Journal of Chromatography A, 1218 (2011) 4071–4076

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Short communication

Liquid chromatographic resolution of 1-aryl-1,2,3,4-tetrahydroisoquinolines on a chiral stationary phase based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid

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ARTICLE INFO

Article history:
Received 16 March 2011
Received in revised form 26 April 2011
Accepted 29 April 2011
Available online 6 May 2011

Keywords:
Chiral stationary phase
Enantiomer
Liquid chromatography
Resolution
1-Aryl-1,2,3,4-tetrahydroisoquinolines

ABSTRACT

A liquid chromatographic chiral stationary phase (CSP) based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid was applied for the first time to the resolution of biologically important 1-aryl-1,2,3,4-tetrahydroisoquinolines. The unusual resolution of cyclic secondary amino compounds on a chiral crown ether-based CSP was quite successful with the use of a mixture of methanol–acetonitrile–triethylamine at a ratio of 30/70/0.5 (v/v/v) as a mobile phase. From the chromatographic behaviours for the resolution of seven 1-aryl-1,2,3,4-tetrahydroisoquinolines, the steric bulkiness of the 1-phenyl ring at the chiral center of analytes was concluded to play an important role in the chiral recognition.

1. Introduction

1-Aryl-1,2,3,4-tetrahydroisoquinolines have been known to show significant pharmacological activities. For example, 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**, Fig. 1) has been reported to show an antagonistic effect at NMDA (*N*-methyl-D-aspartate) receptors by interacting with their phencyclidine binding site [1–3]. Between the two enantiomers, the (*S*)-enantiomer of **1** was reported to show higher affinity than the (*R*)-enantiomer [2]. The (*S*)-enantiomer of **1** has also been incorporated into Solifenacin (**2**, Fig. 1), which is used for the treatment of the symptoms of overactive bladder [3–5]. As an another example, *N*-acetyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3**, Fig. 1) has been known to show an antagonistic effect at AMPA [2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid] receptors and known to be useful as a potential neuroprotective agent in the treatment of neurological diseases, such as epilepsy, ischemia, Parkinson's disease, and multiple sclerosis [3,6,7]. Especially, the anticonvulsant effects of **3** were reported to reside mainly in the (*R*)-enantiomer [8]. Consequently, optically active 1-aryl-1,2,3,4-tetrahydroisoquinolines have been the target in a number of enantioselective synthesis [3,9]. In this instance, during the process of developing chiral drugs related to 1-aryl-1,2,3,4-tetrahydroisoquinolines, the analytical methods for the exact determination of the enantiomeric composition of 1-aryl-1,2,3,4-tetrahydroisoquinolines are very important.

Among the various methods of separating enantiomers, liquid chromatographic separation on chiral stationary phases (CSPs) has emerged as one of the major workhorses for analytical purposes, such as the determination of the enantiomeric composition of chiral drugs or stereoselective pharmacokinetic analysis, and for preparative purposes [10]. For the enantiomeric separation of 1-aryl-1,2,3,4-tetrahydroisoquinolines and/or their derivatives, liquid chromatographic CSPs based on β-cyclodextrin [11] or cellulose tris-(3,5-dimethylphenycarbamate) [6,12] have been utilized. However, crown ether-based CSPs have not been utilized in the resolution of 1-aryl-1,2,3,4-tetrahydroisoquinolines. In this study, we wish to report the resolution of 1-aryl-1,2,3,4-tetrahydroisoquinolines on a crown ether-based CSP for the first time.

