Resolution of Atropisomers of Hindered Naphthamides on an Improved HPLC Chiral Stationary Phase Derived from (S)-Leucine

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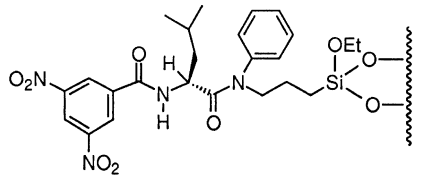
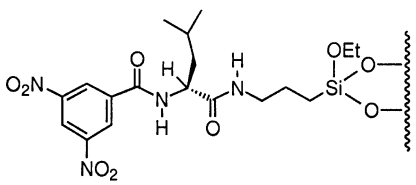
Received July 2, 1999

Liquid chromatographic resolution of enantiomers on chiral stationary phases (CSPs), which is now known as one of the most accurate and convenient means of determining the enantiomeric composition of chiral compounds, owes its success mostly to the availability of the effective CSPs.[1] Consequently, various efforts have been devoted to the development of new effective CSPs and/or to the improvement of the existing CSPs. For example, CSPs based on proteins,[2] cellulose derivatives,[3] cyclodextrins,[4] macro cyclic antibiotics,[5] low molecular mass optically active chiral molecules,[6] and chiral crown ethers7 have been the successful ones for the separation of enantiomers. Our efforts in this area have resulted in the development of new effective CSPs based on α-amino acids,[8] amino alcohols[9] and chiral crown ethers.[10]

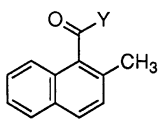
Recently, our research interests have also been focused on the improvement of the existing CSPs and consequently several CSPs improved quite much have been developed. For example, a CSP prepared by bonding (S)-naproxen to silica gel through a tertiary N-phenyl amide linkage was proved more effective than the corresponding CSP developed previously by bonding (S)-naproxen to silica gel *via* a secondary amide linkage or *via* a tertiary dialkylamide linkage.[11] More recently, we developed another improved CSP (CSP **1**) by simply displacing the N-H hydrogen of the connecting amide tether of CSP **2**, which is commercially available, with a phenyl group. CSP **1** was found to be much more effective than CSP **2** in resolving various π-acidic N-(3,5-dinitrobenzoyl)-α-amino amides and esters.[12] In addition, CSP **1** was found to show much greater enantioselectivity than CSP **2** for the resolution of π-basic N-(3,5-dimethoxybenzoyl)-α-amino amides and esters.[13] However, the utility of CSP **1** in the resolution of atropisomers is not tested yet.



CSP **1**



CSP **2**



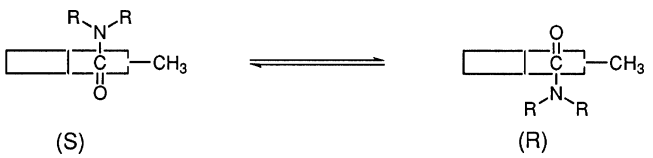
3 [Y = N(R)$_2$]

In this study, we wish to extend the use of CSP **1** to the resolution of atropisomers by demonstrating that CSP **1** is much more effective than CSP **2** in resolving slowly interconverting atropisomers of hindered naphthamides **3**.

Naphthamides **3** are expected to adopt conformations in which the plane of the naphthalene ring and that containing the carboxamide group are approximately perpendicular as proposed previously for hindered naphthyl ketones.[14] In this instance, no element of symmetry is left in the molecules. In addition, the 2-methyl group on the naphthalene ring of naphthamides **3** hinders the rotation around the C(naphthyl)-C(carbonyl) bond. Consequently, a pair of torsional conformers of naphthamides **3** which are in their enantiomeric relationship as shown in Figure 1 is expected to be separable. The barrier to enantiomer interconversion in the case of compound **3a** was reported to be 100.4 kJ/mol at 25.3 ºC in dioxane, which corresponds to an interconversion half-life of about 6 h.[15]

The chromatographic separation of the two enantiomers of compound **3a** was first performed on a column packed with swollen microcrystalline triacetylcellulose.[15] The chromatographic separation of naphthamides **3** on CSP **2** and other CSPs have also been reported.[16] In that study, the degree of enantioselectivity for the two enantiomers of naphthamides **3** on CSP **2** was turned out to be quite low, separation factors, α, being less than 1.20. However, we found that the separation of the two enantiomers of naphthamides **3** on CSP **1** was much more effective than that on CSP **2**.

