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Resolution of Amide Derivatives of Naproxen on Pirkle-Type π-Acidic Chiral Stationary Phases

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A chiral recognition model which explains the chiral resolution behavior of N-alkyl amide derivatives of naproxen on the Pirkle type π-acidic CSPs derived from N-(3,5-dinitrobenzoyl)-(R)-phenylglycine and N-(3,5-dinitrobenzoyl)-(S)-leucine has been proposed. Based on the proposed model, an effort to improve the resolution of racemic naproxen derivatives on the CSP has been devoted and consequently, N-alkyl N-aryl amides of naproxen or N-alkyl N-cyclohexyl amides of naproxen have been found to be resolved quite well on a Pirkle type π-acidic CSP. Based on the reciprocity conception of chiral recognition, CSPs which might show excellent resolving ability for π-acidic racemic compounds have been suggested.

Introduction

Enantiomers of chiral drugs often show different biological activities[1] and, in consequence, the enantiomeric composition of chiral drugs has been an important issue in developing and using them.[2] The nonsteroidal anti-inflammatory drugs (NSAIDs) related to α-arylpropionic acids are one class of pharmaceutical compounds which exhibit the contrasting behavior of the two enantiomers. In general, the (S)-enantiomers of NSAIDs are more active for the desired therapeutic effect than the corresponding (R)-enantiomers and the (R)-enantiomers undergo metabolic inversion of configuration *in vivo*.[3] In this instance, accurate and convenient means of measuring the enantiomeric purity of chiral drugs including NSAIDs has been sought.[4]

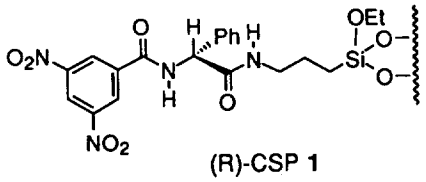
Chiral liquid chromatography based on chiral stationary phases (CSPs) has been most successfully applied to separate the two enantiomers of NSAIDs related to α-arylpropionic acids.[5] Among others, the alkyl amide derivatives of racemic NSAIDs have been resolved on CSP **1** derived from (R)-N-(3,5-dinitrobenzoyl)phenylglycine.[5a~e] To rationalize the chromatographic resolution results of the alkyl amide derivatives of NSAIDs on CSP **1**, Wainer and Doyle proposed a chiral recognition model utilizing the dipole stacking of amide dipoles and the π-π interaction between the dinitrobenzoyl group of the CSP and the aryl substituent of the analyte.[5a] Subsequently, this chiral recognition model was recognized by Pirkle as a "head-to-head" chiral recognition model.[5e] However, resolving a homologous series of alkyl amide derivatives of racemic naproxen on CSP **2** derived from (S)-N-(3,5-dinitrobenzoyl)leucine, we found that the chromatographic resolution results are somewhat different from those on CSP **1**. To rationalize the differences between the chromatographic resolution results on CSP **1** and **2**, we herein propose an improved chiral recognition model utilizing the face-to-edge π-π interaction which has attracted considerable attention as an associative force between aromatic rings in the recent studies[6] and the hydrogen bonding interaction

Table 1. Comparison of the resolution of naproxen alkyl amide derivatives **3** on CSP **1** and **2**[a]

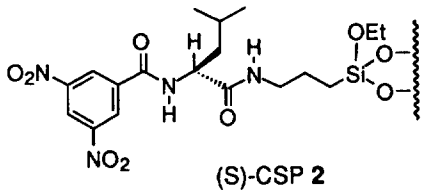
Anal	R	CSP 1				CSP 2			
		k_1'[b]	k_2'[c]	α[d]	Co.[e]	k_1'[b]	k_2'[c]	α[d]	Co.[e]
3a	CH_3	16.62	19.88	1.20	R	9.45	10.22	1.08	R
b	CH_2CH_3	13.65	16.06	1.18	R	6.76	8.02	1.19	R
c	$(CH_2)_2CH_3$	11.33	12.75	1.13	R	4.81	6.28	1.31	R
d	$(CH_2)_4CH_3$	8.30	8.77	1.06	R	3.41	4.94	1.45	R
e	$(CH_2)_6CH_3$	6.86	6.86	1.00		2.77	4.28	1.55	R
f	$(CH_2)_7CH_3$	6.28	6.28	1.00		2.59	4.03	1.56	R
g	$(CH_2)_9CH_3$	5.75	5.75	1.00		2.34	3.81	1.63	R
h	$(CH_2)_{11}CH_3$	5.19	5.19	1.00		2.11	3.47	1.64	R

