

Yuko T. Iwata¹
Agnes Garcia²
Tatsuyuki Kanamori¹
Hiroyuki Inoue¹
Tohru Kishi¹
Ira S. Lurie²

¹National Research Institute
of Police Science,
Chiba, Japan

²Special Testing and
Research Laboratory,
US Drug Enforcement
Administration,
Chantilly, VA, USA

The use of a highly sulfated cyclodextrin for the simultaneous chiral separation of amphetamine-type stimulants by capillary electrophoresis

We investigated the simultaneous chiral separation of nine amphetamine type stimulants (*dl*-norephedrine, *dl*-norpseudoephedrine, *dl*-ephedrine, *dl*-pseudoephedrine, *dl*-amphetamine, *dl*-methamphetamine, *dl*-methylenedioxyamphetamine (MDA), *dl*-methylenedioxymethamphetamine (MDMA), and *dl*-methylenedioxyethylamphetamine (MDEA)) by capillary electrophoresis using highly sulfated γ -cyclodextrin (SU(XIII)- γ -CD) as a chiral selector. Three different approaches using SU(XIII)- γ -CD with 50 mM phosphate background electrolyte were designed; (I) high CD concentration (10 mM SU(XIII)- γ -CD) at neutral pH (pH 7.0) in the normal polarity mode, (II) low CD concentration (1.0 mM) at low pH (pH 2.6) in the normal polarity mode and (III) high CD concentration at low pH (pH 2.6) in the reversed-polarity mode. In mode (II), the effects of adding three neutral CDs (β -CD, dimethyl- β -CD and hydroxypropyl- β -CD) were also investigated. The best separation was obtained after optimizing mode (III) as follows: run buffer of 10 mM SU(XIII)- γ -CD with 50 mM phosphate background electrolyte at pH 2.6, applied voltage of -12 kV and capillary temperature of 15°C .

Keywords: Amphetamine-type stimulants / Capillary electrophoresis / Chiral separation / Sulfated cyclodextrin
EL 4858

1 Introduction

Identification and quantitation of phenethylamines presents analytical difficulties in forensic laboratories due to their low molecular weights, polarity, and their ability to exist as optical isomers. The enantioselective determination of amphetamine type stimulants (ATS) has both legal and intelligence value in forensic laboratories throughout the world. 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 is monitored as a controlled substance present in Khat samples. In addition, high purity *d*-methamphetamine is legally referred to as "Ice" and its possession results in longer sentences. Methamphetamine abuse is rapidly increasing in the United States and it is one of the most popular abused drugs in Asia. The most common manufacturing method of illicit *d*-methamphetamine is the reduction of *d*-pseudoephedrine or *l*-ephedrine, which is

produced from natural resources such as *Ephedrae herba* or by fermentation [1, 2]. This is substantiated by reports [3] describing most seized methamphetamine samples as containing the *d*-isomer. On the other hand, manufacture of methamphetamine from phenyl-2-propanone and methylamine yields the racemic compound, *dl*-methamphetamine [4]. Recently, there has been an influx of seized cases containing *dl*-, *l*-, or mixture of *d*- and *l*-methamphetamine, as well as the *d*-form in Japan and the United States. Thus, chiral information is useful and essential to identify the precursor, the synthetic pathway, and intrinsic characteristics of seized samples.

GC and HPLC have been used for the separation of optical isomers of phenethylamines [5–8]. There are some limitations of GC and HPLC for simultaneous chiral analysis of ATS. In the case of GC, base extraction may be required. 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 cost prohibitive. And HPLC with chiral stationary phase suffers from low theoretical plates, which can result in poor resolution and/or long analysis times.

Recently, CE has been introduced as a powerful analytical tool for the chiral separation of amphetamines using derivatization or in conjunction with an array of CDs as chiral selectors [9–17]. However, some of the ATS in the electropherogram were poorly separated and exhibited signifi-

Correspondence: Yuko T. Iwata, National Research Institute of Police Science, 6-3-1, Kashiwanoha, Kashiwa, Chiba 277-0882, Japan

E-mail: togawa@nrips.go.jp

Fax: +81-471-33-9159

Abbreviations: ATS, amphetamine-type stimulants; **DM- β -CD**, 2,6-di-O-methyl- β -CD; **HP- β -CD**, 2-hydroxypropyl- β -CD; **MDA**, methylenedioxyamphetamine; **MDEA**, methylenedioxyethylamphetamine; **MDMA**, methylenedioxymethamphetamine; **SU(XIII)- γ -CD**, highly sulfated γ -cyclodextrin

