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Chiral analysis of amphetamine-type stimulants using reversed-polarity capillary electrophoresis/positive ion electrospray ionization tandem mass spectrometry

Reversed-polarity (RP) capillary electrophoresis/positive ion electrospray ionization mass spectrometry (CE-ESI+ MS) and tandem mass spectrometry (MS/MS) were utilized for simultaneous chiral separation of nine amphetamine-type stimulants (ATS) (*dl*-norephedrine, *dl*-norpseudoephedrine, *dl*-ephedrine, *dl*-pseudoephedrine, *dl*-amphetamine, *dl*-methamphetamine, *dl*-methylenedioxyamphetamine, *dl*-methylenedioxymethamphetamine, and *dl*-methylenedioxyethylamphetamine). Using highly sulfated γ-cyclodextrin (SU(XIII)-γ-CD) as a chiral selector, the nine ATS were completely separated within 50 min. The migrated ATS-CD complex was dissociated at the ESI interface, and only ATS molecules went into the MS detector so that all 18 individual enantiomers were identified by their mass spectra. The detection limit of MS/MS was 10 times more sensitive than those for single MS. Seized *d*-methamphetamine hydrochloride samples dissolved at high concentration (20 mg/mL) were analyzed. Impurities originating in the precursor such as *l*-ephedrine and *d*-pseudoephedrine were detected and identified by tandem mass spectra.

Keywords: Amphetamine-type stimulants / Chiral separation / Positive ion electrospray ionization / Reversed-polarity capillary electrophoresis / Sulfated cyclodextrin DOI 10.1002/elps.200305431

1 Introduction

Drug abuse is a serious problem in the world, and different types of drugs are used in different countries. The enantioselective determination of amphetamine-type stimulants (ATS) has an important role in identifying illicit drugs because of their medicinal effects and legal regulations. For example, in Japan, different enantiomers of 2-amino-1-phenylpropane-1-ol are controlled by different laws. In the United States, only *d*-norpseudoephedrine (NpEP) is monitored as a controlled substance present in Khat samples. In addition, chiral information on ATS is useful and essential for identifying the precursor, the synthetic pathway, and the intrinsic characteristics of seized drugs. Recently, the seized methamphetamine (MA) samples have contained not only the *d*-isomer but also *dl*-, *l*-, or a mixture of *d*- and *l*- isomers in Japan and the United States [1].

GC(-MS) and HPLC(-MS) have been used for the separation of optical isomers of phenethylamines [2–7]. There are some limitations of GC and HPLC for simultaneous chiral analysis of ATS. In the case of salt samples, such as hydrochloride salt of MA, extraction of the compounds with proper organic solvents under alkaline conditions may be required prior to GC analysis. Derivatizations with chiral reagents are often needed before GC or HPLC analysis. Chiral GC and HPLC columns are commercially available, though those columns are usually specific for a class of compounds and expensive. HPLC with chiral stationary phase suffers from low theoretical plates, which can result in poor resolution. There is no report describing full and simultaneous enantioseparation of racemic ephedrine (EP) and pseudoephedrine (pEP) or racemic norephdrine (NEP) and NpEP using HPLC or LC-MS.

Capillary electrophoresis (CE) is one of the powerful techniques for separating the enantiomers and can be applied to ATS separation [8–16]. We had reported the simultaneous chiral separation of 9 ATS, *dl*-NEP, *dl*-NpEP, *dl*-EP, *dl*-pEP, *dl*-amphetamine (AM), *dl*- MA, *dl*-methylenediox-

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Abbreviations: AM, amphetamine; **ATS,** amphetamine-type stimulants; **EP**, ephedrine; **IS**, internal standard; **MA**, methamphetamine; **MDA**, methylenedioxyamphetamine; **MDEA**, methylenedioxyethylamphetamine; **MDMA**, methylenedioxymethamphetpseudoephedrine; **RP**, reversed-polarity; **SU(XIII)-γ-CD**, highly sulfated γ-cyclodextrin

yamphetamine (MDA), *dl*-methylenedioxymethamphetamine (MDMA) and *dl*-methylenedioxyethylamphetamine (MDEA), by reversed-polarity (RP) CE with a UV detector using highly sulfated γ-cyclodextrin (SU(XIII)-γ-CD) as a chiral selector [1].