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

between the CSP and the analyte instead of the dipole stacking hypothesis. In addition, an effort to improve the separability of the two enantiomers of naproxen derivatives on CSP **2** is described. This effort is expected to be extended to develop an efficient CSP derived from optically pure naproxen based on the reciprocity conception of chiral recognition, which was first employed by Pirkle in rationally designing CSPs.[7]



(R)-CSP **1**



(S)-CSP **2**

Experimental

HPLC analyses were performed with an instrument 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. All chromatographic data were collected using a mixed solvent of 2-propanol and hexane (90 : 20, v/v) as a mobile phase with a flow rate of 2.0 mL/min at 20 ℃. The column void volume was determined by injecting 1,3,5-tri-*tert*-butylbenzene, a presumed unretained solute.[8] Stainless-steel HPLC chiral columns (250 mm×4.6 mm I.D.) packed with CSP **1** or **2** were obtained from Regis (Morton Grove, Illinois, USA).

Analytical samples **3, 4, 5a, 6a** and **7a** were prepared by simply treating the acid chloride of naproxen with appropriate amines in the presence of triethylamine as described

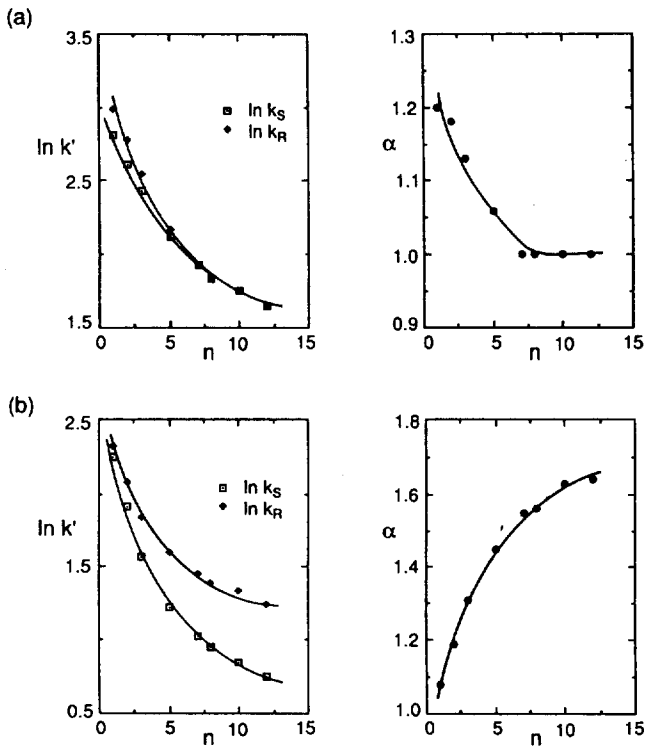


Figure 1. Trends in the retention (ln k') of the two enantiomers and the enantioselectivity (α) for resolving N-alkyl amide derivatives **3** of naproxen on (a) CSP **1** and on (b) CSP **2**. The length of the amide N-alkyl group [-$(CH_2)_n$-H] of analytes is denoted by n on the abscissa. For chromatographic conditions, see the experimental part.

previously.[5a,9] N-Alkylation of amides **5a, 6a** and **7a** were accomplished by treating an amide in dry THF with n-butyllithium and then adding HMPA and appropriate alkylbromide. A typical run for the preparation of **5d** is as follows.

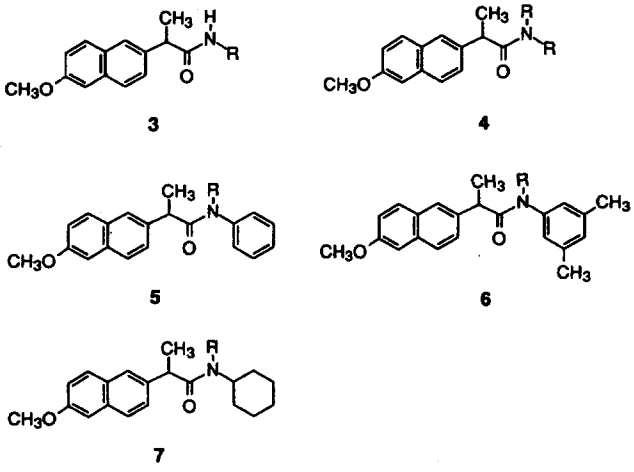
To a stirred solution of 0.50 g of naproxen anilide **5a** (1.64 mmol) in 20 mL dry THF was added 1.05 mL of 1.6 M n-butyllithium (1.68 mmol) in hexane at −10 ℃. The reaction mixture was stirred for 20 min and then 0.29 mL of HMPA (1.64 mmol) was added to the cold basic solution. After stirring the mixture for additional 15 min, 0.45 mL of 1-bromopropane (4.92 mmol) was added at once. The mixture was stirred at room temperature for 28 h and concentrated in vacuo. The final crude product was purified by flash chromatography on silica gel to afford 0.47 g (82.6%) of **5d** as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80-0.95 (m, 5H, CH_2CH_3), 1.47 (d, 3H, CH_3), 3.64 (m, 2H, NCH_2), 3.66 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 6.89-7.64 (m, 11H, ArH). IR ($CDCl_3$) cm^{-1} 3059, 2965, 1657, 1607.