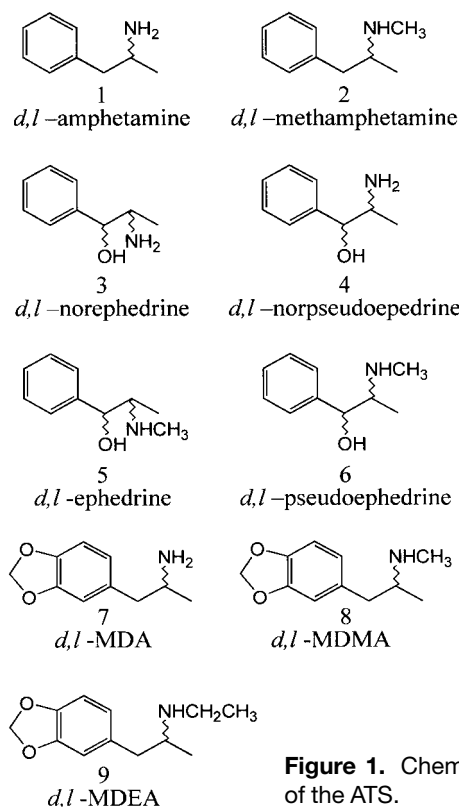


Figure 1. Chemical structures of the ATS.

cant tailing. The number of analytes that could be separated simultaneously was not adequate for some forensic purposes. Therefore, it was necessary to study the chiral separation of ATS in further detail. In the present study, we investigated the simultaneous chiral separation of the nine ATS shown in Fig. 1 by CE using highly sulfated γ -cyclodextrin (SU(XIII)- γ -CD), an anionic CD, as a chiral selector. Stobaugh *et al.* [11] explained that the use of anionic CDs effectively increases the “separation window”, as the maximum opportunity for separation may exist when the analyte and anionic CD migrate in opposite directions. It was demonstrated that SU(XIII)- γ -CD has high resolving power for individual enantiomers of amphetamine-like compounds [13]. Its use is advantageous for forensic purposes because of its commercial availability. Therefore, using SU(XIII)- γ -CD, the effects of CD concentration, addition of neutral CD, pH, ionic strength and temperature were investigated to separate nine ATS.

2 Materials and methods

2.1 Chemicals

Authentic standards of *dl*-norephedrine, *dl*-norpseudoephedrine, *dl*-ephedrine, *dl*-pseudoephedrine, *dl*-amphetamine, *dl*-methamphetamine, *dl*-methylenedioxy-

amphetamine (MDA), *dl*-methylenedioxymethamphetamine (MDMA), and *dl*-methylenedioxyethylamphetamine (MDEA) were acquired from the reference collection of the U.S. Drug Enforcement Administration's Special Testing and Research Laboratory. SU(XIII)- γ -CD was supplied by Beckman Coulter (Fullerton, CA, USA). β -CD, dimethyl- β -CD (DM- β -CD), and hydroxypropyl- β -CD (HP- β -CD) were obtained from Sigma (St. Louis, MO, 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

The CE system used was an Agilent Capillary Electrophoresis system G1600A (Waldbronn, Germany) equipped with a 50 μ m ID $\times$ 32.5 cm (24 cm to the detector) fused-silica capillary (Polymicro Technologies, Phoenix, AZ, USA) and a photodiode array detector. Detection was achieved using UV at 195 nm. The capillaries were conditioned before use by successive washings for 10 min each with 1 M sodium hydroxide and water, followed by a 30 min flush with run buffer. The capillaries were also flushed with run buffer for 2 min between injections. The electropherograms were recorded and processed with an Agilent Chemstation Data system.

2.3 Sample preparation and electrophoretic conditions

Racemic ATS were dissolved in 50 mM phosphate buffer (pH 2.6) at a concentration of about 0.2 mg/mL. All sample solutions were filtered through a Whatman Uniprep 0.45 μ m membrane (Clifton, NJ, USA) before analysis. Pressure injections (50 mbar for 1 s) of standard sample solutions were used. Approximately 1 nL of the sample solution was introduced into the capillary (calculated using the Hagen-Poiseuille equation). SU(XIII)- γ -CD with 50 mM phosphate background electrolyte was used as a run buffer. Changes in pH of run buffer (pH 7.0 and pH 2.6) and SU(XIII)- γ -CD concentration (10, 20 and 5 mM) were evaluated in order to optimize the separation. The run buffer contained 1 mM SU(XIII)- γ -CD and 50 mM phosphate (pH 2.6) with 5 mM neutral CD (β -CD, DM- β -CD or HP- β -CD) were used to see the effects of adding neutral CDs. The optimum voltages were determined by the Ohm's law plot. Temperature of the capillary was initially set to 30°C and changed to 15°C in order to optimize the separation.

