http://dx.doi.org/10.5012/bkcs.2012.33.10.3497

Enantiomeric Separation of 1-(Benzofuran-2-yl)alkylamines on Chiral Stationary Phases Based on Chiral Crown Ethers

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Received July 13, 2012, Accepted July 26, 2012

Key Words : Chiral stationary phase, Chiral crown ether, Enantiomeric separation, Liquid chromatography, 1-(Benzofuran-2-yl)alkylamines

Optically active chiral amines are important as building blocks for pharmaceuticals and as scaffolds for chiral ligands and, consequently, many efforts have been devoted to the development of efficient methods for their preparation. For example, reduction of amine precursors with chiral catalysts,[1] enzymatic kinetic resolution or dynamic kinetic resolution of racemic amines[2] and the direct amination of ketones with transaminases[3] have been developed as the efficient methods for the preparation of optically active chiral amines. During the process of developing or utilizing optically active chiral amines, the methods for the determination of their enantiomeric composition are essential. Among various methods, liquid chromatographic resolution of enantiomers on chiral stationary phases (CSPs) have been known to be one of the most accurate and economic means for the determination of the enantiomeric composition of optically active chiral compounds.[4] Especially, CSPs based on chiral crown ethers have been successfully used for the resolution of racemic primary amines.[5] For example, CSPs based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid (CSP **1**, Figure 1) or (3,3'-diphenyl-1,1'-binaphthyl)-20-crown-6 (CSP **2** and CSP **3**, Figure 1) have been known to be quite effective for the resolution of cyclic and non-cyclic amines, various fluoroquinolone antibacterials containing a primary amino group, tocainide (antiarrhythmic agent) and its analogues, aryl-a-amino ketones and 3-amino-1,4-benzodiazepin-2-ones.[6,7]

Optically active 2-substituted benzofurans might be the precursors of biologically active compounds,[8] and the preparation of optically active 2-substituted benzofurans required during the development of chiral drugs has been reported by a limited number of papers.[9] More recently, the method of preparing 1-(benzofuran-2-yl)alkylamines, one type of 2-substituted benzofurans, was reported.[10] However, the method for the liquid chromatographic resolution of 1-(benzofuran-2-yl)alkylamines on CSPs based on chiral crown ethers has not been reported yet. In this study, we wish to apply the three CSPs (CSPs **1**, **2** and **3**) to the liquid chromatographic resolution of 1-(benzofuran-2-yl)alkylamines and wish to compare their chiral recognition effici-

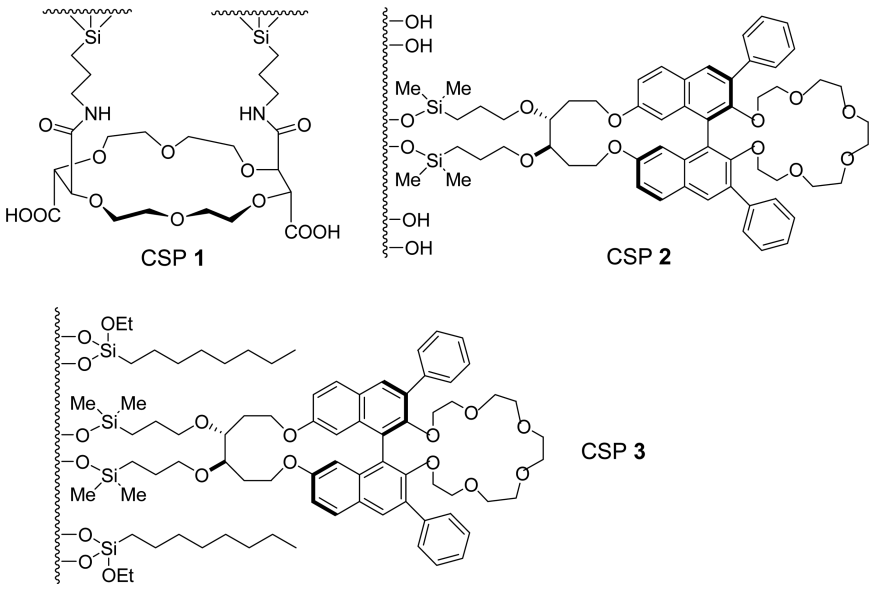

Figure 1. Structures of CSP**1**, CSP **2** and CSP **3**.

