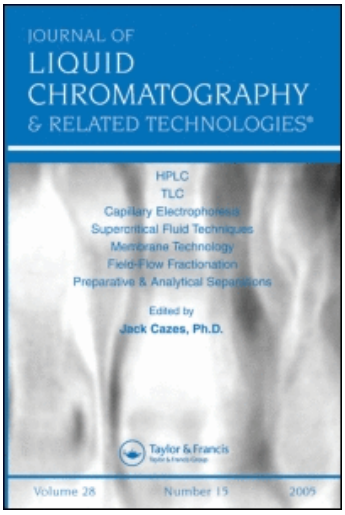

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Enantiomeric Separation of a Series of β-Lactams Using Capillary Zone Electrophoresis

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Enantiomeric Separation of a Series of β-Lactams Using Capillary Zone Electrophoresis

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Abstract: Twelve racemic substituted β-lactam compounds were examined via capillary zone electrophoresis using three chiral selectors: sulfated α-cyclodextrin (SAC), sulfated β-cyclodextrin (SBC), and carboxymethyl β-cyclodextrin (CMBC). Ten of the twelve β-lactams are separated and each of the ten compounds is baseline separated by at least one of the chiral run buffer additives under optimized conditions. SAC was found to be the most effective chiral selector, baseline separating seven of the analytes and partially separating another two. The concentration of the chiral selector had a prominent effect on the resolution, generally higher concentrations gave longer migration times and better resolutions. Addition of organic modifier also increased analyses time but gave lower resolution. Decreasing the pH of the run buffer generally decreased analyses times as well as resolution. Decreasing the applied voltage generally improved resolution.

Keywords: Capillary electrophoresis (CE), β-Lactam, Sulfated α-Cyclodextrin (SAC), Sulfated β-cyclodextrin (SBC), Carboxymethyl β-cyclodextrin (CMBC), Pseudophase separations

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INTRODUCTION

β-Lactams have been a topic of interest in recent years because of their wide application in both pharmaceutical science and synthetic organic chemistry. They are widely used as antibacterial agents and many studies have been published on their antibacterial activity, action mechanism, and clinical applications.[1–7] β-lactams and their derivatives also are widely used as intermediates in the organic synthesis of heterocyclic compounds of medical and chemical interest,[8] amino acids,[9–11] short peptide segments,[12] alkaloids,[13] etc. The synthesis of various β-lactam compounds both chemically[14,15] and through biosynthetic processes[16] has been reported.

Since the two enantiomers of a compound can have very different behaviors in a chiral environment, as in a physiological matrix, one enantiomer of a drug can have different effects than its antipode. Since many chiral compounds are first synthesized in racemic form, it is necessary to separate their enantiomers. Also enantioselective methods are needed for the determination of enantiomeric purities, quality control applications, and some pharmacokinetic and pharmacodynamic studies.[17–19] However, as two enantiomers have identical chemical and physical properties in non-chiral environments, the separation of enantiomers can be challenging. Separation of lactam enantiomers has been reported by HPLC with different CSPs.[20–26] Huang et al.[27] used a β-cyclodextrin based CSP to separate water soluble β-lactams. The β-lactams presented in this paper were separated using HPLC by Péter et al.[28] and Sun et al.[29] using macrocyclic glycopeptide and cyclodextrin CSPs, respectively. However, to our knowledge, there has been no report on these separations of the β-lactam enantiomers by capillary electrophoresis (CE).

As is well known, CE provides rapid analyses with high efficiencies and often high resolutions. Chiral CE, is becoming a popular method for enantiomeric separation.[30–32] Cyclodextrins (CDs) are cyclic oligosaccharides with six (α-CD), seven (β-CD), eight (γ-CD) glucopyranose units forming a hollow truncated cone structure. The open cavity possesses a hydrophobic interior and hydrophilic external surface with five chiral centers per glucose unit. The idea of using CDs as chiral selectors in CE was borrowed from early LC work.[33–36] Because of their excellent stability over a wide pH range (3–14) and minimal UV absorption, CDs and their derivatives have developed into the most prevalent and widely useful class of chiral selectors in CE.[30,37–40] In our study, three anionic chiral selectors, sulfated α-cyclodextrin (SAC), sulfated β-cyclodextrin (SBC), and carboxymethyl β-cyclodextrin (CMBC) were added to the run buffer in order to achieve enantiomeric separations in the capillary zone electrophoresis (CZE) mode. Compared to the results obtained by HPLC on cyclodextrin columns,[29] CE achieved higher resolution under optimized conditions.

