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On-line sample concentration in micellar electrokinetic chromatography using cationic surfactants

Jong-Bok Kim*, Joselito P. Quirino[1], Koji Otsuka, Shigeru Terabe

Faculty of Science, Himeji Institute of Technology, Kamigori, Hyogo 678-1297, Japan

Abstract

Two on-line sample concentration techniques, sample stacking and sweeping, were evaluated using cationic surfactants as pseudostationary phases in micellar electrokinetic chromatography. As cationic surfactant micelles, tetradecyltrimethylammonium bromide and cetyltrimethylammonium chloride were employed. About 10-fold and 1000-fold increases in detection sensitivity in terms of peak heights were observed by sample stacking and sweeping, respectively, without suppression of the electroosmotic flow. In particular, the concentration limits of detection ($S/N=3$) for test naphthalenesulfonic acids obtained with sweeping were from 0.96 to 0.47 ppb with UV detection without any preconcentration procedure.

Keywords: Sample stacking; Sweeping; Sample handling; Surfactants; Naphthalenesulfonic acids; Sulfonic acids; Organosulfur compounds

1. Introduction

Capillary electrophoresis (CE) has been developed as a separation method suitable for routine applications and among several modes of CE micellar electrokinetic chromatography (MEKC) has been accepted as a popular and powerful analytical technique. MEKC, which was first introduced by Terabe et al. [1], is particularly adequate for the separation of neutral solutes, but this technique provides enhanced selectivity for separations of ionic species as well [2–5]. Analytes are separated based on their differential partitioning between the aqueous phase and the micelles. Since the micellar phase is similar to a chromatographic stationary phase, MEKC is an interface between electrophoresis and chromatography [6].

In general, MEKC techniques offer higher efficiencies and faster analysis times than those achieved by high-performance liquid chromatography (HPLC). However, the low concentration sensitivity is one of major problems in MEKC, as in the other modes of CE, due to a short pathlength in on-column UV detection and minute injection volumes to maintain high efficiency. This limits the applicability of MEKC to the analysis of low concentration samples. Thus, method development is indispensable for increasing concentration sensitivity or reducing limits of detection (LODs). With the ordinarily used UV detector and usual injection (ca. 1 mm in the capillary), concentration sensitivity in MEKC is at least an order of magnitude lower than that in HPLC. Various attempts have been conducted to improve concentration sensitivity. These ap-

*Corresponding author. Tel.: +81-791-580-173; fax: +81-791-580-493.

E-mail address: jbkim@sci.himeji-tech.ac.jp (J.-B. Kim).

[1]Present address: Department of Chemistry, Stanford University, Stanford, CA 94305-5080, USA.

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proaches involve, the use of highly sensitive detection methods (e.g., laser-induced fluorescence detection), the installation of capillaries equipped with increased detection pathlength (e.g., Z-shaped cell and bubble cell), and off-line preconcentration methods (e.g., liquid–liquid extraction and solid-phase extraction). However, these methods require high cost or consume time. To improve detection sensitivity in MEKC, two different techniques for on-line sample concentration have been developed: sample stacking [7] and sweeping [8,9]. These on-line concentration techniques have advantages of simplicity and economy because of no requirement of modification in CE instrumentation.

Mechanism of sample stacking is based on the difference in electrophoretic velocities between the high electric field sample zone (low-conductivity zone) and the low electric field running solution zone (high-conductivity zone). Sample ions migrate faster in the sample zone than in the running solution zone and slow down when they reach the running solution zone. The analyte is focused at the boundary of the two zones. To give effective electrophoretic mobilities to neutral analytes, ionic surfactant micelles are employed in MEKC [7]. Stacking under suppressed electroosmotic flow (EOF) conditions enabled more than 100-fold concentration for neutral analytes [7]. Mechanism of sweeping is based on the picking and accumulating of analytes by the micelle entering the sample solution. The sample matrix having similar conductivity to that of the running buffer gave more than 1000-fold concentration under suppressed EOF conditions [8,9]. Recently Palmer et al. reported ''micellar stacking'' with a high salt concentration sample matrix to give a high concentration efficiency [10], although we think the technique is equal to sweeping in total [11]. So far, in many previous reports, the on-line sample concentrations were performed using anionic pseudo-stationary phases only.