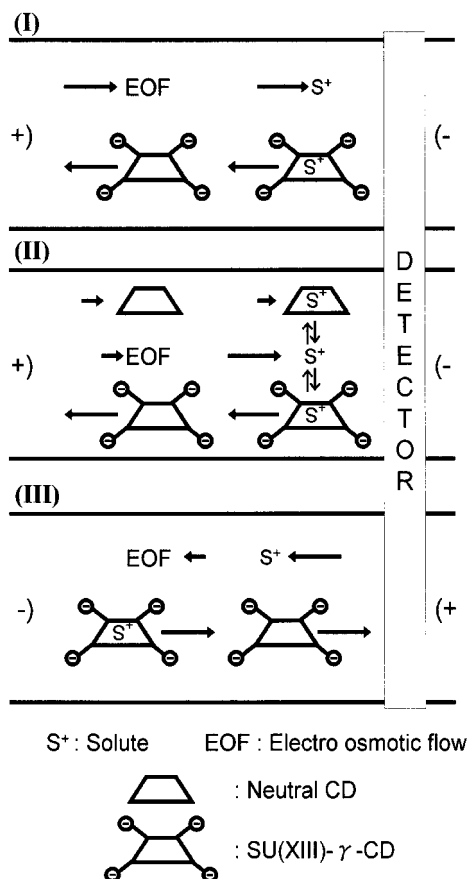


Figure 2. Schematic representation of the separation in mode (I) high CD concentration (10 mM SU(XIII)- γ -CD) at neutral pH (pH 7.0) in the normal-polarity mode, mode (II) low CD concentration (1.0 mM) at low pH (pH 2.6) in the normal-polarity mode and mode (III) high CD concentration at low pH in the reversed-polarity mode.

3 Results and discussion

Three different approaches were designed as shown in Fig. 2. Mode (I) uses high SU(XIII)- γ -CD concentration at neutral pH in normal polarity. As reported by Desiderio and Fanali [18], solutes move toward the cathode and complexes of solute with anionic CDs move in the opposite direction. Mode (II) uses low SU(XIII)- γ -CD concentration with and without neutral CDs at low pH in normal polarity. Under mode (II), as reported by Stobaugh *et al.* [11], complexes of solute with neutral CD move toward the cathode, although complexes with anionic CDs move toward the anode. Mode (III), as noted by Wu and Stalcup [19], uses high SU(XIII)- γ -CD concentration at low pH in the reversed polarity. The movements of solutes and complexes are reversed in comparison with mode (I).

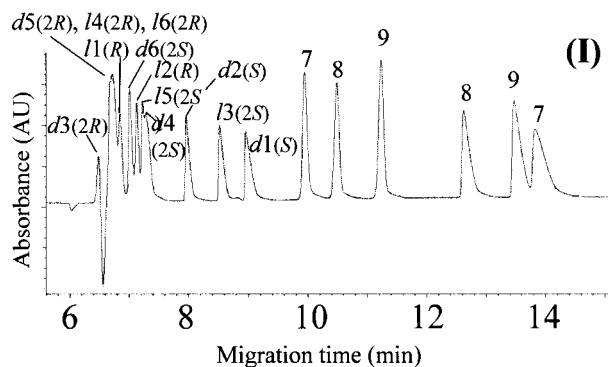


Figure 3. Electropherogram of mode (I). The run buffer contained 10 mM SU(XIII)- γ -CD and 50 mM phosphate (pH 7.0). A 50 μ m ID $\times$ 32.5 cm capillary was used with a running voltage of +6 kV at 30°C. Peaks: $d3$, d -norephedrine; $d5$, d -ephedrine; 14 , l -norpseudoephedrine; 16 , l -pseudoephedrine; 11 , l -amphetamine; $d6$, d -pseudoephedrine; 12 , l -methamphetamine; 15 , l -ephedrine; $d4$, d -norpseudoephedrine; $d2$, d -methamphetamine; 13 , l -norephedrine; $d1$, d -amphetamine; 7 , MDA; 8 , MDMA; 9 , MDEA. The configuration of the β -carbon is included in the figure.

3.1 Mode (I): high SU(XIII)- γ -CD concentration at neutral pH in the normal-polarity mode

Figure 3 shows the electropherogram of mode (I), high CD concentration (10 mM SU(XIII)- γ -CD) at neutral pH (pH 7.0) in the normal-polarity mode (+6 kV). Most of the nonring-substituted ATS (*i.e.* amphetamine, methamphetamine, norephedrine, norpseudoephedrine, ephedrine and pseudoephedrine) were unresolved and moderate to slight peak tailing was observed for most solutes. However, this mode would be suitable for the chiral separation of single racemic compound, since all individual enantiomers are fully resolved with a short analysis time.