Results and Discussion

Resolution results of a homologous series of N-alkyl amide derivatives **3** of naproxen on CSP **1** and **2** are summarized in Table 1. The trends for the capacity factors (k') and the separation factors (α) shown in Table 1 are graphically illustrated in Figure 1. As shown in Figure 1, the chromatographic resolution trends for resolving N-alkyl amide derivatives **3** of naproxen on CSP **1** and **2** are exactly opposite. For

example, the capacity factor of the second eluted enantiomer on CSP **1** decreases more rapidly than that of the first eluted enantiomer and consequently the separation factor decreases as the N-alkyl chain of **3** increases in length. On the contrary, the capacity factor of the first eluted enantiomer on CSP **2** decreases more rapidly than that of the second eluted enantiomer and consequently the separation factor increases continuously as the N-alkyl chain of **3** increases in length. In addition, it should be noted that the elution orders on CSP **1** and **2** are identical as shown in Table 1 even though the absolute configurations of the two CSPs are opposite to each other.

To explain the elution orders of the N-alkyl amide derivatives of NSAIDs on CSP **1**, a chiral recognition mechanism involving the π-π interaction between the 3,5-dinitrobenzoyl group of CSP **1** and the 6-methoxy-2-naphthyl group of the analyte **3** and the head to head dipole stacking interaction between the two amide dipoles of the CSP and the analyte has been proposed.[5a,c] The chiral recognition mechanism proposed previously, however, does not rationalize the opposite trends of chromatographic resolution results shown in Figure 1 and the same elution orders on the two CSPs having opposite absolute configuration. Therefore, in this study, we proposed an improved chiral recognition model based on the chromatographic resolution trends shown in Figure 1 and the elution orders observed on CSP **1** and **2**.



The improved chiral recognition model proposed in this study is shown in Figure 2. In the model, (R)-CSP **1**, (S)-CSP **2** and the N-alkyl amide derivative **3** of naproxen are schematically presented in their lowest energy conformations and assumed to be preferentially populated as described previously.[5c,5h,10] In Figure 2a, (R)-CSP **1** and the analyte are proposed to interact with each other through the face-to-face π-π interaction between the π-basic 6-methoxy-2-naphthyl (NAPH) group of the analyte and the π-acidic 3,5-dinitrophenyl group (DNP) of the CSP and the hydrogen bonding interaction between the carbonyl oxygen (A) of the analyte and the amide N-H hydrogen (B) of the CSP. In this instance, the edge of the 6-methoxy-2-naphthyl group of the (R)-analyte faces the face of the phenyl group at the chiral center of the CSP, inducing the face-to-edge π-π interaction between aromatic rings.[6] Consequently the transient diastereomeric (R,R)-complex is expected to be more stable than the corresponding (S,R)-complex, the (R)-enantiomer being retained longer than the (S)-enantiomer on CSP **1**. However, the stability of the (R,R)-complex decreases more rapidly than the (S,R)-complex as the alkyl chain (R in the Figure) of the N-alkyl amide of naproxen increases in length because the alkyl chain of the (R)-analyte intercalates between the connecting tethers of the CSP while that of the (S)-analyte does not. In this instance the separation factor should decrease continuously. All of these are consistent with those shown in Figure 1a.