Crown ether-based CSPs have been reported to be useful for the resolution of racemic compounds containing a primary amino group [13,14]. Especially, CSP **4** (Fig. 1) based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid has been successfully utilized for the resolution of various racemic α-, β- and γ-amino acids [15–17], primary amines [18], amino alcohols [18], fluoroquinolone antibacterials [19–21], and other racemic compounds containing a primary amino group [22–24]. While crown ether-based CSPs have been known to be useful only for the resolution of racemic compounds containing a primary amino group, CSP **4** was successful for the resolution of non-primary amino compounds such as methoxyphenamine (bronchodilator)

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doi:10.1016/j.chroma.2011.04.088

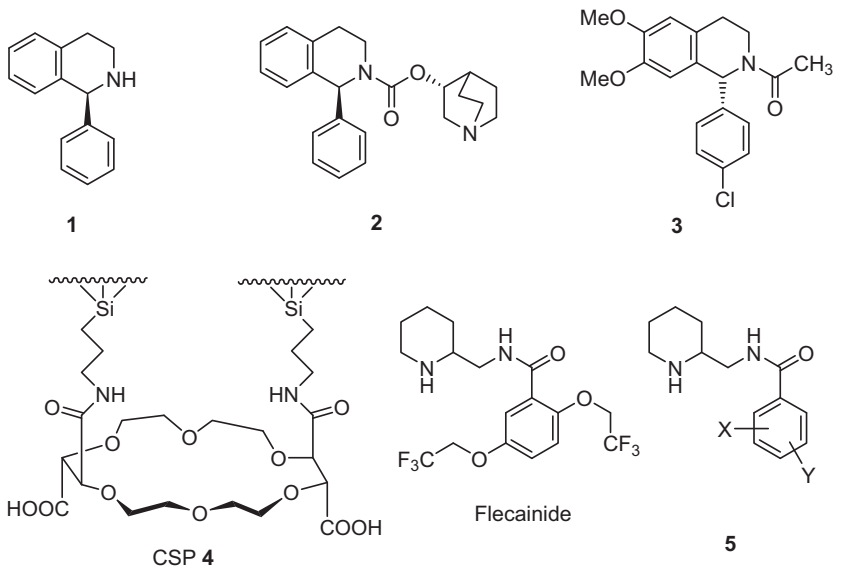

Fig. 1. The structures of compounds **1**, **2**, **3**, **5**, flecainide and CSP **4**.

containing a secondary amino group and secondary amino alcohols related to β-blockers [25–27]. In addition, CSP **4** was successful for the resolution of *N*-(3,5-dinitrobenzoyl)-α-amino acids [28] and *N*-(3,5-dinitrobenzoyl)-α-amino acid amides [29]. Recently, CSP **4** was successfully applied to the resolution of flecainide (antiarrhythmic agent, Fig. 1) and its analogues (**5**, Fig. 1) as the first example of the resolution of cyclic secondary amino compounds on crown ether-based CSPs [30]. 1-Aryl-1,2,3,4-tetrahydroisoquinolines are also cyclic secondary amino compounds, but their structures are quite different from those of flecainide and its analogues (**5**), in that the former are benzopiperidine derivatives while the latter are simple piperidine derivatives. In this instance, the resolution of 1-aryl-1,2,3,4-tetrahydroisoquinolines on CSP **4** is expected to be quite an interesting example of the resolution of secondary amino compounds on crown ether-based CSPs.

2. 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, a Waters model 484 detector (Milford, MA, USA) and a YongLin Autochro Data Module (software: YongLin Autochro 2000). The temperature of the chiral column was set at 20 °C using a Julabo F30 Ultratemp 2000 cooling circulator (Seelbach, Germany). A chiral column packed with CSP **4** [Chirosil RCA(+), 250 mm × 4.6 mm I.D.] was obtained from RS tech (Daejeon, Korea). Racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**) was prepared starting from 2-phenylethylamine and benzoylchloride according to the procedure reported previously [31]. 2-Phenylethylamine was first treated with benzoylchloride in KOH solution and then the resulting amide was cyclized with $ZnCl_2$ and $POCl_3$ in toluene to afford 1-phenyl-3,4-dihydroisoquinoline. Finally 1-phenyl-3,4-dihydroisoquinoline was reduced with $NaBH_4$ to give 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**). Racemic 1-aryl-1,2,3,4-tetrahydroisoquinolines (**6**–**11**) and 1-ethyl-1,2,3,4-tetrahydroisoquinoline (**12**), shown in Fig. 2, were prepared starting from 2-(3′,4′-dimethoxypheny1)ethylamine and para- or ortho-substituted benzaldehydes (or propanal) according to the procedure described in the literature [32]. The mixture of 2-(3′,4′-dimethoxypheny1)ethylamine and appropriate aldehydes was refluxed in anhydrous toluene and then the resulting azomethines were refluxed again with trifluoroacetic acid (TFA) in toluene to give 1-aryl-1,2,3,4-tetrahydroisoquinolines (**6**–**11**) and 1-ethyl-1,2,3,4-tetrahydroisoquinoline (**12**). The structures of