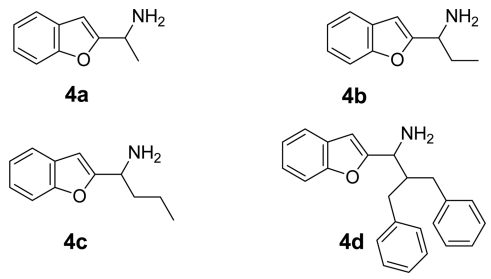

Figure 2. Structures of 1-(benzofuran-2-yl)alkylamines (**4a-4d**).

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1-(Benzofuran-2-yl)alkylamines (**4a-4d**, Figure 2) were prepared by the reductive amination of 2-benzofuranyl methyl ketone or by the mono- or dialkylation of 2-benzofuranyl methyl ketone and then by the reductive amination of the resulting 2-benzofuranyl alkyl ketone as shown in Scheme 1.

1-(Benzofuran-2-yl)alkylamines (**4a-4d**) shown in Figure 2 were resolved on CSPs **1**, **2** and **3**. After testing various mobile phase conditions, 80% methanol in water containing 10 mM perchloric acid and 1 mM ammonium acetate was selected as a most widely applicable mobile phase. The acidic modifier (perchloric acid) added to the mobile phase has been used to protonate the primary amino group of analytes.[5] The enantioselective complexation of the resulting primary ammonium ions ($R\text{-}NH_3^+$) of analytes inside the cavity of the crown ether ring of the CSP has been known to be essential for the chiral recognition.[5] Without ammonium acetate in mobile phase, the retention times of analytes were very long. Consequently, ammonium acetate was added to the mobile phase to control the retention time of analytes.[5] Competition between ammonium ion and a primary ammonium ion ($R\text{-}NH_3^+$) of analytes for the complexation inside the cavity of the crown ether ring of the CSP is expected to reduce the retention times of analytes.

The chromatographic resolution results are summarized in Table 1. All of 1-(benzofuran-2-yl)alkylamines (**4a-4d**) were resolved quite well on CSP **1**. However, analyte **4a** was only slightly resolved on CSP **2** while other three 1-(benzofuran-2-yl)alkylamines (**4b-4d**) were not resolved at all. Analytes **4a** and **4d** were also base-line resolved on CSP **3** even though their separation factors (α) and resolutions (R_S) were much inferior to those on CSP **1** and analyte **4c** was not resolved at all on CSP **3**. As an example, the comparison of the chromatograms for the resolution of **4a** on CSPs **1**, **2** and **3** is illustrated in Figure 3. From these results, CSP **1** is concluded to be quite useful in the resolution of 1-(benzofuran-2-yl)alkylamines while CSP **2** or CSP **3** is concluded to be limited in their general use in the resolution of 1-(benzofuran-2-yl)alkylamines.

The retention factors (k_1) for the resolution of 1-(benzofuran-2-yl)alkylamines (**4a-4d**) on CSPs **1**, **2** and **3** are quite dependent on the alky group of analytes. As the length of the alkyl group attached to the chiral center of analytes increases from methyl to ethyl and then propyl, the retention factors (k_1) usually decrease on CSPs **1**, **2** and **3**. When the primary ammonium ion ($R\text{-}NH_3^+$) of analytes forms complex inside the cavity of the crown ether ring of the CSPs, the sterically

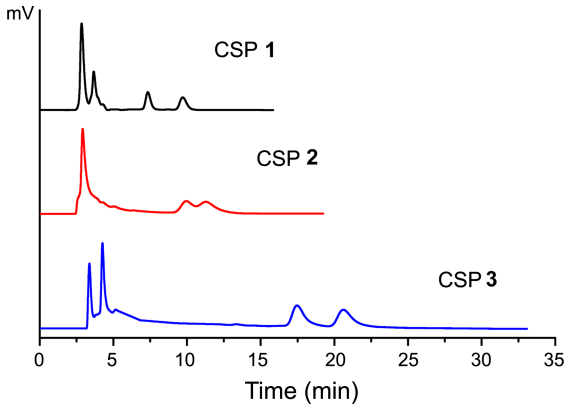
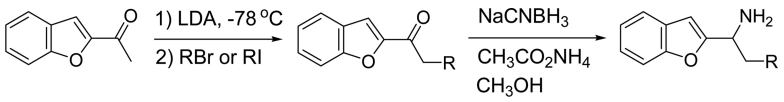


Figure 3. Chromatograms for the resolution of 1-(benzofuran-2-yl)ethylamines (**4a**) on CSP **1**, CSP **2** and CSP **3**. Mobile phase: 80 % Methanol in water containing perchloric acid (10 mM) and ammonium acetate (1 mM). Flow rate: 0.5 mL/min. Temperature: 20 °C. Detection: 254 nm UV.