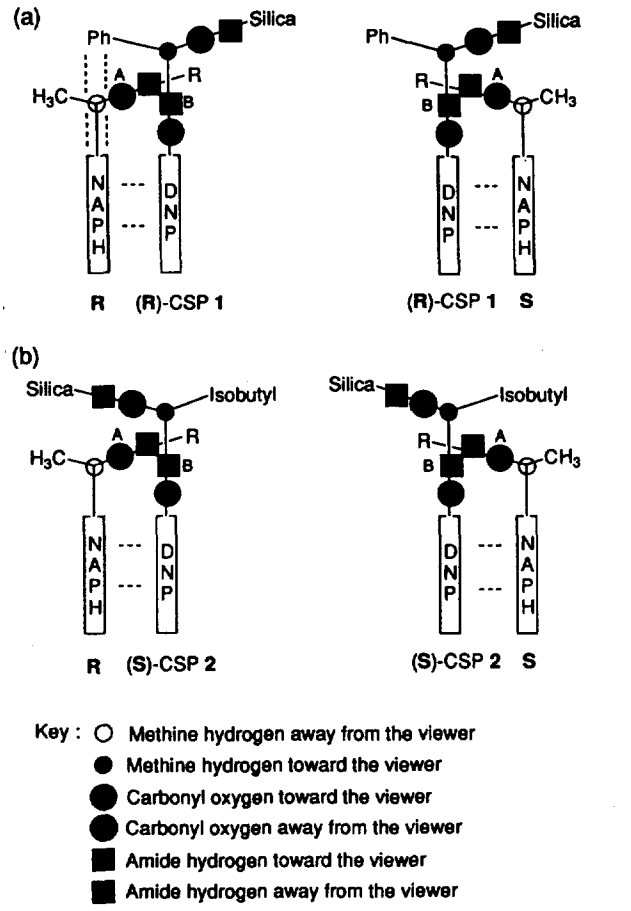


Figure 2. Proposed chiral recognition model for resolving N-alkyl amide derivatives **3** of naproxen on (a) CSP **1** and on (b) CSP **2**. The (R,R)-complex is more stable than the (R,S)-complex on (R)-CSP **1** whereas the (R,S)-complex is more stable than the (S,S)-complex on (S)-CSP **2**.

Similarly, (S)-CSP **2** interacts with N-alkyl amide derivative **3** of naproxen through the face-to-face π-π interaction between the π-basic 6-methoxy-2-naphthyl (NAPH) group of the analyte and the π-acidic 3,5-dinitrophenyl group (DNP) of the CSP and the hydrogen bonding interaction between the carbonyl oxygen (A) of the analyte and the amide N-H hydrogen (B) of the CSP as shown in Figure 2b. However, the face-to-edge π-π interaction which plays some important role in determining the stability difference between the two diastereomeric complexes on CSP **1** is not expected in this event. Instead, the stability difference between the two diastereomeric complexes on CSP **2** may be determined by the steric bulkiness of the isobutyl group and the carboxamide

Table 2. Comparison of the resolution of N,N-dialkyl amide derivatives **4** of naproxen on CSP **1** and **2**[a]

Anal	R	CSP 1				CSP 2			
		k_1'[b]	k_2'[c]	α[d]	Co.[e]	k_1'[b]	k_2'[c]	α[d]	Co.[e]
4a	CH_2CH_3	5.63	5.63	1.00		2.94	3.83	1.30	R
b	$(CH_2)_2CH_3$	4.10	4.10	1.00		1.65	2.44	1.48	R
c	$(CH_2)_3CH_3$	3.09	3.09	1.00		1.24	1.88	1.52	R
d	$(CH_2)_4CH_3$	2.45	2.65	1.06	S	1.03	1.62	1.57	R
e	$(CH_2)_5CH_3$	2.03	2.26	1.11	S	0.89	1.42	1.60	R
f	$(CH_2)_9CH_3$	1.31	1.55	1.18	S	0.58	1.00	1.72	R

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

connecting group at the chiral center of CSP **2**. It has been generally accepted that a carboxamide group is sterically smaller than a simple alkyl or aryl group.[11] Thus, the carboxamide connecting group at the chiral center of CSP **2** is thought to be sterically smaller than the isobutyl group and consequently the diastereomeric (R,S)-complex formed between the (R)-enantiomer and the CSP is expected more stable than the (S,S)-complex. The stability difference between the (R,S)- and the (S,S)-complex becomes greater and greater as the alkyl chain (R in the Figure 2b) of the N-alkyl amide of naproxen increases in length because the alkyl chain of the (S)-analyte intercalates between the connecting tethers of the CSP while that of the (R)-analyte does not, and consequently the separation factor increases continuously as shown in Figure 2b. All of these are exactly opposite to those on CSP **1** and consistent with those shown in Figure 1b.

According to the model shown in Figure 2, the amide N-H hydrogen of the analyte is not necessary in the chiral recognition and likely to be detrimental to the enantioselectivity exerted by the CSP because it can be used for the non-selective hydrogen bonding and consequently for the non-selective retention of the two enantiomers on the CSP. In this instance, replacing the supposedly superfluous amide N-H hydrogen with a simple alkyl group is expected to improve the resolution of the two enantiomers on the CSP. Based on this rationale, to see the effect of the removal of the N-H hydrogen from analyte **3** on the enantioselectivity exerted by CSP **1** and **2**, we prepared N,N-dialkyl amide derivatives **4** of naproxen and resolved them on CSP **1** and **2**.