In criminal cases, drugs are identified by various suitable methods. The Scientific Working Group for Analysis of Seized Drugs (SWGDRUG) recommended minimum standards for forensic drug identification [17]. According to the SWGDRUG recommendations, analytical methods are grouped into three categories (Categories A, B and C) based on their principle and discriminating power. The discriminating power increases from Category C to A. CE is classified in the second Category B and another analytical method from Category A is required to identify the drug; otherwise, two more analytical methods from Category B or C are required to identify the drugs. Practically, modern forensic laboratories are required to use the method classified in Category A, which provides structural information of analytes. Mass spectrometry (MS) is one of the analytical methods classified in Category A. Identification only by CE-UV would be not enough for the evidence submitted to a court. One of the ideal goals for forensic analysts is CE-MS that has high separation efficiency and high identification power. There are few reports for identification of ATS enantiomers by CE-MS. Sheppard *et al.* [18] reported the separation of racemic EP using neutral CD, but it was not adequate to identify each of the isomer. Cherkaoui *et al.* [19] performed chiral separation of some ATS with neutral CD using a partial-filling technique to avoid the introduction of nonvolatile chiral additives into the ion source and a negative effect on MS performance. The mixture of racemic AM, MA, MDA, MDMA, MDEA, and methylenedioxypropylamphetamine were well enantioseparated, though the enantioseparation of EP and pEP or NEP and NpEP were not reported.

In this study, we combined reversed-polarity CE with positive electrospray ionization mass spectrometry (ESI+ MS) and tandem mass spectrometry (MS/MS) for enantioselective identification of the nine ATS to identify the compounds more precisely than with CE-UV analysis [1]. In addition, this method was applied to the analysis of trace precursors in illicit methamphetamine seizures in Japan.

2 Materials and methods

2.1 Chemicals

d- and *l*-NEP hydrochlorides were obtained from Wako Pure Chemical Industries (Osaka, Japan). *dl*- and *l*-EP hydrochlorides were obtained from Fuji Chemical Industries (Toyama, Japan), *dl*-AM sulfate from Takeda Chemical Industry (Osaka, Japan), and *d*-MA hydrochloride from Dainippon Pharmaceutical (Osaka, Japan). *d*- and *l*-NpEP were synthesized from *l*- or *d*-NEP, and *dl*- and *d*-pEP were synthesized from *dl*-EP or *l*-EP [20]. *d*-AM and *dl*-MA were synthesized from *l*-NEP or *dl*-EP [21]. *dl*-MDA hydrochloride, *dl*-MDMA hydrochloride, and *dl*-MDEA hydrochloride were synthesized as previously reported [22]. *d*-Isoproterenol bitartrate was obtained from Sigma (St. Louis, MO, USA). SU(XIII)-γ-CD was supplied by Beckman Coulter (Fullerton, CA, USA). Deionized water treated with a Millipore Milli-Q System (Bedford, MA, USA) was used for preparation of all electrolytes, standards, and samples. All other chemicals used were analytical reagent grade.

2.2 Instrumentation

A CE system G1600A (Agilent Technologies, Waldbronn, Germany) was connected to a Q-Tof Hybrid Quadrupole Time of Flight Mass Spectrometer (Micromass, Manchester, UK) equipped with a CE/CEC sprayer (Micromass, Manchester, UK) and a Z-spray Nanoflow Electrospray Source Flange. A resistor installed in the voltage cable of the CE/CEC Sprayer was replaced from 3 to 33 MΩ. A registor installed in the ground wire was replaced from 33 to 200 MΩ. Since the negative high voltage was applied on the electrophoresis system, the higher resistor was set into the CE sprayer to avoid reverse current (Fig. 1b). Otherwise the ionization voltage was obviously dropped. CE separations were performed with a 50 μm ID × 375 μm OD × 56 cm fused-silica capillary (Polymicro Technologies, Phoenix, AZ, USA). The separation capillaries were conditioned before use by a 30 min flush with run buffer, 2.5 mM SU(XIII)-γ-CD aqueous solution, and were also flushed successively with 1 M formic acid and run buffer for 5 min each between injections. The CE system was operated in RP mode (cathode at the inlet and anode at the outlet) using the current program. The applied current was ramped to −10 μA for 0.5 min, held for 5 min, ramped to −20 μA for 0.5 min and held during the rest of the analysis. The temperature of the separation capillary was set at 15°C. Pressure injections with 50 mbar for 4 s of standard sample solution and 1 s 50 mbar of impurity analysis sample solution at the cathodic end of the separation capillary were used in all experiments. The other end of the separation capillary was connected to the CE/CEC sprayer equipped with a 50 μm ID × 150 μm OD × 12 cm fused-silica capillary (Polymicro Technologies) as a CE extension capillary (Fig. 1a). The extension capillary voltage (ionization voltage) was ramped manually to 4.2 kV after electrophoresis was started. A coaxial sheath liquid, consisting of ethanol/10 mM ammonium formate (1/1 v/v) was delivered by a KDS 100 syringe pump (KD Scientific,

