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Liquid Chromatographic Resolution of Racemic α-Amino Acid Derivatives on an Improved π-Acidic Chiral Stationary Phase Derived from (S)-Leucine

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A chiral stationary phase derived from (S)-N-(3,5-dinitrobenzoyl)leucine N-phenyl N-alkyl amide (CSP **2**) was applied in separating the two enantiomers of various π-basic aromatic derivatives of leucine N-propyl amide in order to evaluate π-basic aromatic groups as an effective derivatizing group for the resolution of α-amino acids. Subsequently N-(3,5-dimethoxybenzoyl) group was found to be very effective as a π-basic aromatic derivatizing group. Based on these results, N-(3,5-dimethoxybenzoyl) derivatives of various α-amino N-propyl amides, N,N-diethyl amides and esters were resolved on the CSP derived from (S)-N-(3,5-dinitrobenzoyl) leucine N-phenyl N-alkyl amide (CSP **2**) and the resolution results were compared with those on the CSP derived from (S)-N-(3,5-dinitrobenzoyl)leucine N-alkyl amide (CSP **1**). The enantioselectivities exerted by CSP **2** were much greater than those exerted by CSP **1**. In addition, racemic N-(3,5-dimethoxybenzoyl)-α-mino N,N-diethyl amides were resolved much better than the corresponding N-(3,5-dimethoxybenzoyl)-α-mino N-propyl amides and esters on both CSPs. Based on these results, a chiral recognition mechanism utilizing the π-π donor-acceptor interaction and the two hydrogen bondings between the CSP and the analyte was proposed.

Introduction

Liquid chromatographic resolution of enantiomers on chiral stationary phases (CSPs) has been known as one of the most convenient and accurate means in evaluating enantiomeric purity of chiral compounds. Consequently, various CSPs for the liquid chromatographic resolution of enantiomers have been developed.[1] Among others, Pirkle-type CSPs have been known to separate two enantiomers by forming energetically different two transient diastereomeric π-π donor-acceptor complexes with two enantiomers.[2] For the effective formation of π-π donor-

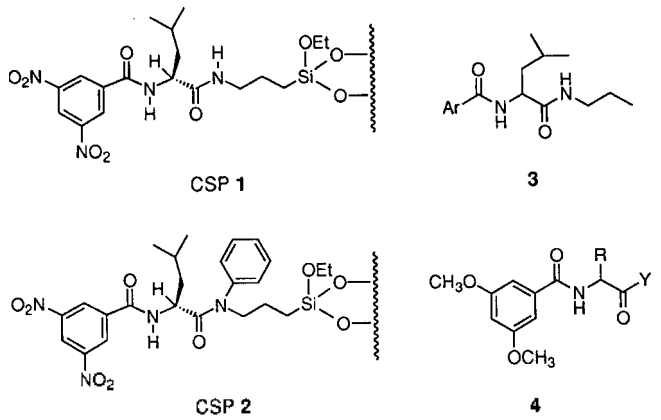

Figure 1. Structures of CSPs **1** and **2** and racemic analytes **3** and **4**.

acceptor complexes between the CSP and racemic analytes, Pirkle-type CSPs have been usually designed to contain π-acidic and/or π-basic aromatic rings.[3] For example, CSP **1** (Figure 1) containing a strong π-acidic 3,5-dinitrobenzoyl group has been successfully employed in separating the two enantiomers of π-basic racemates.[4]

