Polydopamine-Modified TS-1 Zeolite Framework Nanoparticles as a Matrix for the Analysis of Small Molecules by MALDI-TOF MS

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ABSTRACT: Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) using conventional organic matrices for detection of small molecules has some limitations, such as heterogeneous analyte/matrix co-crystals, as well as interference of matrices in the low-molecular-weight range. In this work, a zeolite framework nanomaterial, TS-1, was applied as a MALDI matrix for the analysis of small molecules by MALDI-MS for the first time. To improve the signal intensity and reproducibility, TS-1 was modified with polydopamine (TS-1@PDA). Using TS-1@PDA as a matrix, organic substances in the low-molecular-weight region such as amino acids, nucleosides, peptides, oligosaccharides, and fatty acids can be detected by MALDI-MS in positive ion mode. Compared with traditional organic matrices like 2,5-dihydroxybenzoic acid (2,5-DHB) and α-cyano-4-hydroxycinnamic acid (CHCA), TS-1@PDA has the advantages including the formation of uniform sample spots, small background interference at low molecular weight, and better salt tolerance. Furthermore, this matrix was employed for the analysis of endogenous glucose in urine samples, and the level of glucose was quantified with a linear range of 0–10 mM (R² > 0.98). The results demonstrated that TS-1@PDA has the potential to be used as an effective MALDI matrix for the analysis of small molecules in biological samples with excellent reproducibility and moderate sensitivity.

INTRODUCTION

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a soft ionization technique that was first developed by Karas and Hillenkamp in the 1980s.1 Because of its superior advantages, such as simple operation, high sensitivity, small sample volume, high throughput, and great salt tolerance, MALDI-TOF MS has been widely used in the analysis of biomacromolecules such as proteins, nucleic acids, and polymers.2−5 However, the detection of low-molecular-weight (LMW) compounds (<500 Da) still suffers from some challenges.6 For example, conventional organic matrices like 2,5-dihydroxybenzoic acid (2,5-DHB) and α-cyano-4-hydroxycinnamic acid (CHCA) generate peaks in the low-molecular-weight range due to their self-ionization, leading to strong background interferences to small molecules.7 Heterogeneous sample spots are generated during the co-crystallization of analytes and matrix, therefore causing poor reproducibility and unreliable quantitative analysis results.8

Many efforts have been made to overcome the above problems in recent years. Some organic molecules have been developed as MALDI-TOF MS matrices,9 including 3,4-dimethoxybenzylamine (NHHC).10 However, it is still hard to completely avoid the background interference caused by these matrices. In recent years, a variety of inorganic nanomaterials with different compositions and morphologies, which could avoid most of the drawbacks of conventional organic matrices, were applied for low-mass-range molecule analysis.15,16 Until now, metals and their oxides,17−19 carbon-based nanoparticles,20−22 and silicon-based materials have been proved to be effective MALDI-TOF matrices. Among these matrices, silicon-based materials like porous silicon,23 silicon nanowires,24 and silicon microarrays25 have a large surface area, universal optical absorption property, and weak noise signal, which could be used as a stable and effective matrix.26 However, different nanomaterial-based matrices still suffer some drawbacks. For example, the reproducibility of silicon nanosurfaces is low, and carbon materials have poor water dispersibility. These limitations led to the formation of homogeneous sample spots.27 Besides, the modification of nanomaterials with an

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organic matrix and organic—inorganic binary matrix have also become the focus of research. In a word, further improvement of matrix performance remains an important research direction.

The nanoparticle, TS-1, is a titanium-substituted zeolite framework silica material with an MFI topology, which is extensively applied in production technology and low cost. Due to the significant optical absorption in the ultraviolet region, TS-1 might be used as a matrix for MALDI-TOF MS detection. However, its hydrophobicity may reduce the dispersion of TS-1 in solvent and the reproducibility of MALDI analysis results, which has a great impact on quantitative analysis. Polydopamine coating might be a powerful strategy to improve the properties of nanomaterials as a MALDI matrix because of its great adhesion, biocompatibility, and electrical and optical properties. It cannot only improve the dispersion of nanomaterials and the homogeneity of sample spots but also significantly increase the laser energy absorption capacity in MALDI-TOF MS due to the aromatic ring structure of dopamine.

