Analytica Chimica Acta xxx (2018) 1–8

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Ultrahigh efficient laser desorption ionization of saccharides by Ti-based metal-organic frameworks nanosheets

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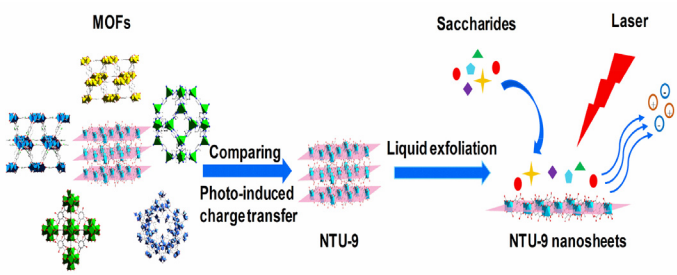
HIGHLIGHTS

- Ti-basedmetal-organic frameworks (MOFs) were first utilized as ultrahigh efficient matrices for MALDI-TOF MS analysis.
- Six water-stable MOFs were selected and tested as MALDI matrices to ionize saccharides.
- The efficiency of MALDI matrix was highly relevant to suitable band gap energy and superior photoabsorption properties.
- A wide range of small molecules were analyzed with NTU-9 nanosheets as the matrices in both positive and negative modes.
- Quantitative determination of glucose was established for diabetic and healthy serum samples.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 2 May 2018
Received in revised form
11 June 2018
Accepted 12 June 2018
Available online xxx

Keywords:
Saccharides
Matrix
Metal-organic frameworks
Nanosheets

ABSTRACT

We proposed some exfoliated Ti-based metal-organic frameworks (MOFs) nanosheets as matrices with ultrahigh ionization efficiency, free matrix background, significant dispersibility and acidic resistance. Combining the features between MOFs and 2-D nanomaterials, the NTU-9 nanosheets matrix also demonstrated suitable band gap energy and superior photoabsorption properties, much better than other representative MOFs. A wide range of small molecules that involving low mass region were also analyzed with NTU-9 nanosheets as the matrices in both positive-ion and negative-ion reflector modes. The ultra-efficient NTU-9 nanosheets matrix was successfully applied to serum for quantitative determination of glucose as a clinical diagnosis indicator of diabetes mellitus.

1. Introduction

Saccharides are the major products of photosynthesis in the

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https://doi.org/10.1016/j.aca.2018.06.035
0003-2670/

biosphere, which are playing an important role in living organisms. Saccharides such as oligosaccharide and glucose are abundant on the cell surfaces, which participating in the cell–cell recognition, cellular developments, cell adhesion and signal transduction [1–3]. At the same time, the glucose level in the blood is an important criterion for human health evaluation and clinical diagnosis of diabetes mellitus [4,5]. Thus the rapid, accurate and high-throughput saccharides analytical method is essentially needed not only for cell biology research but also for clinical practice.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a valuable high-throughput tool, which has been successfully used for the saccharides [6–8]. Conventional matrices for MALDI-TOF MS, α-cyano-4-hydroxycinnamic acid (CHCA) and 2,5-dihydroxybenzoic acid (2,5-DHB) are extensively used in large molecules analysis. However, CHCA and 2,5-DHB are seldom used to the analysis of small molecules ($m/z < 1000$ Da) because they generally have a large number of interfering matrix clusters and precursors [9–16].

The analysis of neutral saccharides by MALDI-TOF is still a challenge due to their low ionization efficiency [17,18]. Usually the time-consuming chemical derivatization is needed in the mass shifting strategy to solve problem [19]. Now, the discovery of the new efficient matrices, such as carbon nanomaterials [20,21], will improve the ionization efficiency as well as avoid the interfering matrix cluster and precursor peaks in the low-mass range. However, new materials with enhanced laser absorption ability and water dispersibility were still in demand to overcome the inhomogeneous co-crystallization of sample and low shot-to-shot reproducibility. Metal–organic frameworks (MOFs) are porous materials that are built from metal ions and organic ligands with an impressive number of applications, such as catalysis [22–24], separation [25–27], sensing [28,29], imaging [30,31] as well as MALDI matrix [32–34]. So far, the MOF MALDI matrices have not been tried for saccharides analysis due to the limited water dispersibility.

Two-dimensional (2-D) MOF nanosheets are emerging nanomaterials by combining the features of 2-D materials and MOFs [35,36]. It exhibited larger surface area, ultrahigh porosity, tunable pore sizes, good solubility, single atom/molecule activity, which makes them ideal for various applications in electronics [37], sensors [38], catalysis [39], energy storage [40] and separation [41,42]. We utilized 2-D MOF nanosheets as excellent matrix for the MALDI-MS analysis of bio-related bases and acids [43]. Not like them, the ionization efficiency of neutral saccharides are extremely low. To tackle the problem, 2-D MOF nanosheets with suitable laser absorption wavelength and efficient light-induced electron or proton transfer ability were needed.