In this study, to extend the applicability of these on-line sample concentration techniques, cationic surfactant micelles such as tetradecyltrimethylammonium bromide (TTAB) or cetyltrimethylammonium chloride (CTAC) were employed. Cationic surfactants have been introduced for the analysis of phenylthiohydantoin (PTH)-amino acids [12], nucleotides [13], inorganic anions [14], glucosinolates [15], herbicides [16] and steroids in urine [17]. The addition of cationic surfactants to the running buffer caused the reversal of EOF owing to positively charged capillary wall by the adsorption of cationic surfactants [12,18]. The reversed EOF directs toward the positive electrode, whereas the micelle has the electrophoretic mobility in the opposite direction. The analytes are brought to the detector by the EOF since the magnitude of the EOF is greater than the electrophoretic velocity of the micelle. Under this condition, low retention factor (k) analytes are eluted faster than high k analytes as in MEKC with anionic micelles although the migration direction is different. In this paper normal stacking mode (NSM) [19], one of sample stacking modes, and sweeping with cationic micelles are presented.

2. Materials and methods

2.1. Apparatus

All experiments were performed with a Hewlett-Packard 3D capillary electrophoresis system (Waldbronn, Germany). Fused-silica capillaries (50 μm I.D.× 360 μm O.D.) were purchased from Polymicro Technologies (Phoenix, AZ, USA) and used without surface modification. The temperature of the capillary was maintained at 25°C by the instrument thermostatting system. Samples were introduced by pressure injection (50 or ~1000 mbar). An optimum detection wavelength was selected for each analyte based upon the spectra recorded by the diode-array detector. Conductivities were measured with a Horiba ES-12 conductivity meter (Kyoto, Japan).

2.2. Chemicals

CTAC, salicylic acid, 1-naphthalenesulfonic acid sodium salt (1-NSA), Tris(hydroxymethyl)-aminomethane (Tris), 1,5- and 2,6-naphthalenedisulfonic acid disodium salts (1,5- and 2,6-NDSA) were purchased from Wako (Osaka, Japan). TTAB, 2,7-naphthalenedisulfonic acid disodium salt (2,7-NDSA), diphenylglycolic acid, and Yellow OB were obtained from Tokyo Kasei Kogyo (Tokyo, Japan). Other reagents were obtained from Nacalai Tesque (Kyoto, Japan). All reagents were of ana-

lytical-reagent grade and used without further purification. Water was purified with a Milli-Q system (Millipore, Bedford, MA, USA).

Buffers were prepared from stock solutions of Tris and hydrochloric acid. Stock solutions of nitrobenzene, resorcinol, 2-naphthol, and *o*-, *m*-, *p*-nitroanilines were prepared in purified water at concentrations depending on the water solubility of each analyte. Stock solutions of steroids (cortisone, hydrocortisone, testosterone) were prepared with methanol. Stock solutions of naphthalenesulfonate derivatives (1-NSA, 1,5-, 2,6-, and 2,7-NDSAs) were prepared in purified water. Stock solutions of aromatic acids (salicylic acid, diphenylglycolic acid, and 2-naphthoic acid) were prepared in 50% aqueous methanol or methanol. Retention factors were determined using methanol as the marker of EOF and Yellow OB as the marker of the micelle [12]. Buffer solutions were sonicated and filtered through 0.45-μm filters before use.

2.3. Procedure

The new capillary was rinsed with 1 *M* NaOH for 20 min, followed by methanol for 20 min, 0.1 *M* NaOH for 20 min, purified water for 20 min, and finally the background solution (BGS) for 10 min. To assure reproducibility, at the end of each run the capillary was flushed with 0.1 *M* NaOH (2 min), methanol (2 min), purified water (2 min) and then with the BGS (3 min). For NSM, samples prepared in purified water are injected for much longer time compare to the normal injection, after conditioning the capillary with micellar BGS at neutral pH. Sample solutions were introduced at the cathodic end of the capillary at the 50 mbar and then separation potential was applied with negative polarity at the injection end. The plug length of the sample solution was optimized in terms of peak shapes by injecting the sample for different times. For the sweeping experiments, test analytes prepared in Tris–HCl solutions having the conductivity similar to that of the BGS were pressure injected into the capillary at the cathodic end. The velocities of a liquid in the capillary at 50 or ~1000 mbar pressure were determined by using a neutral marker to approximate the length of the zones injected at different intervals. Then the BGS vials were set to both ends of the capillary and the voltage was applied at negative polarity. Other experimental conditions are described in the text or figures.

