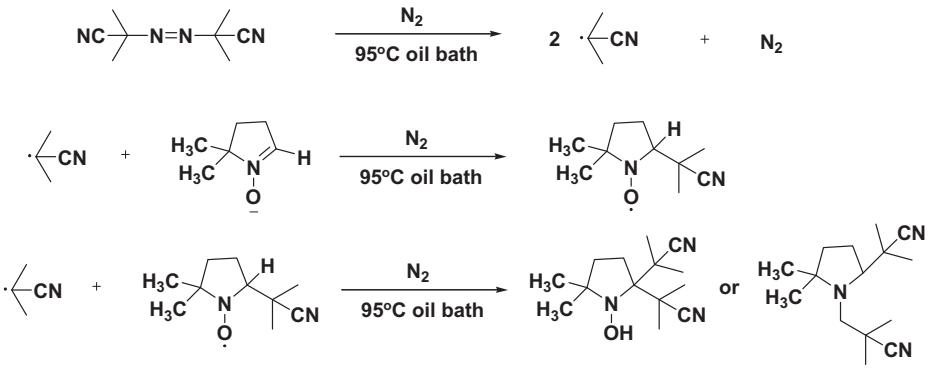

Fig. 7. The mechanism of trapping of •CH(CH3)2CN with AIBN in the solution of benzene at 95 °C by DMPO and the trapping product could be studied by the MALDI-FTICR-MS.

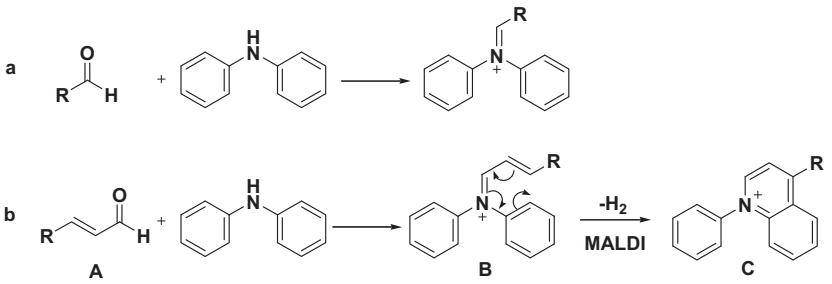

Fig. 8. (a) The reaction pathways between diphenylamine and low molecular weight aldehydes (R = substituent group). (b) The possible formation mechanism of C. While R = H, A is acrolein, B is the ion at *m/z* 208, and C is the ion at *m/z* 206; while R = CH_3, A is crotonaldehyde, B is the ion at *m/z* 222, and C is the ion at *m/z* 220.

solution of diphenylamine, 2,5-dihydroxybenzoic acid was used for the extraction/derivatization of SMAs. The micro-drop of the extraction solution containing ionic derivatization products of SMAs could be directly deposited in the sample target to perform the measurement of SMAs in the cigarette smoke on puff level by MALDI-FTICR-MS. SMAs were derived with diphenylamine to a stable Schiff base bearing a quaternary ammonium group. Thus the sensitivity of analysis for SMAs was significantly improved. Good sample homogeneity in in-dot was achieved by adding diphenylamine into the solvent for EDSD and a satisfying repeatability of MALDI-FTICR-MS signals was obtained. The EDSD procedure combining the derivatization/extraction into one step to form the related quaternary ammonium product ions significantly increases the analysis sensitivity and the signal repeatability.

4. Omics analysis based on MALDI-FTICR-MS

4.1. Proteomics by MALDI-FTICR-MS

MALDI MS is a central tool for proteomic analysis. Nowadays, the combination of MALDI with the powerful mass detector FTICR-MS is widely used and developed in the proteomics researches. Proteomics can be defined as the direct qualitative and quantitative analysis of the full complement or subset of the proteins present in an organism, tissue, or cell under a given set of physiological or environmental conditions. Proteomics by FTICR-MS in both top down and bottom up strategies were developed rapidly and wildly applied in many cases [173]. MALDI-FTICR-MS, combined with separation techniques, such as liquid chromatography (LC) or capillary electrophoresis (CE) to better address the complexity of most biological samples, has become preeminent for proteomics analyses. Offline HPLC-MALDI-FTICR/MS provides the means to rapidly analyze complex mixtures of peptides, such as the products of a proteome via proteolytic digestion [174]. The dissociation of peptide ions in MS/MS is currently a significant focus with the difficult that the singly protonated tryptic peptide ions produced by MALDI are significantly more difficult to dissociate for MS/MS than the corresponding multiply protonated ions. A MS/MS technique termed CIRCA (combination of infrared and collisional activation) coupling with high-resolution, high mass accuracy FTICR-MS by Lebrilla have been applied on proteomic analysis and effectively overcome these difficulties [175].