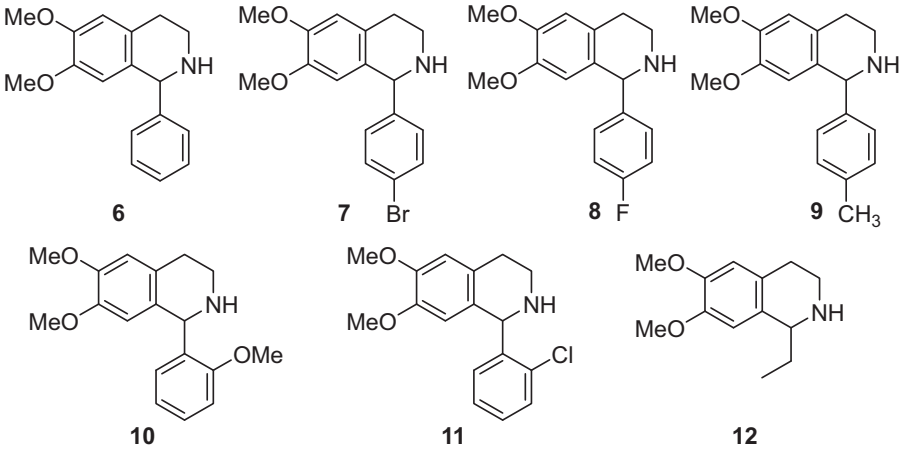

Fig. 2. The structures of analytes **6**–**12** tested for their resolutions on CSP **4**.

Table 1
Resolution of selected analytes (**6** and **7**) on CSP **4** with the use of 50% methanol, ethanol or 2-propanol in acetonitrile containing TFA (0.1%) and TEA (0.5%) as a mobile phase.[a]

Alcohol type in mobile phase	**6**			**10**		
	k_1	α	R_S	k_1	α	R_S
Methanol	1.77	1.21	1.49	1.64	1.96	5.44
Ethanol	2.16	1.18	1.18	1.72	1.92	4.85
2-Propanol	4.11	1.23	1.14	3.33	2.18	4.10

[a] Flow rate, 1.0 ml/min; detection, 254 nm UV; column temperature, 20 °C; k_1, retention factor of the first eluted enantiomer; α, separation factor; R_S, resolution.

1-aryl-1,2,3,4-tetradydroisoquinolines (**1** and **6**–**11**) and 1-ethyl-1,2,3,4-tetrahydroisoquinoline (**12**) thus prepared were identified by ^{1}H NMR spectra. Each of 1-aryl-1,2,3,4-tetradydroisoquinolines (**1** and **6**–**11**) and 1-ethyl-1,2,3,4-tetrahydroisoquinoline (**12**) was dissolved in methanol (usually 1.0 mg/ml) and then used for the resolution experiments on CSP **4**. The usual injection volume was 2.0 μl.

