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RESEARCH ARTICLE

Analysis of Compounds Dissolved in Nonpolar Solvents by Electrospray Ionization on Conductive Nanomaterials

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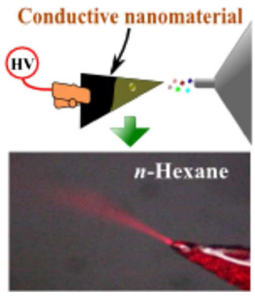

Abstract. Electrospray ionization mass spectrometry (ESI-MS) technique has limitations in analysis of compounds that are dissolved in nonpolar solvents. In this study, ambient ionization of compounds in solvents that are not "friendly" to electrospray ionization, such as *n*-hexane, is achieved by conductive nanomaterials spray ionization (CNMSI) on nanomaterial emitters, including carbon nanotubes paper and mesodendritic silver covered metal, which applies high voltages to emitters made of these materials without the assistance of polar solvents. Although the time intensity curves (TIC) commonly vary from 4.5% to 23.7% over analyses, protonated molecular ions were found to be the most abundant species, demonstrating good reproducibility of the technique in terms of ionized species. Higher mass spectrometric responses are observed in analyzing nonpolar systems than polar systems. 2-Methoxyacetophenone, 4-methylacetophenone, benzothiazole, quinolone, and cycloheptanone as low as 2 pg in *n*-hexane can be directly detected using the developed method. The developed technique expands the analysis capability of ESI-MS for direct, online analysis of nonpolar systems, such as low polarity extracts, normal phase liquid chromatography eluates, and synthetic mixtures.

Keywords: Conductive nanomaterials, Electrospray ionization, Nonpolar solvents

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Introduction

As a powerful mass spectrometric technique, electrospray ionization (ESI) has been demonstrated to have significant advantages in speed and sensitivity among other chemical analysis methods, and it has been widely applied in many scientific fields to analyze a great variety of compounds. Traditionally, these compounds are dissolved in aqueous mixtures of polar organic solvents (e.g., methanol and acetonitrile) prior to ESI. However, ESI is limited to analyzing compounds dissolved in nonpolar solvents due to the solvents' poor conductivities and low dielectric constants. As a result, the nonpolar solvents that are widely used in organic reactions, normal phase liquid chromatography (NPLC), gel permeation chromatography (GPC), sample extraction and NMR analysis, are less amenable for use in ESI-MS. To analyze nonpolar systems using ESI-MS, adding polar solvents or ionic liquids to solution was reported to facilitate ionization of dissolved species [1–3]. However, it changes the solvent system of the samples that may lead to deviations from the prior conditions.

In recent years, much effort has been made, in combination with the emergence of ambient ionization techniques, to detect chemicals in nonpolar solvents. Previous research on recently developed solvent-assisted, electrospray-based ionization methods illustrated that extractive electrospray ionization (EESI) [4, 5], solvent-assisted electrospray ionization (SAESI) [6], and continuous flow-extractive desorption electrospray ionization (CF-EDESI) [7, 8] could be used for the direct analysis of compounds in "non-ESI-friendly" solvents. In these ionization methods, introduction of the nonpolar system's sample and ionization are independent processes, which prevent the sample conditions from changing. However, complicated instrument modifications or complex parameter adjustments to these methods are still required. In addition to solvent-assisted ESI, solid substrate ESI techniques such as wooden tip ESI [9–11], probe electrospray ionization (PESI) [12–16], and paper spray ionization (PSI) [17–19] have been extended to directly sample and ionize various types of samples. By first sampling and then

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subjecting samples to ESI-MS analysis with the assistance of polar solvents or polar solvent vapor would be a promising approach for these techniques to analyze analytes in nonpolar solvents. It is worth noting that among the above methods, paper substrate-based PSI is capable of directly ionizing insoluble drugs, peptides, nucleotides, and phospholipids as solids from paper wetted with nonpolar solvent [20]. Nevertheless, according to our repeated trials, the ionization efficiency of PSI is quite limited concerning such use.

Discovered in 1991 [21], carbon nanotubes (CNTs) have been recognized for their low weight [22], good heat conductance [23], various electronic properties that depend on their structure, and the ability to transfer charge at relatively low voltages due to their high aspect ratios and nanometer-sized tips [24]. Recently, CNTs have mainly been used in matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) as a matrix [25]. In addition, based on CNTs, field emission, chemical ionization (CI) [26], electron ionization (EI) [27], as well as field emission ionization [28] were developed. In ESI field, paper substrates are capable of generating spray ionization under an electronic potential of just a few volts after the paper is coated with CNTs [29]. We speculate the conductive nanostructure (as that of CNTs) may play an important role in facilitating ionization, and thus may be used in ionization of "non-ESI-friendly" systems. However, the potential of using conductive nano-materials for the ionization of analytes dissolved in nonpolar solvents has not yet been investigated. After evaluating many materials in our preliminary experiments, we ultimately found that ionization efficiency of "non-ESI-friendly" systems significantly improved compared with conventional technologies when using conductive nanomaterials such as CNTs and mesodendritic silver-covered metal as ESI emitters.

