Liquid chromatographic resolution of 2-hydroxycarboxylic acids on a new chiral stationary phase derived from (*S*)-leucine

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Abstract

Enantiomers of racemic 2-hydroxycarboxylic acids have been resolved as their *O*-ethoxycarbonyl π-basic anilide derivatives on a new chiral stationary phase (CSP) derived from *N*-(3,5-dinitrobenzoyl)leucine *N*-phenyl *N*-alkylamide and the resolution results have been compared with those on various commercial π-acidic CSPs. The resolution results demonstrate that the new CSP derived from *N*-(3,5-dinitrobenzoyl)leucine *N*-phenyl *N*-alkylamide is most effective among the five CSPs tested for the resolution of 2-hydroxycarboxylic acid derivatives. In order to elucidate the chiral recognition mechanism exerted by the new CSP, the resolution of slightly differently modified derivatives of 2-hydroxycarboxylic acids on the new CSP has been investigated. Based on the resolution results, a chiral recognition mechanism utilizing three simultaneous interactions such as the face to face π–π interaction and the two hydrogen bonding interactions between the CSP and the more retained enantiomer of the analyte has been proposed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Enantiomer separation; Chiral stationary phases, LC; 2-Hydroxycarboxylic acids; Leucine

1. Introduction

Liquid chromatographic direct separation of enantiomers on chiral stationary phases (CSPs) has been known to be the most accurate and convenient means in solving the problems related to stereochemistry including the determination of enantiomeric composition of chiral compounds [1,2]. Consequently, significant efforts have been devoted to the development of effective CSPs for the liquid chromatographic direct separation of enantiomers [3]. Among others, Pirkle-type CSPs have been known to be effective for the resolution of racemates containing π-acidic or π-basic aromatic groups [4,5].

Our efforts in this area have also resulted in several successful Pirkle-type CSPs [6–8].

Recently, we developed a new π-acidic Pirkle-type CSP based on (*S*)-leucine (CSP **1**) by simply replacing the superfluous adsorption site, the N–H hydrogen of the connecting tether of commercial π-acidic CSP **2**, with a phenyl group [9]. CSP **1** thus developed has shown much greater enantioselectivity for the enantiomers of π-acidic racemates such as *N*-(3,5-dinitrobenzoyl)-α-amino amides and esters [9,10] and for the enantiomers of π-basic racemates such as *N*-(3,5-dimethoxy)-α-amino *N*,*N*-dialkyl amides than CSP **2** [11]. In this study, we wish to extend the use of CSP **1** to the resolution of α-hydroxycarboxylic acids.

Optically active 2-hydroxycarboxylic acids are important as starting materials, chiral building blocks

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or intermediates in the synthesis of biologically active substances and consequently various enzymatic and chemical methods have been employed for the preparation of optically active 2-hydroxycarboxylic acids [12–15]. During the process of preparing or utilizing α-hydroxycarboxylic acids, the methods for the rapid and accurate assessment of enantiomeric composition of chiral 2-hydroxycarboxylic acids are essential. To this end, NMR chiral shift reagent methods [16] and methods of chromatographic separation of diastereomers [17,18] have been utilized. However, all of these methods have shortcomings in convenience and/or accuracy. In this context, the chromatographic direct separation of enantiomers on chiral stationary phases (CSPs) might be the choice for the assessment of enantiomeric composition of chiral 2-hydroxycarboxylic acids.

Previously gas chromatographic direct separation of the two enantiomers of 2-hydroxycarboxylic acids as their volatile derivatives on CSPs has been used for the assessment of enantiomeric composition [17]. Liquid chromatographic separation of the two enantiomers of 2-hydroxycarboxylic acids or their derivatives has also been successfully applied for the assessment of enantiomeric composition [19–21]. However, the degree of separation was only moderate and the derivatization process utilized was somewhat complicated. Recently, we developed a very attractive process of derivatizing α-hydroxycarboxylic acids [22] and found the derivatives of α-hydroxycarboxylic acids thus prepared were easily resolved on CSP **1**. In this study, we report the resolution of the derivatives of 2-hydroxycarboxylic acids on CSP **1** and the comparison of the resolution results with those on various other commercially available Pirkle-type CSPs.