EXPERIMENTAL

Materials

The 12 racemic β-lactams, *cis*-6-azabicyclo[3.2.0]heptan-7-one (1), *cis*-7-azabicyclo[4.2.0]octan-8-one (2), *cis*-7-azabicyclo[4.2.0]oct-3-en-8-one (3), *cis*-7-azabicyclo[4.2.0]oct-4-en-8-one (4), *cis*-8-azabicyclo[5.2.0] nonan-9-one (5), *cis*-9-azabicyclo[6.2.0]decan-10-one (6), *cis*-9-azabicyclo [6.2.0]dec-4-en-10-one (7), *cis*-3,4-benzo-6-azabicyclo[3.2.0]heptan-7-one (8), *cis*-4,5-benzo-7-azabicyclo[4.2.0]octan-8-one (9), *cis*-5,6-benzo-8-azabicyclo[5.2.0] nonan-9-one (10), *exo*-3-azatricyclo[4.2.1.$0^{2,5}$]nonan-4-one (11) and *exo*-3-azatricyclo [4.2.1.$0^{2,5}$]non-7-en-4-one (12) (Structures–refer to Table 1) were prepared in our laboratory by cycloaddition of chlorosulfonyl isocyanate to the sorresponding cycloalkanes and cycloalkadienes by Peter el al.[28,41,42]; α-cyclodextrin hydrate, sulfated, sodium salt and β-cyclodextrin, sulfated, sodium salt (SAC and SBC) were purchased from Aldrich Chemical Company (Milwaukee, WI, USA). SBC is with a degree of substitution of 7–11 moles/mole β-CD. Sodium phosphate, dibasic anhydrous, and sodium hydroxide were all obtained from Fisher Scientific (St. Louis, MO, USA). Capillaries were purchased from Polymicro Technologies (Phoenix, AZ, USA).

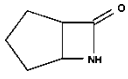
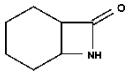
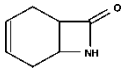
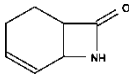
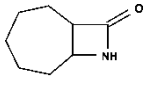
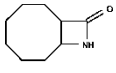
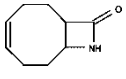
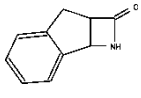
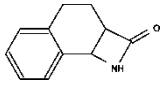
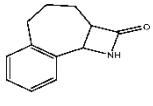
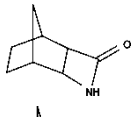
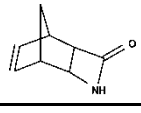
Equipment

All the separations were performed on a Beckman P/ACE 5000 (Fullerton, CA, USA) or P/ACE 2050 CE instrument (Fullerton, CA, USA) using normal polarity. Capillaries with the dimension of 50 μm ID × 358 OD, 37 cm in length (30 cm to detector) were used. All samples were detected by UV absorbance at 214 nm. All the data were analyzed with Beckman System Gold Software.

Method

The separation resolution (Rs) was calculated as: $Rs = 2(t_{m2} - t_{m1})/(w_1 + w_2)$, where t_{m2} and t_{m1} are the migration times of the second and first observed enantiomers, w_1 and w_2 are the extrapolated peak width at baseline. The apparent mobility μ_{app} was calculated as: $\mu_{app} = L^*L_{total}/(t_m{}^*V)$, and the electroosmotic mobility μ_{os} was calculated as: $\mu_{os} = L^*L_{total}/(t_{os}{}^*V)$ where L is the length of capillary from the injection end to the window, 30 cm, L_{total} is the total length of capillary, 37 cm, t_{os} is the migration time of EOF marker, t_m is the enantiomer migration time, and V is the voltage applied across the capillary. The efficiency N was calculated as $N = 16^*(t_{m1}/w_1)^2$. The selectivity α was calculated as $\alpha = t_{m2}/t_{m1}$. Anhydrous dibasic sodium phosphate was dissolved in deionized, filtered water to make a 5 mM solution and adjusted to the desired pH with 0.1 M hydrochloric acid or

Table 1. Separations of β-lactams using SAC. Separation conditions: 154 mg/mL SAC in 5 mM sodium phosphate buffer, pH 8.0; +6 kV. Other details refer to experimental part

	154 mg/mL SAC		
Structure	t_{m1}(min)	t_{m2}(min)	Rs
1 	33.69	36.30	2.4
2 	33.11	36.55	1.8
3 	22.55	24.72	2.9
4 	29.44	33.42	3.3
5 	—		
6 	24.08	25.90	2.1
7 	15.77	16.55	1.7
8 	19.90	21.04	2.2
9 	22.15	22.96	1.0
10 	21.74	22.36	1.1
11 	30.26	32.66	1.5
12 	22.57	22.84	0.2

0.1 M sodium hydroxide, and used as buffer solutions to maintain the pH during running. Sample solutions were made by dissolving samples directly in deionized water (from 1 to 5 mg/mL).