Most of the ATS have a chiral center at the β -carbon with respect to the aromatic ring system. Stobaugh *et al.* [11] reported that the resolution of stereoisomers is due to the association with chiral selector. The migration orders of individual nonring-substituted ATS enantiomers in Fig. 3 indicate that the isomers possessing the *S*-configuration at the β -carbon have a stronger association with SU(XIII)- γ -CD, which results in a longer migration time.

3.2 Mode (II): low SU(XIII)- γ -CD concentration at low pH in the normal-polarity mode (with and without neutral CDs)

Figure 4 shows the electropherogram of mode (II), low CD concentration (1.0 mM SU(XIII)- γ -CD) at low pH (pH 2.6) in the normal-polarity mode (+9 kV). Most of the nonring-

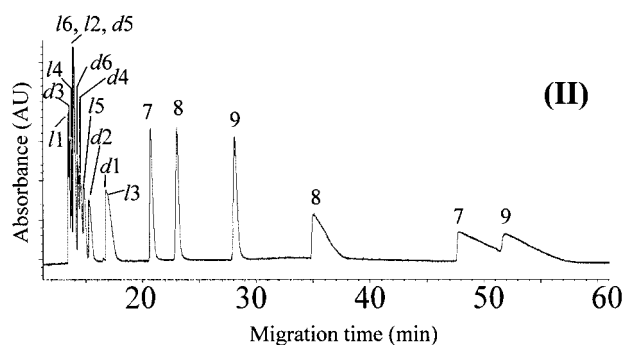


Figure 4. Electropherogram of mode (II). The run buffer contained 1 mM SU(XIII)- γ -CD and 50 mM phosphate (pH 2.6) with a running voltage of +9 kV at 30°C. Peaks are as described in Fig. 3.

substituted ATS were incompletely resolved, and severe to moderate peak tailing for most solutes was observed. All individual enantiomers are fully resolved but the running time was rather long because of the longer migration time due to the low EOF at pH 2.6. The effects of adding three neutral CDs (β -CD, DM- β -CD and HP- β -CD) were also investigated (Fig. 5). Adding β -CD to 1.0 mM SU(XIII)- γ -CD did not loose the resolution of the individual enantiomers and it improved the peak shapes slightly with shortening analytical time (Fig. 5a). Addition of DM- β -CD to 1.0 mM SU(XIII)- γ -CD made the resolution of MDMA (8) and MDEA (9) worse than that in Fig. 4, although the addition did not loose the resolution of the individual enantiomers (Fig. 5b). All 18 peak tops were observed only when HP- β -CD was added to 1.0 mM SU(XIII)- γ -CD, though the resolutions were insufficient (Fig. 5c). Among these mode (II), adding DM- β -CD only enabled to resolve *d*-amphetamine (*d*1) and *l*-norephedrine (*l*3) completely.

There are several reports concerning the effect of neutral CDs on the resolution of ATS. Chinaka *et al.* [16] reported that β -CD itself had no resolving power for individual enantiomers of neither norephedrine nor ephedrine and DM- β -CD alone partially resolved individual enantiomers of MDA, MDMA and MDEA. HP- β -CD, which was frequently used as a chiral selector for ATS, showed no ability in resolving enantiomers of norephedrine [10, 14, 16, 17]. As previously reported by Lurie *et al.* [12], major changes were observed in selectivity, including changes in migration order of solutes, especially for the nonring-substituted ATS by adding neutral CDs. On the other hand, migration order of individual enantiomers did not change with the addition of neutral CDs. It also revealed that migration times of the ring-substituted ATS (*i.e.* MDA, MDMA and MDEA) were shortened by adding neutral CDs, as compared to those of the nonring-substituted ATS. The neutral CD competed with SU(XIII)- γ -CD for complexation of ATS, resulting in a shorter analysis time.