2. Experimental

Chromatography was performed with an HPLC system consisting of a Waters model 515 HPLC pump, a Rheodyne model 7125 injector with a 20 μl sample loop, a Younglin M720 Absorbance detector (variable wavelength) and a Youngin D520B computing integrator. The chiral columns used in this study are available from the previous study (CSP **1**) or commercially available (CSPs **2**, **3**, **4**, and **5**) from

Regis Chemical Company (Morton Grove, IL) (see Fig. 1 for the structures of CSPs). All chromatographic resolution experiments were performed using a mixed solvent of 2-propanol–hexane (20–80, v/v) as a mobile phase at a flow-rate of 2 ml/min at room temperature. Column void volume was measured by injecting 1,3,5-tri-*tert.*-butylbenzene.

In this study, ten 2-hydroxycarboxylic acids (see Fig. 2 for the structures) were purchased from Aldrich or Sigma chemical company and used for the resolution experiment after derivatization. Derivatives **6**, **7**, **8** and **9** of 2-hydroxycarboxylic acids were prepared by simply stirring 2-hydroxycarboxylic acids with EEDQ [2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline] in the presence of the appropriate aryl amine such as aniline, 3,5-dimethylaniline, 3,5-dimethoxyaniline, *N*-methyl aniline or *N*-ethyl aniline in methylene chloride at room temperature for 5 h as described in our previous study [22]. The racemization during the process of derivatization of optically active 2-hydroxycarboxylic acids such as lactic acid and mandelic acid was not detected as reported in our previous study [22]. Derivatives **10** were prepared by stirring α-methoxyphenylacetic acid obtained from Aldrich chemical company with EEDQ in the presence of aniline, 3,5-dimethylaniline or 3,5-dimethoxyaniline in methylene chloride at room temperature.

3. Results and discussion

For the enantioselective separation, CSPs should interact with racemic analytes through a minimum of three simultaneous interactions, at least one of these interactions being stereochemically dependent [1]. Various types of interactions between the CSP and racemic analytes can be utilized for the chiral recognition. Among others, π–π interaction between the CSP and analytes has been known to be of prime importance for the chiral recognition on Pirkle-type CSPs [4,5]. In this context, derivatization of 2-hydroxycarboxylic acids with a reagent containing aromatic groups might be useful for the chiral recognition on Pirkle-type CSPs.