RESULTS AND DISCUSSION

Enantiomeric Separation of Substituted β-Lactam Compounds by CZE

As can be seen from the analyte structures in Table 1, each compound consists of a polar lactam moiety fused to a hydrophobic ring system. Hence, these compounds are somewhat soluble in the bulk run buffer solution and can form inclusion complexes with cyclodextrins as well. To obtain an enantiomeric separation, the analyte must have a different mobility than the chiral selectors.[38] Since these chiral analytes have no ionizable groups and are uncharged in buffer solution, the simplest CE system would utilize a charged chiral selector. In the normal polarity mode, the bulk solution moves toward the cathode due to electroosmotic flow (EOF), while the anionic chiral cyclodextrin, moves towards the anode, providing two phases (a bulk solution phase and a cyclodextrin pseudophase) for the analyte distribution.

Effect of Chiral Selector Structure and Analyte Structure

The results of the optimized separations are presented in Tables 1–3. This includes the structures of the β-lactams, migration times, and resolutions

Table 2. Separations of β-lactams using SBC. Separation conditions: 60 mM SBC in 5 mM sodium phosphate buffer, pH 8.0; +7 kV. Other details refer to experimental part

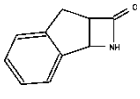
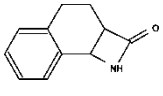
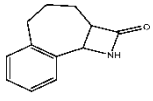
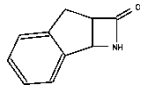
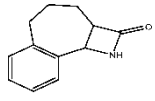
	60 mM SBC		
Structure	t_{m1}(min)	t_{m2}(min)	Rs
8 	10.52	10.68	0.7
9 	11.30	14.00	3.4
10 	12.49	15.19	9.5

Table 3. Separations of β-lactams using CMBC. Separation conditions: 20 mM CMBC in 5 mM sodium phosphate buffer, pH 8.0; +10 kV. Other details refer to experimental part

	20 mM CMBC		
Structure	t_{m1}(min)	t_{m2}(min)	Rs
8 	9.11	9.53	1.5
10 	10.68	10.97	1.3

under optimized separation conditions. Corresponding electropherograms under optimized conditions using different kinds of chiral selectors are shown in Figures 1–3 (Fig. 1 for SAC, Fig. 2 for SBC, and Fig. 3 for CMBC).

As shown in Tables 1–3 and Figures 1–3, ten of the twelve racemic compounds are separated and each of them is baseline separated using at least one of the chiral selectors under optimized conditions. SAC is the best overall chiral selector for enantioseparation of the substituted β-lactams, giving 8 baseline separations and 2 partial separations. Among these

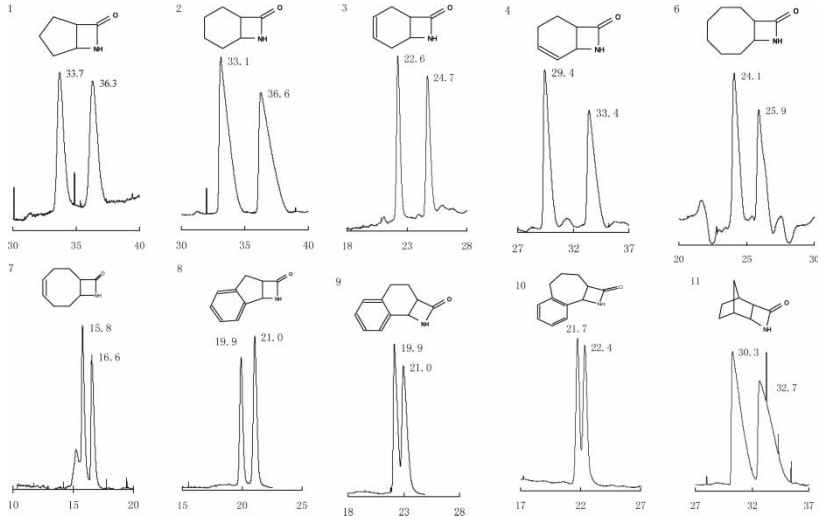


Figure 1. Electropherograms of β-lactams **1**$\sim$**4** and **6**$\sim$**11**. Experimental conditions: 154 mg/mL SAC in 5 mM sodium phosphate concentration buffer, pH 8.0; +6 kV; Details refer to experimental part.