In this work, TS-1 modified with polydopamine (TS-1@PDA) was investigated as a novel matrix for the detection of small molecules by MALDI-TOF MS (Figure 1). The synthesized TS-1@PDA nanoparticles were characterized by ultraviolet—visible (UV—vis) absorption and scanning electron microscopy (SEM), and their performance as a matrix was evaluated by comparing with unmodified TS-1 nanoparticles and traditional organic matrices like 2,5-DHB and CHCA. Then, TS-1@PDA nanoparticles were applied to detect a series of small biomolecules in positive ion mode, as well as quantitative analysis of glucose in healthy human urine samples. The results showed that TS-1@PDA has the potential to be applied in complex biological sample analysis with good sensitivity and reproducibility.

EXPERIMENTAL SECTION

Reagents and Materials. L-Aspartic acid, L-glutamic acid, L-histidine, L-phenylalanine, L-tyrosine, L-tryptophan, thymidine, cytidine, uridine, adenosine, guanosine, and trifluoroacetic acid (TFA) were purchased from Sigma-Aldrich (St. Louis, MO). Peptides including Tyr−Gly−Gly (YG-3), Tyr−Phe (YF-2), and Phe−Gly−Phe−Gly (FG-4) were purchased from Shanghai Apeptide Co. Ltd. (Shanghai, China). Glutathione, glucose, sucrose, and raffinose were obtained from J&K Scientific Co. Ltd. (Beijing, China). TS-1 was supplied by XFNano, Inc. (Nanjing, China). Dopamine hydrochloride, tris(hydroxymethyl)aminomethane (Tris), sodium dihydrogen phosphate (NaH2PO4), disodium hydrogen phosphate (Na2HPO4), sodium hydroxide (NaOH), sodium chloride (NaCl), and fatty acids (FAs), including cis-10-heptadecenoic acid (17:1), α-linolenic acid (18:3), linoleic acid (18:2), trans-vaccenic acid (18:1), and arachidonic acid (20:4), were purchased from Aladdin (Shanghai, China). Matrices including 2,5-dihydroxybenzoic acid (2,5-DHB) and α-cyano-4-hydroxycinnamic acid (CHCA) were purchased from Bruker Daltonics GmbH (Bremen, Germany). Ethanol, methanol, and acetonitrile (ACN) were purchased from Merck (Darmstadt, Germany). Bond Elut phenylboronic acid (PBA) columns were obtained from Varian (Agilent, Santa Clara, CA). Ultrapure deionized water (18 MΩ) used in all experiments was prepared by a Milli-Q water purification system (Millipore, Bedford, MA).

Preparation of TS-1@PDA. TS-1 nanoparticles were coated with polydopamine by self-polymerization of dopamine described in the literature. Briefly, 50.0 mg of TS-1 nanoparticles were dispersed in 50.0 mL of Tris buffer (10.0 mM) by 30 min ultrasonication, and the pH of the solution was adjusted to 8.5 by HCl. Then, 50.0 mg of dopamine was quickly added into the above solution under continuous magnetic stirring and the same volume of suspension was separated from the reaction system at different reaction times (2, 4, 6, 8, and 10 h). The final product was collected by centrifugation at 800 rpm for 10 min and washed with water and ethanol several times to remove unreacted dopamine. The obtained TS-1@PDA was dialyzed to remove impurities and dried at 50 °C for further MALDI-TOF MS analysis.

TS-1 and TS-1@PDA Characterization. A scanning electron microscope (SEM, Hitachi S-4800, Japan) was used to characterize the particle size and surface morphology of TS-1 and TS-1@PDA nanoparticles. The surface morphology was observed and photographed using an Olympus BX51M upright metallurgical microscope (Japan). UV—vis absorption spectra were recorded using a Shimadzu UV-3600 spectrophotometer. MALDI-TOF MS (Bruker Daltonics GmbH, Bremen, Germany) experiments were performed with a reflector mode using a 355-nm Nd:YAG laser. 

Figure 1. Procedures of MALDI-TOF MS analysis using TS-1@PDA as the matrix.
of the TS-1 and TS-1@PDA suspension were, respectively, measured using an Agilent Cary 100 UV–vis spectrophotometer at room temperature in a 1.0 cm path length.