3. Results and discussion

The eight racemic 1-aryl- (or 1-ethyl)-1,2,3,4-tetrahydroisoquinolines (**1**, and **6**–**12**) shown in Figs. 1 and 2 were resolved on CSP **4**. First of all, in order to find out the most widely applicable mobile phase condition, we selected two analytes (**6** and **10**) and resolved them on CSP **4**. Previously, secondary amino compounds including β-blockers and flecainide analogues were resolved on CSP **4** using methanol, ethanol or 2-propanol in acetonitrile containing a small amount of TFA and triethylamine (TEA) as a mobile phase [25–27,30]. In the resolution of the selected analytes (**6** and **10**) on CSP **4**, methanol, ethanol or 2-propanol in acetonitrile containing a small amount of TFA and TEA was also tested as a mobile phase and the chromatographic resolution results are summarized in Table 1. The representative chromatograms for the resolution of analyte **10** on CSP **4** for each type of alcohol in acetonitrile in the mobile phase are presented in Fig. 3. The separation factors (α) were the greatest when the 2-propanol-containing mobile phase was used. However, the resolutions (R_S) were the greatest when the methanol-containing mobile phase was used. The retention times of the first eluted enantiomers denoted by the retention factors (k_1) were found to increase when methanol in the mobile phase was changed to ethanol and then to 2-propanol, as shown in Table 1 and Fig. 3. By changing methanol in the mobile phase to ethanol and to 2-propanol, the mobile phase polarity is expected to decrease and, consequently, the

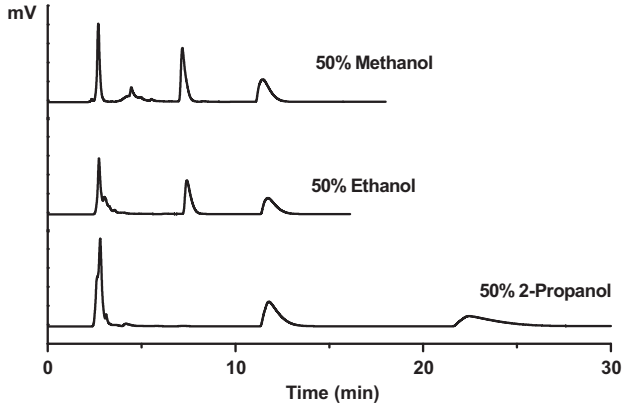

Fig. 3. Representative chromatograms for the resolution of analyte **10** on CSP **4** with the use of 50% alcohol in acetonitrile containing 0.1% TFA and 0.5% TEA. Flow rate: 1.0 ml/min. Detection: 254 nm UV. Column temperature: 20 °C.

Table 2
Resolution of selected analytes (**6** and **10**) on CSP **4** with the variation of the content of methanol (MeOH) in acetonitrile (ACN) and with the variation of the content of TFA and TEA in the mixed solvent of methanol and acetonitrile as a mobile phase.[a]

	Mobile phase (MeOH/ACN/TFA/TEA)	**6**			**10**		
		k_1	α	R_S	k_1	α	R_S
a	80/20/0.1/0.5	2.56	1.18	1.40	2.43	1.89	5.38
b	50/50/0.1/0/5	1.77	1.21	1.49	1.64	1.96	5.44
c	30/70/0.1/0.5	1.71	1.23	1.63	1.62	2.06	5.77
d	30/70/0.0/0.5	2.36	1.29	1.73	2.19	2.36	6.32
e	30/70/0.3/0.5	1.19	1.00	–	1.21	1.87	4.04
f	30/70/0.1/0.3	3.73	1.22	1.70	3.53	2.01	6.06
g	30/70/0.1/0.4	2.32	1.23	1.71	2.18	2.05	5.90

[a] Flow rate, 1.0 ml/min; detection, 254 nm UV; column temperature, 20 °C; k_1, retention factor of the first eluted enantiomer; α, separation factor; R_S, resolution.

interaction of the analytes with the mobile phase decreases. In this instance, the enantiomers are retained longer. After considering the three chromatographic parameters for the resolution of the selected analytes on CSP **4**, we selected methanol in acetonitrile containing a small amount of TFA and TEA as the best mobile phase condition.

Additionally we endeavoured to determine the optimum content of methanol in acetonitrile and the content of TFA and TEA in the mobile phase. The selected analytes (**6** and **10**) were resolved on CSP **4** with the variation of the content of methanol in acetonitrile and with the variation of the content of TFA and TEA in the mobile phase and the chromatographic resolution results are summarized in Table 2.