3. Results and discussion

3.1. NSM

The principle of the NSM with a cationic surfactant is the same as that with an anionic surfactant except for the electrode polarity [19]. The neutral analyte in sample solution can be quickly carried to the boundary between the BGS and sample solution by the faster migrating cationic micelle entering into the sample solution from the anodic end of the sample solution. Since the electric field strength in the BGS zone is low, the velocity of the micelle slow down and the analyte is focused at the boundary between BGS and the cathodic end of the sample solution zone. Fig. 1 compares the peak heights and shapes between different sample matrices. The concentration of test analytes in Fig. 1B and 1C is a 10-fold dilution of the corresponding sample solution in Fig. 1A. Fig. 1A shows an electropherogram of conventional MEKC analysis with 1 s injection. As shown in Fig. 1B, where the analytes were dissolved in the BGS and then injected for 30 s, broader peaks were observed without significant improvement of sensitivity. This was due to the similar conductivities between the sample matrix and BGS and due to the presence of the micelle in the sample matrix, thus no focusing effect occurred. On the other hand, when the analytes were dissolved in water, about 15-fold improvements of peak heights were achieved by sample stacking (Fig. 1C) as expected. It should be noted that although the conductivity ratio between the BGS and sample solution is about 2300 to 1, the stacking efficiency was far below the ratio. The discrepancy can be explained in terms of the mismatch of the EOF between in the sample solution and in the BGS, which causes partial mixing at the boundary.

The effects of the injection time on corrected peak area (peak area divided by the migration time) and peak height are given in Fig. 2. The corrected peak area increased in proportion to the injection time (Fig. 2A). The peak height, as shown in Fig. 2B,

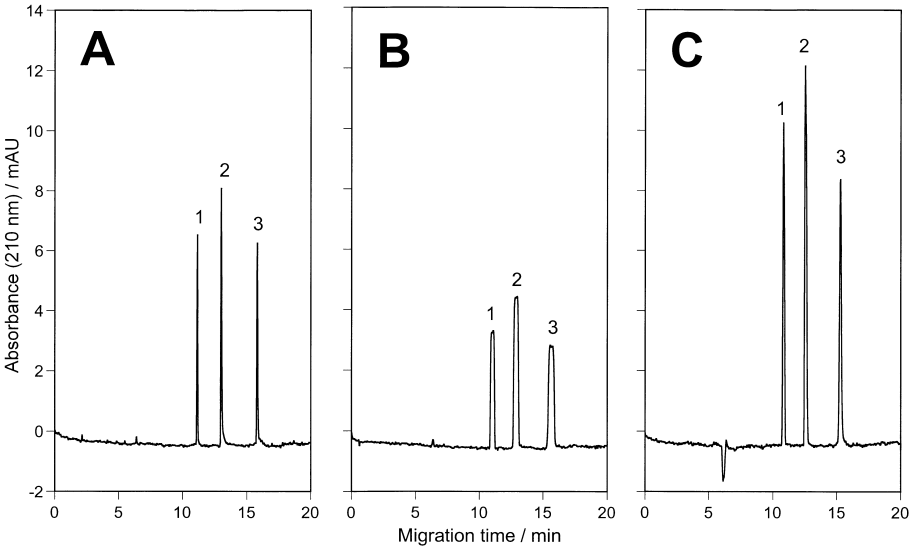

Fig. 1. Comparison of peak heights and shapes between different sample matrices. BGS, 50 m*M* phosphate (pH 7.0) containing 50 m*M* CTAC; sample matrix, (A, B) BGS, (C) water; injection time, (A) 1 s, (B, C) 30 s; concentration of samples, (A) nitrobenzene (peak 1, 157 ppm), resorcinol (peak 2, 122 ppm), 2-naphthol (peak 3, 58.5 ppm), (B, C) 10-fold dilution of samples in A; capillary, 61 cm (52.5 cm to detector)×50 μm I.D.; detection, 210 nm; applied voltage, −20 kV; temperature, 25°C.

