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Secondary Electrospray Ionization Ion Mobility Spectrometry/Mass Spectrometry of Illicit Drugs

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A secondary electrospray ionization (SESI) method was developed as a nonradioactive ionization source for ion mobility spectrometry (IMS). This SESI method relied on the gas-phase interaction between charged particles created by electrospray ionization (ESI) and neutral gaseous sample molecules. Mass spectrometry (MS) was used as the detection method after ion mobility separation for ion identification. Preliminary investigations focussed on understanding the ionization process of SESI. The performance of ESI-IMS and SESI-IMS for illicit drug detection was evaluated by determining the analytical figures of merit. In general, SESI had a higher ionization efficiency for small volatile molecules compared with the electrospray method. The potential of developing a universal interface for both GC- and LC-MS with an addition stage of mobility separation was demonstrated.

Ambient pressure ion mobility spectrometry (IMS) has been developed as a powerful method for analysis of volatile and semivolatile compounds.[1,2] In particular, illicit drugs, explosives, and chemical warfare agents have been the major target compounds for detection by ambient pressure IMS. Ion mobility measurement for investigating gas-phase conformations of large biomolecules has been reported with low-pressure mobility instruments,[3−5] and high molecular weight compounds have also been successfully introduced into ambient pressure IMS by an electrospray ionization method.[6] Recently, a high-resolution ambient pressure ion mobility spectrometer/mass spectrometer with an electrospray ionization source was reported for gas-phase separation of multiple charged biomolecules.[7] To date, the mass range of compounds that can be analyzed by IMS has been extended to tens of kilodaltons.[8,9] Although most electrospray ionization studies have focussed on biological applications, ESI has also been used for analyzing a broad range of compounds of lower molecular weight.[10,11] Illicit drugs have been studied to understand the dependence of ion intensity on sample concentration in ESI-MS experiments.[12]

The detection of illicit drugs is one of the major areas in which IMS has been applied. Karasek, Hill, and coworkers[13] first demonstrated the potential of using IMS for drug analysis in which gas-phase heroin and cocaine ions created by a ^{63}Ni radioactive ionization source were mass-identified. Significant advances in drug detection by IMS were made by Hill's[14,15] and Lawrence's group[16−18] in the 1980s. Because of its high sensitivity, specificity, and portability, IMS has become one of the primary methods used for detecting illicit drugs. In most IMS applications, a ^{63}Ni radioactive source has been the ionization source of choice. Although it has significant advantages, the radioactivity of the ^{63}Ni source restricts handling and limits applications. A nonradioactive ionization source having response chemistries similar to that of the ^{63}Ni ionization source is highly desirable.

Because the ESI source is a nonradioactive ionization source for IMS, this investigation focuses on its use as an IMS ionization source for the detection of illicit drugs. Although ESI for mass spectrometers has been well-studied, the ionization process in the ESI-IMS[6,19] has not been investigated. Thus, one objective of this research was to investigate the ionization mechanism and its efficiency and analytical figures of merit of electrospray ionization for drug detection with IMS. Traditionally, ESI has been for the detection of analytes in liquids. Drugs, however, are commonly detected in the vapor phase as well as the liquid phase. Thus, a

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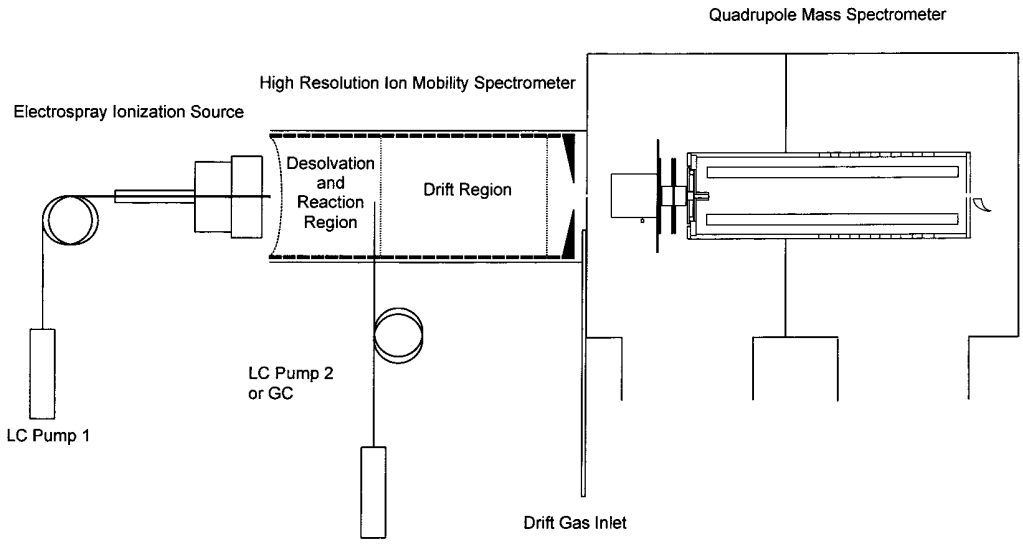

Figure 1. Schematic diagram of electrospray/secondary electrospray ionization ion-mobility spectrometry mass spectrometry.

second objective of this research was to test a novel ionization scheme, secondary electrospray ionization (SESI), which used electrosprayed solvent droplets to ionize sample molecules in the gas phase. The potential of ionizing gas-phase compounds in this manner has previously been demonstrated.[19]