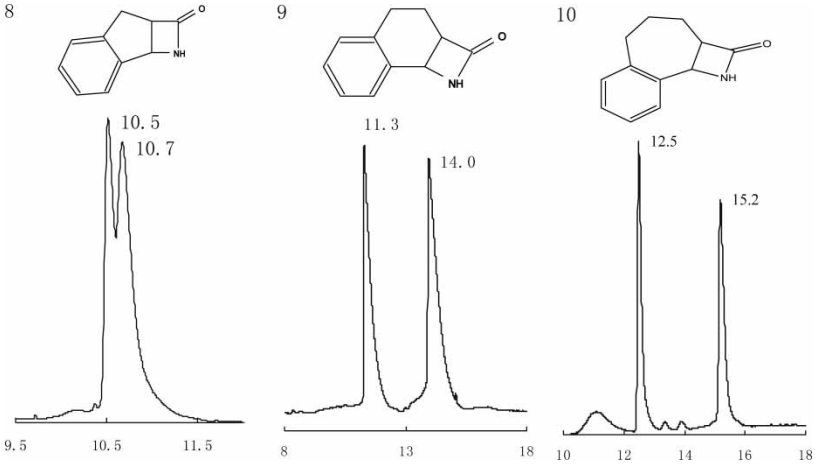


Figure 2. Electropherograms of β-lactams **8**$\sim$**10**. Experimental conditions: 60 mM SBC in 5 mM sodium phosphate buffer, pH 8.0; +7 kV; Details refer to experimental part.

separations, the highest resolution, Rs = 9.5, was achieved for compound **10** using SBC within 16 minutes. SBC produces baseline or partial separations only for **8**, **9,** and **10**, which are tricyclic compounds that possess an aromatic ring. CMBC separates two of the tricyclic aromatic β-lactams (i.e., **9** and **10**). Neither SBC nor CMBC separates any compound that does not contain an aromatic ring.

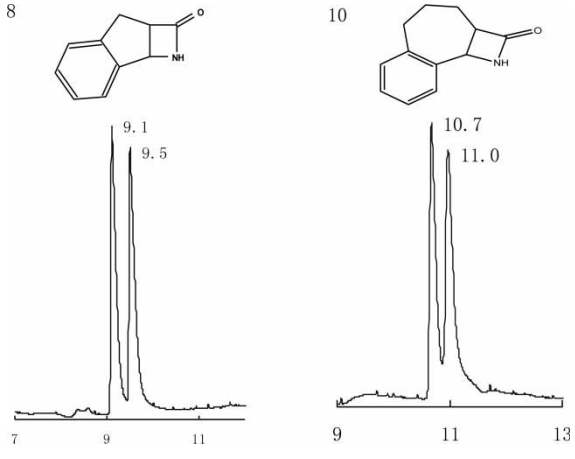


Figure 3. Electropherograms of β-lactams **8** and **10**. Experimental conditions: 20 mM CMBC in 5 mM sodium phosphate buffer, pH 8.0; +10 kV; Details refer to experimental part.

In aqueous solution, hydrophobic analytes can form hydrophobic inclusion complexes with cyclodextrins.[43,44] To obtain enantioselectivity, additional simultaneous interactions such as hydrogen bonding and steric interactions must occur, often at the mouth of the cyclodextrin cavity.[34,43,44] Therefore, to obtain enantiomeric separation, it is beneficial for the hydrophobic group of the analyte to have a comparable size with the cyclodextrin cavity.[34,43,44] This may explain why only the three tricyclic compounds with a rigid aromatic ring (compounds **8**, **9**, and **10**, Table 1) are separated with SBC or CMBC. Compounds **1**$\sim$**7** have only a cyclic alkane ring attached to the lactam moiety, compounds **11** and **12** are relatively small tricyclic entities. As observed (results not shown), all the analytes had a longer migration time than EOF marker (DMSO) when SBC or CMBC were present. This suggests that all the compounds formed an inclusion complex with SBC and CMBC. However, no enantioseparations for compounds **1**–**7**, **11**–**12** were observed. As found previously, this is probably due to the fact that they can easily undergo free rotation in the cavity of the CD.[34,43]