increased with an increase in the injection time up to 50 s. However, for much longer injection time (60 s), peak heights leveled off and peaks showed asymmetric and distorted shapes. The 30 s injection (1.7 cm) was the most suitable in terms of peak shapes. This result confirmed previous studies [19,20], which suggested that the injected length of the sample zone was limited by the dispersive effect brought about by the local electroosmotic velocity mismatch between the low- and high-conductivity zones. LODs, percentage relative standard deviations (RSDs), and sensitivity enhancement factors in terms of peak heights (SEF_{height}) obtained for the test analytes with NSM (30 s injection) are summarized in Table 1. 2-Naphthol was eluted at the same migration time as that of Yellow OB. It indicates that 2-naphthol is totally associated with the TTAB micelle under this condition. Acceptable reproducibility was achieved, as RSD values obtained with five successive experiments in migration times, corrected peak areas, and peak heights were less than 7% for all analytes. All computed values of SEF_{height} for the test analytes with different retention factors were relatively close (~15 fold). SEF_{height} was therefore independent of retention factors in NSM. This is consistent with the result of the NSM using an anionic micelle [19].

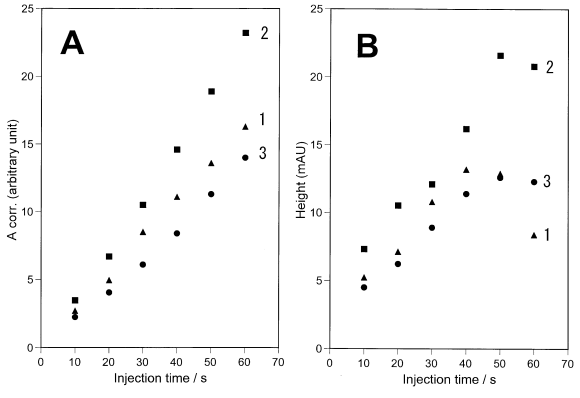

Fig. 2. Effects of injection time on corrected peak area (A) and peak height (B). Conditions are as in Fig. 1C except for injection time.

3.2. Sweeping

3.2.1. Sweeping of neutral and positively chargeable analytes

Fig. 3 shows the sweeping MEKC analysis of the three structurally related and hydrophobic neutral

Table 1
Limits of detection (LODs), RSDs, and SEF_{height} for the test samples in NSM[a]

	Nitrobenzene	Resorcinol	2-Naphthol
Calibration line[b]	$y=0.71x-0.54$	$y=0.97x+0.37$	$y=1.58x-0.32$
Correlation coefficient (r)	0.9984	0.9977	0.9996
LOD ($S/N=3$)	$7.15\cdot10^{-7}$ M	$5.90\cdot10^{-7}$ M	$2.77\cdot10^{-7}$ M
RSD ($n=5$)			
(a) Migration time (%)	0.63	0.66	0.64
(b) Peak height (%)	1.7	6.7	3.4
(c) Corrected peak area (%)	2.5	2.1	2.4
Retention factor (k)	2.73	6.01	∞
SEF_{height}[c]	15	14	13

[a] Conditions as in Fig. 1C.
[b] Calibration line: concentration (ppm)=slope·peak height (mAU)+y-intercept.
[c] SEF_{height}=(peak height obtained with concentration/peak height obtained with usual MEKC injection)·dilution factor.

steroids. In order to obtain a good separation between hydrocortisone and testosterone, methanol was added to the BGS. Note that the concentrations of analytes in Fig. 3B are 100-fold dilutions of those in Fig. 3A. Fig. 3A shows the electropherogram of a normal injection MEKC analysis. Detector responses were improved about 100-fold (~150-fold for testosterone) in terms of peak heights. Sweeping MEKC analysis of some steroids derivatives using an anionic micelle, sodium dodecyl sulfate (SDS), in the presence of EOF gave about 200-fold (for testosterone) sensitivity enhancement [9]. On the other hand, high sensitivity enhancement, about 1500-fold for testosterone, was obtained under suppressed EOF [8]. Table 2 summarizes the results of the LODs, RSDs, and SEF_{height} obtained for the test analytes with sweeping MEKC (6.27 cm injection length). Sensitivity enhancement factors were calculated by simply getting the ratio of the peak heights obtained from sweeping and normal injection and correction by the dilution factor. The LODs for the test steroids were in the range from 29 to 13 ppb ($S/N=3$). A high number of theoretical plates of $5.3\cdot10^5$ was obtained for testosterone. The high plate number is partly ascribed to the short length of the capillary used for the separation or to the short separation time after the focusing of the analyte zone.