In this study, we report the developed use of conductive nanomaterials spray ionization mass spectrometry (CNMSI-MS) in the analysis of analytes in nonpolar solvents. Conductive nanomaterial is first cut into a triangle, and a silica capillary connected to a syringe pump is used to supply analyte solution to the center of the triangle through contact with its surface. Analytes transport to the triangle tip via capillary action through micro-channels in the emitter substrate, and then a high electric field is applied to perform ionization. CNMSI-MS studies of compounds dissolved in solutions, such as methanol, *n*-hexane, and dichloromethane (CH_2Cl_2), were investigated. Chiral molecules separated by NPLC were also detected by CNMSI-MS without any polar assistant solvent, and intense signals of $[M+H]^+$ ions from each racemic compound is clearly observed in positive ionization mode.

Experimental

Materials

Perphenazine (**1**) and 5-acrylamide-1,10-phenanthroline (**2**) were synthesized in our laboratory and confirmed structurally using UV spectroscopy, MS, ^{1}H NMR, and ^{13}C NMR. The purity of each compound was verified as being higher than 98% using HPLC–UV analysis. 2-Methoxyacetophenone (**3**), 4-methylacetophenone (**4**), 1-indanone (**5**), acetophenone (**6**), 4'-dimethylaminoacetophenone (**7**), 5-methylindole (**8**), benzothiazole (**9**), quinolone (**10**), cycloheptanone (**11**), 2,2'-dipyridyl (**12**), and silver nitrate (**13**) were purchased from Aladdin Reagent Co., Ltd. (Shanghai, China). Single-walled carbon nanotubes (SWCNTs) were obtained from Aladdin Reagent Co., Ltd. (Shanghai, China). Grade ET31 chromatography paper (0.50 mm thick) was purchased from Whatman International Ltd. (Maidstone, England). Water was prepared using a Milli-Q system (Millipore Laboratory, Bedford, MA, USA). HPLC-grade methanol, acetonitrile, ethanol, and acetone were obtained from Merck Co. (Darmstadt, Germany). *n*-Hexane and CH_2Cl_2 of analytical reagent grade were obtained from Changzheng Chemical Reagent Corp. (Chengdu, China). HPLC grade methanol was purchased from Fisher Co. (Fisher Scientific, Hampton, NH, USA). N-(2-(hydroxymethyl)-1-(2-methoxyphenyl)-3-methylbut-3-en-1-yl)P,P-diphenylphosphinic amide raceme (**14**) was synthesized in our laboratory. Other reagents were of analytical grade and used without further purification.

Apparatus

The conductive nanomaterial was cut into triangles measuring 3 × 8 mm (base × height). The triangles were held in place such that the distance from the tip to the MS inlet was 2.0–11.0 mm using a 3D-printed holder mounted on a manual XY stage. An external high voltage supply (0–4.0 kV) was connected to the emitter via a copper clip (Figure 1). Sample solution was supplied to the center of the emitter using a silica capillary connected to a syringe pump. The solvent volume was delivered in 2 μL aliquots, and repeated measurements were conducted using the same emitter. For paper spray, all parameters were kept the same with the exception of substituting grade ET31 chromatography paper for the conductive nanomaterial.

Preparation of CNTs Sheet and Mesodendritic Silver Covered Metal

CNTs sheet (10–50 μm thick) was produced by multiple steps of tube dispersion and suspension filtration as described previously [30]. SWCNTs were sonicated for 5 h in 5 M hydrochloric acid (HCl) to dissolve residual iron catalyst particles. Concentrated nitric acid (HNO_3) was added to the acid etch and kept between 55 and 60 °C for 5 h to increase the effectiveness of the purification and populate the nanotube surface with carboxylic acid groups. The material was neutralized through a series of deionized water washes, then filtered, dried, and reground into powder. Using nanosperse AQ surfactant (Waltham, MA, USA), the purified nanotubes were suspended in deionized water and sonicated. An aliquot of the suspension was then removed and vacuum-filtered through a microporous membrane (0.45 μm) to fabricate a free-standing, round film of CNTs. Subsequent washes with deionized water and methanol were performed. After washing, the CNTs sheet was carefully peeled off from the filter membrane. Finally, the paper was