Derivatization of 2-hydroxycarboxylic acids was achieved by the method developed in our laboratory [22]. For example, anilide derivatives **6** of 2-hy-
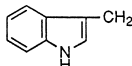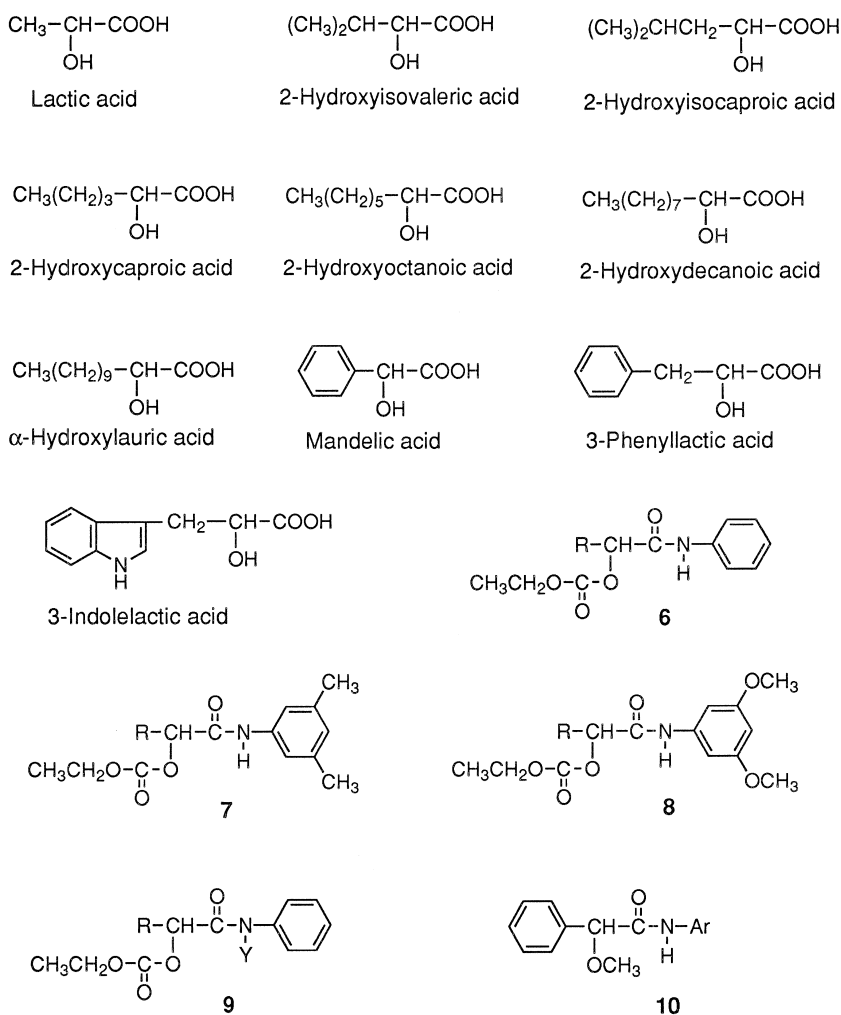
Fig. 1. Structures of CSPs **1**–**5** used in this study.

droxycarboxylic acids were easily prepared by just stirring 2-hydroxycarboxylic acids with EEDQ in the presence of aniline in methylene chloride at room temperature. Anilide derivatives **6** of 2-hydroxy-carboxylic acids thus prepared contain a π-basic anilide functional group. Therefore, they are expected to be resolved on Pirkle-type π-acidic CSPs. The chromatographic resolution of anilide derivatives **6** of various 2-hydroxycarboxylic acids was performed on CSP **1** and the chromatographic resolution results were compared with those on four other commercial Pirkle type π-acidic CSPs (CSP **2**, **3**, **4**, and **5**) in Table 1. The configuration of the first eluted enantiomers indicated in Table 1 was determined by injecting configurationally known samples. In Table 1, CSP **1** shows the best enantio-selectivity for the two enantiomers of derivatives **6** of 2-hydroxycarboxylic acids. CSPs **2** and **3**, which are derived from *N*-(3,5-dinitrobenzoyl)-α-amino

acids, show moderate enantioselectivity for the two enantiomers of derivatives **6** of 2-hydroxycarboxylic acids. However, the enantioselectivity exerted by CSP **2** or **3** is not as effective as CSP **1**. CSP **4**, which is commercially available as Whelk-O1, has been known to show excellent enantioselectivity for various types of racemic compounds [23]. However, in resolving derivatives **6** of 2-hydroxycarboxylic acids, CSP **4** was not effective as shown in Table 1. CSP **5**, the commercial name of which is Pirkle 1J, is known to resolve various racemic β-blockers such as alprenolol and propranolol [24]. However, CSP **5** was also not effective in resolving derivatives **6** of 2-hydroxycarboxylic acids.

CSP **1** retains the integrity of the structure of CSP **2** except for the N–H hydrogen of the connecting tether. In place of the N–H hydrogen of the connecting tether of CSP **2**, CSP **1** has a phenyl group. This structural difference between CSP **1** and **2** might