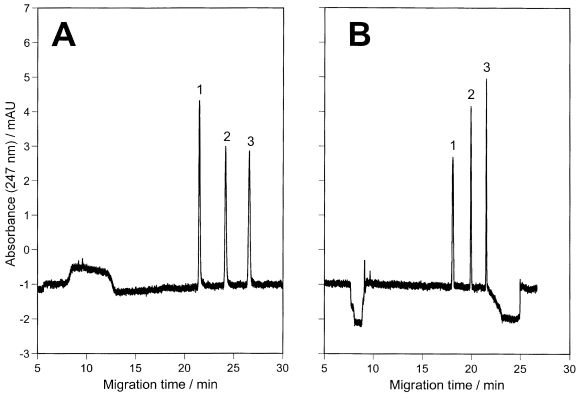

Fig. 3. Sweeping MEKC analysis of test steroids. BGS, 100 mM Tris–HCl (pH 7.0) containing 50 mM TTAB and 10% methanol; sample solution, steroids in Tris–HCl buffer (pH 7.0) having conductivity equal to that of the BGS (7.0 mS/cm); injected length, (A) 0.57 mm, (B) 6.27 cm; concentration of samples, (A) ~100 ppm, (B) ~1 ppm; identification of peaks, (1) cortisone, (2) hydrocortisone, (3) testosterone; detection, 247 nm; applied voltage, −15 kV. Other conditions as described in Fig. 1.

Fig. 4 shows the separation of isomers of *o*-, *m*-, *p*-nitroanilines by conventional (Fig. 4A) and sweeping MEKC (Fig. 4B). The BGS, a 100 mM Tris–HCl buffer (pH 7.0) containing 50 mM TTAB, provided complete separation of isomers of nitroanilines. On the contrary, when the anionic SDS micelle was employed, *m*-, *p*-nitroanilines were coeluted without baseline separation (data not shown). Concentrations of the analytes in Fig. 4B are 10-fold dilutions of those of Fig. 4A. Low sensitivity enhancement (~20-fold) were obtained due to low k values (around 4 for *m*-, *p*-nitroanilines and about 6 for *p*-nitroaniline).

3.2.2. Sweeping of anionic analytes

Sweeping of positively charged amines with anionic SDS micelles provided high k values because

Table 2
LODs, RSDs, and number of theoretical plates, and SEF_{height} for the test steroids[a]

	Cortisone	Hydrocortisone	Testosterone
Calibration line[b]	$y=2.50x+0.12$	$y=4.34x+0.17$	$y=5.76x-0.06$
Correlation coefficient (r)	0.9991	0.9989	0.9997
LOD ($S/N=3$)			
(a) ppb	29	17	13
(b) $\cdot 10^{-8}$	8.0	4.7	4.5
RSD			
(a) Migration time ($n=10$) (%)	1.7	1.8	1.9
(b) Peak height ($n=3$) (%)	4.4	4.4	7.2
(c) Corrected peak area ($n=3$) (%)	3.8	3.2	5.9
Number of theoretical plates	$8.7\cdot 10^4$	$2.4\cdot 10^5$	$5.3\cdot 10^5$
SEF_{height}[c]	65	120	150

[a] Conditions as in Fig. 3B.
[b] See Table 1.
[c] See Table 1.

of the strong electrostatic interaction between oppositely charged amines and SDS [9]. According to the same principle, sweeping of negatively chargeable analytes with cationic TTAB micelles will give high k values and the higher SEF. Fig. 5 shows that about 1000-fold sensitivity improvement was obtained for some aromatic carboxylic acids. The concentrations of analytes in Fig. 5B are 1000-fold dilutions of those of Fig. 5A. A usual injection (Fig. 5A) was included for comparison. The k values of negatively chargeable compounds in MEKC with an anionic SDS micelle were very small, e.g., 0.06 for benzoic acid and 0.08 for salicylic acid, due to the electrostatic repulsion between the anionic analytes and anionic SDS micelle [9].