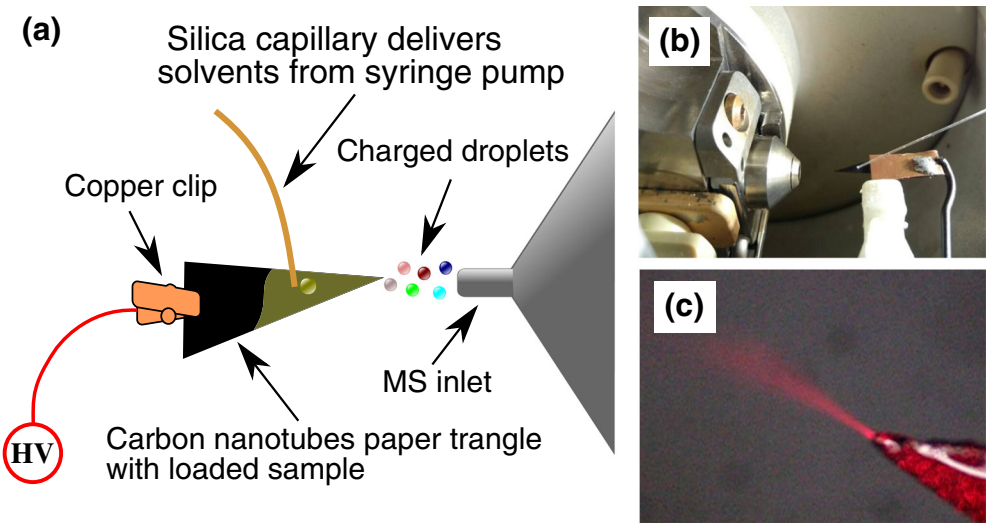

Figure 1. **(a)** Schematic presentation of CNMSI-MS; **(b)** photograph of the experimental setup; **(c)** electrospray plume under red laser illumination when using *n*-hexane as solvent

dried in an oven at 30 °C for 24 h in vacuo to remove excess moisture.

Mesodendritic silver-covered zinc sheet was synthesized in the same procedure as reported in our previous work [31].

Mass Spectrometry

The study was performed on a Waters Xevo TQ mass spectrometer (Waters, Manchester, UK) equipped with an orthogonal Z-spray electrospray ionization source (ESI). For conventional ESI-MS experiments, the parameters were set as follows: 500 L/h desolvation gas flow rate; 500 °C desolvation gas temperature; 150 °C source temperature; 3 kV capillary voltage; and 30 V cone voltage. The accumulation time for the ion signal to acquire a single mass spectrum record was set to 0.2 s. Tandem mass spectra were obtained by collision-induced dissociation (CID) of selected precursor ions with argon as collision gas. For CNMSI-MS experiments, desolvation and nebulization gases were turned off. Because an external high voltage supply was used for ionization, the capillary voltage was also turned off. Other parameters were the same as those for conventional ESI-MS experiments. Data acquisition and processing were performed using Masslynx 4.1 software (Waters Corp., Milford, MA, USA). All experiments were carried out in triplicate or more in an air-conditioned room with constant temperature and humidity.

Results and Discussion

Characterization of CNTs Paper

CNTs sheet was chosen as a solid substrate CNMSI-MS emitter for its various structurally dependent electronic properties and for its ability to transfer charge at relatively low voltages due to the high aspect ratios and nanometer-sized tips. After processing, CNTs were fabricated in the form of a film, i.e., CNTs sheet (Figure 2a). The morphology and structure of the as-prepared CNTs sheet was characterized using scanning electron microscopy (SEM). Figure 2b depicts the SEM image of a randomly oriented CNTs sheet that entangled into disordered ropes and bundles by Van der Waals forces [32]. The individual rope size (30–60 nm) and structure of the CNTs sheet were uniform, indicating that tube dispersion in the suspension had been successful. The CNTs sheet surface had pores that averaged 100–200 nm in diameter, which made for large specific surface areas. These structures endowed the CNTs sheet with nanomaterials characteristics, such as larger surface area, smaller pore diameter, and greater conductivity [33–37]. Mesodendritic silver-covered metal was also chosen for its nanomaterial characteristics and conductive nature.

Evaluation Experiments of Conductive Nanomaterials

A series of evaluation experiments were conducted using CNMSI-MS analysis of standard compounds dissolved in different solutions. The emitter tip-to-MS inlet distance and spray voltage were investigated.