CH₃−CH−COOH
  |
  OH
Lactic acid

(CH₃)₂CH−CH−COOH
    |
    OH
2-Hydroxyisovaleric acid

(CH₃)₂CHCH₂−CH−COOH
     |
     OH
2-Hydroxyisocaproic acid

CH₃(CH₂)₃−CH−COOH
    |
    OH
2-Hydroxycaproic acid

CH₃(CH₂)₅−CH−COOH
    |
    OH
2-Hydroxyoctanoic acid

CH₃(CH₂)₇−CH−COOH
    |
    OH
2-Hydroxydecanoic acid

CH₃(CH₂)₉−CH−COOH
    |
    OH
α-Hydroxylauric acid

Ph−CH−COOH
  |
  OH
Mandelic acid

Ph−CH₂−CH−COOH
    |
    OH
3-Phenyllactic acid

Indole−CH₂−CH−COOH
     |
     OH
3-Indolelactic acid

6

7

8

9

10

Fig. 2. Structures of ten 2-hydroxycarboxylic acids used in this study and their derivatives **6**, **7**, **8**, **9** and **10**. See the Experimental for the chromatographic condition.

suggest that the N–H hydrogen of the connecting tether of CSP **2** is just a superfluous interaction site and just leads to the non-stereoselective retention. This assumption is evidenced by the greater capacity factors, k'_1, on CSP **2** for the first eluted enantiomers of all analytes tested in this study.

As an effort to elucidate the chiral recognition mechanism exerted by CSP **1** for the resolution of racemic 2-hydroxycarboxylic acid derivatives **6**, slightly modified derivatives **7–10** were prepared and their resolution behaviors on CSP **1** were investigated. First of all, the effect of the π-basicity of the π-basic aromatic functional group of analytes on the

chiral recognition was investigated by preparing 3,5-dimethylanilide and 3,5-dimethoxyanilide derivatives **7** and **8** and then resolving them on CSP **1**. The chromatographic results for the resolution of 3,5-dimethylanilide and 3,5-dimethoxyanilide derivatives **7** and **8** of 2-hydroxycarboxylic acids on CSP **1** and the comparison with those on other CSPs are summarized in Tables 2 and 3. The comparison of chromatograms for the resolution of anilide (**6h**), 3,5-dimethylanilide (**7h**) and 3,5-dimethoxyanilide derivative (**8h**) of mandelic acid is illustrated in Fig. 3. As shown in Tables 2 and 3 and in Fig. 3, 3,5-dimethylanilide derivatives **7** and 3,5-dimethoxy-

Table 1
Resolution of derivatives **6** of 2-hydroxycarboxylic acids on CSPs (**1–5**)[a]

6	R	CSP **1**		CSP **2**		CSP **3**		CSP **4**		CSP **5**	
		k_1' [b]	α [c]	k_1' [b]	α [c]	k_1' [b]	α [c]	k_1' [b]	α [c]	k_1' [b]	α [c]
a	CH_3	1.13 (R)	2.45	1.55 (R)	1.46	3.31 (S)	1.27	1.90	1.00	3.94 (S)	1.05
b	$(CH_3)_2CH$	0.83 (R)	3.16	1.03	1.58	1.80	1.16	1.29	1.13	2.60	1.00
c	$(CH_3)_2CHCH_2$	0.87 (R)	3.16	1.02 (R)	1.65	2.05 (S)	1.34	1.20 (S)	1.15	2.64	1.00
d	$CH_3(CH_2)_3$	0.76	2.41	0.85	1.42	1.80	1.21	1.28	1.00	2.33	1.00
e	$CH_3(CH_2)_5$	0.87	2.56	1.00	1.48	2.16	1.26	1.39	1.00	2.68	1.00
f	$CH_3(CH_2)_7$	0.64	2.02	0.79	1.43	1.33	1.18	1.24	1.00	2.38	1.00
g	$CH_3(CH_2)_9$	0.57	2.02	0.70	1.41	1.15	1.16	1.14	1.00	2.12	1.00
h	C_6H_5	1.57 (R)	3.90	1.76 (R)	1.66	4.54 (S)	1.31	2.29 (R)	1.17	5.86 (S)	1.11
i	$C_6H_5CH_2$	1.28 (R)	2.79	1.39 (R)	1.50	3.72 (S)	1.41	1.79	1.00	4.88	1.00
j	⟨indol-3-yl⟩–CH2	3.07	2.62	4.20	1.44	10.68	1.35	4.41	1.00	24.96	1.00