As the content of methanol in acetonitrile is decreased from 80% to 50% and then to 30%, the retention factors decrease, but the separation factors and resolutions increase continuously (see entries a–c in Table 2). As the content of methanol in acetonitrile is decreased, the mobile phase polarity increases. In this instance, the interaction of the analytes with the mobile phase should increase and, consequently, the retention times of analytes should decrease. However, the reason for the trends of the separation factors and resolutions is not clear yet. Overall, 30% methanol in acetonitrile seems to be the promising condition.

The variation of the content of TFA and TEA in the mobile phase consisting of the mixed solvent of methanol–acetonitrile (30/70, v/v) was also found to affect the chiral recognition behaviours for the resolution of the selected analytes (**6** and **10**) on CSP **4**. As the content of TFA was increased from 0.0% to 0.1% and then to 0.3% at a constant content of TEA (0.5%), all three chromatographic parameters (k_1, α and R_S) decreased (see entries c–e in Table 2). In addition, as the content of TEA in the mobile phase was increased from 0.3% to 0.4% and then to 0.5% at a constant content of TFA (0.1%), the retention factors also decreased, whereas the separation factors and resolutions remained almost constant (see entries c, f and g in Table 2). The trends of the retention factors with the variation of the contents of TFA and TEA in the mobile phase might be explained by the ion-exchange process. The ion-exchange process has been utilized to rationalize the retention behaviours of cationic analytes on a strong cation-exchange type CSP containing a sulfonic acid group [33]. The pK_a values of the four carboxylic acid groups of (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid are 2.13, 2.84, 4.29 and 4.88 [34]. In this instance, the two carboxylic acid groups of CSP **4** are expected to be dissociated under the mobile phase condition. In the presence of TFA in the mobile phase, the analytes are also expected to be protonated. In this instance, the ionic interaction between the cationic analyte and anionic carboxylate of the CSP might be the primary cause for the retention of the analyte. The protonated TEA in the mobile phase can compete with the cationic analyte for the interaction with the anionic carboxylate of