The chromatographic results for the separation of the two enantiomers of naphthamides **3** on CSP **1** are summarized and compared with those on CSP **2** in Table 1. The elution order of the two enantiomers of naphthamide **3a** on CSP **1** was found to be consistent with that on CSP **2** by collecting the two fractions for the resolution of naphthamide **3a** on CSP **1** and then injecting each into CSP **2**. From these results, we assumed that the (S)-enantiomer is retained longer on the CSP as described previously.[16] As shown in Table 1, the degree of the enantioselectivity (represented by separation factors, α) for the two enantiomers of naphtha-



(S) (R)

Figure 1. A schematic presentation of the slowly interconverting (S)- and (R)-enantiomers of naphthamides **3**.

Table 1. Comparison of the liquid chromatographic resolution of naphthamides **3** on CSP **1** and CSP **2**[a]

Analyte	Y	CSP **1**			CSP **2**		
		k_1[b]	k_2[c]	α[d]	k_1[b]	k_2[c]	α[d]
3a	$N(CH_3)_2$	6.50	9.59	1.48	15.90	19.30	1.22
3b	$N(CH_2CH_3)_2$	4.00	5.68	1.42	8.57	9.96	1.16
3c	$N(CH_2CH{=}CH_2)_2$	2.75	3.95	1.44	6.00	7.11	1.19
3d	N(n-Butyl)$_2$	2.41	3.42	1.42	4.15	4.73	1.14
3e	N(n-Pentyl)$_2$	2.15	2.98	1.39	4.36	4.96	1.14
3f	N(n-Hexyl)$_2$	1.93	2.64	1.37	3.77	4.24	1.12
3g	N(n-Decyl)$_2$	1.41	1.78	1.26	2.67	2.91	1.09
3h		5.51	7.38	1.34	14.49	16.15	1.11
3i		5.54	7.39	1.33	14.63	16.37	1.12
3k		8.81	11.60	1.31	18.68	22.50	1.20

[a]See the experimental part for the chromatographic conditions. [b]Capacity factor of the first eluted enantiomer. [c]Capacity factor of the second eluted enantiomer. [d]Separation factor.

mides **3** on CSP **1** is greater than that on CSP **2**. Another interesting results to note are that the retention (represented by capacity factors, k_1 and k_2) of the two enantiomers on CSP **1** is much lower than that on CSP **2**. From these results, it is clear that the N-H hydrogen of the connecting amide tether of CSP **2** does not play any significant role in the chiral recognition except for the nonstereoselective retention.

Actually, the chiral recognition mechanism proposed previously for the resolution of naphthamide **3a** on CSP **2** does not utilize the N-H hydrogen of the connecting amide tether.[16] Instead, the mechanism proposed utilizes the N-H hydrogen of the 3,5-dinitrobenzamide for the hydrogen bonding interaction with the analytes. Based on the chiral recognition mechanism proposed previously[16] and with the aid of CPK molecular model study, the interactions between the model compound of the chiral selector of CSP **1** and the (S)- and (R)-enantiomer of naphthamide **3a** are proposed in Figure 2. The exact geometrical structure of the N-phenyl N-propyl amide part of the CSP is not confirmed yet. However, the N-phenyl N-propyl amide part of the model compound of the CSP is assumed to retain the E-conformation as shown in Figure 2 in order to avoid the steric hindrance between the N-propyl chain and the chiral moiety and the electronic repulsion between the carbonyl lone pair electrons and the phenyl π-electrons as described previously.[11b,17] In addition, the N-phenyl ring of the N-phenyl N-propyl amide part of the model compound of the CSP is assumed to take a perpendicular conformation with respect to the plane of the amide part of the CSP as shown in Figure 2, based on the ab initio molecular orbital calculation concerning the conformational preference of the phenyl ring of N-methylacetanilide[17] and based on the CPK molecular model study. The steric bulk of the isobutyl side chain of CSP **1** is presumed to control the approach of an analyte to the two faces of the planar π-acidic dinitrobenzamide ring of the CSP as proposed previously.[16] In this instance, the (S)-enantiomer of naphthamide **3a** approached from the sterically more accessible side can undergo simultaneous π-π interaction and the hydrogen bonding interaction with the CSP. However, the simultaneous π-π interaction and the hydrogen bonding interaction between the CSP and the (R)-enantiomer of naphthamide **3a** are hampered because of the steric repulsion between the 2-methyl group of the analyte and the connecting amide tether of the CSP as shown in Figure 2b. The steric repulsion between the 2-methyl group of the analyte and the connecting amide tether of the CSP might be extended even more by the N-phenyl group of the connecting amide tether of CSP **1**. In this instance, the difference in the stability of the two transient diastereomeric complexes formed between CSP **1** and the two enantiomers of naphthamide **3a** shown in Figure 2 increases and consequently the enantioselectivity on CSP **1** becomes greater than that on CSP **2**.