**Sample Preparation for MALDI-TOF MS Analysis.** The standard solutions of amino acids, nucleosides, oligosaccharides, peptides, and anticancer drugs were prepared by directly dissolving them with ultrapure deionized water, while fatty acids were dissolved in H2O-ACN (50:50, v/v) at a concentration of 10.0 mM as stock solutions. All analyte solutions were prepared by mixing and diluting the stock solutions with corresponding solvents to obtain the final concentration of 1.0 mM for each analyte. A urine sample was collected from a healthy 22-year-old male volunteer and the sampling time was 2 h after lunch. Urine was mixed with 3-fold amount of methanol for protein precipitation. Then, the precipitated proteins were removed by centrifuging at 16 000 rpm for 30 min. To ensure the accuracy of the analytical results, impurities are removed by solid-phase extraction. The Bond Elut PBA-SPE column was preconditioned with a mixture of H2O-ACN (70:30, v/v) with 1% trifluoroacetic acid at a concentration of 20.0 mg mL⁻¹, and washed with a mixture of 10.0 mM phosphate buffer (pH 10.0), and then the sample was loaded into the column and washed with a mixture of 10.0 mM phosphate buffer (pH 8.5) with 5% ACN. Finally, the sample was eluted with H2O-ACN (70:30, v/v) solution containing 1% trifluoroacetic acid and collected for further analysis. For matrix preparation, TS-1 and TS-1@PDA NPs were redispersed in deionized water in the concentration range from 1.0, 2.5 to 5.0 mg mL⁻¹ and TS-1@PDA NPs were redispersed in deionized water in and collected for further analysis. For matrix preparation, TS-1 and TS-1@PDA nanoparticles were characterized using UV–vis absorption spectroscopy and scanning electron microscope (SEM). As shown in Figure 2b,c, respectively. Monodispersed TS-1 nanoparticles range in size from 150 to 300 nm. After polydopamine modification, the surface of the nanoparticles became smoother but the size did not increase significantly, which indicates that a thin layer of polydopamine film was formed to cover the surface of TS-1 nanoparticles. Due to the above properties, both TS-1 and TS-1@PDA nanoparticles have the potential to be applied as MALDI matrices for MALDI-TOF MS detection, which was further verified and compared in subsequent experiments.

### RESULTS AND DISCUSSION

**Characterization of TS-1 and TS-1@PDA.** After the synthesis of novel nanomaterial matrix TS-1@PDA, the changes before and after modification were characterized and compared. Unmodified TS-1 and the synthesized TS-1@PDA nanoparticles were characterized using UV–vis absorption spectroscopy and scanning electron microscope (SEM). As shown in Figure 2a, both TS-1 and TS-1@PDA have significant UV absorption in the range of 200–400 nm, and the absorption of TS-1@PDA is much stronger than that of TS-1. This allowed TS-1@PDA to absorb the laser energy and transfer energy to the analyte more efficiently than TS-1, causing molecular ionization easily. The size and morphology comparison of TS-1 nanoparticles and TS-1@PDA are shown in Figure 2b,c, respectively. Monodispersed TS-1 nanoparticles in Figure 2a, respectively. Monodispersed TS-1 nanoparticles range in size from 150 to 300 nm. After polydopamine modification, the surface of the nanoparticles became smoother but the size did not increase significantly, which indicates that a thin layer of polydopamine film was formed to cover the surface of TS-1 nanoparticles. Due to the above properties, both TS-1 and TS-1@PDA nanoparticles have the potential to be applied as MALDI matrices for MALDI-TOF MS detection, which was further verified and compared in subsequent experiments.
Figure 3. Mass spectra of an amino acid mixture using (a) 2,5-DHB, (b) CHCA, (c) TS-1, and (d) TS-1@PDA as the matrix in positive ion mode (Asp, [M+Na]+ m/z 156.0; Glu, [M+Na]+ m/z 170.0; His, [M+H]+ m/z 156.0, [M+Na]+ m/z 178.0, [M+K]+ m/z 194.0; Phe, [M+H]+ m/z 166.1, [M+Na]+ m/z 188.0; Tyr, [M+Na]+ m/z 204.0; Trp, [M+H]+ m/z 205.0, [M+Na]+ m/z 227.0). The concentration of each analyte was 1.0 mM. Matrix-related ions are marked with asterisks. Laser intensity of 30% was applied for all.