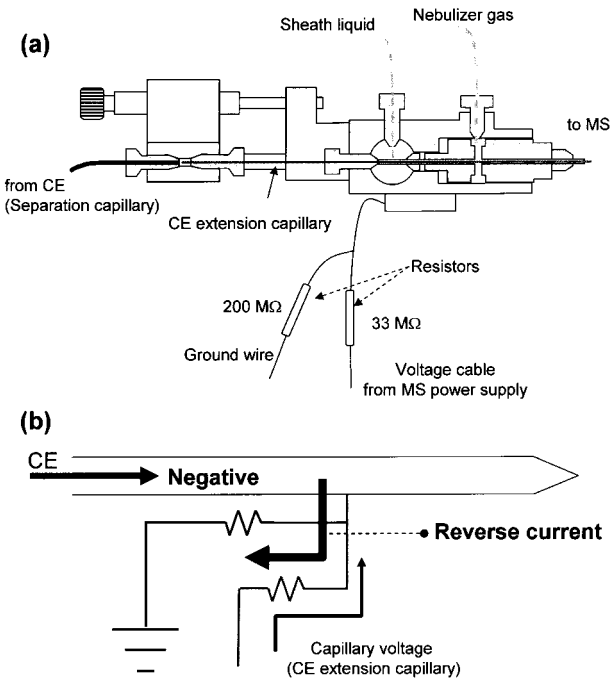

Figure 1. Schematics of the CE/CEC sprayer. (a) Diagram of the CE/CEC sprayer with CE extension capillary. Separation capillary (from CE) was connected from the left side. (b) Electrical relations between separation capillary and CE extension capillary at the CE/CEC sprayer.

PA, USA) at 1 μL/min. The nebulizer gas was nitrogen. The cone voltage was maintained at 20 V. MS and MS/MS were done in the positive ion mode. Argon was used as the collision gas at a pressure of 5 psi with a collision energy of 15 eV for MS/MS detection. The mass electropherograms were recorded and processed with a Micromass MassLynx NT Data System.

2.3 Sample preparation

Standard ATS were dissolved in deionized water at a concentration of 100 μg/mL for MS analysis and 10 μg/mL for MS/MS analysis (as individual enantiomers). Seized MA hydrochloride samples were dissolved at a high concentration of 20 mg/mL with internal standard solution (20 μg/mL of *d*-isoproterenol hydrochloride). All sample solutions were filtered through a GL Chromatodisc 13A 0.25 μm membrane (GL Science, Tokyo, Japan) before analysis.

3 Results and discussion

In CE-MS with run buffer containing nonvolatile compounds such as CD or surfactant, the polarity of the CE was selected so that the compounds did not go into the ion source [23–26]. Therefore, normal polarity (NP) is preferable for CE-MS with anionic compounds such as SU(XIII)-γ-CD because they countermigrate to the detector. The normal polarity mode in previous work [1] or other CE works [8–16] could separate one or some racemic compounds of the ATS with a short analysis time. However, simultaneous chiral separation of the nine ATS using CE needed to be run under RP mode [1].

In the RP mode, ATS-CD complexes migrated to the cathode and were detected as the complexes, anionic compounds, by UV detector. The RP mode is normally used for detecting anions, and the electrical potential for electrospray is reasonable when combined with negative electrospray ionization (ESI−). If ESI− had been combined with our CE conditions, the sampling cone of the ion source would attract a large excess of anionic CD, and the MS detector would be seriously contaminated. In addition, it would be difficult to identify ATS-CD complexes because the molecular weights of the ATS are much smaller than that of CD, and the number of sulfonyl substituents of SU(XIII)-γ-CD varied.