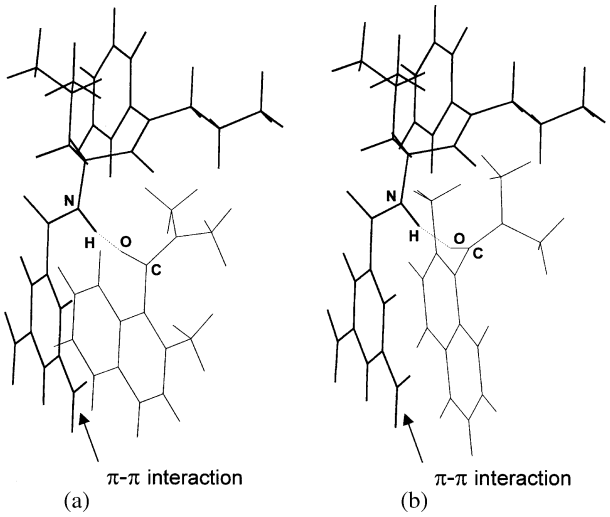


Figure 2. A proposed chiral recognition model for the resolution of naphthamide **3a** on CSP **1**. (a) The (S)-enantiomer and (b) the (R)-enantiomer of naphthamide **3a** (represented with thin lines) interact with (S)-N-(3,5-dinitrobenzoyl)leucine N-phenyl N-propyl amide (represented with thick lines), a model compound of the chiral selector of CSP **1**, through the π-π interaction and the simultaneous hydrogen bonding interaction. However, in this instance, the 2-methyl group of the (R)-enantiomer directing toward the N-phenyl N-propyl amide group of the model compound of CSP **1** hinders the effective interaction as shown in (b), the transient diastereomeric (S,R)-complex being less favorable than the (S,S)-complex.

In summary, in this study, we demonstrated that CSP **1** is more effective than CSP **2** in separating the two enantiomers of naphthamides **3**. The greater enantioselectivity exerted by CSP **1** was rationalized by the decreased nonstereoselective retention and the increased steric hindrance imposed on the interaction between the less retained enantiomer and CSP **1**.

Experimental Section

Chromatography was performed using an HPLC system consisting of a Waters model 510 pump, a Rheodyne model 7125 injector with a 20 μL sample loop, a Youngin model 710 absorbance detector with a 254 nm UV filter and a

Youngin D520B computing integrator. Preparation of CSP 1 was described in the previous study.[12] A chiral column packed with CSP **2** was obtained from Regis Tech. Inc. (Morton Grove, Illinois, U. S. A.). All chromatographic experiments were performed by using 2-propanol-hexane (20 : 80, v/v) as a mobile phase with a flow rate of 2 mL/min at room temperature. Column void volume was measured by injecting 1,3,5-tri-tert-butylbenzene.[18] Naphthamides **3** used in this study were prepared via the reaction of 2-methyl-1-naphthoyl chloride with appropriate dialkylamines or cyclic amines as described previously.[16]

Acknowledgment. This work was supported by the grants from the Basic Science Research Program (BSRI-98-3410) and from the Korea Science and Engineering Foundation (96-0501-08-01-3).

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