EXPERIMENTAL SECTION

The schematic diagram of the apparatus used in this study is shown in Figure 1. It consisted of three parts: an electrospray ionization source, an IMS tube, and a mass spectrometer. The ionization source was a water-cooled electrospray system, which was developed at Washington State University several years ago.[6] In this design, a water-cooled jacket surrounded the spray needle assembly and water-cooled nitrogen flowed along the axis of and in contact with the spray needle. The objective of cooling the spray needle and spray was to prevent solvent evaporation inside the needle. Desolvation was accomplished by a high-temperature (250 °C) counter flow of nitrogen gas, which also served as the drift gas for the IMS tube. The flow rates of the cooling and drift gases were carefully adjusted to achieve the best desolvation. Two LC pumps (Microgradient System, BrownLee Labs, Applied Biosystems, Santa Clara, CA) were used in this experiment. LC pump no. 1 was the liquid supplier for the electrospray needle, and LC pump no. 2 was used to introduce volatile sample solutions or reagent gases into the reaction region of the IMS for the SESI experiments. In a separate experiment, a HP 5890 gas chromatograph equipped with a DB-5ms (J&W Scientific, Folsom, CA) capillary column was also used for the secondary electrospray ionization experiments. The column was 0.32 mm in inner diameter, 30 m in length, and 0.5 μm in film thickness. A meter of 1/8" copper tubing was used as the heating jacket for the GC column, which extended through the copper heating jacket and into the IMS. The heating jacket was held at 250 °C. The typical injection volume was 1 μL. The GC oven temperature was at 200 °C and column flow rate was at 1.6 mL/min. A detailed description of the IMS tube and electronics can be found in ref 6.

For the ion mobility spectrometer, a stacked ring design drift tube was constructed with a repeat distance of 9 mm, including an 8-mm stainless steel ring and a 1-mm gap. Relatively short repeat distances in this design helped create a uniform electric field in the drift region. The dimensions of the rings were machined to be 49-mm i.d. and 57-mm o.d. The total length of the desolvation region was 72 mm and that of the drift region was 130 mm. At the end of the drift tube, a novel ion extraction ring served as a defocusing electrode in front of the pinhole interface for the mass spectrometer. The function of this ring was to neutralize ions that were close to the wall and only allow those ions from the center of the tube to pass through the pinhole. The drift-gas inlet was located at the end of the drift tube near the pinhole leak. It served to disrupt the diffusion layer around the pinhole leak and to keep the leak clean and free from clogging. The pinhole leak was 40 μm in diameter and served as the barrier between the atmospheric region of the ion-mobility spectrometer and the vacuum region of the mass spectrometer. The center part of the interface was mounted on a 16-cm flange by a specially designed metal−glass seal. An electrical potential could thus be applied to the pinhole leak. On the low-pressure side of the pinhole leak, a set of lenses, designed for atmospheric pressure ionization sources, guided the ions into a quadrupole mass spectrometer (ABB Extrel, Pittsburgh, PA). Two Diffstak 160/700 diffusion pumps (Edwards High Vacuum Inc., Grand Island, NY) were closely mounted to the upper chamber in order to achieve the highest pumping efficiency. Two ion gauges (Granville-Phillips, model 274006, Boulder, Colorado) were installed on the internal and external chambers for pressure measurements.

The mass spectrometer was an Extrel C50-Q equipped with a quadrupole mass filter that was 20 cm in length and 0.95 cm in diameter. For mobility studies, the output signal was connected to a Keithley 427 amplifier (Keithley Instruments, Cleveland, OH) instead of the preamp from the original mass spectrometer electronics. The amplified signal was sent to the data acquisition system constructed at WSU. A detailed description of the IMS control and the data acquisition system can be found in reference 6.

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The electrospray ionization source was normally operated with a potential difference of 4000 V between the needle tip and the target screen, e.g., 5500 V on the screen and 9500 V on the needle. For the direct electrospray. experiments, the electrospray solvent by which the sample was introduced into the spray needle was 49.5% water, 49.5% methanol, and 1% acetic acid. Electrospray solvent flow through the needle was controlled at 5 μL/min. The cooling gas flow was controlled at 630 mL/min, and the counter-flow drift gas was maintained at 800 mL/min. The temperature of the electrospray needle was held at 40 °C. For the SESI experiments, the samples were introduced into the high-temperature reaction region by LC pump no. 2, where they were evaporated and ionized. In general, the samples were introduced into the reaction region with the same flow rate and solvent composition as used for the electrospray ionization experiment.

The electric field was maintained at 280 V/cm throughout the desolvation region and the ion-drift region of the IMS tube. The electrical lenses in vacuum consisted of 6 elements (the pinhole leak served as the first lens) with potentials of +7.9, −4.9, −20.1, −7.4, −99.9, −23.2 V in order of the ion-migration direction. The quadrupole mass filter operated at a bias potential of −5.2 V and a frequency of 1.2 MHz. The electron multiplier was operated at a potential of 1.75 KV and −4 KV for the collision dynode. Pressures were measured to be 2.2×10^{-4} Torr in the ion optical region and 1.5×10^{-5} Torr in the detector region.