Therefore, we tried to apply positive electrospray ionization (ESI+) for the MS detection to solve these problems. Figure 2 shows the idea of the "RP CE-ESI+ MS". In the RP mode, anionic ATS-CD complexes migrated to the cathodic end of the separation capillary through the CE sprayer. ATS-CD complexes were sprayed straight forward to baffle at the ion source from the end of the CE sprayer supported by coaxial sheath liquid and nebulizer gas. We expected that the ATS (cationic compounds) would be drawn by the sample cone that was placed orthogonally to the CE sprayer and would be positively charged in ESI+ mode. The ATS would be dissociated from the CD complex and would go into the MS detector

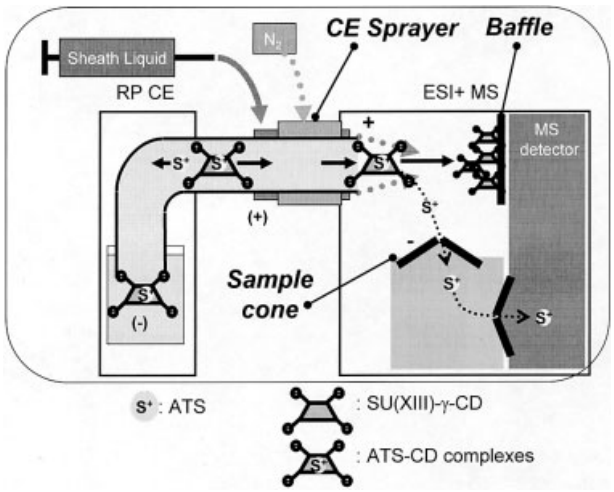

Figure 2. Schematic representation of the RP CE-ESI+ MS/MS.

alone. The dissociated or excess CD would keep going straight to the baffle and would not be introduced into the MS detector. Prior to the CE-MS experiment, we analyzed a running buffer containing SU(XIII)-γ-CD with direct infusion in the ESI+ mode. No ions related to SU(XIII)-γ-CD (~2350 M_r) were detected, implying that the CDs were not introduced into the MS detector in the ESI+ mode (data not shown).

3.1 Optimization of RP CE conditions for ESI+MS

For the CE-UV experiments, the analytical conditions for the best separation were as follows: run buffer of 10 mM SU(XIII)-γ-CD with 50 mM phosphate background electrolyte at pH 2.6, an applied voltage of −12 kV, and a capillary temperature of 15°C [1]. Optimization for CE-MS analysis started from these conditions. The electrophoresis current was about 85–95 μA during the CE-UV analysis. The electrophoresis current had to be kept at less than 20 μA, otherwise the ionization voltage for the electrospray could not be applied in the combination of RP CE and ESI+ MS. To lower the current, the concentration of the background electrolyte was changed. The standard ATS mixture was analyzed using the run buffer of 10 mM SU(XIII)-γ-CD with the formate background electrolyte. The concentration of background electrolyte gradually decreased from 50 mM. The total analysis time became longer, though the resolution was maintained even when using the run buffer without the background electrolyte, *i.e.*, water (data not shown). However, the electrophoresis current using 10 mM SU(XIII)-γ-CD aqueous solution was still higher than 20 μA, because the SU(XIII)-γ-CD itself is a highly charged electrolyte. We also lowered the concentration of SU(XIII)-γ-CD step by step. The minimum CD concentration for the complete chiral separation of nine ATS was 2.5 mM (data not shown).

Reducing the concentration of SU(XIII)-γ-CD increased the total analysis time to more than 1 h. The current of the CE gradually increased during electrophoresis, and the applied voltage had to be set rather low in a constant voltage mode. The electrophoresis condition was changed from voltage control to current control to shorten the total analysis time. In addition, the separation capillary was bypassed the UV-detector to shorten the capillary length (Fig. 3).

The optimized conditions of RP CE for ESI+ MS were as follows: run buffer, 2.5 mM SU(XIII)-γ-CD aqueous solution (the pH of the solution was 3.1); the applied current was ramped to −10 μA for 0.5 min, held for 5 min, ramped to −20 μA for 0.5 min and held during the rest of the analysis; capillary temperature, 15°C; length of the separation capillary, 56 cm.