Effect of Concentration of Chiral Selectors

The concentration of the chiral selector has a pronounced effect on the separation of the twelve chiral lactams. The separation of compound **10**

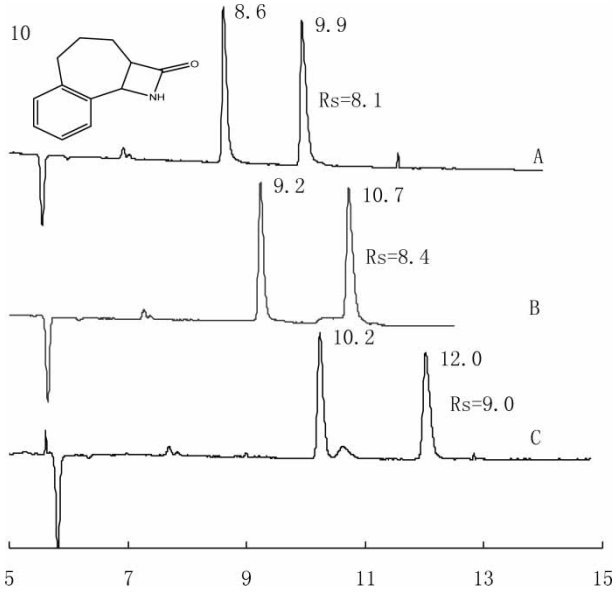


Figure 4. Electropherograms of β-lactam **10** separated at different SBC concentration: A: 50 mM SBC; B: 60 mM SBC; C: 70 mM SBC. Experimental conditions: 5 mM sodium phosphate buffer, pH 8.0; +10 kV. Details refer to the experimental part.

with SBC is used as an example. Electropherograms and other separation data for compound **10** under different SBC concentrations are shown in Fig. 4. Other factors such as buffer concentration, pH, and applied voltage are kept the same in order to focus on the effect of selector concentration. According to the experimental data (Fig. 4), higher concentrations of the chiral selector generally increase the migration times. This is due to the fact that, as the concentration of chiral selector increases, a higher percentage of analyte will be included into the CDs. This inclusion complex has a mobility opposite that of the EOF, thereby increasing the migration time of any neutral analyte that forms a dynamic complex.[45] Also, the higher amounts of SBC increase the ionic strength and viscosity of the run buffer. This slows the EOF, which also contributes to longer migration times. As can be seen from Fig. 4, as the concentration of SBC increases from 50 mM to 70 mM, the resolution also increases from 8.1 to 9.0. This trend is consistent with the work by Wren and Rowe.[46,47]

Effect of Organic Modifier

Organic modifiers can affect enantiomeric separations in many ways.[40] As can be seen from Table 4, upon addition of ethanol, the EOF is decreased, as are the migration times of analytes. The selectivity, α, and resolution, Rs, both decrease when higher percentages of ethanol are present. This can be explained by the fact that organic additives can modify the interaction between the CD cavity and analyte.[40] The ethanol tends to compete with the analyte for the CD cavity, thus decreasing the binding constants between the analyte and CD.[34] In turn, the mobility difference between the two enantiomers, and thus the selectivity, decreases as does the resolution.

Effect of Running Buffer pH

The pH of the run buffer is known to affect the separation in several ways. The pH controls the charge state of ionizable analytes and the chiral selectors.[38] It

Table 4. Effect of addition of organic modifier ethanol on the separation of β-lactam **10**. Separation conditions: 60 mM SBC in 5 mM sodium phosphate buffer, pH 7.2; +5 kV

EtOH V/V	$t_{m1(min)}$	$t_{m2(min)}$	$t_{eo(min)}$	Rs	N	α
0%	13.60	16.30	10.54	8.9	38000	1.20
5%	15.82	18.10	13.07	7.0	40000	1.14
10%	17.69	19.43	15.43	4.8	41000	1.10