There were three operational modes used in IMS-MS experiments. First, by leaving both ion gates of the IMS open, the mass spectrometer could be operated in normal scan mode to obtain ESI-MS like mass spectra of ions formed in the desolvation region of the IMS tube. Second, by leaving the second gate (which was closest to the mass spectrometer) opened, by pulsing the first gate to permit a small portion of ions into the drift region, and by turning the DC voltage of the mass analyzer, off, nonmass-selective ion mobility spectra were obtained. In this mode, the quadrupole MS was used as a high-pass filter that allowed a broad m/z range of ions to reach the detector. It should be noted here that even though a broad spectrum of ions can pass through the mass filter, transmission efficiency decreased as a function of ion mass. The third mode of operation was similar to the second, except that the mass spectrometer was operated in a single ion monitoring (SIM) mode. In this manner, mass-selective ion mobility spectra were obtained. In addition, the SIM mode was used to obtain mobility spectra for quantitative studies.

The electrospray solvents including methanol, water, and acetic acid were reagent-grade chemicals obtained from JT Baker (Phillipsburg, NJ). Drug standards: heroin hydrochloride, lysergic acid diethylamide (LSD), morphine. sulfate, phencyclidine hydrochloride (PCP), and tetrahydrocannabinol (THC) were purchased from Supelco (Bellefonte, PA) and amphetamine, methamphetamine, and cocaine from RBI (Natick, MA). Unless specified, samples were prepared at a concentration of ~0.01 mg/mL in methanol and water (1:1) with 1% acetic acid (v/v).

RESULTS AND DISCUSSION

The behavior of eight representative illicit drugs (heroin, morphine, cocaine, amphetamine, methamphetamine, THC, LSD, and PCP) was evaluated in the IMS/MS system. These analytes were ionized either by the electrospray ionization method or the secondary electrospray ionization method. First, all of the test compounds were studied by ESI-IMS where final forms of electrosprayed ions were identified by mass spectrometry (Table 1). Ko values of test compounds were determined. Then, a comparison of the ESI and SESI processes was performed with respect to ion identification, ionization efficiency, and analytical figures of merit.

Table 1. Product Ions Illicit Drugs Created by ESI and SESI

compounds	MW	m/z	ion identity	Ko (cm^2/V s)
amphetamine	135	136	$[M + H]^+$	1.665
methamphetamine	149	150	$[M + H]^+$	1.630
PCP	243	84	$[M - C_{12}H_{16} + H]^+$	2.010
		244	$[M + H]^+$	1.255
morphine	285	268	$[M - H_2O + H]^+$	1.254
		286	$[M + H]^+$	1.214
		302	$[M + O + H]^+$	1.195
		308	$[M + Na]^+$	1.164
cocaine	303	304	$[M + H]^+$	1.150
THC	314	315	$[M + H]^+$	1.040
LSD	323	324	$[M + H]^+$	1.070
		346	$[M + Na]^+$	1.028
heroin	369	310	$[M - CH_3COOH + H]^+$	1.135
		370	$[M + H]^+$	1.037

As a gentle ionization method, most ions created by this electrospray ionization source were simply protonated molecular ions. All of the drugs tested generated singly charged ions in the ESI source. However, some compounds decomposed under acidic and high-temperature conditions. Figure 2a shows ion mobility spectra of PCP obtained under electrospray conditions. In the lower spectrum, four major peaks were identified. The first and second peaks were identified as the electrospray solvents: protonated water ($m/z = 19$) and methyl acetate ($m/z = 75$). Peaks at drift times of 11.7 and 18.6 ms corresponded to product ions of PCP. The 11.7-ms peak was a decomposition product ion from the cleavage between nitrogen and the tertiary carbon; the peak at 18.6 ms was simply the protonated molecular ion. The peak at 11.7 ms tailed until 18.6 ms indicating that decomposition was occurring in the drift region of the ion-mobility spectrometer. Ion-mobility spectra representing these two species monitored in the SIM mode are shown in the middle and upper spectra in Figure 2a. Well-defined mobility peaks were observed in the SIM mode, which indicated both of these ions formed before entering the drift region.

For heroin, shown in Figure 2b, except for some solvent-related clusters appearing in the short drift time region, two major peaks at $m/z = 310$ and 370 were detected corresponding to $[M - CH_3COOH + H]^+$ and $[M + H]^+$, respectively. Similarly, loss of 59 has been commonly observed both in EI and ^{63}Ni ionization sources.[13] Since these two peaks were well defined in the ion mobility spectra, decomposition occurred either in the solution-phase or desolvation region of the IMS tube. The ion mobility spectra for morphine, shown in Figure 2c, was complicated with the presence of a sodium adduct ion and the oxidized form of the molecule. The oxidized form of the ion has been reported as being formed in the corona discharge region around the electrospray needle.[20] This product ion can be avoided by adjusting the voltage