Another negatively chargeable samples, naphthalenesulfonic acids (NSAs), were subjected to

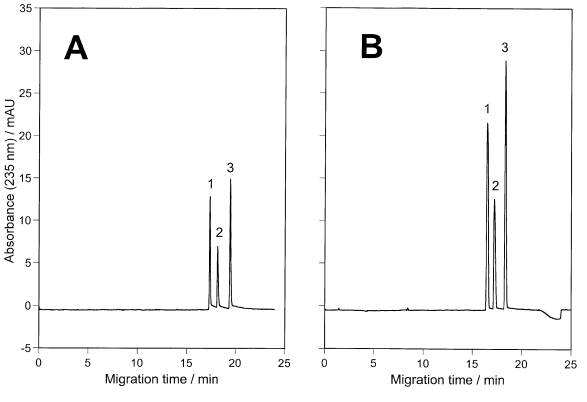

Fig. 4. Sweeping and separation of *o*-, *m*-, *p*-nitroanilines. BGS, 100 m*M* Tris–HCl (pH 7.0) containing 50 m*M* TTAB; sample solution, samples in Tris–HCl buffer (pH 7.0) having conductivity equal to that of the BGS (10.0 mS/cm); injected length, (A) 0.57 mm, (B) 2.28 cm (B); concentration of samples, (A) ~100 ppm, (B) ~10 ppm; identification of peaks, (1) *m*-nitroaniline, (2) *p*-nitroaniline, (3) *o*-nitroaniline; detection, 235 nm; applied voltage, −15 kV. Other conditions as described in Fig. 1.

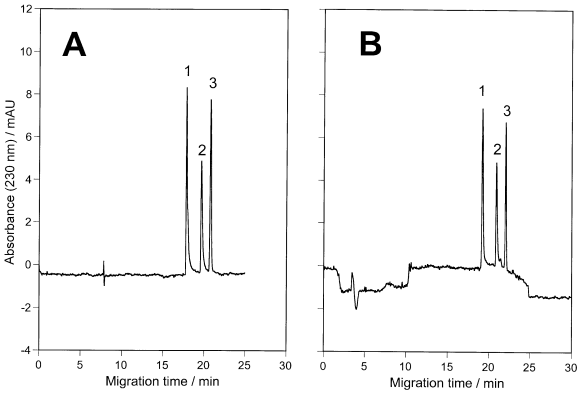

Fig. 5. Sweeping MEKC analysis of three aromatic carboxylic acids. BGS, 100 m*M* Tris–HCl (pH 7.0) containing 50 m*M* TTAB and 20% methanol; sample solution, acids in Tris–HCl buffer (pH 7.0) having conductivity equal to that of the BGS (6.20 mS/cm); injected length, (A) 0.57 mm, (B) 34.7 cm; concentration of samples, (A) salicylic acid (peak 1, 753 ppm), diphenylglycolic acid (peak 2, 936 ppm), 2-naphthoic acid (peak 3, 54 ppm), (B) 1000-fold dilution of samples in A; detection, 230 nm. Other conditions as described in Fig. 1.

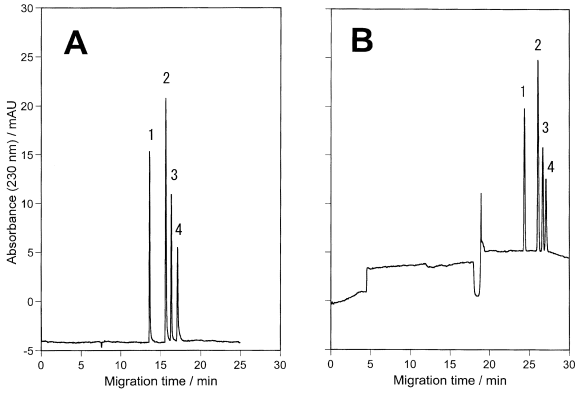

Fig. 6. Sweeping MEKC analysis of NSAs. BGS, 100 m*M* Tris–HCl (pH 7.0) containing 50 m*M* TTAB and 20% acetonitrile; sample solution, samples in Tris–HCl buffer (pH 7.0) having conductivity equal to that of the BGS (8.30 mS/cm); injected length, (A) 0.57 mm, (B) 45.6 cm; concentration of samples, (A) 2,6-NDSA (peak 1, 106 ppm), 1,5-NDSA (peak 2, 328 ppm), 2,7-NDSA (peak 3, 91 ppm), 1-NSA (peak 4, 112 ppm), (B) 1000-fold dilution of samples in A; detection, 230 nm; applied voltage, −15 kV. Other conditions as described in Fig. 1.