Our interest related to CSP **1** has been focused on the elucidation of the chiral recognition mechanism for the resolution of π-basic racemates and finally one possible chiral recognition mechanism for the separation of the two enantiomers of N-acyl-α-aylalkylamines on CSP **1** has been proposed.[5] According to the chiral recognition mechanism proposed, the amide N-H hydrogen of the connecting tether of CSP **1** does not play any significant role in the chiral recognition except for the nonstereoselective retention. In this instance, the deletion of the amide N-H hydrogen of the connecting tether of CSP **1** was expected to improve the chiral recognition ability of the CSP. Based on this rationale and our previous study concerning the use of an N-phenyl N-alkyl amide group as a very effective connecting tether of a CSP,[3b,6] we prepared a new CSP (CSP **2**) by simply replacing the N-H hydrogen of the connecting tether of CSP **1** with a phenyl group. CSP **2** has actually been found to show much greater enantioselectivity for the enantiomers of π-acidic racemates such as N-(3,5-dinitrobenzoyl)-α-amino amides and esters than CSP **1**.[7] However, the chiral recognition ability of CSP **2** for the two enantiomers of π-basic analytes has not been evaluated yet. CSP **2** contains a strong π-acidic group which can be utilized for the π-π donor-acceptor interaction with the π-basic racemic analytes. In this context, CSP **2** is expected to resolve π-basic racemic compounds very well. In this study, we demonstrate that CSP **2** is very excellent in resolving the π-basic aromatic derivatives of various racemic α-amino acids.

Experimental

Chromatography was performed with 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. A chiral column packed with CSP **1** was commercially available from Regis Tech. Inc. (Morton Grove, Illinois, U. S. A.). CSP **2** was available from the previous study.[7] 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.[8] all analytes employed in this study were prepared from α-amino acids by a well known simple derivatizing process utilized in preparing the chiral selector, N-(3,5-dinitrobenzoyl)leucine N-phenyl N-allylamide, of CSP **2**.[7]

Results and Discussion

CSP **2** containing a strong π-acidic N-(3,5-dinitrobenzoyl) group was expected to separate the two enantiomers of π-basic aromatic derivatives of various racemic α-amino acids through enantioselective π-π donor acceptor interaction between the CSP and an analyte. Various π-basic aromatic groups which can be utilized for the derivatization of α-amino acids are available. Therefore, it is necessary to determine which π-basic derivatizing group is most effective for the chromatographic resolution of α-amino acids on CSP **2**. In order to evaluate various π-basic derivatizing groups, we prepared various π-basic aromatic derivatives **3** of leucine N-propyl amide and resolved them on CSP **2**. The chromatographic results for the resolution of various π-basic aromatic derivatives **3** of leucine N-propyl amide on CSP **2** are summarized in Table 1. The resolution results summarized in Table 1 demonstrate that the chromatographic resolutions are significantly influenced by the π-basicity of the aromatic derivatizing group. For example, changes of the π-basic aromatic derivatizing group from benzoyl (**3e**) to 4-methoxybenzoyl (**3c**) and then to 3,5-dimethoxybenzoyl (**3a**) significantly enhance the retention of the two enantiomers (denoted by the capacity factors, k_1' and k_2') and the separation factor (α). Similarly, changes of the π-basic aromatic derivatizing group from benzoyl (**3e**) to 4-methylbenzoyl (**3d**) and then to 3,5-dimethlybenzoyl (**3b**) improve the retention of the second eluted enantiomer (denoted by the capacity factor, k_2') and the separation factor (α), but diminish the retention of the first eluted enantiomer (denoted by the capacity factor, k_1'). Therefore, it is concluded that the retention of the second eluted enantiomer which forms more stable (S,S)-complex with the (S)-CSP and the separation factor increase as the π-basicity of the aromatic derivatizing group increases. One thing to note from the resolution behavior summarized in Table 1 is that methoxy group attached to the aromatic derivatizing

Table 1. Resolution of racemic analytes **3** on CSP **2**[a]

Analyte	Ar	k_1'[b]	k_2'[c]	α[d]	Conf.[e]
3a	3,5-dimethoxyphenyl	0.97	8.51	8.77	S
b	3,5-dimethylphenyl	0.38	3.21	8.42	S
c	4-methoxyphenyl	0.69	4.87	7.06	S
d	4-methylphenyl	0.44	2.90	6.59	S
e	phenyl	0.46	2.44	5.31	S
f	1-naphthyl	1.08	1.87	1.72	S

[a] See the experimental part for the chromatographic conditions. [b] Capacity factors of the first eluted enantiomers. [c] Capacity factors of the second eluted enantiomers. [d] Separation factors. [e] Absolute configuration of the second eluted enantiomers.