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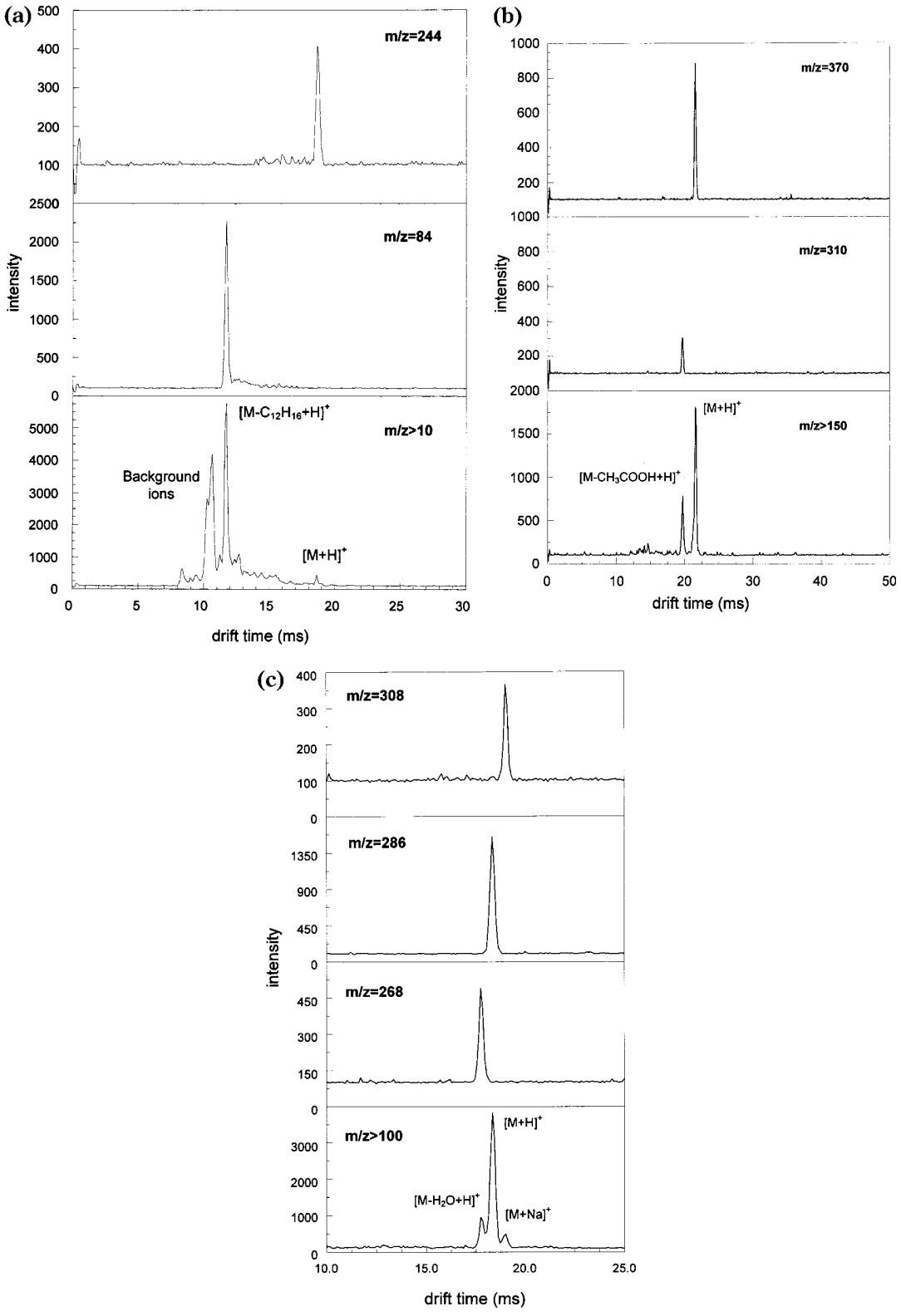

Figure 2. (a) Ion mobility spectra of PCP· with mass identification. Top: mass selective detection of protonated PCP at $m/z = 244$. Middle: mass selective detection of $m/z = 84$, a decomposition product. Bottom: ion-mobility spectrum of PCP related and background ions without mass-selective detection. (b) Ion-mobility spectra of heroin with mass identification. Top: mass-selective detection of $m/z = 370$. Middle: mass selective detection of $m/z = 310$, a decomposition product. Bottom: ion-mobility spectrum of heroin-related and background ions without mass-selective detection. (c) Ion-mobility spectra of morphine with mass identification. Top: mass-selective detection of $m/z = 308$, the sodium adduct. Upper middle: mass-selective detection of $m/z = 286$. Lower middle: mass-selective detection of $m/z = 268$, a decomposition product. Bottom: ion-mobility spectrum of morphine-related ions after elimination of background ions.

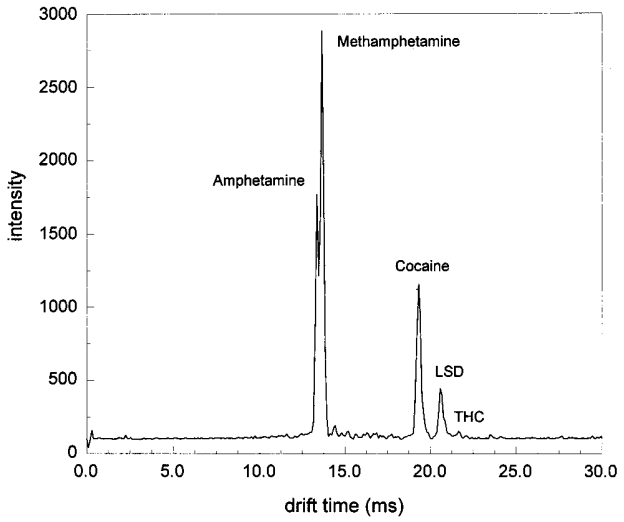

Figure 3. Ion mobility spectrum of a drug mixture ionized by an ESI source. A mixture of amphetamine, methamphetamine, cocaine, LSD, THC was prepared at a concentration of 11.5−23 ppm in methanol and water (1:1 v/v) with 1% acetic acid addition. Sample was introduced at a flow rate of 5 μL/min. The ion-mobility spectrometer was operated at a total sampling time of 51 ms and a gate pulse width of 0.2 ms.

applied between the electrospray needle and the target screen. Even though the spectrometer was operated below its maximal resolution,[7] ions that differed by a water molecule or sodium ion were well resolved from the protonated molecular ion peak.