A typical CNMSI-MS spectrum is provided by analyzing the **1** and **2** sample solution (20 μg mL^{-1} in CH_2Cl_2). Sample (2 μL) was introduced to the center of the emitter. A potential of 1.5 to 3.5 kV was then applied to obtain a quality spectrum (data shown in Figure 3a and b). The protonated molecules ($[M + H]^+$ at *m/z* 404 and 250 for **1** and **2**, respectively) are clearly observed with no interfering background or fragment ions. No signal was observed in ESI-MS for the two analytes (Figure 3c). In addition, the CNMSI-MS spectra are provided by analyzing the **3-12** sample solution (20 μg mL-1 in CH_2Cl_2) in Supplementary Figure S23. They have similar results that relative proton adduct peak of compounds **3-12** could also be clearly found. Subsequently, the relationship between the emitter tip distance from the MS inlet and the intensity of the ion

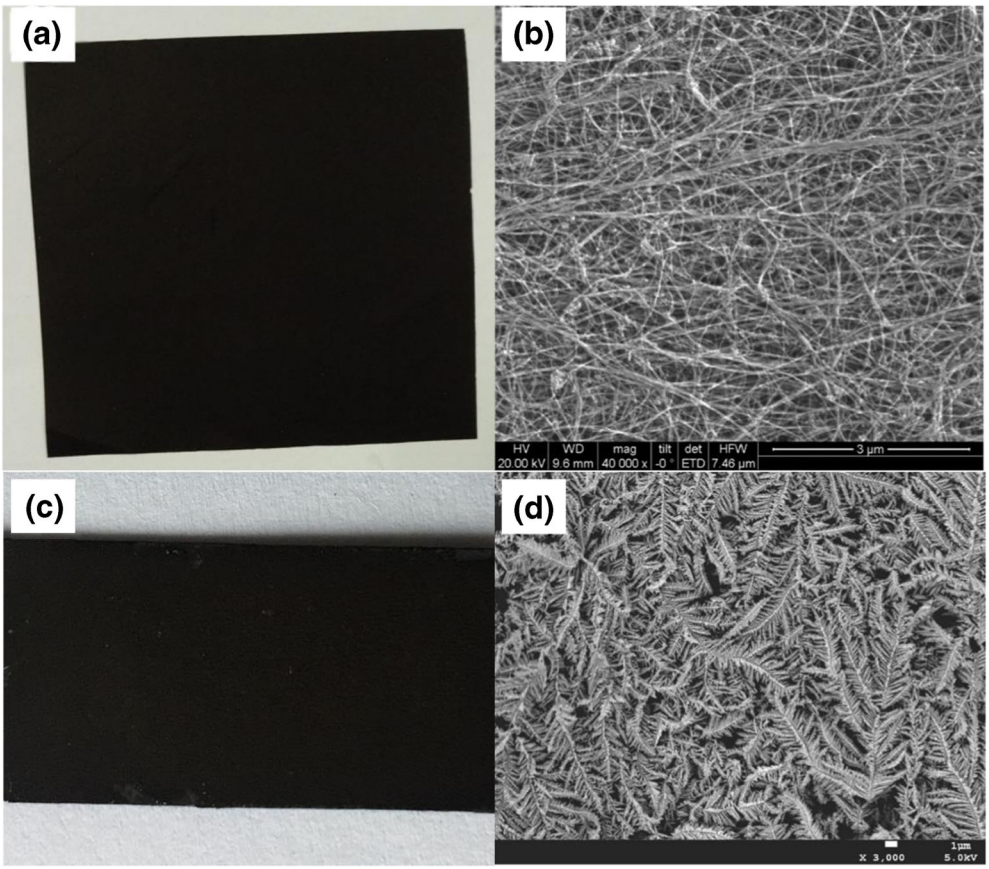

Figure 2. **(a)** The prepared CNTs sheet (cut into 10 cm × 10 cm size); **(b)** SEM image of the CNTs sheet surface; **(c)** prepared mesodendritic silver-covered zinc (width 15 mm × height 0.25 mm); **(d)** SEM image of the mesodendritic silver

signals, corresponding to ionization efficiency, was investigated. Using a high voltage set to 3.0 kV, the distance was adjusted from 2.0 to 11.0 mm in 1.0 mm steps to record different ion intensities, shown in Figure 4. Ion intensities increased as a function of distance from 2.0 to 6.0 mm, reaching the highest intensities at 6.0 and 8.0 mm for **1** (*m/z* 404) and **2** (*m/z* 250), respectively. When the distance went above 8.0 mm, ion intensities sharply reduced. It is known that when the distance of ESI emitter increases, ion transfer efficiency falls, leading to decreased ion intensities. However, when at a relatively close distance, electric fields at the tip of the emitter would become high enough to produce types of ions seen from atmospheric pressure chemical ionization (APCI, Supplementary Figure S1). Thus, CNMSI-MS ionization performance is limited by the background peaks generated through the APCI effect. The competition between generating APCI types of ions and analyte ions is presumably the main reason that ion intensities change between 2.0 and 6.0 mm.