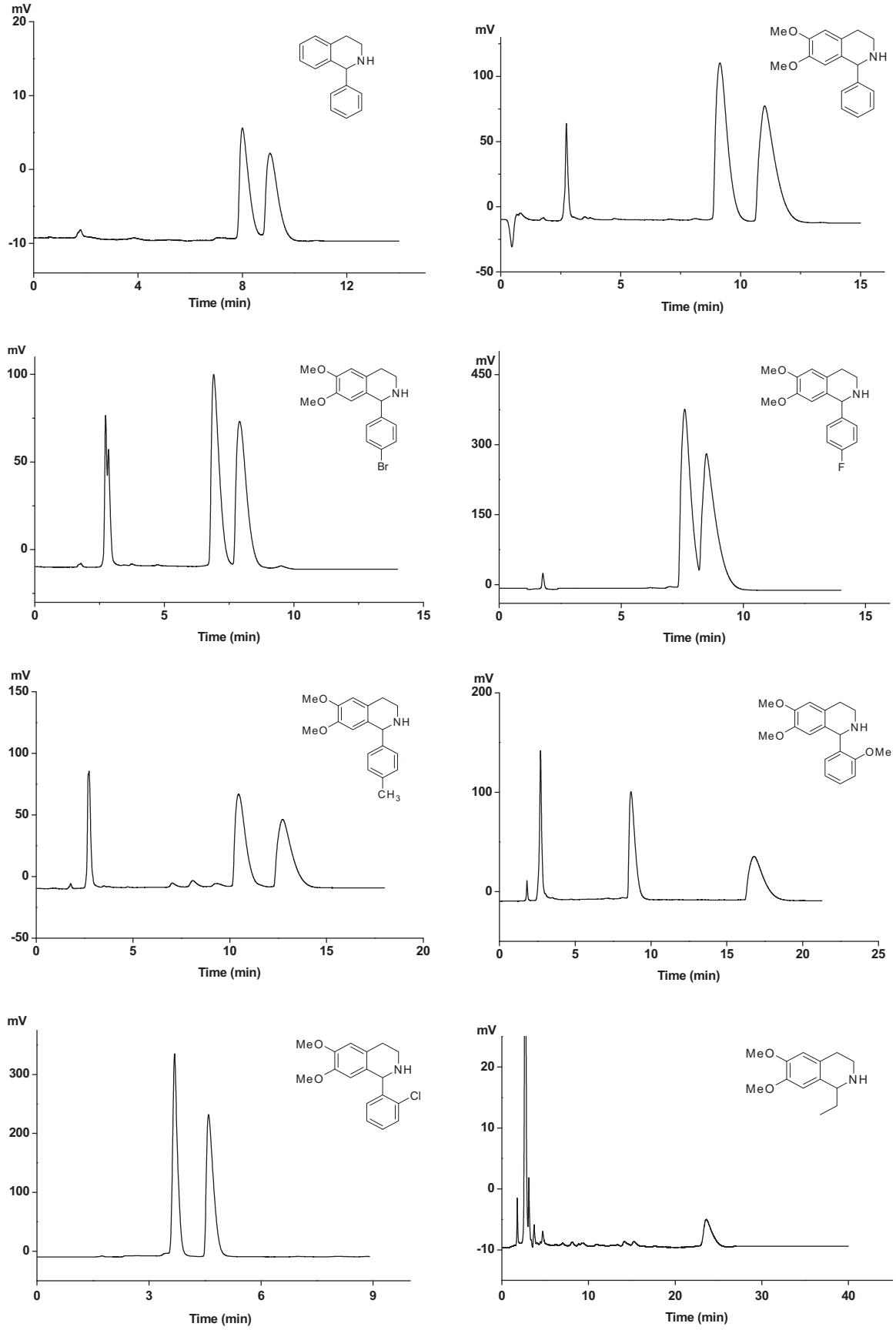

Fig. 4. Chromatograms for the liquid chromatographic resolution of 1-aryl (or ethyl)-1,2,3,4-tetrahydroisoquinolines (**1** and **6**–**12**) on CSP **4**. Mobile phase: 30% methanol in acetonitrile containing TEA (0.5%). Flow rate: 1.0 ml/min. Detection: 254 nm UV. Column temperature: 20 °C.

Table 3
Resolution of 1-aryl (or ethyl)-1,2,3,4-tetrahydroisoquinolines (**1** and **6**–**12**) on CSP **4** with the use of 30% methanol in acetonitrile containing TEA (0.5%) as a mobile phase.[a]

Analytes	k_1	k_2	α	R_S
1	1.94	2.33	1.20	1.49
6	2.36	3.04	1.29	1.73
7	1.84	1.91	1.24	1.59
8	1.79	2.11	1.18	0.99
9	2.85	3.68	1.31	1.88
10	2.19	5.17	2.36	6.32
11	0.35	0.68	1.94	2.61
12	7.68	7.68	1.00	–

[a] Flow rate, 1.0 ml/min; detection, 254 nm UV; column temperature, 20 °C; k_1, retention factor of the first eluted enantiomer; α, separation factor; R_S, resolution.

the CSP and consequently, the retention factors should decrease as the content of TEA in mobile phase is increased. By increasing the content of TFA in the mobile phase, the content of protonated TEA increases and, consequently, the retention of analytes should decrease. Additionally, the interaction between the cationic analyte and mobile TFA anion can decrease the retention of the analyte. However, the reason for the trends of the separation factors and resolutions is not clear. Based on the chromatographic results summarized in Tables 1 and 2, the optimal mobile phase condition was concluded to be a mixture of methanol–acetonitrile–triethylamine at a ratio of 30/70/0.5 (v/v/v). Under the optimum mobile phase condition, the eight 1,2,3,4-tetrahydroisoquinolines (**1** and **6**–**12**) were resolved on CSP **4**, and the corresponding chromatograms and chromatographic resolution results are given in Fig. 4 and Table 3, respectively.