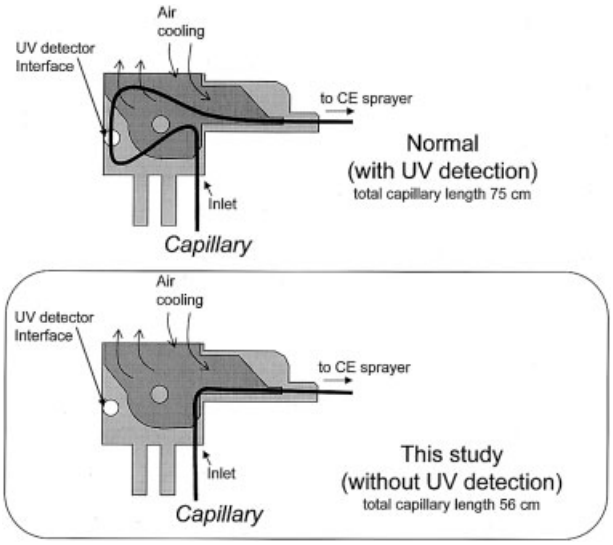

Figure 3. Schematics of the CE-MS cassette of Agilent CE. Upper: normal, lower: this study.

3.2 Simultaneous chiral separation of nine ATS using CE-MS and CE-MS/MS

For ESI+, the cone voltage was set to 20 V, the most sensitive value for detecting $[M+H]^+$ ions (precursor ions) of the ATS. For collision-induced dissociation, the gas pressure and the energy were set to 5 psi and 15 eV, respectively, to make the relative intensity of $[M+H]^+$ ions in MS/MS spectra around 10%. Because the ESI method is more difficult to apply to the RP CE-ESI+ MS than NP CE-ESI+ MS or RP CE-ESI− MS because of their electrical potential condition, the organic solvent of the sheath liquid was examined. Among the organic solvents examined (methanol, ethanol 2-propanol, and acetonitrile), ethanol is the best for stable spray. The sheath liquid was set to ethanol/10 mM ammonium formate (1/1 v/v). The ionization voltage was set to almost maximum of the system (4.2 kV) because the RP mode caused reverse current to the CE sprayer and it needed higher electrical potential than normal values.

Figure 4 shows the CE-MS electropherograms of the standard ATS solution (100 μg/mL as individual enantiomers) under the optimized conditions as shown in Section 2.2. All 18 individual enantiomers were resolved and identified. No ions related to SU(XIII)-γ-CD (~2350 M_r) were detected just as with direct infusion, implying that the migrated ATS-CD complex was dissociated at the ESI interface and SU(XIII)-γ-CD in the run buffer did not go into the MS detector.

MS/MS analysis was also examined for selectivity and sensitivity. Figure 5 shows the MS/MS spectra and the expected fragmentation of ATS. NEP and NpEP or EP

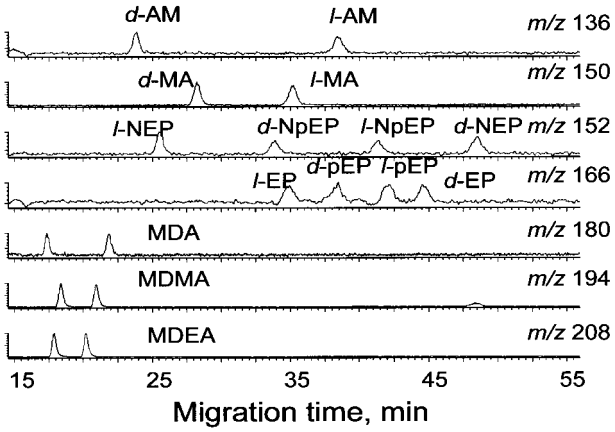

Figure 4. CE-MS mass traces of the standard ATS solution (100 μg/mL as individual enantiomers). The run buffer was 2.5 mM SU(XIII)-γ-CD aqueous solution (pH 3.1). Capillary, 50 μm ID × 56 cm; running current, −20 μA; capillary temperature, 15°C. The sample was injected at a pressure of 50 mbar for 4 s (*ca*. 400 pg).