In addition, the ionization efficiency of CNMSI-MS at different spray voltages was investigated. Filter paper, copper sheet, and mesodendritic silver-covered metal triangles of the same size were also evaluated under the same conditions. The distance between the tip of the emitter and the MS inlet was set to 6.0 mm, and the voltage was adjusted in the range of 1.5 to 3.5 kV in 0.5 kV increments to record differences in ion intensities. As shown in Figure 5a (for **2**) and Figure 5b (for **1**), the CNMSI-MS (on CNTs and mesodendritic silver-covered metal) signal intensity of both analytes first showed a slow increase (1.5–2.5 kV) followed by a more rapid increase (2.5–3.5 kV). However, signal intensity of PSI-MS showed only slight increases over the entire 1.5–3.5 kV spray voltage range. Not surprisingly, almost no signal was observed for the two analytes on the copper sheet emitter, in agreement with the result of the same analytes in solution obtained by conventional ESI-MS (Figure 3c). Notably, the signal of CNMSI-MS is approximately 10 times higher than that of PSI-MS in terms of ion intensity, indicating the superior ionization efficiency of this CNMSI-MS method of analyzing chemicals in nonpolar solvents.

A variety of other compounds (**3**–**12**) in pure solvents (including methanol, *n*-hexane, and CH_2Cl_2) have been analyzed by conventional ESI-MS and CNMSI-MS. In ESI-MS, only methanol showed some degree of ionization for the analytes. The ionization performance of nonpolar ESI is limited. Nonpolar systems, such as *n*-hexane solution, failed to ionize by conventional ESI, as only background signals were observed (Supplementary Figure S2). With the assistance of conductive nanomaterials, ionization efficiency increased dramatically, especially for those nonpolar systems. Figure 6 demonstrated the CNMSI-MS (on CNTs) results of the analyzed

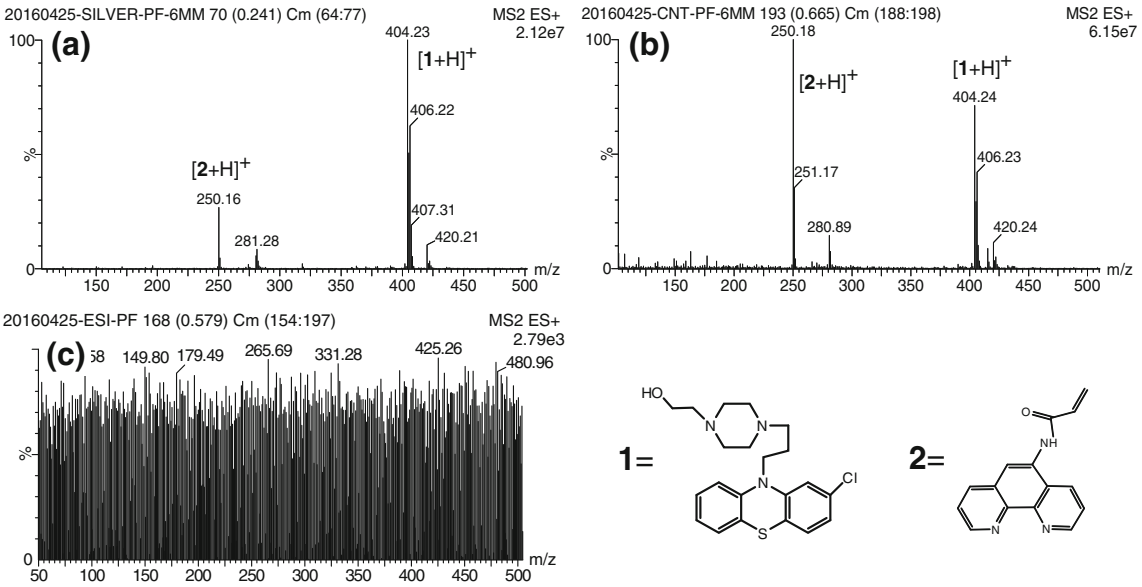

Figure 3. Mass spectrum of **1** and **2** dissolved in CH_2Cl_2 by **(a)** CNMSI-MS (on mesodendritic silver); **(b)** CNMSI-MS (on CNTs) and **(c)** conventional ESI-MS. The distance between the emitter tip and the MS inlet is 6.0 mm. The spray voltage used is 3.0 kV

