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A novel type of matrix for surface-assisted laser desorption–ionization mass spectrometric detection of biomolecules using metal-organic frameworks

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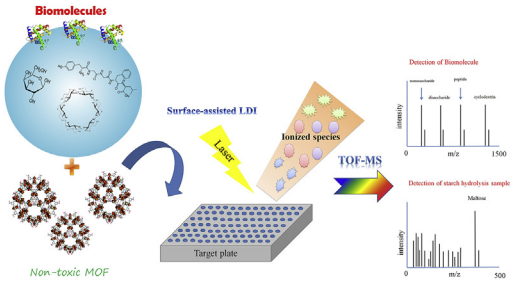
HIGHLIGHTS

- This is the first report on the SALDI-MS analysis of polar carbohydrates using MOF as matrix.
- 3D MOF for SALDI-MS matrix was developed for biomolecule analysis without chemical modification.
- Good signal reproducibility and low background interferences were achieved.
- MOF for SALDI-MS can be used for quantitative and qualitative analysis of polar carbohydrate molecules.

GRAPHICAL ABSTRACT



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ABSTRACT

A 3D metal-organic framework (MOF) nanomaterial as matrix for surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS) and tandem mass spectrometry (MS/MS) was developed for the analysis of complex biomolecules. Unlike other nanoparticle matrices, this MOF nanomaterial does not need chemical modification prior to use. An exceptional signal reproducibility as well as very low background interferences in analyzing mono-/di-saccharides, peptides and complex starch digests demonstrate its high potential for biomolecule assays, especially for small molecules.

1. Introduction

Carbohydrates play a significant role in a variety of biological functions such as cell–cell recognition, protein targeting, and metabolic diseases [1–6]. Mass spectrometry is one of the analytical techniques used for analyzing carbohydrates due to its precision, high sensitivity and flexibility. With the aid of ionization techniques such as electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI), identification and

Abbreviations: MOF, metal-organic framework; SALDI, surface-assisted laser desorption ionization; CD, cyclodextrin; CHCA, α-cyano-4-hydroxycinnamic acid; DHB, 2,5-dihydroxybenzoic acid; CUS, coordinatively unsaturated metal sites.

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quantitative analysis of saccharide variations in biological systems is possible. MALDI, which is a matrix dependent, has been widely applied for the analysis of various macromolecules such as polymers, proteins and lipids [7–11]. The typical matrices used in MALDI-MS are α-cyano-4-hybroxycinnamic acid (CHCA) and 2,5-dihydroxybenzoic acid (DHBA) that have strong laser absorbing capacity at 337 nm, which makes it more efficient in proton transfer and creating high-intensity signals in almost the whole mass range [12]. These common organic matrices are easily ionized under laser irradiation but in general may form an inhomogeneous co-crystallization with analytes (i.e. presence of "sweet spots"), which are associated to some serious background interference at the low mass region (<500 Da) and poor shot-to-shot reproducibility. As a result, this would make the quantitative analysis of small saccharide molecules very difficult [13]. On account of these drawbacks and limitations, surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS) [14,15] has been introduced that uses nanoparticles and nanostructured materials as matrices. One of the successful examples is the analysis of neutral, low molecular weight carbohydrates, which is rather difficult by MALDI-MS due to the absence of basic or acidic group in the structure (i.e. carbohydrates have low ionization efficiency because of their low proton affinity), while an efficient ionization is usually observed when SALDI-MS is used with the aid of nanoparticles (Au [16] and ZnS [17]) and nanostructures (carbon nanotube [18,19] and HgTe [20]) as matrices thereby improving its signal reproducibility and sensitivity during the analysis.

Metal-organic frameworks (MOFs) are one type of novel crystalline nanomaterials constructed from clusters of metal ions and organic ligands [21]. The unique properties of these highly ordered crystalline materials, such as high surface area (up to thousands $m^2\ g^{-1}$), porosity, tunable pore sizes (meso- and micro-sized pores), and with specific adsorption affinities, have offered a wide range of highly promising applications in gas storage, separation, catalysis, magnetism, adsorption, chromatography and so on [22–33]. In our previous research in discovering the other significance of MOFs [34], a potential nanoporous MOFs for SALDI-MS was found to be effective as matrix for the determination of hydrophobic polycyclic aromatic hydrocarbons (PAHs). As part of our continuing research in MOFs application, we further explore the other type of MOF nanoparticles as matrix for SALDI-MS in the analysis of highly polar carbohydrates and peptides. To the best of our knowledge, there are no reports about the analysis of polar carbohydrates (glucose, sucrose, galactose, lactose, fructose, maltose, α-, β- and γ-cyclodextrins (α-, β- and γ-CD)) using MOF nanoparticles to assist laser desorption/ionization process.