Table 2. Comparison of the resolution of racemic analytes **4** on CSP **1** and **2**[a]

Analyte	Amino acid (R)	Y	CSP 1				CSP 2			
			k_1'[b]	k_2'[c]	α[d]	Conf.[e]	k_1'[b]	k_2'[c]	α[d]	Conf.[e]
4a	Alanine (CH_3)	$NHCH_2CH_2CH_3$	4.29	10.87	2.02	S	2.97	8.96	3.02	S
b		$N(CH_2CH_3)_2$	6.31	17.19	2.72	S	2.91	28.96	9.95	S
c		OCH_2CH_3	4.04	7.18	1.78	S	2.72	9.19	3.64	S
d	Valine	$NHCH_2CH_2CH_3$	1.70	3.33	1.96	S	1.01	7.87	7.79	S
e	($CH(CH_3)_2$)	$N(CH_2CH_3)_2$	3.07	5.67	1.85	S	2.10	10.76	5.12	S
f		OCH_2CH_3	2.47	3.92	1.59	S	2.07	6.21	2.96	S
g[f]	Leucine	$NHCH_2CH_2CH_3$	1.59	4.38	2.75	S	0.97	8.51	8.77	S
h	($CH_2CH(CH_3)_2$)	$N(CH_2CH_3)_2$	2.92	10.33	3.54	S	1.83	21.83	11.93	S
i		OCH_2CH_3	2.24	4.50	2.01	S	1.89	7.30	3.86	S
j	Phenylglycine	$NHCH_2CH_2CH_3$	3.63	4.02	1.11	S	3.58	6.23	1.74	S
k	(C_6H_5)	$N(CH_2CH_3)_2$	4.36	8.52	1.95	S	2.86	12.83	4.49	S
l		OCH_2CH_3	3.36	4.51	1.34	S	3.03	5.86	1.93	S
m	Phenylalanine	$N(CH_2CH_3)_2$	3.19	9.28	2.91	S	1.95	17.91	9.18	S
n	Serine	$N(CH_2CH_3)_2$	9.78	24.36	2.49		3.16	17.41	5.51	
o	Threonine	$N(CH_2CH_3)_2$	7.38	15.52	2.11		2.58	11.01	4.26	
p	Tryptophan	$N(CH_2CH_3)_2$	11.81	22.21	1.88		5.01	42.63	8.51	
q	Cysteine	$N(CH_2CH_3)_2$	2.02	2.31	1.14		1.01	1.18	1.17	

[a,b,c,d,e] See the footnote to Table 1. [f] Analyte **4g** is the same compound as analyte **3a**.

group seems to be more effective than the methyl group in increasing the π-basicity of the aromatic derivatizing group. From all of these observations, it is concluded that the π-π donor-acceptor interaction between the CSP and the analyte is responsible for the chiral recognition and N-(3,5-dimethoxybenzoyl) group should be the choice as an effective π-basic aromatic derivatizing group.

Application of CSP **2** to the resolution of N-(3,5-dimethoxybenzoyl) derivatives of various α-amino amides and esters was very successful. The chromatographic results for the resolution of N-(3,5-dimethoxybenzoyl) derivatives of various α-amino amides and esters on CSP **2** are summarized and compared with those on CSP **1** in Table 2. The chromatograms shown in Figure 2 are illustrating the comparison of the enantioselectivities exerted by CSP **1** and CSP **2** for the resolution of racemic N-(3,5-dimethoxybenzoyl)leucine N,N-diethyl amide (**4h**). As shown in Table 2 and Figure 2, the enantioselectivities exerted by CSP **2** are much greater than those by CSP **1**. Consequently, it is assumed that the N-H hydrogen of the amide connecting tether of CSP **1** is not involved in the chiral recognition, but the carbonyl oxygen of the amide connecting tether of the CSP is assumed to play a role as a hydrogen bond acceptor as reported previously.[7]

The chromatographic resolution results summarized in Table 2 also illustrate that N-(3,5-dimethoxybenzoyl)-α-amino N,N-diethyl amides are resolved much better as denoted by the separation factors (α values) than the corresponding N-propyl amides and ethyl esters except for the resolution of N-(3,5-dimethoxybenzoyl)valine