**Performance of TS-1 and TS-1@PDA as a MALDI-TOF MS Matrix.** Various TS-1@PDA nanoparticles were obtained by modification with polydopamine for different reaction times ranged from 2 to 10 h. As shown in Supporting Figure S2, we found that TS-1@PDA with the modification time of 4 h as the MALDI matrix has the best detection sensitivity for glucose. We first compared the background signals generated from TS-1 and TS-1@PDA with those from organic matrices. The performances of the organic matrix (2,5-DHB, CHCA) and nanoparticle-based matrix (TS-1 and TS-1@PDA nanoparticles) were compared under the same condition including the used AnchorChip target plate. As shown in Supporting Figure S3, TS-1 and TS-1@PDA did not produce significant background, whereas 2,5-DHB and CHCA generated a large number of intense background signals in the LMW region (m/z <600). Dopamine was polymerized on the surface of TS-1 nanoparticles into an adhesive polymer, and matrix fragment ions were hardly generated during the analysis, which ensured the clean background in the LMW region. To evaluate whether TS-1 and TS-1@PDA have the potential for analysis of multifarious small molecules, a series of representative analytes covering both polar and nonpolar molecules like amino acids, nucleosides, oligopeptides, oligosaccharides, and fatty acids were detected in both positive and negative ion modes. Their chemical structures are shown in Supporting Figures S4–S8.

A mixed aqueous solution of six amino acids at a concentration of 1.0 mM was first detected using TS-1@PDA as the MALDI-TOF MS matrix. Its performance in positive ion mode was first compared with that using TS-1 nanoparticles and two organic matrices, 2,5-DHB and CHCA. As shown in Figure 3, when using 2,5-DHB or CHCA as the matrices separately, amino acids produced ion signals [M+H]+, [M+Na]+, and [M+K]+ simultaneously, which overlapped with each other, seriously increasing the difficulty of understanding the spectra. The situations using TS-1 and TS-1@PDA as the matrices are significantly different. [M+H]+ signals were effectively suppressed and rendered clear analyte-related spectrum mainly of [M+Na]+ at m/z 156.0 [Asp+Na]+, m/z 170.0 [Glu+Na]+, m/z 178.0 [His+Na]+, m/z 188.0 [Phe+Na]+, m/z 194.0 [His+K]+, m/z 204.0 [Tyr+Na]+, and m/z 227.0 [Trp+Na]+. The [His+K]+ signal was observed, which might be induced by the basicity of histidine, whereas the other selected amino acids were neutral or acidic. Moreover, we can clearly see that the signal intensities of these amino acids and signal-to-noise ratio (S/N) are significantly improved after polydopamine modification, indicating the better performance of TS-1@PDA than TS-1 as a matrix. The signal-to-noise ratio data of the relevant signals are shown in Supporting Table S1.

We suggest the reason to be the fact that the rich aryl groups of polydopamine provide a π–π conjugate structure, which greatly improves the energy transfer efficiency during the desorption–ionization process. In addition, the amino acid mixture was also detected using negative ion mode. The results are shown in Supporting Figure S9, which produce clear analyte signals and clear background. However, the signals of these analytes in negative ion mode were generally lower than those in positive ion mode. Therefore, we chose the positive ion mode for the subsequent study.

To further confirm that the performance of TS-1 nanoparticles as a MALDI-TOF MS matrix was improved after polydopamine modification, a mixture of five nucleosides (thymidine, MW = 242.23, cytidine, MW = 243.22, uridine, MW = 244.20, adenosine, MW = 267.25, guanosine, MW = 283.24) at a concentration of 1.0 mM was further detected by MALDI-TOF MS in positive ion mode using the above four matrices and their performances were compared. As shown in Supporting Figure S10, when using 2,5-DHB or CHCA as the matrix, the proton, sodium, and potassium adducts were...
displayed in the spectra, making them especially difficult to interpret. When using TS-1 and TS-1@PDA as the matrices, only a low background appeared in the analyte region, and the spectra were dominated by [M+Na]+ signals. Mass spectra signals and S/N were higher when using TS-1@PDA as the matrix compared to that using TS-1, which indicated that TS-1@PDA was a better choice than TS-1 as the matrix. The signal-to-noise ratio data of the relevant signals are shown in Supporting Table S2.