[a] Chromatographic condition is given in the Experimental.
[b] Capacity factor of the first eluted enantiomer. Absolute configuration of the first eluted enantiomer is given in parenthesis.
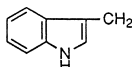[c] Separation factor.

anilide derivatives **8** are resolved better than the corresponding simple anilide derivatives (**6**) on CSP **1**. These results demonstrate that the degree of enantioselectivity exerted by CSP **1** is strongly dependent on the π-basicity of the aromatic anilide derivatizing group. From these results, it is concluded that the π–π interaction between the *N*-(3,5-dinitrobenzoyl) group of the CSP and the anilide group of analytes is important for chiral recognition.

The role of the N–H hydrogen of the anilide

derivatizing group of 2-hydroxycarboxylic acid derivatives **6** in the chiral recognition is expected to be demonstrated by the resolution behaviors of 2-hydroxycarboxylic acid derivatives **9**, which do not contain the N–H hydrogen, on CSP **1**. The resolution of 2-hydroxycarboxylic acid derivatives **9** on CSP **1** was performed with samples derived from lactic and mandelic acid and the results are summarized in Table 4. As shown in Table 4, 2-hydroxycarboxylic acid derivatives **9** which contain methyl or ethyl

Table 2
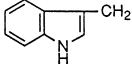Resolution of derivatives **7** of 2-hydroxycarboxylic acids on CSPs (**1–5**)[a]

7	R	CSP **1**		CSP **2**		CSP **3**		CSP **4**		CSP **5**	
		k_1' [b]	α [c]	k_1' [b]	α [c]	k_1' [b]	α [c]	k_1' [b]	α [c]	k_1' [b]	α [c]
a	CH_3	1.44 (R)	2.80	1.66 (R)	1.64	3.25 (S)	1.34	1.80	1.14	4.11 (S)	1.08
b	$(CH_3)_2CH$	0.94 (R)	3.74	1.09	1.81	2.01	1.48	1.37	1.00	2.75	1.00
c	$(CH_3)_2CHCH_2$	1.04 (R)	3.90	1.06 (R)	1.90	1.92 (S)	1.44	1.24 (S)	1.15	2.71	1.00
d	$CH_3(CH_2)_3$	1.04	2.96	1.04	1.65	1.99	1.34	1.41	1.07	2.87	1.00
e	$CH_3(CH_2)_5$	0.88	2.71	0.87	1.60	1.68	1.27	1.28	1.09	2.79	1.00
f	$CH_3(CH_2)_7$	0.70	2.34	0.81	1.57	1.31	1.24	1.29	1.09	2.30	1.00
g	$CH_3(CH_2)_9$	0.63	2.25	0.72	1.53	1.14	1.21	1.19	1.10	2.10	1.00
h	C_6H_5	1.61 (R)	5.60	1.78 (R)	2.02	4.03 (S)	1.45	2.36 (R)	1.09	6.90	1.00
i	$C_6H_5CH_2$	1.45 (R)	3.11	1.43 (R)	1.64	3.38 (S)	1.56	1.78	1.08	5.54	1.00
j	⟨indol-3-yl⟩–CH2	3.31	3.28	4.15	1.57	9.82	1.46	4.34	1.00	28.33	1.00

[a] Chromatographic condition is given in the Experimental.
[b] Capacity factor of the first eluted enantiomer. Absolute configuration of the first eluted enantiomer is given in parenthesis.
[c] Separation factor.