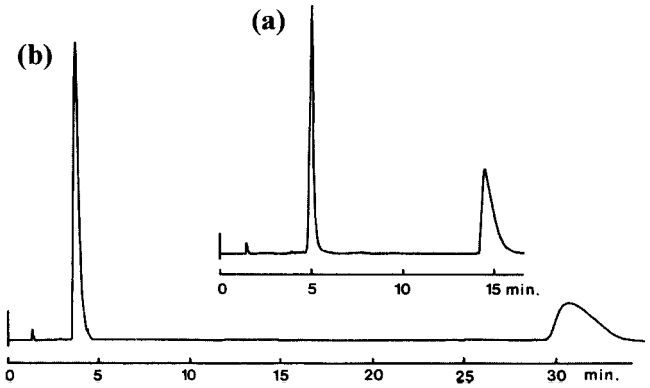

Figure 2. Representative chromatograms for the resolution of N-(3,5-dimethoxybenzoyl) leucine N,N-diethyl amide (**4h**) on (a) CSP **1** and (b) CSP **2**. See the footnote to Table 1 for the chromatographic conditions.

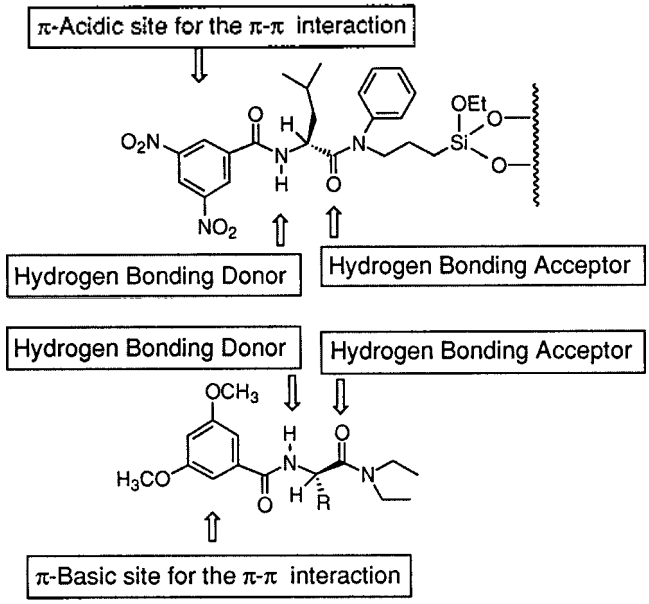

Figure 3. Proposed interaction sites of CSP **2** and analytes, N-(3,5-dimethoxybenzoyl)-α-amino N,N-diethyl amides, for the chiral recognition.