sweeping (see Fig. 6). Fig. 6A shows the electropherogram of normal injection MEKC analysis. The BGS was a 100 m*M* Tris–HCl buffer (pH 7.0) containing 50 m*M* TTAB and 20% (v/v) acetonitrile. As shown in Fig. 6A, the optimum concentration of acetonitrile was 20%, under that condition the four NSAs were completely separated. The migration order of the 1-NSA and NDSA indicates that the 1-NSA interact with cationic micelle more strongly than the NDSA. However, from the viewpoint of electrostatic interaction, it is unreasonable that the 1-NSA interact with cationic micelles more strongly than NDSA. In ion-exchange electrokinetic chromatography with polymer cations for the separation of the NSAs gave the reversed migration order of the 1-NSA and NDSA (the NDSA interacted with the polymer cation more strongly than the 1-NSA) [21]. However, the hydrophobic interaction may contribute more strongly to the incorporation of the naphthalenemonosulfonate ion by TTAB. It is difficult to reasonably explain the migration order without further study. The electropherogram obtained after the sweeping (45.6 cm injected) is depicted in Fig. 6B. Detector responses were improved about 700-fold in terms of peak heights. When the sample solution was more injected, peak heights leveled off and peaks showed incomplete separation. This is considered to be a result of the sample zone passed the detector before the complete concentration. Note that the concentrations of analytes in Fig. 6B are 1000-fold dilutions of those of Fig. 6A. A ghost peak, appeared before the peaks of interest (around 18 min) in Fig. 6B, is probably due to isotachophoretic focusing of ions or impurities in the sample solution [8]. As can be observed by comparison of Fig. 6A and B, the

Table 3
LODs, RSDs, number of theoretical plates, and SEF_{height} for the test NSAs[a]

	2,6-NDSA	1,5-NDSA	2,7-NDSA	1-NSA
Calibration line[b]	$y=0.10x+0.54$	$y=0.063x+0.16$	$y=0.083x+0.33$	$y=0.13x+0.42$
Correlation coefficient (r)	0.9994	0.9996	0.9959	0.9998
LOD ($S/N=3$)				
(a) ppb	0.58	0.96	0.72	0.47
(b) $\cdot 10^{-9}$	1.7	2.6	2.2	2.0
RSD				
(a) Migration time ($n=9$) (%)	0.90	0.92	0.98	0.93
(b) Peak height ($n=3$) (%)	3.3	6.2	6.3	3.2
(c) Corrected peak area ($n=3$) (%)	2.5	0.17	1.0	0.38
Number of theoretical plates	$1.9\cdot10^5$	$2.0\cdot10^5$	$2.0\cdot10^5$	$1.9\cdot10^5$
SEF_{height}[c]	750	760	750	670

[a] Conditions as in Fig. 6B.
[b] See Table 1.
[c] See Table 1.

change in migration time is probably due to change in the magnitude of EOF between the sample and BGS zones.

As shown in Table 3, we obtained the LODs of the test NSAs in the range from 0.96 to 0.47 ppb ($S/N=3$) with UV detection without any preconcentration procedure. These LODs are almost the same level as that given in a previous report, where laser-induced fluorescence detection was used in combination with solid-phase extraction for the environmental analysis of NSAs in river water samples [22,23]. The plate numbers of the peaks were in the range from 190 000 to 200 000 and the resolution was almost unaffected by sweeping even with long injected lengths close to the effective length of the capillary. Table 3 summarizes the results of sweeping, which are acceptable, except for the SEF. The SEF of 1-NSA is smaller than that of NDSAs in spite of the retention factor higher than that of NDSAs. This result is inconsistent with the theory; the SEF increases with an increase in the retention factor [8,9]. Therefore, further investigations are needed to explain this discrepancy.

4. Conclusion

In the present study, we have shown that cationic surfactants can be used as pseudostationary phases for on-line sample concentration in MEKC without suppression of EOF. Ten to 100-fold sensitivity enhancements were obtained with NSM and sweeping of neutral analytes. Sweeping of some anionic analytes gave high concentration factors up to 1000-fold without any preconcentration step. Therefore, application of sweeping with cationic surfactants for anionic analytes is promising. Previous results have shown that high concentration factors are obtained under suppressed EOF by simply lowering the pH for anionic SDS micelles [7–9]. However, it was difficult to suppress EOF even under acidic conditions in the presence of cationic surfactants.

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