Table 3
Resolution of derivatives **8** of 2-hydroxycarboxylic acids on CSPs (**1–5**)[a]

8	R	CSP **1**		CSP **2**		CSP **3**		CSP **4**		CSP **5**	
		$k_1'^b$	α^c	$k_1'^b$	α^c	$k_1'^b$	α^c	$k_1'^b$	α^c	$k_1'^b$	α^c
a	CH_3	2.76 (R)	3.67	3.74 (R)	1.95	10.53 (S)	1.49	3.71	1.13	10.25 (S)	1.12
b	$(CH_3)_2CH$	1.98 (R)	5.16	2.43	2.18	6.43	1.70	2.69	1.00	6.41	1.11
c	$(CH_3)_2CHCH_2$	2.23 (R)	5.89	2.41 (R)	2.33	6.35 (S)	1.69	2.48 (S)	1.10	6.46	1.09
d	$CH_3(CH_2)_3$	2.38	3.95	2.34	1.98	5.58	1.52	2.80	1.09	6.70	1.09
e	$CH_3(CH_2)_5$	2.09	3.52	1.95	1.69	4.75	1.44	2.55	1.09	5.81	1.07
f	$CH_3(CH_2)_7$	1.31	2.89	1.87	1.86	3.57	1.37	2.56	1.10	6.81	1.07
g	$CH_3(CH_2)_9$	1.19	2.74	1.69	1.79	3.08	1.33	2.36	1.10	5.78	1.06
h	C_6H_5	3.67 (R)	6.76	3.83 (R)	2.34	10.36 (S)	1.64	4.54 (R)	1.13	14.07 (S)	1.14
i	$C_6H_5CH_2$	3.63 (R)	4.35	3.31 (R)	1.97	9.61 (S)	1.75	3.62	1.00	14.06	1.00
j	(indole-CH₂ structure)	6.19	4.23	9.97	1.86	25.37	1.90	8.61	1.00	69.22	1.00

[a] Chromatographic condition is given in the Experimental.
[b] Capacity factor of the first eluted enantiomer. Absolute configuration of the first eluted enantiomer is given in parenthesis.
[c] Separation factor.

a)

b)

c)
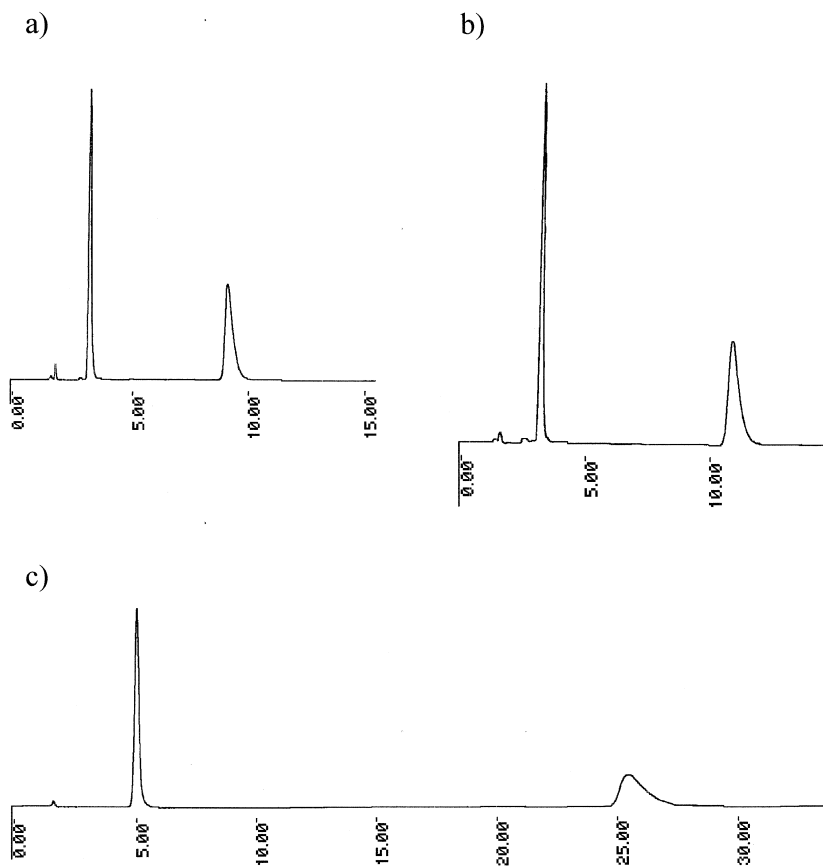
Fig. 3. Comparison of the chromatograms for the resolution of derivatives (a) **6h**, (b) **7h**, and (c) **8h** of mandelic acid on CSP **1**.