compounds (**3**–**12**) in three different solvents. The TIC intensity of compounds **3**-**12** varying from 4.5% to 23.7% (RSD, n = 3) over analyses of the same sample, protonated molecular ions were found to be the most abundant species, demonstrating good reproducibility of the technique in terms of ionized species. Further identification was performed by MS/MS to confirm these compounds (Supplementary Figure S3–12). The high ionization efficiency allowed for sensitive detection of compounds dissolved in nonpolar solvents. In this study, pg level limits of detection are achieved, e.g., in n-hexane, 2 pg of compounds **3** and **10** can be detected. Compared with ESI-MS, sample ionization in CNMSI-MS showed different features. When spraying solvents of different polarities (such as methanol, n-hexane, and CH_2Cl_2), droplets are visible in the spray plume under natural illumination. As illustrated in Supplementary Video S1, polar solvent methanol presented disperse spray plume, whereas the nonpolar solvents (n-hexane and CH_2Cl_2) generated longer and more focused spray plume. More volatile solvents, such as CH_2Cl_2, have been observed to continuous form dendritic ice crystals in addition to spray, as a result of the rapid cooling of water vapor during solvent droplets vaporization (Supplementary Video S1). This is in agreement with the phenomenon reported in nonpolar PSI [20], and could explain the origin of the proton added to the analytes. Penning ionization of atmospheric water vapor might play an important role in the ionization process of CNMSI; this explains why almost all compounds were protonated and barely any sodiated and potassiated species were observed. In CNMSI-MS, nonpolar solvents tend to generate a higher response for all 10 analytes compared with polar solvents. This could be explained by the differences in dielectric constant between nonpolar and polar solvents. Nonpolar solvents commonly have low dielectric constant (ε = 9.1, 1.9, and 2.0 for dichloromethane, hexane, and cyclohexane, respectively), which means lower ability to stabilize charges than polar solvents (ε = 32.7 and 37.5 for methanol and acetonitrile, respectively), which made the generated droplets poorly charged and reduced the charge repulsion between droplets, thus facilitate the formation of focused and longer spray plume. Supplementary Video S1 agrees with the assumption, as polar solvent methanol showed disperse spray plume, whereas the nonpolar solvents (n-hexane and CH_2Cl_2) generated longer and more focused spray plume. In addition to Penning ionization, field desorption from the CNTs sheet nano-structures (i.e., CNTs) is also presumed to play an important role in the ionization process [38]; this explains why almost no signal was observed for the analytes on the copper sheet emitter, which is supposed to present similar Penning

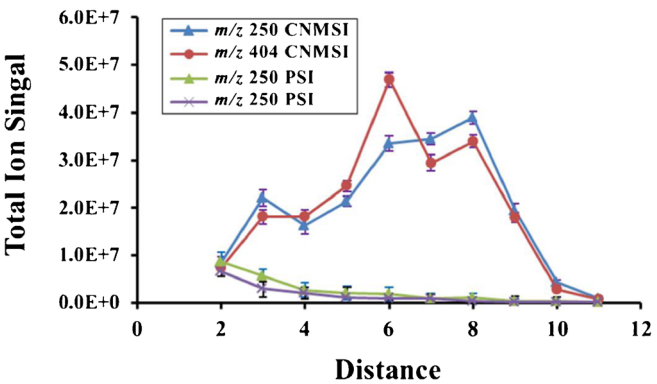

Figure 4. The impact of distance between the emitter tip of PSI and CNMSI and MS inlet on the intensities of [**1** + H]$^+$ (m/z 404) and [**2** + H]$^+$ (m/z 250) (20 μg mL^{-1} CH_2Cl_2 solutions). The spray voltage used is 3.0 kV