4.2. Metabolomics by MALDI-FTICR-MS

Metabolomics investigations always are challenges for analytical chemistry because of its comprehensive analysis of numerous metabolites which have very diverse physicochemical properties and occur at different abundance levels in biological samples [176]. FTICR-MS, is an increasingly useful technique in metabolomics research, due to its highest mass resolution, mass resolving power, mass accuracy, and sensitivity of present MS technologies [39,177]. Acutely, most high-throughput analytical methods for intracellular metabolites are based on MALDI-TOF-MS, due to its suitable quantitative performance and dynamic range for the characterizing of intracellular metabolism trends and the monitoring of the changes of metabolite concentrations responding to different conditions [178]. The MALDI-MS-based analytical methods developed herein have been shown as a suitable tool for high-throughput analysis of dynamic intracellular metabolism events of *Escherichia coli* by analyzing whole cell samples taken consecutively before and after a perturbation of the environmental carbon source [179].

However, its low resolution of MALDI-TOF compared with FTICR-MS, makes MALDI-FTICR-MS an important tool to identify the elemental compositions of detected metabolites to support the reliability of the MALDI-MS-based analysis [180]. MALDI FTICR-MS presents many advantages to a wide range of applications in various biological fields. The analysis of the endogenous and exogenous metabolic compounds in tissues by detecting the molecular specificity with MALDI-MS based imaging methods maintained their spatial orientation. As for applications in small molecular compounds, the two-dimensional visualization of the distribution of a drug and first-pass metabolites in wholebody sections of animals could be achieved [181].

Recently, Guo reported a metabolomics study to detect acute cellular renal allograft rejection using a noninvasive method by investigating small molecule analysis of urinary samples. MALDI-FTICR-MS was used to analyze 15 urinary samples from transplant patients with different grades of biopsy showing improved clinical acute cellular rejection (ACR) and 24 urinary samples from 8 transplant patients without evidence of rejection [182]. Seven small molecules demonstrated highly successful diagnostic performance. Kidney transplant patients with ACR could be distinguished from those without ACR using four individual small molecules with a high specificity. Thus, the patient groups could be clear defined by the detection of the small molecules in urine associated with ACR using MALDI-FTICR-MS technology.

Meanwhile, a novel pyrimidine-based stable-isotope labeling reagent, [d_0]/[d_6]4,6-dimethoxy-2-(methylsulfonyl)pyrimidine ([d_0]/[d_6]-DMMSP, shown in Fig. 9), was developed for comparative quantification of proteins [183,184] and peptides [185]. Then, [d_0]/[d_6]-DMMSP were used as derivatization agent for the studies of different expression levels of keratins in tongue coating samples of Hepatitis B patients by MALDI-MS and western-blot analysis. The results showed the higher expression level of these keratins in tongue coating samples of hepatitis B patients than healthy adults [186]. These results provided additional information

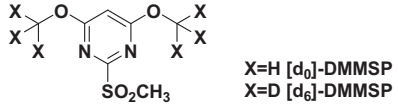

Fig. 9. Structure of the novel stable-isotope labeling reagent ([d_0]/[d_6]-DMMSP).

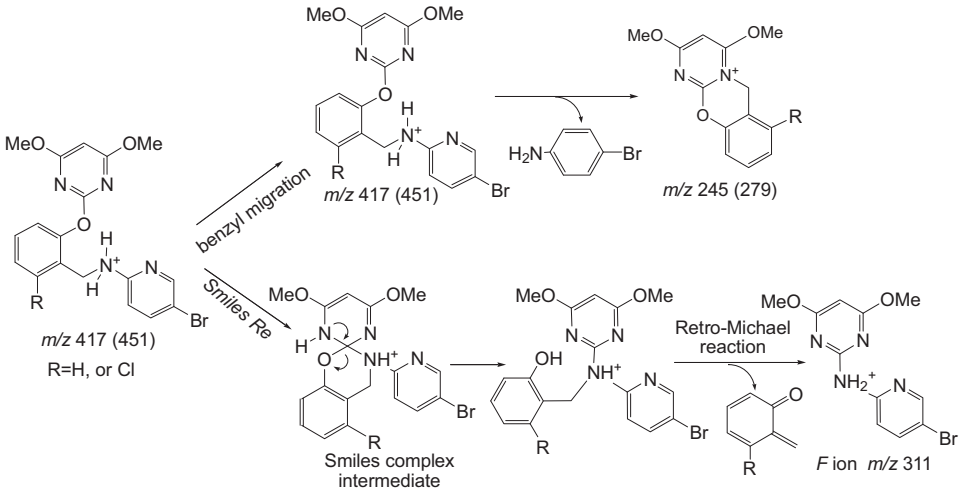

Fig. 10. The dissociation modes of ions at *m*/*z* 417 (451). The formation mechanism of the ions at *m*/*z* 245 (279) from parent ions at *m*/*z* 417 (451) is a gas phase benzyl migration reaction. Meanwhile the formation mechanism of the ions at *m*/*z* 311 from parent ions at *m*/*z* 417 (451) is a gas phase *Smiles* rearrangement reaction.

to understand the medical diagnosis depending on the tongue coating. The metabolomics researches for small molecules with $[d_0]/[d_6]$-DMMSP by MALDI-FTICR-MS are in progress in our research group.