Table 4
Resolution of 2-hydroxycarboxylic acid derivatives **9** and **10** on CSP **1**[a]

Analyte	R	Y or Ar	k'^{b}_1	k'^{c}_2	α^{d}	Conf.[e]
9a	CH_3	CH_3	0.92	0.92	1.00	
9b	CH_3	CH_2CH_3	0.70	0.70	1.00	
9c	C_6H_5	CH_3	0.89	0.89	1.00	
9d	C_6H_5	CH_2CH_3	0.72	0.72	1.00	
10a		Phenyl	1.13	1.40	1.24	*S*
10b		3,5-Dimethylphenyl	1.18	1.30	1.10	*S*
10c		3,5-Dimethoxyphenyl	2.36	2.60	1.10	*S*

[a] Chromatographic condition is given in the Experimental.
[b] Capacity factor of the first eluted enantiomer.
[c] Capacity factor of the second eluted enantiomer.
[d] Separation factor.
[e] Absolute configuration of the second eluted enantiomer.

groups in the place of the N–H hydrogen of 2-hydroxycarboxylic acid derivatives **6** are not resolved at all on CSP **1**. From these results, the N–H hydrogen of the anilide derivatizing group of 2-hydroxycarboxylic acid derivatives **6** is concluded to play a very important role probably as a hydrogen bonding donor site in the chiral recognition.

The role of the carbonyl oxygen of the carbonate group of 2-hydroxycarboxylic acid derivatives **6** in the chiral recognition has also been similarly demonstrated by resolving 2-hydroxycarboxylic acid derivatives **10**, which do not contain the carbonate group, on CSP **1**. The results for the resolution of 2-hydroxycarboxylic acid derivatives **10** on CSP **1** are included in Table 4. As shown in Table 4, 2-hydroxycarboxylic acid derivative **10** is not resolved well on CSP **1**. The separation factors, α, are very small compared with those for the resolution of corresponding 2-hydroxycarboxylic acid derivatives **6h**, **7h** and **8h**. Consequently, it is concluded that the carbonyl oxygen of the carbonate group of 2-hydroxycarboxylic acid derivatives **6** is very important as a hydrogen bonding acceptor site in the chiral recognition.

Based on the interaction sites of CSP **1** and 2-hydroxycarboxylic acid derivatives **6** discussed above and with the aid of a CPK molecular model study, a chiral recognition mechanism is proposed as shown in Fig. 4. Fig. 4 shows the (*S*,*S*)-complex formed between the model compound of the chiral selector of CSP **1**, (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-phenyl *N*-propyl amide and the (*S*)-enantiomer of lactic acid derivative **6a**. In Fig. 4, the model compound of the chiral selector of CSP **1** interacts with the (*S*)-enantiomer of the 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 anilide group of the analyte. Simultaneously, the model compound of the chiral selector of CSP **1** interacts with the (*S*)-enantiomer of the analyte through the two hydrogen bonding interactions. One hydrogen bonding is presumed to be formed between the N–H hydrogen of the anilide group of the analyte and the carbonyl oxygen of the amide tethering group of the model compound of the chiral selector of CSP **1** while another hydrogen bonding is assumed to be formed between the carbonyl oxygen of the carbonate group of the analyte and the N–H hydrogen of the 3,5-dinitrobenzoyl amide group, the only hydrogen bonding donor site of the model compound of the chiral selector of CSP **1**. However, the three simultaneous interactions such as shown in Fig. 4 is not possible with (*R*)-enantiomers because of the inadequate three dimensional positions of the functional groups of (*R*)-enantiomers. In this instance, the (*S*,*S*)-complex is more stable than the (*S*,*R*)-complex and consequently the (*S*)-enantiomer is retained longer on the column.