The reduced ion mobilities for all of the drugs tested are summarized in Table 1. The molecular weights of the drugs ranged from 135 to 369. None formed multiply charged ions under the experimental conditions. In addition to the decomposition cases discussed above, formation of sodium adducts for drugs of relatively higher molecular weight were common. In the mass range of protonated drugs, reduced mobility has been reported to be inversely proportional to ion mass.[2] One significant exception to this rule found in these experiments was for THC. THC had a molecular weight of 314, which is smaller than that of LSD (323). However, its reduced mobility was measured to be lower than that of LSD. According to the Ko, the calculated collisional cross section for THC and LSD was 153 and 148 Å^2, respectively. A discussion of the relationship between gas-phase ion structure and reduced ion mobility can be found in ref 2. From this data, it was clear that the strict relation between mass and mobility is incorrect and must be used with caution.

Figure 3 demonstrated the ion mobility spectrometric separation of a drug mixture that contained amphetamine, methamphetamine, cocaine, LSD, and THC. As discussed above, THC had a lower Ko value compared with LSD and therefore arrived after LSD. In the mixture, amphetamine, methamphetamine, cocaine, and LSD were at the same concentration, 11.5 μg/mL. The response of the THC peak was weaker compared with the others and so was used at twice the concentration as the other analytes. The ionization efficiency of compounds in the electrospray ionization process depends on their proton affinities, and THC has a lower proton affinity compared with those of other components in the tested mixture. The difference in response intensity among these compounds (Figure 3) was a result of charge competition in the electrosprayed droplets. Figure 3 demonstrated a fast separation of drugs with resolution comparable to that of traditional HPLC methods.[21]

One interesting result occurred when neutral acetic acid was introduced into the desolvation region via LC pump no. 2. Figure 4a shows the ion-mobility spectra of electrospray solvents before and after adding acetic acid in the reaction region. The left spectrum showed three major peaks resulting from the electrospray ionization of a mixture of methanol, water, and acetic acid (49.5:49.5:1 v/v). They were mass identified as $[H_2O + H]^+$, $[CH_3COOCH_3 + H]^+$, and some clusters of these ions. Under good desolvation conditions, the methyl acetate was always the most dominant peak created by this ESI source. The right spectrum shows the product ions when acetic acid was introduced into the reaction region. The methyl acetate peak was enhanced while the $[H_2O + H]^+$ ion peak was reduced in intensity. This result suggested that the esterification reaction occurred during the desolvation process in the high-temperature environment.

When the analytes were added to the electrospray solution and a gas-phase acetic acid modifier was, introduced in the reaction region, similar profiles of tracing A and B (Figure 4b) indicated a similar ionization process with or without the addition of gaseous acetic acid. However, the total ion intensity increased about 80% when acetic acid was added. The reaction process of this gas-phase modification can be explained by the change in acid−base equilibrium in the droplets. Under the guidance of the electric field, the analytes and solvents in the electrosprayed droplets drifted through the desolvation region in contact with the acetic acid vapor. When acetic acid molecules collided with the charged droplets, they dissolved into the droplets and ionized. As a result, the pH in each droplet was lowered, similar to the effect observed for solvent evaporation,[22] increasing the efficiency of ionization.

Adding acetic acid into the reaction region of the IMS provided an opportunity to modify the ionization process prior to mobility and mass analysis. For separations that require high pH chromatographic conditions, the acid modifier introduced from the gas phase may improve electrospray ionization efficiency.

For the investigation of SESI, the ESI source was operated under the same conditions as described above. As shown in Figure 1, the LC pump no. 1 delivered 5 μL/min of solvent for creating charged droplets and reactant ions. LC pump no. 2 pumped sample solution into the reaction region at the same flow rate. The resulting ion-mobility spectrum (Figure 5a) was similar to that which resulted from direct electrospray ionization (Figure 3). There are two mechanisms that can be proposed for the secondary ionization process. First is the gas-phase interaction between droplets and analytes. Similar to the case of acetic acid modification, analyte molecules can be dissolved into the droplets when they contact the charged droplets in the desolvation region of the spectrometer. Since the electrospray ionization process produces an abundance of charge at the droplet surface, interaction of the analyte vapor with the charged droplet surface can produce a more efficient ionization process than can ordinary electrospray ionization.[22]