Six water-stable MOFs with different metal clusters and ligands were selected and tested as MALDI matrices to ionize saccharides, such as NTU-9 (Ti, NTU = Nanyang Technological University), MIL-125(Ti, MIL = Matérial Institut Lavoisier), MIL-125-NH_2 (Ti), UiO-66-$(OH)_2$(Zr, UiO = University of Oslo), MIL-100(Fe) and ZIF-8(Zn, ZIF = zeolitic imidazolate frameworks). NTU-9(Ti) demonstrated high ionization efficiency towards saccharides in the positive-ion reflector mode, while low peak intensities and background interference peaks were observed with other MOFs. Thus, NTU-9 was further exfoliated to 2-D nanosheets, which was introduced as a matrix for MALDI-TOF MS for the first time. The 2-D NTU-9 nanosheets exhibited significant advantages, such as high ionization efficiency, free matrix background and high acidic resistance. A variety of small molecules that involving low mass region were tested to evaluate the matrix performance in both positive-ion and negative-ion reflector modes. This 2-D NTU-9 nanosheets was also successfully applied in the quantitative determination of glucose in human serum which was the clinical indicator of diabetes.

2. Experimental section

2.1. Preparation of NTU-9

The NTU-9 was synthesized by an improved hydrothermal method [44]. H_4DOBDC (2,5-dihydroxyterephthalic acid) (0.95 g, 5 mmol) and DEF (*N*,*N*-Diethylformamide) (3 mL) were added in 25 mL Teflon autoclave. The mixture was stirred at room temperature for 5 min before titanium isopropoxide (0.35 mL 1.16 mmol) was introduced. The solution was sealed and heated at 200 °C for 20 h in an oven. Then the obtained product was cooled to room temperature. The dark red solid of NTU-9 was obtained and collected by centrifugation, then thoroughly washed with DMF and methanol. Finally, the product was dried at 120 °C for 24 h in a vacuum oven. The detailed synthesis information of other MOFs is shown in Electronic Supplementary Information.

2.2. Exfoliation of NTU-9 into nanosheets

In a typical process of liquid exfoliation [45], 50 mg of NTU-9 was ultrasonicated in 50 mL of isopropanol for a total of 48 h. After centrifuged at 3000 rpm for 5 min, the collected supernatant was further centrifuged at 12000 rpm for 20 min. The precipitant of the NTU-9 nanosheets was obtained and dried at 50 °C overnight. The average exfoliation yield of NTU-9 nanosheets was 10%.

2.3. Matrix preparation for MALDI-TOF MS

To compare the performance of several materials as matrices for MALDI-MS, the matrices of NTU-9 nanosheets, NTU-9, MIL-125, MIL-125-NH_2, UiO-66-$(OH)_2$, ZIF-8, MIL-100(Fe) and $Zn_2(bim)_4$ were all dispersed in ethanol/H_2O (1:1, v/v) and sonicated for 10 min to form matrix suspension (1.0 mg mL^{-1}). The CHCA matrix (0.7 mg mL^{-1}) was dissolved in water/acetonitrile (15/85, v/v) containing 0.1% trifluoroacetic acid (TFA). 2,5-DHB matrix aqueous solution (20 mg mL^{-1} DHB in 1% H_3PO_4 aqueous solution) was prepared. The analyte solution of 1 μL was deposited on a MTP AnchorChip 384 plate and air-dried. Then, 1 μL of matrix suspension was deposited on the top of analytes.

2.4. Preparation of sample solutions

The concentrations of stock solutions for all the following analytes were 10 mM. The glucose ($C_6H_{12}O_6$, molecular weight (MW) = 180.16, pK_a = 12), maltose ($C_{12}H_{22}O_{11}$, MW = 342.32, pK_a = 12.05) and saccharides of maltotriose ($C_{18}H_{32}O_{16}$, MW = 504.44, pK_a = 11.55), maltotetraose ($C_{24}H_{42}O_{21}$, MW = 666.58, pK_a = 11.19), α-cyclodextrin ($C_{36}H_{60}O_{30}$, MW = 973.00, pK_a = 11.56), and β-cyclodextrin ($C_{42}H_{70}O_{35}$, MW = 1135.00, pK_a = 12.1) were all dissolved in water at a concentration of 10 mM as stock solution. Solvents were water/MeOH (1:1, v/v) for amino acids. Four nucleobases were dissolved in hot water. Fatty acids including dodecanoic acid (C12), hexadecanoic acid (C16) and icosanoic acid (C20) were dissolved in anhydrous ethanol. All solutions were stored at 4 °C for further use.

The serum samples were obtained by Jiangsu Province Hospital of TCM (Affiliated Hospital of Nanjing University of Chinese Medicine) according to their standard clinical procedures. The standard addition method with internal standard of isotope D-glucose-1-^{13}C was employed. The collected serum (10 μL) was added with the isotope D-glucose-1-^{13}C (final concentration 5 mM). Thereafter, different concentrations of glucose (1, 2, 3 and 4 mM) were added to the above mixtures, respectively. Finally, the mixture were added with acetonitrile (acetonitrile: serum = 3: 1, v/v) to remove the high-abundance proteins from the serum samples. After

Please cite this article in press as: Y.-J. Chang, et al., Ultrahigh efficient laser desorption ionization of saccharides by Ti-based metal-organic frameworks nanosheets, Analytica Chimica Acta (2018), https://doi.org/10.1016/j.aca.2018.06.035