4.3. Lipidomics by MALDI-FTICR-MS

Lipids, playing the important roles such as bilayer cell membrane, energy reservoirs, messengers, are essential cellular constituents that have multiple distinct yet critical roles in cellular function [187,188]. Lipidomics, after genomics and proteomics, is a newly and rapidly expanding research field that studies cellular lipids and the organizational hierarchy of lipid and protein constituents mediating life processes [189]. FTICR-MS is becoming an established tool for the investigation of lipids. Wilkins and his coworkers using MALDI-FTICR-MS examined and analyzed phospholipids profiles of different mammalian tissues [190,191] as well as those of whole cell organisms [192,193]. In the monitoring of the quality of the museum environment, the oxidative changes of triacylglycerols and diacylphosphatidylcholines in egg tempera paint strips can be used for chemical dosimetry. Van den Brink and Heeren used high resolution MALDI-FTICR-MS as a method for rapid determining the exact elemental composition of the alteration products from diacylphosphatidylcholines and triacylglycerols [194]. Leavell and Leary developed a computer algorithm dedicated to the analysis of FTICR-MS spectral data from lipid extracts [195]. This algorithm, termed FAAT (Fatty Acid Analysis Tool), has been successfully used to investigate complex lipid extracts containing thousands of components, from various species of mycobacteria.

4.4. MALDI FTICR-MS imaging for bio-active small molecular compounds

The concept of MALDI mass spectrometric imaging (MSI) was introduced in 1997 by Caprioli et al. [196] for rapid and direct profiling of the endogenous and exogenous compounds in tissues by MALDI MS to obtain their spatial orientation. This operation mode is often referred to as the mass microprobe mode with the spatial resolution of 50–200 mm. An alternative to the mass

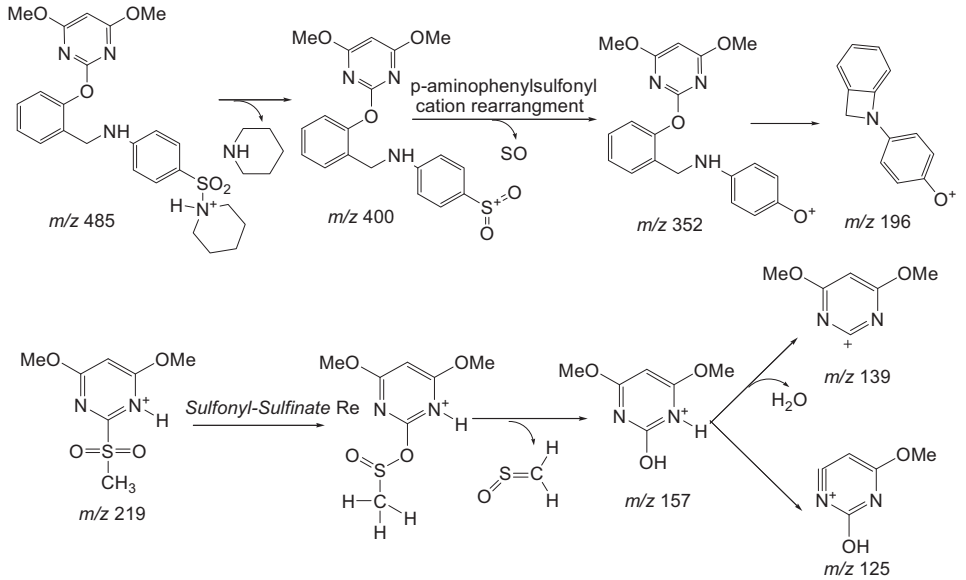

Fig. 11. The dissociation modes of ions at *m*/*z* 485 and 219. The formation mechanism of the ion at *m*/*z* 352 from the ion at *m*/*z* 400 is a gas phase rearrangement of *p*-aminophenylsulfonyl cation. The formation mechanism of the ion at *m*/*z* 157 from parent ions at *m*/*z* 219 is a gas phase *sulfonyl-sulfinate* rearrangement.

microprobe approach, the mass microscope approach has been pioneered by Heeran, who used a 150–300 mm diameter ion beam is used to map a magnified image of the spatial distribution of a selected m/z value onto a two-dimensional detector [197]. Imaging mass spectrometry is a powerful tool for localizing compounds of biological interest with molecular specificity and relatively high resolution. The determination of the localization of various low molecular weight compounds in a whole animal is valuable for many applications, including pharmaceutical absorption, distribution, metabolism, and excretion (ADME) studies and biomarker discovery [198].