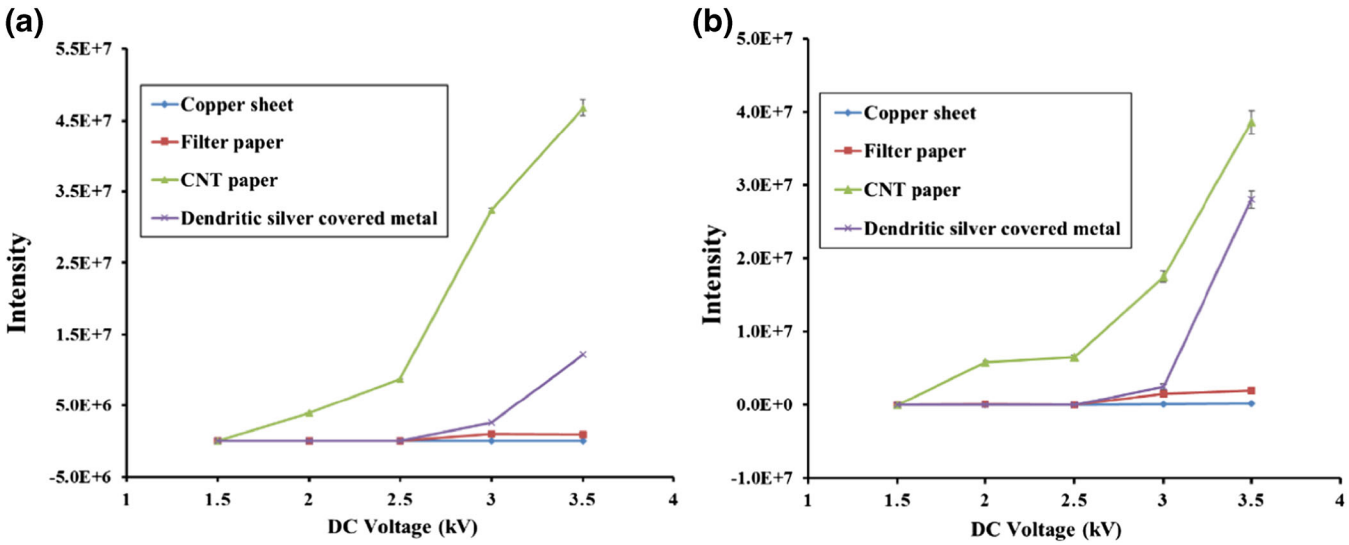

Figure 5. The impact of spray voltage on the intensities of **(a)** [**1** + H]$^+$ (*m/z* 404) and **(b)** [**2** + H]$^+$ (*m/z* 250) (20 μg mL^{-1} CH_2 Cl_2 solutions). The distance between the emitter tip and MS inlet is 6.0 mm

ionization performance with CNTs paper and mesodendritic silver-covered metal. However, the detailed ionization mechanism of CNMSI-MS is still not well known and needs further study.

The Practical Application of Low Polarity Compounds Analyzed by CNMSI-MS Methods

Nonpolar solvents are extensively used in organic synthesis and NPLC separations, and this makes desirable the ability to directly detect solution-phase samples with MS under ambient conditions. Although more polar solvents such as isopropanol, EtOAc, or chloroform were mixed with nonpolar mobile phase, the incompatibility of the mobile phase with ESI restricts the combination of NPLC with ESI-MS. Proven to have the capability to ionize nonpolar solution system while avoiding the difficulty of ESI arising from incompatible solvent choices, CNMSI-MS provided an option to NPLC-MS analysis. After racemic compounds (**14**) dissolved in hexane/*i*-PrOH (9:1, v/v) were enantio-separated by NPLC and transferred to the center of CNMSI-MS emitter (made of CNTs) by silica capillary, chiral molecules could be detected by CNMSI-MS. Without any polar assistant solvent, stable signals of [M+H]$^+$ ions from each racemic compound are clearly observed in positive ionization mode. (Figure 7, the NPLC elutes were transferred only when the UV peak was shown, otherwise the mobile phase was switched to waste by a tee valve). However, no analyte signal was found in conventional ESI-MS when analyzing the hexane/*i*-PrOH (9:1, v/v) solution of the raceme. More examples of NPLC-CNMSI-MS can be found in Supplementary

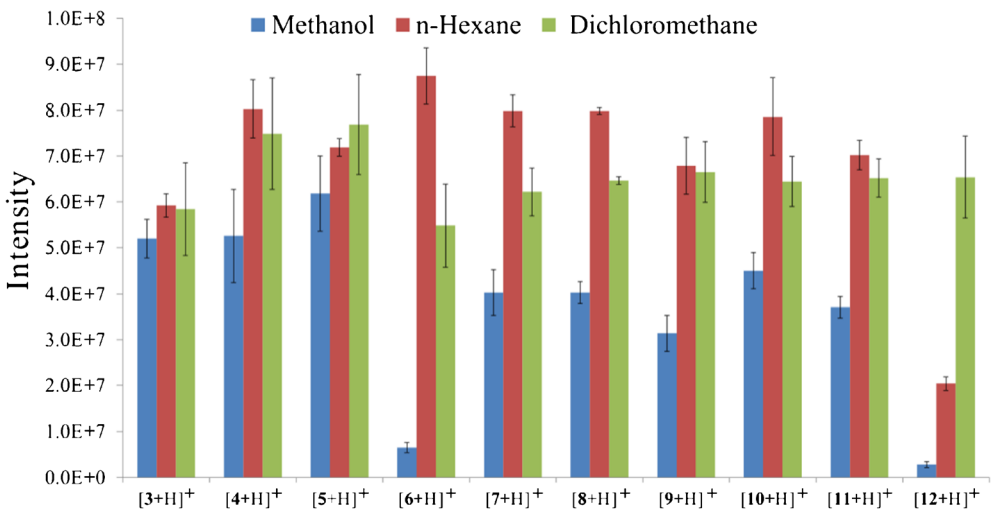

Figure 6. Effect of spray solvent on the analysis of compounds **3**-**12** by CNMSI-MS (on CNTs, *n* = 3). Concentration of each compound was 20 μg mL^{-1}