To extend the application range of TS-1@PDA as a MALDI-TOF MS matrix for detecting more kinds of small molecules, oligopeptides, oligosaccharides, and fatty acids were detected. Three oligopeptides with the main sodium adduct ions (YG-3, m/z 318.1; YF-2, m/z 351.2; FG-4, m/z 449.2) and one potassium adduct ion (FG-4, m/z 465.2) were displayed in the spectra (Supporting Figure S11a). For the solution of three oligosaccharides mixture, the main sodium adduct ions (glucose, m/z 203.1; sucrose, m/z 365.1; raffinose, m/z 527.2) and a small amount of potassium adduct ion (rafinose, m/z 543.2) were detected (Supporting Figure S11b), which made the positive ion spectrum easy to interpret. For the selected five fatty acids (FA 17:1, MW = 268.44, FA 18:3, MW = 278.44, FA 18:2, MW = 280.45, FA 18:1, MW = 282.47, FA 20:4, MW = 304.47), mainly, the [M+Na]⁺ peaks and [M+K]⁺ peaks were detected (Supporting Figure S11c), but the ion signals of sodium adducts were much higher than the potassium adducts. The above results indicated that TS-1@PDA has the potential to be applied as a MALDI-TOF MS matrix for the detection of a wide range of chemicals with small molecular weight.

From the above results, we found that when using TS-1@PDA nanoparticles as a matrix for the detection of small molecules in positive ion mode by MALDI-TOF MS, the sodium adduct ions were dominant in the mass spectra, which completely inhibited the generation of [M+H]⁺. This may be due to the introduction of sodium ions during the synthesis of TS-1 nanoparticles and the PDA modification under alkaline conditions containing sodium hydroxide, which increased the sodium ion concentration in the system. Therefore, the sodium adduct ions easily appeared in the mass spectra.

**Sample Spot Uniformity and Signal Reproducibility Evaluations.** The uniformity of matrix-forming sample spots has a significant impact on the repeatability of MALDI-TOF MS detection. For nanoparticles, the uniformity of the sample spots is mainly affected by the dispersibility of nanoparticles in solvent, so the changes of water dispersibility for TS-1 after polydopamine modification were visually assessed. The same amount of TS-1 and TS-1@PDA nanoparticles were ultrasonically dispersed in ultrapure water and statically placed for a few minutes. Comparing the photos after different time periods, TS-1 cannot disperse well in water and quickly precipitate out of the aqueous dispersion, whereas TS-1@PDA exhibits excellent water dispersibility (Supporting Figure S12).

Glucose (1.0 mM) was chosen as a model molecule to compare the co-crystalline morphology with different matrices, and their sample spots were obtained by an upright metallurgical microscope (Olympus BX51M, Japan). As shown in Supporting Figure S13, the organic matrix 2,5-DHB and CHCA formed irregular co-crystals with the analyte, resulting in the inability to quantitatively analyze the sample. For the TS-1 situation, the edge has a distinct coffee ring effect (Figure 4a). As shown in Figure 4b, after modification by polydopamine, the sample spots formed by TS-1@PDA and 1.0 mM glucose have overall uniformity without the coffee ring effect, which is due to the improved water dispersibility, probably making it better for quantitative analysis.

To confirm this hypothesis, the reproducibility was explored using glucose as a model analyte, and TS-1 and TS-1@PDA as the matrix separately. When using TS-1 as the matrix, the intensities from 18 acquisitions were stabilized at around 5000 with a relative standard deviation (RSD) of 37.3% (Figure 4c). For the TS-1@PDA situation, the intensity distribution was stabilized at around 60 000 and showed a better reproducibility with the RSD of 10.8% (Figure 4d). The results showed that the reproducibility of TS-1@PDA as a MALDI-TOF MS matrix was improved compared to TS-1 and the quantitative results were consistent with the corresponding crystalline morphologies of different matrices with 1.0 mM glucose. In addition, the center positions of 12 different sample spots using TS-1 and TS-1@PDA as the matrix were also detected, and the RSD of signal intensity was 23.3 and 5.0%, respectively (Supporting Figure S14). The results indicated that TS-1@PDA as the MALDI matrix has the capability to increase shot-to-shot and spot-to-spot intensity reproducibility.