The three chromatographic parameters including the retention factors, separation factors and resolutions were found to be dependent on the structures of the analytes. By comparing the chromatographic resolution results for analytes **1**, **6**, **7**, **8** and **9**, it can be inferred that the electron donating substituents on the benzo ring and/or at the para-position of the 1-phenyl ring of 1,2,3,4-tetrahydroisoquinolines improve the retention factors, separation factors and resolutions, while the electron withdrawing substituents reduce them. However, both the electron donating (methoxy group) and electron withdrawing substituents (chloro group) at the ortho-position of the 1-phenyl ring of 1,2,3,4-tetrahydroisoquinoline (analyte **10** or analyte **11**) were found to reduce the retention factor, but improve the separation factor and resolution significantly compared to those for the resolution of analyte **6**. Between the two substituents at the ortho-position of the 1-phenyl ring of 1,2,3,4-tetrahydroisoquinolines, the chloro substituent was found to reduce the retention factor more than the methoxy substituent, whereas the methoxy substituent improves the separation factor and resolution more than the chloro substituent.

Although the exact chiral recognition mechanism is not clear yet, the ionic interaction between the cationic analyte and anionic carboxylate of the CSP is thought to play an important role for the enantioselective formation of transient diastereromeric complexes. The interaction between the analytes and the CSP might be hindered enantioselectively by the 1-aryl group at the chiral center of the analytes. The steric bulkiness of the 1-aryl group of the analytes is expected to become more significant when the 1-aryl group contains an ortho-substituent. Consequently, the retention factor of analyte **10** is less than that of analyte **6,** though the former contains an electron donating methoxy group at the ortho-position of the 1-phenyl group. The retention factor of analyte **11** is much less than that of analyte **7** or **8** because of the ortho-substitution of the 1-phenyl group with an electron withdrawing group. In contrast, the separation factors and resolutions for the resolution of analytes **10** and **11** are much greater than those for the resolution of analyte **6**, **7**, **8** or **9**. The two enantiomers of analytes **10** and **11** are expected to be recognized more significantly by CSP **4** than those of the other analytes, because of the sterically large ortho-substituted 1-phenyl ring at the chiral center of analytes **10** and **11**.

Analyte **12** shows quite a large retention factor and no resolution on CSP **4**. The relatively small 1-ethyl group at the chiral center of the analyte is not expected to hinder the interaction of the analyte with the CSP. In this instance, the analyte interacts strongly with the CSP and is retained on it for a longer period of time. However, the two enantiomers are not recognized because of the relatively small size of the ethyl group at the chiral center of the analyte.

In summary, CSP **4** was successfully applied to the resolution of 1-aryl-1,2,3,4-tetrahydroisoquinolines, which have not been previously resolved on crown ether-based CSPs. The optimum mobile phase condition was a mixture of methanol–acetonitrile–triethylamine at a ratio of 30/70/0.5 (v/v/v). 1-Aryl-1,2,3,4-tetrahydroisoquinolines containing an ortho-substituted 1-phenyl group at the chiral center were resolved much better than those containing non-substituted or para-substituted 1-phenyl ring. From these results, it can be concluded that the steric bulkiness of the 1-phenyl ring at the chiral center of the analytes plays an important role in the chiral recognition. However, the exact chiral recognition mechanism is not clear yet.

Acknowledgement

This work 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).