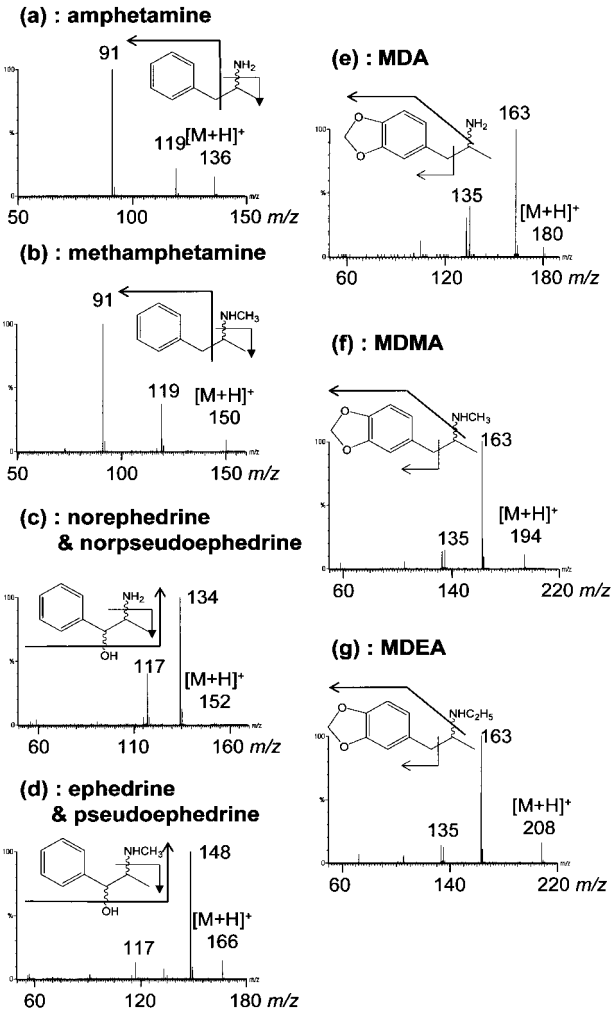

Figure 5. MS/MS spectra and expected fragmentation of ATS.

and pEP showed the same MS/MS spectra as shown in Fig. 5c or d. Product ions of ATS are given in Table 1. The base peaks of the product ions were selected for determination of the sensitivity of MS/MS. Figure 6 depicts the CE-MS/MS electropherograms of the standard ATS solution (10 μg/mL as individual enantiomers). The detection sensitivities of ATS with MS/MS detector was 10 times higher than those with single MS detection. Additionally, poor peak shapes of EPs and NEPs in CE-MS were improved (Fig. 4). This is the first report that racemic EP and pEP or racemic NE and NpE were enantioseparated simultaneously using an MS detector. The analysis time is rather long, but it would be used complementary to the CE-UV [1]. The CE-UV would be for routine analysis and quantitative analysis, and the CE-MS/MS for confirmation.

Table 1. Product ions of ATS

Compound	Precursor ion $[M+H]^+$ (*m/z*)	Product ions[a] (*m/z*)
AM	136	91, 119
MA	150	91, 119
NEP	152	134, 117
NpEP	152	134, 117
EP	166	148, 117
pEP	166	148, 117
MDA	180	163, 135
MDMA	194	163, 135
MDEA	208	163, 135
d-Isoproterenol	212	194, 152

a) Ions underlined were base peaks.

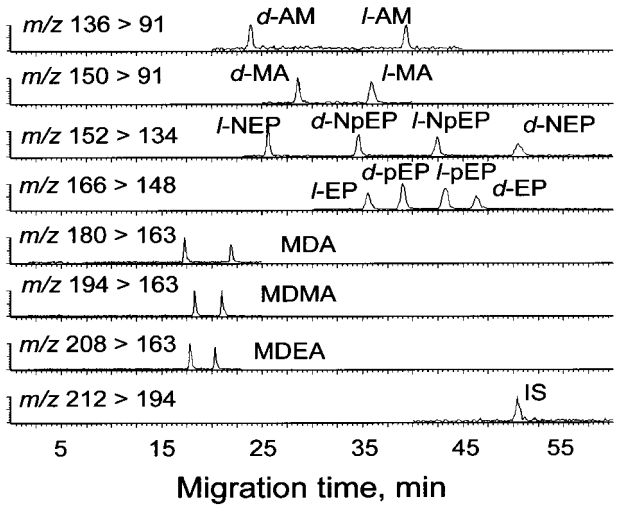

Figure 6. CE-MS/MS mass electropherogram of the standard ATS solution (10 μg/mL as individual enantiomer). CE conditions and peaks are as described in Fig. 2. The sample was injected *via* application of 50 mbar for 4 s (*ca*. 40 pg).