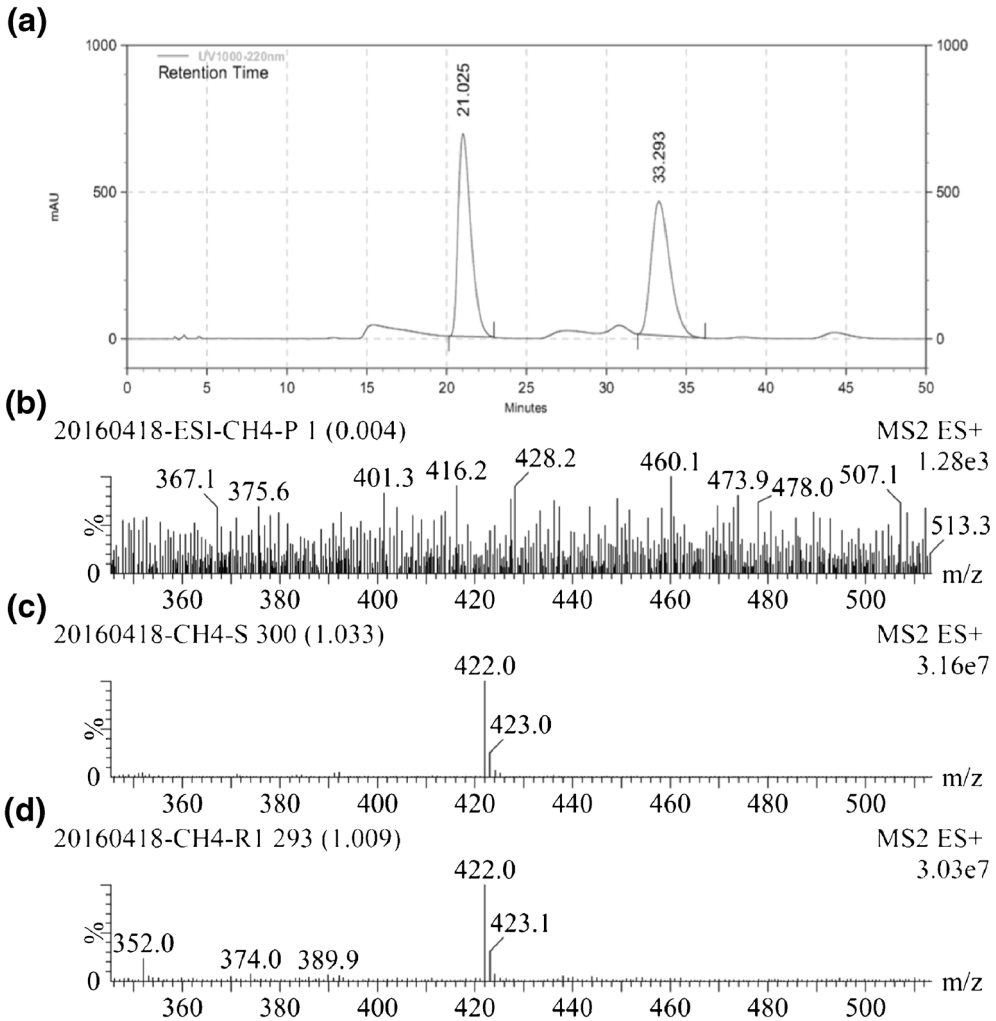

Figure 7. NPLC-UV-CNMSI-MS of N-(2-(hydroxymethyl)-1-(2-methoxyphenyl)-3-methylbut-3-en-1-yl)-P,P-diphenylphosphinic amide raceme (**14**): **(a)** UV chromatogram; **(b)** ESI-MS result of hexane/i-PrOH (9:1, v/v) solution of the raceme; **(c)** CNMSI-MS taken at 21.02 min; **(d)** 33.29 min

Figure S13 and S14. In brief, NPLC-CNMSI-MS provides a powerful tool for enantio-selective analysis of chiral compounds, especially those without UV absorption.

Conclusion

CNMSI-MS can ionize chemicals dissolved in nonpolar solvents, such as hexane, without any assistance from polar solvents. The developed ambient ionization technique expands the analytic capability of ESI-MS to the direct, online analysis of nonpolar systems, such as low polarity extracts, NPLC elutes, and synthetic mixtures. Compared with conventional PSI-MS, CNMSI-MS produces superior signals in terms of ion intensity and limit of detection, indicating the higher ionization efficiency and sensitivity of this method for analytes in nonpolar solvents. Field desorption from nano-structures within the conductive nanomaterials is presumed to be one of the key factors. Further applications of this technology are ongoing, and should broaden the analytical scope of a commercial mass spectrometer with only minor modifications.

Acknowledgments

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