Scheme 1. The scheme for the preparation of 1-(benzofuran-2-yl)alkylamines.

Table 1. Resolution of 1-(benzofuran-2-yl)alkylamines (**4a-4d**) on CSP **1**, CSP **2** and CSP **3**[a]

Analytes	CSP **1**			CSP **2**			CSP **3**		
	k_1	α	R_S	k_1	α	R_S	k_1	α	R_S
4a	1.63	1.52	3.08	2.11	1.21	0.75	2.59	1.25	1.76
4b	1.44	1.39	1.72	1.85	1.00	-	2.07	1.12	0.77
4c	1.40	1.41	2.36	1.77	1.00	-	2.15	1.00	-
4d	2.61	1.63	3.72	2.91	1.00	-	6.37	1.13	1.07

[a]Mobile phase: 80% Methanol in water containing perchloric acid (10 mM) and ammonium acetate (1 mM). Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer. α: Separation factor. R_S: Resolution.

Table 2. Resolution of 1-(benzofuran-2-yl)alkylamines (**4a-4d**) on CSP **1** with the variation of methanol content in mobile phase[a]

Methanol content	4a			4b			4c			4d		
	k_1		R_S	k_1		R_S	k_1	a	R_S	k_1	a	R_S
80%	1.63	1.52	3.08	1.44	1.39	1.72	1.40	1.41	2.36	2.61	1.63	3.72
50%	2.23	1.42	2.45	1.80	1.32	1.19	1.86	1.30	1.53	5.92	1.56	3.45
30%	3.17	1.29	1.44	2.53	1.22	0.87	3.32	1.20	1.18	13.32	1.50	2.16

[a]Mobile phase: 80%, 50% or 30% Methanol in water containing perchloric acid (10 mM) and ammonium acetate (1 mM). Flow rate: 0.5 mL/min. Detection: 254 nm UV. Temperature: 20 °C. k_1: Retention factor of the first eluted enantiomer. α: Separation factor. R_S: Resolution.

bulky or long alkyl group seems to hinder the complexation. In this instance, the retention factors (k_1) can be reduced when the length of the alkyl group attached to the chiral center of analytes increases from methyl to ethyl and then propyl. However, when the alkyl group becomes highly lipophilic as analyte **4d**, the lipophilic interaction of analyte with the CSPs seems to become important for the retention of analytes under reversed mobile phase condition. Consequently, the retention factors (k_1) for the resolution of analyte **4d** should be greater than those for the resolution of other analytes. Especially, the retention factor for the resolution of analyte **4d** is quite large on CSP **3**, which is highly lipophilic because of the residual silanol group-protecting *n*-octyl groups on the silca surface of the CSP.[7b]

The importance of the lipophilic interaction of analytes with the CSPs for the retention of analytes might be proved by changing the polarity of mobile phase. When the polarity of mobile phase was increased by decreasing the content of methanol in mobile phase, the retention factors (k_1) for the resolution of analytes **4a-4d** increased quite much while the separation factors (a) and resolutions (R_S) decreased as shown in Table 2. These results clearly demonstrate the importance of the lipophilic interaction of analytes with the CSPs for the retention of analytes. However, the lipophilic interaction of analytes with the CSP seems to be non-enantioselective and, consequently, not to make a contribution to the chiral recognition.

In conclusion, CSP **1** based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid can be successfully used for the resolution of 1-(benzofuran-2-yl)alkylamines. However, CSP **2** or CSP **3** based on (3,3'-diphenyl-1,1'-binaphthyl)-20-crown-6 is limited in its general use in the resolution of 1-(benzofuran-2-yl)alkylamines.

Experimental

Chromatography was performed with an HPLC system consisting of a Waters model 510 HPLC Pump (Milford, MA, USA), a Rheodyne model 7725i injector (Rohnert Park, CA, USA) with a 20 μL sample loop, Waters 486 tunable absorbance detector (Milford, MA, USA) and Younglin Autochro data module (Software: YoungLin Autochro-WIN 2.0 plus) (Seoul, Korea). Chiral columns packed with CSP **1**, CSP **2** and CSP **3** were available from prior study.[6d] The temperature of the chiral columns was maintained at 20 °C by using a Julabo F30 Ultratemp 2000 cooling circulator (Seelbach, Germany).