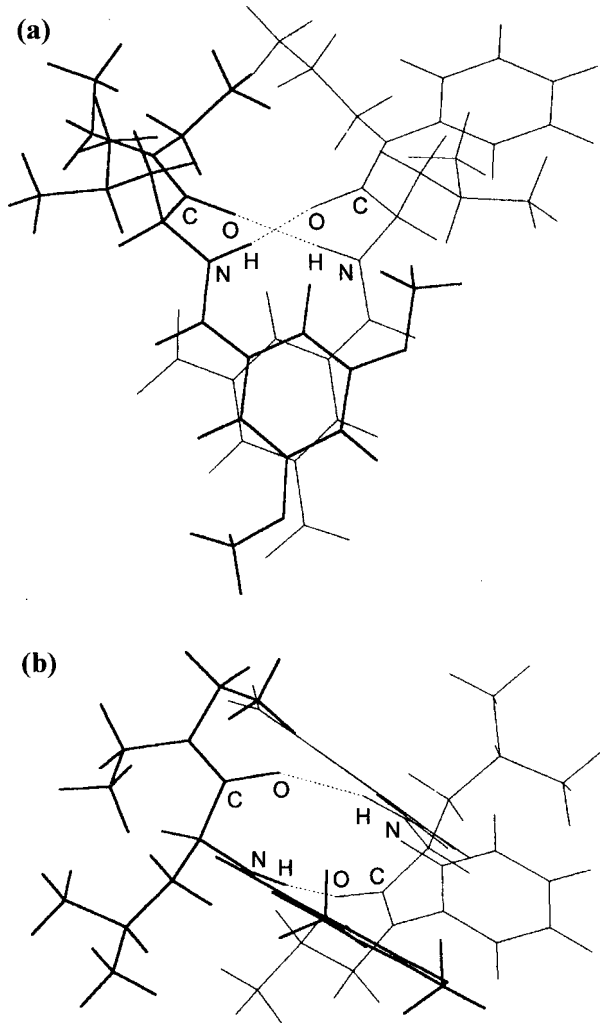

Figure 4. A computer generated (HyperChem 3.0) stick chiral recognition model for the more stable (S,S)-complex formed between (S)-N-(3,5-dinitrobenzoyl)leucine N-phenyl N-propyl amide (represented with thin lines), a model compound of the chiral selector of CSP **2**, and analyte, (S)-N-(3,5-dimethoxybenzoyl)leucine N,N-diethyl amide (represented with thick lines). (a) A stick molecular model viewed from the angle showing the π-π interaction between the 3,5-dimethoxyphenyl group of the analyte and the 3,5-dinitrophenyl group of the CSP and the two hydrogen bonds (side view). (b) The same stick molecular model as in (a), but viewed from the different angle (top view).

derivatives. In the case of the resolution of N-(3,5-dimethoxybenzoyl)valine derivatives, however, the retention of the second enantiomer of N-(3,5-dimethoxybenzoyl) valine N,N-diethyl amide (**4e**) is greater than that of N-(3,5-dimethoxybenzoyl)valine N-propyl amide (**4d**). From these results it is also assumed that the N-H hydrogen of the N-propyl amide of the analytes is not involved in the chiral recognition. Instead, the carbonyl oxygen of the N,N-diethyl amide part, the N-propyl amide part or the ethyl ester part of the analyte is assumed to be involved in the chiral recognition as a hydrogen bond acceptor, based on the fact that the electron density of the carbonyl oxygen of the N,N-dialkyl amide is greater than that of the N-alkyl amide or the ester.[9]

The interaction sites of CSP **2** and N,N-diethyl amide of N-(3,5-dimethoxybenzoyl)-α-amino acids discussed above are summarized in Figure 3. With the aid of CPK molecular model study, a chiral recognition mechanism is proposed by correlating the interaction sites of CSP **2** shown in Figure 3 with their complementary sites of the analyte, N-(3,5-dimethoxybenzoyl)-α-amino N,N-diethyl amide. Figure 4 shows the chiral recognition model for the more stable (S,S)-complex formed between the model compound of the chiral selector of CSP **2**, (S)-N-(3,5-dinitrobenzoyl)leucine N-phenyl N-propyl amide, and the analyte, (S)-N-(3,5-dimethoxybenzoyl)leucine N,N-diethyl amide. In Figure 4, the model compound of the chiral selector of the CSP and the analyte are presumed to be in their lowest energy conformation.[5,6b] As shown in Figure 4, the model compound of the chiral selector of (S)-CSP **2** interacts with the (S)-analyte through the face-to-face π-π donor-acceptor interaction between the π-acidic 3,5-dinitrophenyl group of the CSP and the π-basic 3,5-dimethoxyphenyl group of the analyte. Simultaneously, the model compound of the chiral selector of (S)-CSP **2** interacts with the (S)-analyte through the two hydrogen bonding interactions between the hydrogen bond acceptor sites proposed in Figure 3 and the only hydrogen bond donor sites of the CSP and the analyte. In this instance, both the isobutyl groups at the chiral center of the analyte and the model compound of the chiral selector of the CSP are directed away from the interaction sphere.