References

[1] N.M. Gary, B.K. Cheng, S.J. Mick, C.M. Lair, P.C. Contreras, J. Med. Chem. 32 (1989) 1242.
[2] B. Wunsch, S. Nerdinger, Eur. J. Org. Chem. (1998) 711.
[3] S. Wang, M.R. Onaran, C.T. Seto, Org. Lett. 12 (2010) 2690.
[4] M. Maniscalco, D. Singh-Franco, W.R. Wolowich, R. Torres-Colon, Clin. Ther. 28 (2006) 1247.
[5] F. Chu, N. Smith, T. Uchida, Curr. Ther. Res. 70 (2009) 405.
[6] M. Gao, D. Kong, A. Clearfield, Q.-H. Zhang, Bioorg. Med. Chem. Lett. 16 (2006) 2229.
[7] R. Gitto, R. Caruso, B. Pagano, L.D. Luca, R. Citraro, E. Russo, G.D. Sarro, A. Chimirri, J. Med. Chem. 49 (2006) 5618.
[8] R. Gitto, R. Ficarra, R. Stancanelli, M. Guardo, L.D. Luca, M.L. Barreca, B. Pagano, A. Rotondo, G. Bruno, E. Russo, G.D. Sarro, A. Chimirri, Bioorg. Med. Chem. 15 (2007) 5417.
[9] M. Chrzanowska, M.D. Rozwadowska, Chem. Rev. 104 (2004) 3341.
[10] M. Lammerhofer, J. Chromatogr. A 1217 (2010) 814.
[11] W. Stammel, B. Woesle, H. Thomas, Chirality 7 (1995) 10.
[12] P. Donato, R. Stancanelli, M.L. Calabro, S. Tommasini, P. Cutroneo, M. Guardo, B. Pagano, A. Chimirri, P. Ficarra, R. Ficarra, J. Pharm. Biomed. Anal. 42 (2006) 543.
[13] M.H. Hyun, Bull. Kor. Chem. Soc. 26 (2005) 1153.
[14] H.J. Choi, M.H. Hyun, J. Liq. Chromatogr. Rel. Technol. 30 (2007) 853.
[15] M.H. Hyun, J.S. Jin, W. Lee, J. Chromatogr. A 822 (1998) 155.
[16] M.H. Hyun, Y.J. Cho, J.S. Jin, J. Sep. Sci. 25 (2002) 648.
[17] S.J. Lee, H.S. Cho, H.J. Choi, M.H. Hyun, J. Chromatogr. A 1188 (2008) 318.
[18] M.H. Hyun, J.S. Jin, H.J. Koo, W. Lee, J. Chromatogr. A 837 (1999) 75.
[19] M.H. Hyun, J.S. Jin, W. Lee, Bull. Korean Chem. Soc. 19 (1998) 819.
[20] M.H. Hyun, S.C. Han, J.S. Jin, W. Lee, Chromatographia 52 (2000) 473.
[21] M.H. Hyun, S.C. Han, Y.J. Cho, J.S. Jin, W. Lee, Biomed. Chromatogr. 16 (2002) 356.
[22] M.H. Hyun, H.J. Min, Y.J. Cho, Bull. Korean Chem. Soc. 24 (2003) 911.
[23] M.H. Hyun, G. Tan, Y.J. Cho, J. Liq. Chromatogr. Rel. Technol. 27 (2004) 1671.
[24] J.Y. Jin, W. Lee, M.H. Hyun, J. Liq. Chromatogr. Rel. Technol. 29 (2006) 841.
[25] R.J. Steffeck, Y. Zelechonok, K.H. Gahm, J. Chromatogr. A 947 (2002) 301.
[26] D. Zhang, F. Li, D.H. Kim, H.J. Choi, M.H. Hyun, J. Chromatogr. A 1083 (2005) 89.
[27] H.J. Choi, Y.J. Park, M.H. Hyun, J. Chromatogr. A 1164 (2007) 235.
[28] M.H. Hyun, G. Tan, J.Y. Xue, J. Chromatogr. A 1097 (2005) 188.
[29] G. Tan, J.Y. Xue, M.H. Hyun, J. Sep. Sci. 29 (2006) 1407.
[30] A. Lee, H.J. Choi, M.H. Hyun, Chirality 22 (2010) 693.

[31] U.R. Mach, A.E. Hackling, S. Perachon, S. Ferry, C.G. Wermuth, J.-C. Schwartz, P. Sokoloff, H. Stark, ChemBioChem 5 (2004) 508.
[32] R.K. Tiwari, D. Singh, J. Singh, A.K. Chhillar, R. Chandra, A.K. Verma, Eur. J. Med. Chem. 41 (2006) 40.
[33] C.V. Hoffmann, M. Laemmerhofer, W. Lindner, J. Chromatogr. A 1161 (2007) 242.
[34] Y. Machida, H. Nishi, K. Nakamura, H. Nakai, T. Sato, J. Chromatogr. A 805 (1998) 85.