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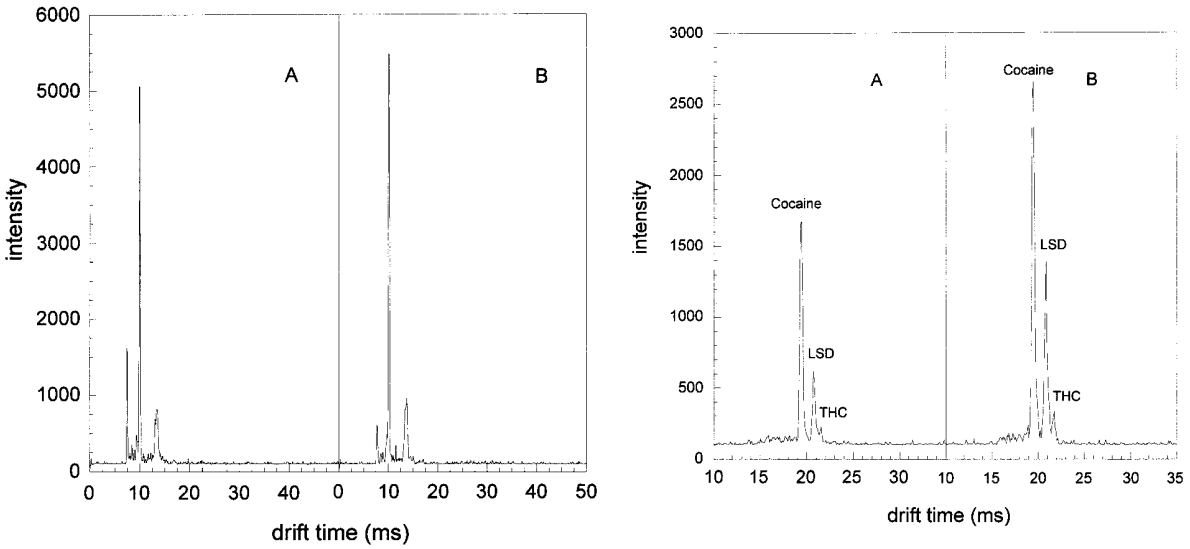

Figure 4. (a) Ion-mobility spectra of electrospray solvents (A) and that with addition of acetic acid from the gas phase (B). (b) Ion-mobility spectra of a drug mixture without vapor-phase acetic acid (A) and that with the addition of vapor-phase acetic acid (B). Mass-selective detection of $m/z > 250$. Detected ion intensity of the drug mixture was improved by 80% after addition of acetic acid in the gas phase.

The second process of secondary ionization may simply be the gas-phase ion-molecular reactions between the neutral analyte and the electrospray-produced reactant ions. At a desolvation region temperature of 250 °C, well-desolvated solvent ions, as shown in Figure 4a, will lose protons when they collide with analytes that have higher proton affinities. Figure 5a shows SESI spectra of the same drug mixture as that used to obtain Figure 3.

Higher ionization efficiency for these drugs was observed in the SESI source. However, the relative response intensity of each compound in the mixture was similar in ESI and SESI. The mass spectrum of the mixture is shown in Figure 5b. The relative peak intensities of each individual analyte were similar to that observed in the ion-mobility spectrum, and the identities were the same as those for the direct ESI source.

As shown in Figure 6, depending on the analytes, a plateau was reached at a concentration in the 10−100 μg/mL range. Note that a similar upper limit of the dynamic range was achieved for both ESI and SESI method, indicating that, in both processes, a finite and similar quantity of charge was produced for the ionization process. In the case of ESI, the relationship between sample concentration and signal intensity has been extensively studied. The upper limit of the dynamic range has been explained by competition for an insufficient amount of charge between analytes and background electrolytes.[23,24] On the other hand, surface-area-limited analytes can escape from charge droplets.[25] In this study, the upper limit of the dynamic range of cocaine and morphine by ESI-IMS was about 100 μg/mL. This is one order of magnitude higher than that obtained by an ordinary ESI-MS experiment.[11] This extension of the upper limit may have been due to significant proton-transfer reactions among analytes, charged droplets, and background ions in the high-temperature (250 °C) reaction region. As demonstrated in ref 26,[26] increasing the analyte concentration caused the nebulizer current to increase, but the detected analyte current reached a plateau at 10^{-5} M. Analyte molecules at the surface of droplets were ionized. Compared with ordinary ESI-MS, in the ESI-IMS instrument neutral analytes released to the vapor state have more time to interact with charged droplets and other solvent-related reactant ions. Thus, gas-phase proton- and charge-transfer reactions can play a more important role in these experiments.

In ESI-IMS experiments, the detected ion population was observed to increase under higher desolvation temperature conditions (Table 2). Increasing the desolvation temperature, of course, increased the solvent evaporation rate. It has been shown that a higher evaporation rate will increase the number of charges on multiply charged proteins.[22] But the effect on ion intensity has not been reported. One explanation of this phenomenon is that rapid evaporation of the solvent more efficiently converts the charged droplets into the gas-phase ions before loss of charge by neutralization of the droplets on the instrument surfaces occurs.

Figure 7 shows ion-mobility spectra of amphetamine taken at two concentrations in the SESI source. At the lower concentration, solvent-cluster ions and $[M + H]^+$ of amphetamine were observed. When the amphetamine concentration was increased, four more product-ion peaks were observed. These ion species were identified as cluster ions associated with amphetamine, acetic acid, and methanol molecules. The upper limit of the dynamic range was established by the formation of these cluster ions in the reaction region. The reproducibility of the method was determined to be ±10% RSD.