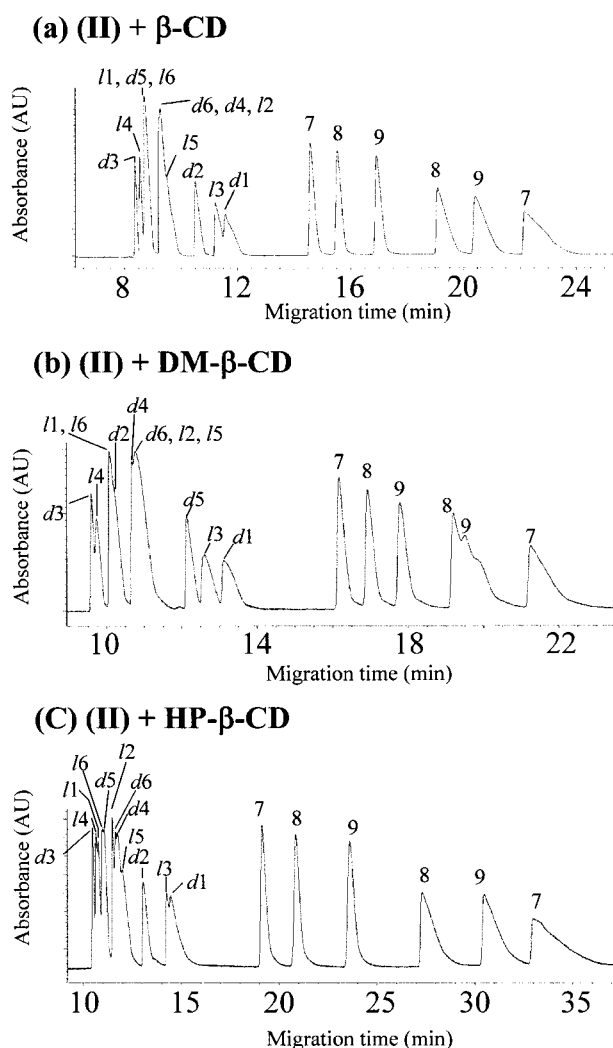


Figure 5. The effect of addition of neutral CDs to mode (II). The run buffer contained 1 mM SU(XIII)- γ -CD and 50 mM phosphate (pH 2.6) (a) with 5 mM β -CD (+9.5 kV); (b) with 5 mM DM- β -CD (+9.5 kV); (c) with 5 mM HP- β -CD (+8 kV); at 30°C. Peaks are as described in Fig. 3.

The electrophoretic conditions adding the neutral CDs presented have their individual advantages and disadvantages. Mode (II) is rather an economical mode since the SU(XIII)- γ -CD is a relatively expensive reagent. It would be useful to select the electrophoretic conditions from the mode (II) (with or without neutral CD) for the chiral separation of certain ATS combinations.

3.3 Mode (III): high SU(XIII)- γ -CD concentration at low pH in the reversed-polarity mode

Figure 6 shows the electropherograms of mode (III), high CD concentration at low pH (pH 2.6) in the reversed-polarity mode. In the reversed-polarity mode, the migration

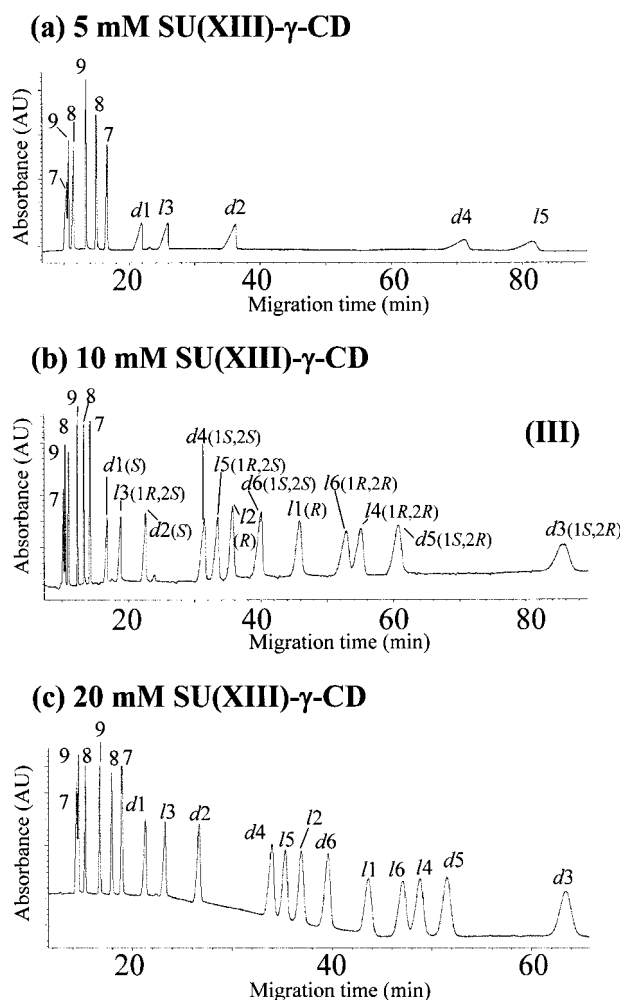


Figure 6. The effect of changing SU(XIII)- γ -CD concentration of mode (III). The run buffer contained 50 mM phosphate (pH 2.6) and (a) 5 mM SU(XIII)- γ -CD (–7 kV); (b) 10 mM SU(XIII)- γ -CD (–6 kV), (c) 20 mM SU(XIII)- γ -CD (–4 kV); at 30°C. Peaks are as described in Fig. 3.