**Salt Tolerance Evaluation.** Biological samples typically contain higher concentrations of salt, which results in reduced ionization efficiency and analyte signal inhibition in MALDI-TOF MS analysis. The salt tolerance of TS-1@PDA in positive ion mode was evaluated using cytidine as a model analyte, which was diluted using a 0–100 mM NaCl solution for further analysis. As shown in Figure 5, with increasing concentration of NaCl, the signal intensity of cytidine at m/z 266.1 decreased slightly. When the concentration of the NaCl solution increased to 100.0 mM, a high signal-to-noise ratio cytidine signal could still be detected. It showed that TS-1@PDA as a MALDI-TOF MS matrix can accommodate the needs of most biological samples. Besides, when the sample containing no exogenous NaCl showed a significant [M+K]⁺ signal, the addition of NaCl inhibited the [M+K]⁺ signal, which made the spectrum easier to explain. The results indicated that NaCl can be used as an additive to the TS-1@PDA matrix to make the spectrum easier to explain through obtaining the main sodium adduct ions.
Quantitative Detection of Glucose and Nucleosides in Urine Samples. To further validate the suitability of the TS-1@PDA matrix for biological samples, cis-diols of a urine sample from a healthy male were extracted and followed by MALDI-TOF MS detection. As shown in Figure 6a, several molecular ion peaks identified in the mass spectrum might be glucose ([glucose+Na]+, m/z 203.1), thymidine ([M+Na]+, m/z 265.1), cytidine ([M+Na]+, m/z 266.1), uridine ([M+Na]+, m/z 267.1), adenosine ([M+Na]+, m/z 290.1), and guanosine ([M+Na]+, m/z 306.1). To confirm their structures, their tandem mass spectra obtained from MALDI-TOF/TOF MS/MS were compared with those of their corresponding standards. The types of identification (the calculated mass and fragment ions of the metabolites) are summarized in Supporting Table S3. To accurately quantify glucose in the urine sample, 1.0 mM D-glucose-13C6 was added to 0−10 mM glucose solution and a calibration curve was plotted by the ion intensity ratio of D-glucose ([M+Na]+, m/z 203.1) to D-glucose-13C6 ([M+Na]+, m/z 209.1). As shown in Figure 6b, the regression equation was \( y = 0.84798x + 0.26924 \), and good linearity was obtained with \( R^2 > 0.98 \), which could meet the analytical demand of glucose in human urine samples. For the quantification of glucose in the urine sample, 1.0 mM D-glucose-13C6 was added into the sample, pretreated, and detected by MALDI-TOF MS using TS-1@PDA as the matrix. Taking the average of six repeated analysis results to calculate the glucose content in the urine, the result was 0.548 ± 0.02 mM, which was consistent with previous research.37

CONCLUSIONS

The zeolite framework nanoparticle, TS-1, was modified by polydopamine to obtain a novel MALDI-TOF MS matrix TS-1@PDA for the analysis of small molecules in positive ion mode. A wide range of small molecules like amino acids, nucleosides, peptides, oligosaccharides, and fatty acids were investigated. Unlike conventional organic matrices, TS-1 and TS-1@PDA showed lower background, higher signal-to-noise ratio, good salt tolerance, and repeatability. Compared to the TS-1 matrix, TS-1@PDA obtained by the modification of TS-1 with PDA significantly improved the signal intensity and reproducibility through a more homogeneous matrix−analyte co-crystal for small-molecule detection. The good performance of the TS-1@PDA matrix provides the potential for small-molecule detection in biological samples, which was demonstrated by the detection of glucose and nucleosides and quantification of glucose in a human urine sample. Our results showed that TS-1@PDA could be an efficient matrix for the analysis of a wide range of small molecules in clinical samples.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00992.

Optimization of the nanomaterial matrix concentration (Figure S1); optimization of polydopamine modification time (Figure S2); matrix background signal comparison (Figure S3); chemical structures of amino acids, nucleosides, oligopeptides, oligosaccharides, and fatty acids (Figures S4−S8); MALDI spectrum of amino acids (Figure S9); MALDI spectra of nucleosides (Figure S10); mass spectra of peptides, oligosaccharides, and FAs (Figure S11); dispersity of TS-1 and TS-1@PDA in water (Figure S12); images of sample spots of 2,5-DHB and CHCA (Figure S13); signal reproducibility between different sample spots (Figure S14); S/N data of amino acids and nucleosides (Tables S1 and S2); MS/MS fragment analysis (Table S3) (PDF)
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Notes

The authors declare no competing financial interest.

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