1-(Benzofuran-2-yl)alkylamines (**4a-4d**) was prepared starting from 2-benzofuranyl methyl ketone as shown in Scheme 1. The intermediates, 2-benzofuranyl alkyl ketones were prepared as following. For example, 2-benzofuranyl methyl ketone (1.0 g, 6.3 mmol) was dissolved in 50 mL of tetrahydrofuran. To the cooled solution in dry ice-acetone bath was added lithium diisopropylamide (LDA) (1.2 equiv) under an argon atmosphere. The whole mixture was stirred at −78 °C for 1 h and then methyl iodide (1.0 g, 7.0 mmol) was added. The whole mixture was stirred for 24 h. After addining water (20 mL) to quench the reaction, the reaction mixture was extracted with methylene chloride. The organic solution was dried over anhydrous $MgSO_4$ and then evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/3, v/v) to afford 2-benzofuranyl ethyl ketone (0.74 g, 68%) as a major product. ^{1}H-NMR ($CDCl_3$, ppm) δ 7.72-7.69 (m, 1H), 7.57 (m, 1H), 7.50-7.47 (m, 1H), 7.33-7.31 (m, 2H), 3.04 (q, 2H), 1.25 (t, 3H). 2-Benzofuranyl propyl ketone was similarly obtained. ^{1}H-NMR ($CDCl_3$, ppm) δ 7.73-7.70 (m, 1H), 7.60-7.57 (m, 1H), 7.51-7.45 (m, 1H), 7.34-7.30 (m, 2H), 2.95 (t, 2H), 1.85-1.78 (m, 2H), 1.03 (t, 3H). When benzyl bromide was used as an alkylating agent, the dialkylated ketone, 2-benzofuranyl dibenzylmethyl ketone, was obtained as a major product. ^{1}H-NMR ($CDCl_3$, ppm) δ 7.67 (m, 1H), 7.61-7.55 (m, 1H), 7.51-7.49 (m, 1H), 7.48-7.40 (m, 2H), 7.34-7.12 (m, 10H), 4.13-4.10 (m, 1H), 3.31-3.11 (m, 4H).

Reductive amination of the ketones thus obtained was performed as following. A solution of 2-benzofuranyl methyl ketone (1 g, 6.2 mmol), ammonium acetate (2 g, 26 mmol) and sodium cyanoborohydride ($NaCNBH_3$, 1 g, 16 mmol) in 20 mL of methyl alcohol was stirred at reflux for 48 h. After cooling, concentrated HCl was slowly added to the mixture until pH < 2. Methanol was removed by an evaporator. Water (30 mL) was added to the residue and the resulting solution was extracted with ether twice. The aqueous layer was made to be basic (pH > 10) by adding KOH pellets. The basic solution was extracted with ether (40 mL) twice. The combined ethereal solution was dried over anhydrous $MgSO_4$ and then evaporated to give 1-(benzofuran-2-yl)ethylamine (**4a**) (1 g, 100%). ^{1}H-NMR ($CDCl_3$, ppm) δ 7.67-7.64 (m, 1H), 7.60-7.57 (m, 1H), 7.46-7.31 (m, 2H), 6.64 (s, 1H), 4.35 (m, 1H), 1.66 (d, 3H). Similarly, **4b-4d** were obtained.

Compound 4b: ^{1}H-NMR ($CDCl_3$, ppm) δ 7.60-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.26-7.22 (m, 2H), 6.51 (m, 1H), 4.04 (t, 1H), 1.92-1.81 (m, 2H), 1.79-1.69 (m, 2H) 0.95 (t, 3H).

Compound 4c: ^{1}H-NMR ($CDCl_3$, ppm) δ 7.60-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.26-7.22 (m, 2H), 6.51 (m, 1H), 4.04 (t, 1H), 1.92-1.81 (m, 2H), 1.79-1.69 (m, 2H), 0.95 (t, 3H).

Compound 4d: ^{1}H-NMR ($CDCl_3$, ppm) δ 7.55-7.49 (m, 1H), 7.46-7.39 (m, 1H), 7.33-7.19 (m, 12H), 6.54 (m, 1H), 4.07 (d, 1H), 2.36-1.99 (m, 1H), 1.62 (m, 2H) 1.25 (m, 2H).

Acknowledgments. This research was supported by NCRC (National Core Research Center) program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (grant number: 2011-0006-254).

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