SESI-IMS can also be used after gas chromatography (GC). Figure 8 shows SESI ion mobility spectra after the GC separation of a cocaine sample that contained an impurity. Ion-mobility spectra A, B, and C were IMS spectra taken in order of GC elution time. In spectrum A, the first peak, at a drift time of about 11 ms, was an ion related to the electrospray solvent. The second peak was an impurity in the cocaine sample. In spectrum B, cocaine

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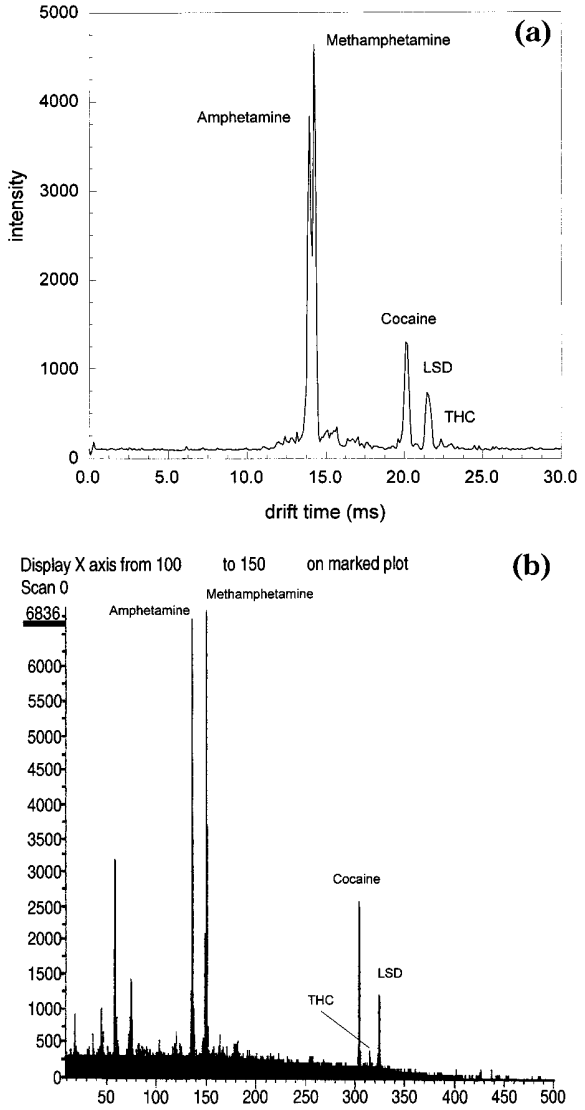

Figure 5. (a) Ion-mobility spectrum of a drug mixture ionized by an SESI source. Under the same operation conditions shown in Figure 3A, the drug mixture was introduced into the spectrometer from gas phase. (b) Mass spectrum of the drug mixture (same as shown in Figure 5a) ionized by SESI.

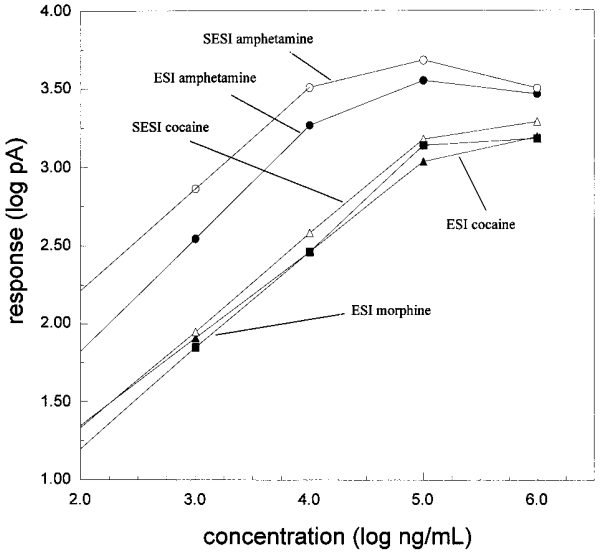

Figure 6. Dynamic response range of amphetamine, cocaine, and morphine in ESI- and SESI-HRIMS/MS. Plateau was reached at a concentration of 10−100 μg/mL.

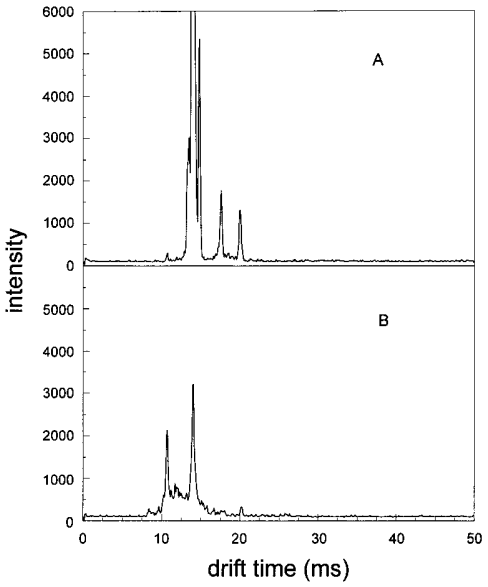

Figure 7. Product ions of amphetamine in the SESI source with different sample concentrations. (A) 1000 μg/mL; (B) 1 μg/mL. Clusters form at a high sample concentration limited dynamic response range in the SESI source.