order was opposite and the peak shapes were improved. All 18 solutes were well resolved, especially for nonring-substituted ATS such as ephedrine, norpseudoephedrine and pseudoephedrine (Fig. 6b), as compared to mode (I) (Fig. 3), though slight peak leading was observed. Mode (III) resulted in the best separation among the three approaches evaluated. As discussed in Section 3.1, Fig. 6b also indicates that the isomers possessing the S-configuration at the β -carbon have a stronger association with SU(XIII)- γ -CD, which results in a shorter migration time. Ephedrine (compound 3, 4, 5 and 6 in Fig. 1) have two chiral centers at the α -carbon and the β -carbon with respect to the aromatic ring system. The baseline resolution of four diastereomers such as *dl*-norephedrine (3) and *dl*-norpseudoephedrine (4) shows that the α -carbon also contributes to the interaction between ATS and

SU(XIII)- γ -CD. When a common configuration occurs at the β -carbon, the presence of the *R*-configuration at the α -carbon led to a stronger interaction with SU(XIII)- γ -CD. For example, the migration order of *dl*-norephedrine (3) and *dl*-norpseudoephedrine (4) was as follows; *l*-norephedrine (1*R*, 2*S*), *d*-norpseudoephedrine (1*S*, 2*S*), *l*-norpseudoephedrine (1*R*, 2*R*), *d*-norephedrine (1*S*, 2*R*).

It is apparent from Sections 3.1 through 3.3 that nonring-substituted ATS and ring-substituted ATS exhibited completely different behaviors. Factors such as hydrophobicity, configuration at the β -carbon (*S* > *R*), configuration at the α -carbon (*R* > *S*), hydrogen bonding, dipole interactions and Van der Waals forces probably contribute to the interaction between ATS and SU(XIII)- γ -CD. The reversed-polarity mode enhanced the separation of the weakly interacting nonring-substituted ATS solutes. The reversed-polarity mode *versus* the normal-polarity mode at low pH allowed us to run the higher anionic CD concentration, which contributed to the overall resolution of the solutes. The effect of SU(XIII)- γ -CD concentration on the separation is also shown in Fig. 6. With increasing SU(XIII)- γ -CD concentration, the analysis time was shortened and peak shapes improved (Fig. 6c). Taking into account the separation of the first MDA peak (7) and MDEA peak (9), best overall separation of 18 solutes was obtained at 10 mM of SU(XIII)- γ -CD in mode (III) (Fig. 6b).

Several chiral applications using anionic CDs as chiral selectors have utilized the reversed-polarity mode, under conditions of suppressed electroosmotic flow [20–30]. Some of these applications have made comparisons of peak shape and the resolution in normal-polarity mode *versus* reversed-polarity mode and have found more optimum separations for certain solutes using the later technique [29, 30]. Dolezalova and Fanali [29] showed for a certain acid carbidopa that a reversed-polarity separation at pH 2.5 is preferred over one performed at pH 3.0 using normal polarity. Christians and Holzgrabe [30] reported for neutral dihydropyridines that reversed-phase separations at pH 3.0 are preferred over normal-phase separations at pH 8.0. They also showed that a higher concentration of anionic CD improved peak shapes in both reversed- and normal-polarity modes.

3.4 Optimization of mode (III)

All 18 individual enantiomers were well resolved in mode (III) at 10 mM SU(XIII)- γ -CD, but the analysis time was too long for practical use. In mode (III), the free solutes (ATS) migrated in opposite direction of the detector, and solute-SU(XIII)- γ -CD complex migrate to the detector (Fig. 2). The electrophoretic conditions were optimized by changing the phosphate background electrolyte concentration,

the applied voltage and the capillary temperature. The analysis time was shortened by decreasing the phosphate concentration, which decreased the EOF. In addition, a low concentration of ions in background buffer could promote the ion-pair formation between the opposite charges of the analyte and the CD [26]. However, the resolution of *l*-pseudoephedrine (*l*6) and *l*-norpseudoephedrine (*l*4) became worse (data not shown). Thus the phosphate concentration was set at 50 mM. The voltage was increased from –6 kV to –10.5 kV. The applied voltage was not more than –10.5 kV at 30°C, since an excessive current of over 100 μ A would be obtained. The analysis time decreased by almost one-third but the resolution of *l*-ephedrine (*l*5) and *l*-methamphetamine (*l*2), and the resolution of *l*-pseudoephedrine (*l*6) and *l*-norpseudoephedrine (*l*4) became worse (data not shown). Since the –6 kV (the voltage of the analysis in Fig. 6b) was determined by the Ohm's law plot, the Joule heating seemed to cause the bad resolution as well as the shorter analysis time. Excessive Joule heating could cause a change in partition coefficients which could decrease resolution. Therefore, lowering the temperature of the cassette to 15°C, which lowered Joule heating (increased viscosity), resulted in more favorable partition coefficients. All the solutes were completely resolved even at the running voltage –10.5 kV and the analysis time was still half of that of the Fig. 6b (data not shown).