In summary, in this study, two enantiomers of racemic 2-hydroxycarboxylic acids were demonstrated to be resolved very well as their *O*-ethoxycarbonyl π-basic anilide derivatives **6** on a new chiral stationary phase (CSP **1**) derived from *N*-(3,5-dinitrobenzoyl)leucine *N*-phenyl *N*-alkylamide and the resolution results were compared with those on four other commercial π-acidic CSPs (**2–5**). The res-
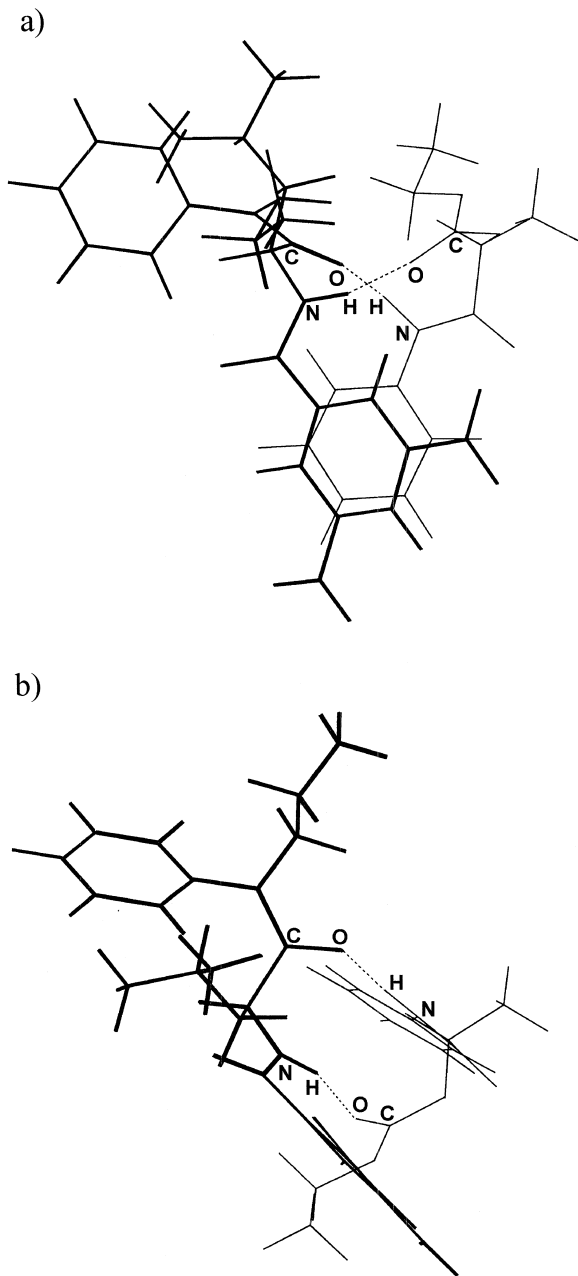
a)

b)

Fig. 4. A proposed chiral recognition model for the more stable (*S*,*S*)-complex formed between a model compound (represented with thick lines) of the chiral selector of CSP **1**, (*S*)-*N*-(3,5-dinitrobenzoyl)leucine *N*-phenyl *N*-propyl amide, and the (*S*)-enantiomer of analyte **6a** (represented with thin lines). (a) A stick molecular model viewed from the angle showing the π–π interaction between the 3,5-dinitrophenyl group of the CSP and the anilide phenyl group of the analyte and the two hydrogen bonds (side view). (b) The same stick molecular model as in (a), but viewed from a different angle (top view).

olution results demonstrate that CSP **1** is most effective among the five CSPs tested for the resolution of 2-hydroxycarboxylic acid derivatives **6**. As an effort to elucidate the chiral recognition mechanism exerted by CSP **1**, the resolution of slightly differently modified derivatives of 2-hydroxycarboxylic acids such as derivatives **7**, **8**, **9** and **10** on CSP **1** was investigated. Based on the resolution results, a chiral recognition mechanism utilizing three simultaneous interactions such as the face to face π–π interaction and the two hydrogen bonding interactions between the CSP and the more retained enantiomer of the analyte was proposed.

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