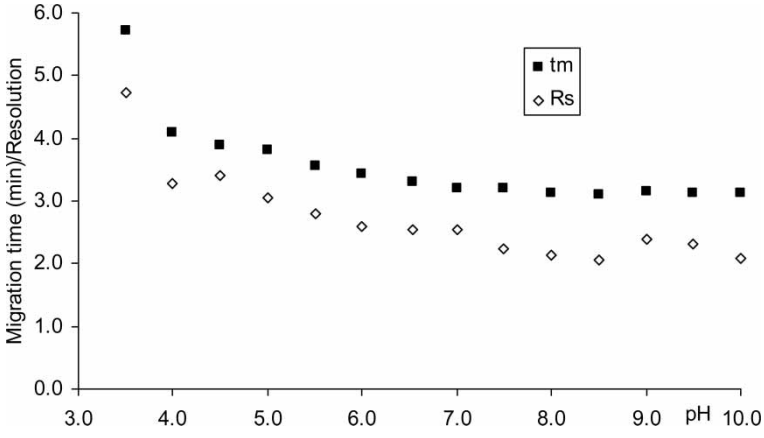


Figure 5. Effect of buffer pH when separating β-lactam **10**. Conditions: 20 mM SBC in 5 mM phosphate buffer, +10 kV. Details refer to the experimental part.

also controls the magnitude of the EOF,[48] which in turn affects the time of the separation. Figure 5 shows the effect of pH when SBC is used to separate compound **10**. All other parameters are kept the same while the running buffer pH varies from 3.5 to 10.0. As can be seen from the graph, when the pH is increased, generally both the resolution and analyses time decrease. This is due to the fact that, electroosmotic mobility, μ_{os} is increased at higher pH. As reported by Rizzi,[49] the selectivity is the ratio of the apparent mobility of the two enantiomers, $\alpha = \mu_{app1}/\mu_{app2}$ (>1), while $\mu_{app} = \mu_e + \mu_{os}$, in which μ_e is the electrophoretic mobility due to its binding to cyclodextrin. Therefore, higher pH increases μ_{os} and thus increases both μ_{app1} and μ_{app2} in same amount. Overall, the enantioselectivity is decreased and it also decreases the resolution.

Effect of Applied Voltage

The applied voltage also affects the enantioseparation by altering the efficiency and selectivity. As the applied voltage decreases, the current will decrease, thereby decreasing Joule heating, which in turn suppresses the adverse effect of parabolic temperature profile inside the capillary and thus improves the efficiency.[48] At the same time, when the voltage is decreased, the migration time will increase, which allows more time for analyte diffusion which can decrease efficiency.[48] Therefore, there is an optimal applied voltage when the combination of the two factors is minimized. Table 5 summarizes the results when using 20 mM SBC to separate compound **9**. As shown in Table 5, when voltage is decreased from 16 kV to 4 kV, the efficiency first increases and then decreases, reaching an

Table 5. Effect of applied voltage on the separation of β-lactam **9**. Separation conditions: 20 mM SBC in 5 mM sodium phosphate buffer, pH 7.2

Voltage(kV)	$t_{m1(min)}$	$t_{m2(min)}$	Rs	N	α
16	1.55	1.60	1.2	19000	1.03
15	1.76	1.83	1.3	22000	1.04
14	2.00	2.09	1.6	25000	1.04
12	2.52	2.64	2.0	28000	1.05
11	3.01	3.18	2.3	30000	1.05
10	3.48	3.69	2.6	33000	1.06
9	4.06	4.32	2.8	34000	1.06
8	4.74	5.06	3.0	35000	1.07
7	5.62	6.01	3.0	34000	1.07
6	6.77	7.25	3.1	34000	1.07
5	8.16	8.75	3.1	32000	1.07
4	10.68	11.48	3.1	30000	1.08

optimum at a voltage of 8 kV. The selectivity term also increases when the voltage is decreased. Therefore, the resolution, which is the combination of efficiency and selectivity increased as the voltage is decreased, and then reaches a plateau between voltages of 6 kV to 4 kV.

CONCLUSION

The separation of twelve racemic, substituted β-lactam compounds were examined via capillary zone electrophoresis using SAC, SBC, and CMBC as chiral selectors. Ten of the twelve compounds are separated and optimized to baseline. Overall, SAC is the most effective chiral selector, separating the greatest number of compounds as well as obtaining the greatest number of baseline separations. SBC and CMBC only separate the three tricyclic aromatic lactams but none of the other smaller aliphatic substituted lactams in this group. Increasing chiral selector concentration is the most effective way to improve resolution but it also increases the analyses time. Addition of organic modifier decreases resolution and increases the analyses times. Higher pHs accelerate the analyses but also hurt resolution. Decreasing voltage can affect efficiency and improve enantioselectivity. Generally higher resolution can be obtained at lower voltages.

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