2. Material and methods

2.1. Preparation of standard and organic matrix solutions

Stock solution of 5 mM carbohydrates were prepared in deionized (D.I.) water and diluted at desired concentration prior to analysis. A 2.5 mM peptide was prepared in D.I. water then diluted to 100 μM with 15 mM ammonium formate buffer and 50% ethanol in the volume ratio of 1:1. Matrix solution: 10 mg CHCA was dissolved in 1 mL of 50% acetonitrile (ACN) solution with 0.1% trifluoroacetic acid (TFA); 10 mg 2,5-dihydroxybenzoic acid (DHB) was dissolved in 1 mL 30% ACN solution with 0.1% TFA; and 1 mg MOFs were suspended in 2 mL ethanol.

2.2. Sample preparation for MALDI- or SALDI-TOF MS

2.2.1. Dried droplet method

One (1) μL sample solution was pre-mixed with 1 μL matrix in the eppendorf tube and placed on target plate.

2.2.2. Matrix first method

One (1) μL matrix was placed on the target plate, dried and subsequently added with 1 μL of sample on the same plate.

2.2.3. Sandwich method

One (1) μL sample was placed on the target plate, dried and added with 1 μL of matrix on the same plate. When dried completely, another 1 μL of sample was added on target plate.

2.3. Preparation of starch hydrolysis sample

A 0.25% starch solution was digested with 1086 ppm α-amylase and stirred for 30 min at 25 °C.

2.4. Experimental condition of mass spectrometry

Ultraflextreme MALDI-TOF mass spectrometer (BrukerDaltonics) equipped with a 355 nm Nd:YAG-laser was used. All oligosaccharides were detected in reflectron positive-ion mode and the accelerating voltage used was +25 kV. In order to obtain a good signal-to-noise ratio (S/N), the laser power was optimized such that the offset laser used was 30% with corresponding laser range of 25% and subsequent manipulation was conducted with respect to the laser range (i.e. 55%–70% of 25% laser range).

3. Results and discussion

3.1. Detection and analysis of mono-/di-saccharides with various MOFs as matrix

Six mono-/di-saccharide molecules (glucose, sucrose, galactose, lactose, fructose and maltose) were used as test analytes to evaluate the efficiency of MOF as matrix for SALDI-MS. The result for low-mass carbohydrates exhibited no ion signals either with or without the conventional organic matrix (CHCA or DHBA) as co-crystallizing agent (Figs. S1–S3), instead serious background signals were observed. In our previous report [34], the cage-type MOFs (MIL-100 and MIL-101) was utilized as matrices for SALDI-MS analyses of PAHs and nonpolar analytes, which eliminated the background interferences and subsequently produced a high mass signal intensities. Therefore, in this study, several cage-type MOFs (MIL-100(Fe), MIL-100(Cr), MIL-100(Al), MIL-101(Cr), and UiO-66(Zr)) were synthesized based on the literature and used as matrix for SALDI-MS analysis of all test carbohydrates (Scheme 1 shows the procedure for polar carbohydrates measurement). These carbohydrates were detected from the adduct formation of alkali metal ion signals ($[M+Na]^+$ and $[M+K]^+$) with less or suppressed background signals observed when MOF particles are used as matrix (Figs. S4–S7). The formation of $[M+Na]^+$ and $[M+K]^+$ signals (without the addition of extra sodium or potassium ion) are sodium/potassium adduct mechanism which is similar with the previous nanoparticles used as matrix for carbohydrate assay [16–20]. However, the cage-type MOFs exhibited different ionization capacity for carbohydrates. Most MOFs can absorb laser energy at 355 nm and at the same time can effectively transfer its energy to the carbohydrate molecules resulting in the formation of the carbohydrate-alkali metal adduct. For example, chromium centered MOFs (MIL-100(Cr) and MIL-101(Cr)) had lower analyte signals than iron (Fe) or aluminum (Al) centered MIL-100. When different MOFs were used as matrices coupled with different laser power intensities ranging from 55% to 70% for carbohydrate detection (Fig. 1 and Figs. S4–S7), an increase in laser power did not only enhance the ionization of glucose for each MOF matrix but also