Table 2. Charge Detected in Single Ion Mobility Spectrum

drift tube temp (°C)	detected charge (10^{-4} C)
110	8.49
150	11.6
200	12.2
250	12.9

and the impurity co-eluted. In spectrum C, only one peak, the cocaine-related peak, was observed. As described in the Experimental Section, the GC was not operated at the optimal conditions for chromatographic separation in order to demonstrate the additional separating power obtained when using IMS after chromatography. In addition, successful ionization of vapor-phase analytes after a GC separation enabled the IMS to be used as a universal mass spectrometry interface for both GC and HPLC. Note, however, that Figure 8 was obtained on a different instrument[19] without mass identification.

As reported by Kebarle and coworkers,[23] detected ion intensity did not correlate well with the droplet current. Although droplet current increased, the ion intensity remained the same or even decreased at higher sample flow rates. This phenomenon was rationalized as an increase in droplet size under high-flow-rate conditions. Figure 9 showed ion-mobility spectra of cocaine under different sample flow rates using the SESI source. The sample solution was continuously introduced into the SESI source at a concentration of 1 μg/mL. By increasing the sample flow rate from 5 to 20 μL/min, the signal intensity increased 110%. Thus, the SESI process did not rely on initial droplet size created by the ESI source. Increasing sample flow rate increased ion intensity

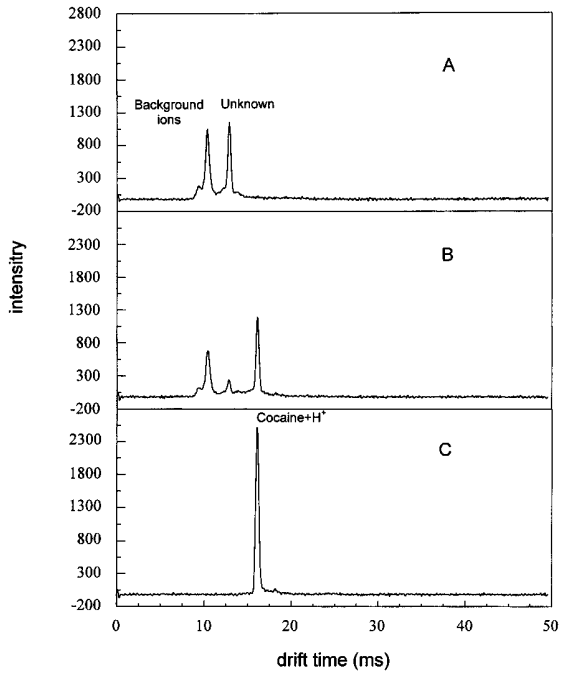

Figure 8. Ion-mobility spectra of cocaine by SESI-IMS after GC separation. Spectra A, B, and C are in order of GC elution time.

by increasing the total amount of analyte in the SESI source.

In summary, ESI response was enhanced when acetic acid vapor was added to the reaction region presumably due to lowering the pH in the droplets. As the acetic acid is volatilized and swept back to the source of the spray, where the droplets are largest, it can be adsorbed by the droplet and lower the pH. While we have not characterized the system completely and this explanation of increased electrospray ionization efficiency is therefore somewhat speculative, it does seem to be a reasonable explanation of the enhanced response that was observed. With respect to the SESI, both gas-phase and liquid-phase ionization may be possible. Nevertheless, the approach of using secondary electrospray ionization is novel and appealing as a practical, alternative ion source for radioactive sources.

CONCLUSIONS

Illicit drugs were ionized and analyzed by ESI/SESI-IMS-MS. The SESI source was developed by utilizing interactions between electrosprayed charged droplets and gas-phase analytes in the reaction region of the IMS tube. Our initial studies comparing ESI with SESI indicated that SESI might be a more sensitive

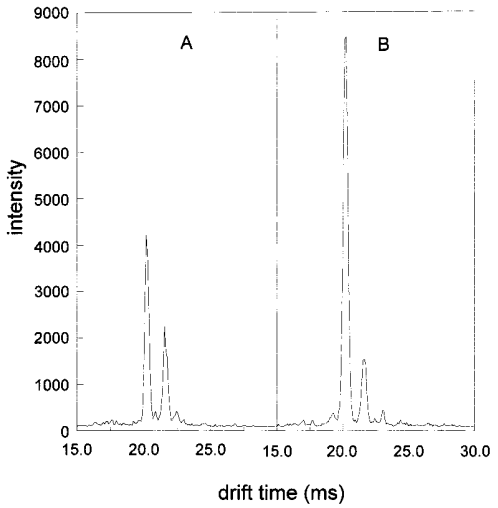

Figure 9. Ion-mobility spectra of cocaine with different sample flow rates with a secondary electrospray ionization source. (A) 5 μL/min; (B) 20 μL/min. Higher ion intensity was detected at higher sample flow rate.

ionization technique than ESI. More investigations are needed. Preliminary investigations of the ionization process demonstrated that gas-phase proton- and charge-transfer reactions play an important role in both ESI and SESI. Employing a mass spectrometer as a detection and identification method, both qualitative and quantitative data were obtained in a single experiment. The SESI ionization source can be used instead of a conventional radioactive ionization source for IMS. In addition, this study opened a new field of multiple interfacing capability of ESI-IMS, i.e., either by direct ionization of a sample in solution by ESI or by indirect ionization of a sample vapor by SESI. The ESI/SESI-IMS shows promise as a interface for both GC- and LC-MS experiments.

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