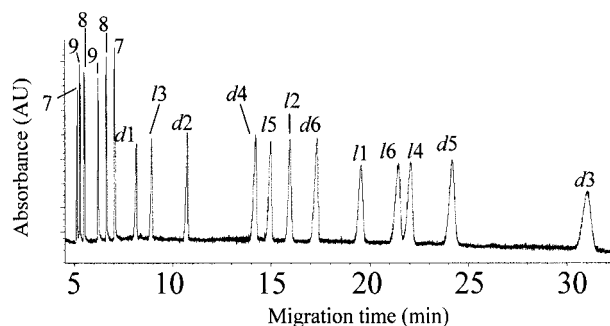


Figure 7. The separation in optimized conditions for simultaneous chiral separation of the nine ATS. The run buffer contained 10 mM SU(XIII)- γ -CD and 50 mM phosphate (pH 2.6) in the running voltage –12 kV at 15°C. Peaks are as described in Fig. 3.

Figure 7 indicates the optimum chiral separation of the ATS with complete resolution of all 18 solutes examined. Within a 32 min run time, all 18 solutes were baseline-resolved. The optimized conditions were as follows: run buffer of 10 mM SU(XIII)- γ -CD with 50 mM phosphate background electrolyte at pH 2.6, applied voltage of –12 kV and capillary temperature of 15°C. The intra-day repeatabilities ($n = 5$) of migration time and peak area under the optimized conditions are shown in Table 1. *d*-Norpseudoephedrine was used as the pseudo internal

Table 1. Reproducibility of the migration time and peak area under optimized conditions

Compound	Migration time (min)		Relative migration Time		Relative peak area	
	Mean	%RSD	Mean	%RSD	Mean	%RSD
MDA ^{a)}	4.993	1.2	0.363	0.3	0.293	5.4
MDEA ^{a)}	5.131	1.1	0.373	0.2	0.436	5.5
MDMA ^{a)}	5.362	1.1	0.389	0.2	0.446	2.9
MDEA ^{a)}	6.017	1.0	0.437	0.3	0.553	1.2
MDMA ^{a)}	6.427	1.2	0.467	0.2	0.563	3.2
MDA ^{a)}	6.834	1.2	0.496	0.2	0.462	2.8
<i>d</i> -Amphetamine	7.932	1.1	0.576	0.2	0.536	3.4
<i>l</i> -Norephedrine	8.695	1.0	0.631	0.3	0.525	2.6
<i>d</i> -Methamphetamine	10.410	1.2	0.756	0.1	0.662	2.2
<i>d</i> -Norpseudoephedrine	13.772	1.2	1.000	–	1.000	–
<i>l</i> -Ephedrine	14.496	1.3	1.053	0.0	0.963	0.9
<i>l</i> -Methamphetamine	15.404	1.5	1.119	0.3	0.988	2.0
<i>d</i> -Pseudoephedrine	16.745	1.4	1.216	0.2	1.336	1.6
<i>l</i> -Amphetamine	18.809	1.8	1.366	0.6	1.246	2.2
<i>l</i> -Pseudoephedrine	20.591	1.7	1.495	0.5	1.436	2.0
<i>l</i> -Norpseudoephedrine	21.207	1.7	1.540	0.5	1.340	1.2
<i>d</i> -Ephedrine	23.123	2.0	1.679	0.8	1.617	2.7
<i>d</i> -Norephedrine	29.249	2.5	2.124	1.4	1.767	4.1

Data represent mean of 5 determinations. Relative migration times and peak areas were calculated using *d*-norpseudoephedrine as an internal standard.

a) Enantiomeric determination of MDA, MDEA, and MDMA was not performed.

standard for the calculation of the relative migration time and area. The repeatability was fair with less than 2.5% of the RSD for migration times and with less than 5.5% of the RSD for relative peak areas. Significantly improved precision was obtained using relative migration times with RSD for most solutes under 0.9%, except *d*-norephedrine (RSD 1.4%). For analysis of real samples, an internal standard that is different from the analytes in this study must be used. Coated capillaries have been used with SU(XIII)- γ -CD to improve precision [31].

In the present study, about 100 pg of each ATS isomer was injected into the capillary. The detection limit for *d*-norephedrine (the smallest peak) is approximately 12 pg on column (S/N = 3). This method has high resolving power for the enantiomers of ATS and would be applicable for some forensic samples, such as powders or tablets of methamphetamine. Figure 7 also suggested that the large resolution between *d*-methamphetamine and other solutes allows for methamphetamine sample overload and it would allow the qualitative and quantitative analysis of methamphetamine precursors that are trace impurities of seized samples. Further studies on forensic applications, as well as a possibility of lot-to-lot variability of the CD, will be presented in a later report. In conclusion, this study resulted in a vastly improved separation over existing GC, HPLC or CE techniques. It was useful to gain insight into which of the three modes of analysis using charged CDs gave the best result for a complex mixture of enantiomers.