Volny developed automated ambient desorption-ionization platform for surface imaging with MALDI-FTICR-MS [199] and the outstanding performance of this instrument allowed screening on the basis of exact masses in imaging mode. The main novel aspect was in the integration of the atmospheric pressure ionization imaging into the current software for MALDI FTICR-MS imaging. Due to the high resolution and mass accuracy of the FTICR-MS instrument it was possible to resolve several ions at the same nominal mass in the MS spectra of brain tissue. These isobaric interferences at low resolution are due to the overlap of ions from different lipid classes with different biological relevance. It was demonstrated that with the use of high-resolution MS fast imaging screening of lipids can be achieved without any pre-separation steps. Lebrilla used aglycomic approach to identify oligosaccharide markers for ovarian cancer by rapidly profiling globally released oligosaccharides and changes in glycosylation of glycoproteins shed by cancer cells are monitored by MALDI-FTICR-MS [200]. It is demonstrated that the presence of at least 15 unique serum glycan markers in all patients but absent in normal individuals. To determine the structure of the glycan biomarkers, a number of the ions were isolated and further analyzed using IRMPD.

Heeren applied FTICR-MS for the spatially resolved mass analysis of rat brain tissue with the aim to optimize protein identification by the high mass accuracy and online MS/MS capabilities of this technique [201]. The spatial distributions of biomolecules differing in mass by less than 0.1 Da could be resolved, and are shown to differ significantly. Online MS/MS analyses of selected ions were demonstrated. A comparison of the FTICR-MS imaging results with TOF imaging on the same sample is presented. To reduce the extended measuring times involved, it is recommended to restrict the FTICR-MS analyses to areas of interest as can be preselected by other, faster imaging methods.

5. Study of dissociation/rearrangement processes of low molecular weight compounds by MALDI-FTICR-MS

During study of dissociation/rearrangement processes of low molecular weight compounds by MALDI-FTICR-MS, information about the energetics of gas phase reactions and fragmentation pathways can be investigated by controlling the energy deposited into precursor ions, the time-scale and target gas in collision. As a typical example, MALDI-FTICR-MS has been used to study 2-pyrimidinyloxy-N-arylbenzylamines with IRMPD or SORI-CID. DHB was used as matrix during these studies, and one shot of laser could reach enough ion abundances even for MS^3 and also achieve high mass accuracy for determining the elemental compositions of the fragment ions. Moreover, the high-resolution data from the MALDI-FTICR MS help to provide critical and important information for the elemental compositions of product ions from the gas phase reactions.

Many interesting and novel gas phase reactions were revealed and discussed (shown in Figs. 10 and 11), such as: the benzyl migration reaction [202], *Smiles* rearrangement reaction [203], rearrangement of *p*-aminophenylsulfonyl cation [204], *sulfonyl-sulfinate* rearrangement [205], retro-*Michael* type fragmentation reaction [206] and gas phase dehydration reactions. Based on comparison of IRMPD/SORI-CID spectra with the In-source CID spectra, the mechanisms of gas-phase *Smiles* rearrangement were elucidated and highlighted based on the different timescales of the three dissociation techniques.

Certain analogies between mechanisms in the gas phase and in solution have been known for a long time [207], and sometimes it is possible to correlate the behavior of charged species formed in the gas phase and in the solution phase [208]. Therefore, mass spectrometry, especially MALDI-FTICR MS, can also act as an important gas-phase "physical organic" tool for mechanistic studies of organic unimolecular reactions under solvent-free conditions [209]. The studies shown above represented a significant association between gas-phase reactions and the analogous reactions in solution. The SORI-CID or IRMPD behaviors of protonated or deprotonated compounds in MALDI FTMS appears to proceed in a fashion similar to the corresponding process induced by acid/base-catalyzed conditions of these compounds in solution [210].

6. Conclusions and future prospects

This review covered the most recent applications of MALDI-FTICR-MS on the low molecular weight compounds analysis for chemical and biochemical researches. The MALDI-FTICR-MS detection-oriented extraction and derivatization techniques for detecting low molecular weight compounds were fully discussed. The tolerance of sample contamination and the potential automated procedure represent the orientation for high throughput character of MALDI technology. Meanwhile the high resolution measurements power and the convenient CID function of FTICR-MS provide highly qualified and accurate MS characterization for target compounds. The introducing of analytical derivatization significantly increases the detection sensitivity and selectivity, as well as provides "charge tags" or "isotopically labeled tags". Thus, low molecular weight compounds analysis by MALDI-FTICR-MS with suitable analytical derivatizations with MALDI-FTICR-MS would provide valuable information to explore the new field of the chemical worlds and offer new opportunities for the innovation of relative scientific researches.

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