In summary, CSP **2**, which has the same structure as that of CSP **1** except for the N-phenyl group instead of the N-H hydrogen, was applied in separating the two enantiomers of various π-basic aromatic derivatives of leucine N-propyl amide and as results the N-(3,5-dimethoxybenzoyl) group was found to be very effective as a π-basic aromatic derivatizing group. From the chromatographic resolution experiments for the two enantiomers of N-(3,5-dimethoxybenzoyl)-α-amino N-propyl amides, N,N-diethyl amides and esters on CSP **1** and CSP **2**, it was found that the enantioselectivities exerted by CSP **2** are much greater than those of CSP **1** and N-(3,5-dimethoxybenzoyl)-α-amino N, N-diethyl amides are resolved much better than the corresponding N-propyl amides and esters. Based on these results, a chiral recognition mechanism which utilizes the π-π donor-acceptor interaction and the simultaneous two hydrogen bondings between the CSP and the analyte was proposed.

From the great chiral recognition ability of CSP **2** for the two enantiomers of π-basic racemates, the chiral selector of CSP **2** might be expected to be utilized in other chiral discriminating techniques such as separating two enantiomers through chiral liquid membrane or monitoring the enantiomeric composition of chiral compounds by NMR with a chiral solvating agent. Application of the chiral selector of CSP **2** to other chiral discriminating techniques is underway in our laboratory.

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Anchimeric Assistance in the Rearrangement of Dichloro-3-methyl-1,4-oxathianes to 2-Chloromethyl Dihydro-1,4-oxathiins

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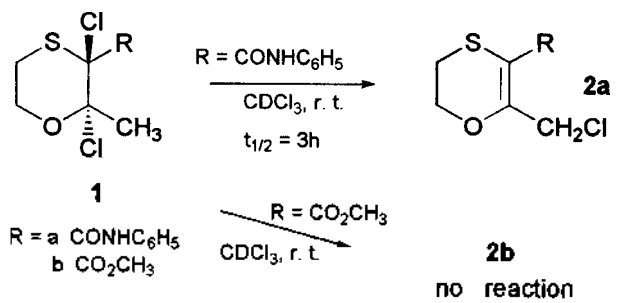
An anchimeric assistance of anilide in the rearrangement of dichloro-1,4-oxathaines **1** to 2-chloromethyl dihydro-1,4-oxathiins **2** is described. The inductive effect of the carbonyl group of anilide was negligible in the rearrangement. A rate of the rearrangement depended on the basicity of anilide nitrogen. A hydrogen bonding between the anilide hydrogen and an oxygen atom of those substituents make the nitrogen less basic, resulting in the slower rearrangement.

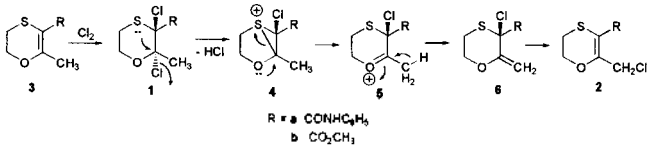
Introduction

A neighboring group participation by a heteroatom or heterosubstituent at a remote position from the reaction center is a well-known phenomenon that generally enhances the reactivity of certain classes of reactions.[1] In our previous paper,[2] we reported that dichloro-1,4-oxathiane anilide **1a** was gradually ($t_{1/2}$=3h) rearranged to chloromethyl compound **2a** at room temperature while the corresponding ester **1b** was fairly stable under the same reaction condition. As an extension of our studies on the reactivity of the dichloro-1,4-oxathianes **1** we now report an anchimeric assistance of anilide in the rearrangement.



Results and Discussion

Syntheses of starting materials, dihydro-1,4-oxathiins **3** were achieved by the previously known method.[3] Chlorination of **3** either by sulfuryl chloride or by chlorine in methylene chloride at 0 °C gave the dichloro-1,4-oxathiane **1** in quantitative yield. The ester dichloride **1b** was fairly stable at room temperature. In contrast, we were unable to isolate the probable intermediate dichloride anilide **1a** as a pure compound but immediately after work-up there were present in the ^{1}H NMR spectrum of the crude reaction mixture a methyl signal, NH, and four methylene hydrogens (ABCD spin patterns) assignable to the structure of this compound. The anilide dichloride **1a** was gradually converted to the chloromethyl compound **2a**. The plausible mechanism of the rearrangement is shown in Scheme 1.



Scheme 1