The authors gratefully acknowledge Beckman Coulter Inc. (Fullerton, CA, USA) for providing SU(XIII)- γ -CD.

Received November 5, 2001

5 References

- [1] Kishi, T., Inoue, T., Suzuki, S., Yasuda, T., Oikawa, T., Niwaguchi, T., *Eisei Kagaku* 1983, 29, 400–406 (in Japanese).
- [2] Kobayashi, K., Iwata, Y., Kanamori, T., Inoue, H., Kishi, T., *Report of the National Research Institute of Police Science* 2000, 53, 1–9 (in Japanese).
- [3] McKibben, T. D., *Drug Enforcement Administration – Special Testing and Research Laboratory*, personal communication 2001.
- [4] Skinner, H. F., *Forensic Sci. Int.* 1990, 48, 123–134.
- [5] Shin, H. S., Donike, M., *Anal. Chem.* 1996, 68, 3015–3020.
- [6] Doyle, T. D., Adama, W. M., Fry, F. S., Wainer, I. W., *J. Liq. Chromatogr.* 1986, 9, 455–471.
- [7] Noogle, F. T., Clark, C. R., *J. Forensic Sci.* 1986, 31, 732–742.
- [8] Herráez-Hernández, R., Campíns-Falcó, P., Tortajada-Genaro, L. A., *Analyst* 1998, 123, 2131–2137.
- [9] Lurie, I. S., *J. Chromatogr.* 1992, 605, 269–275.
- [10] Flurer, C. L., Lin, L. A., Satzger, R. D., Wolnik, K. A., *J. Chromatogr. B* 1995, 669, 133–139.
- [11] Tait, R. J., Thompson, D. O., Stobaugh, J. F., *Anal. Chem.* 1994, 66, 4013–4018.
- [12] Lurie, I. S., Klein, R. F. X., Dal Cason, T. A., LeBelle, M. J., Brenneisen, R., Weinberger, R. E., *Anal. Chem.* 1994, 66, 4019–4026.
- [13] Lurie, I. S., Odeneal II, N. G., McKibben T. D., Casale, J. F., *Electrophoresis* 1998, 19, 2918–2925.
- [14] Aumatell, A., Wells, R. J., Wong, D. K. Y., *J. Chromatogr. A* 1994, 686, 293–307.
- [15] Szökő, É., Gyimesi, J., Barcza, L., Magyar, K., *J. Chromatogr. A* 1996, 745, 181–187.
- [16] Chinaka, S., Tanaka, S., Takayama, N., Komai, K., Ohshima, T., Ueda, K., *J. Chromatogr. B* 2000, 749, 111–118.
- [17] Varesio, E., Veuthey, Jean-Luc, *J. Chromatogr. A* 1995, 717, 219–228.
- [18] Desiderio, C., Fanali, S., *J. Chromatogr. A* 1995, 716, 183–196.
- [19] Wu, W., Stalcup, A. M., *J. Liq. Chromatogr.* 1995, 18, 1289–1315.
- [20] Liu, L., Nussbaum, M. A., *J. Pharm. Biomed. Anal.* 1995, 14, 65–72.
- [21] Gahm, Kyung-Hyun, Stalcup, A. M., *Chirality* 1996, 8, 316–324.
- [22] Janini, G. M., Muschik, G. M., Issaq, H. J., *Electrophoresis* 1996, 17, 1575–1583.
- [23] Gahm, Kyung-Hyun, Chang, L. W., Armstrong, D. W., *J. Chromatogr. A* 1997, 759, 149–155.
- [24] Jin, Y., Stalcup, A. M., *Electrophoresis* 1998, 19, 2119–2123.
- [25] Gratz, S. R., Stalcup, A. M., *Anal. Chem.* 1998, 70, 5166–5171.
- [26] Tamisier-Karolak, S. L., Stenger, M. A., Bommar, A., *Electrophoresis* 1999, 20, 2656–2663.
- [27] Sutton, K. L., Sutton, R. M., Stalcup, A. M., Caruso, J. A., *Analyst* 2000, 125, 231–234.
- [28] Xu, X., Stewart, J. T., *J. Pharm. Biomed. Anal.* 2000, 23, 735–743.
- [29] Dolezalova, M., Fanali S., *Electrophoresis* 2000, 21, 3264–3269.
- [30] Christians, T., Holzgrabe, U., *Electrophoresis* 2000, 21, 3609–3617.
- [31] Chen, F. T. A., Evangelista, R. A., *J. Chin. Chem. Soc.* 1999, 46, 847–860.