As previously reported, the detection limit for *d*-norephedrine using CE-UV was approximately 12 pg on column (S/N = 3) [1]. In the present CE-MS/MS study, about 400 pg of each ATS isomer was injected into the capillary. The detection limit for *d*-norephedrine is ~7 pg on column (S/N = 3). Table 2 shows the repeatability of the relative migration time of MS/MS analysis. *d*-Isoproterenol was used as an internal standard (IS). The interday repeatability study was done on the same separation capillary and extension capillary. The intraday and interday repeatability of the relative migration time (n = 5) was less than 1.49% and 2.64%, respectively.

Table 2. Repeatability of the relative migration time (MT) under optimized conditions

Compound	MT (min) (Ave.)	Relative MT (min) (Ave.)	Relative MT	
			intraday (RSD%)	interday (RSD%)
MDA	17.2	0.340	1.48	2.64
MDEA	17.8	0.350	1.49	2.58
MDMA	18.2	0.360	1.40	2.54
MDEA	20.0	0.395	1.28	2.48
MDMA	20.8	0.410	1.14	2.35
MDA	21.7	0.428	1.22	2.45
d-AM	24.0	0.473	1.04	2.44
l-NEP	25.8	0.508	1.16	2.55
d-MA	28.6	0.564	1.11	2.28
d-NpEP	34.9	0.689	0.82	1.92
l-MA	36.1	0.713	0.54	1.60
l-EP	36.2	0.714	0.71	1.88
l-AM	39.4	0.778	0.39	1.07
d-pEP	39.8	0.785	0.50	1.42
l-NpEP	42.7	0.843	0.25	0.72
l-pEP	43.7	0.863	0.25	0.84
d-EP	46.2	0.912	0.04	0.46
d-NEP	50.3	0.993	0.26	0.29
d-Iso-proterenol	50.7	1.000	–	–

3.3 Application to analysis of seized methamphetamine samples

The optimized CE-MS/MS analysis was applied to real forensic samples. Seized *d*-MA hydrochloride samples dissolved in IS solution at high concentration (20 mg/mL) were analyzed by this method. Small peaks (~1/1000 of MA) of impurities were detected in the mass electropherograms (Fig. 7a) and identified by MS/MS spectra (Figs. 7b and c). These impurities were identified to be *l*-EP and *d*-pEP. Both compounds were synthetic precursors of the *d*-MA. Their presence would reflect the synthetic routes of the drug. This revealed that the present method could support impurity-profiling analysis of seized MA [27] that examined the relationship between seized materials and identification of the sources of supply.

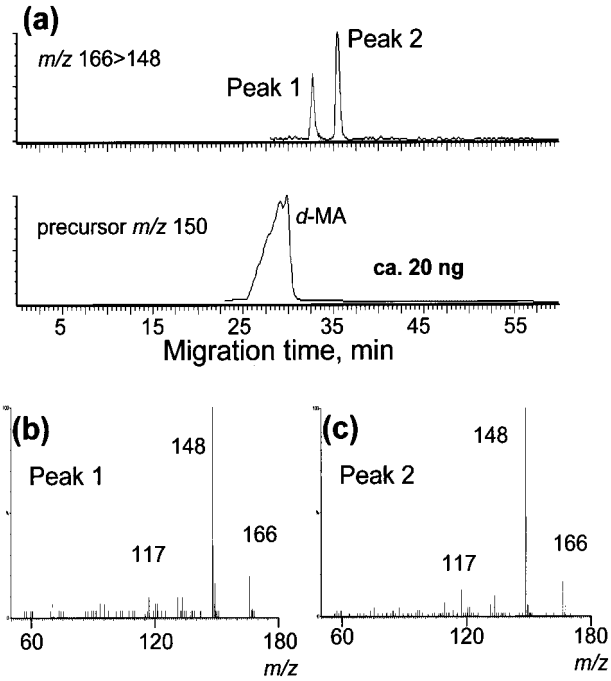

Figure 7. (a) CE-MS/MS electropherogram obtained for the analysis of seized MA hydrochloride (20 mg/mL). MS/MS spectra of (b) peak 1 and (c) peak 2. CE conditions are as described in Fig. 4. The sample was injected at a pressure of 50 mbar for 1 s (*ca*. 20 ng).

4 Concluding remarks

RP CE and ESI+ MS (MS/MS) were combined to analyze cationic ATS with anionic SU(XIII)-γ-CD as a chiral selector. Nine ATS were simultaneously separated and identified by their MS/MS spectra. The detection limit of this method is slightly better than CE-UV, and the MS/MS spectra provide structural information that is necessary for forensic drug analysis. The present method would be applicable to the analysis of precursors in seized MA.

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