Table 2 summarizes the results for resolving N,N-dialkyl amide derivatives **4** of naproxen on CSP **1** and **2**. As shown in Table 2, the resolution of the racemic N,N-dialkyl amide derivatives **4** of naproxen on CSP **1** are not significantly improved compared with those for resolving N-alkyl amide derivatives **3** of naproxen even though the capacity factors are reduced quite much. However, note that the trends in the separation factors for resolving N,N-dialkyl amide derivatives **4** of naproxen on CSP **1** are significantly shifted and consequently N,N-dialkyl amide derivatives **4** of naproxen with a longer amide alkyl group than a butyl group are resolved with the inversion of elution order on CSP **1** whereas those with a shorter amide alkyl group are not resolved as shown in Table 2.

Removal of the amide N-H hydrogen from N-alkyl amide derivatives **3** of naproxen significantly improved the enantioselectivities for the two enantiomers of naproxen derivatives on CSP **2**. As shown in Table 2, the separation factors for resolving N,N-dialkyl amide derivatives **4** of naproxen on CSP **2** are generally greater than those for resolving corresponding N-alkyl amide derivatives **3** of naproxen on CSP **2** and these are consistent with our expectation based on the chiral recognition model in Figure 2.

When the amide N-H hydrogen of N-alkyl amide derivatives **3** of naproxen was replaced by aromatic ring or cyclohexyl group, the two enantiomers of naproxen derivatives were resolved even better on CSP **2**. Table 3 shows the resolution of homologous series of naproxen amide derivatives **5**, **6** and **7**. As shown in Table 3, N-cyclohexyl-N-alkyl amide derivatives **7** of naproxen are resolved best on CSP **2** when the N-alkyl chain is short even though the length

Table 3. Resolution of naproxen derivatives **5**, **6** and **7** on CSP **2**[a]

entry	R	**5**			**6**			**7**		
		k_1'[b]	k_2'[c]	α[d]	k_1'[b]	k_2'[c]	α[d]	k_1'[b]	k_2'[c]	α[d]
a	H	8.57	10.96	1.28	8.46	10.49	1.24	8.14	13.22	1.62
b	CH_3	5.14	7.92	1.54	3.53	5.58	1.58			
c	CH_2CH_3	3.63	6.58	1.81	2.63	4.66	1.77	2.76	4.18	1.51
d	$(CH_2)_2CH_3$	2.73	5.56	2.04	2.09	4.04	1.93	2.19	3.50	1.60
e	$(CH_2)_4CH_3$							1.81	2.93	1.62
f	$(CH_2)_6CH_3$	1.66	4.06	2.45	1.37	3.07	2.24	1.58	2.66	1.68
g	$(CH_2)_7CH_3$							1.52	2.57	1.69
h	$(CH_2)_9CH_3$	1.33	3.40	2.56	1.16	2.74	2.36	1.40	2.37	1.69
i	$(CH_2)_{11}CH_3$	1.20	3.17	2.64	1.06	2.59	2.44	1.30	2.23	1.72
j	$(CH_2)_{13}CH_3$	1.15	3.12	2.71	0.99	2.43	2.45	1.22	2.10	1.72

[a] For the chromatographic conditions, see the experimental part. For the blanks, chromatographic resolution data have not been collected. In every case, the second eluted enantiomer has been found to have (R)-configuration. [b] Capacity factor of the first eluted enantiomer. [c] Capacity factor of the second eluted enantiomer. [d] Separation factor.

of the N-alkyl chain of **7** does not influence the enantioselectivities significantly. However, the length of the N-alkyl chain of N-phenyl-N-alkyl amide derivatives **5** or N-(3,5-dimethylphenyl)-N-alkyl amide derivatives **6** of naproxen influence the enantioselectivities for resolving the two enantiomers of naproxen amide derivatives on CSP **2** significantly, the separation factors being increased continuously as the N-alkyl chain of the analyte increases in length. The increasing trends are more significant for the N-phenyl-N-alkyl amide derivatives **5** than for N-(3,5-dimethylphenyl)-N-alkyl amide derivatives **6** of naproxen as shown in Table 3 and consequently, N-phenyl-N-alkyl amide derivatives **5** of naproxen with a long amide N-alkyl chain are resolved best on CSP **2**.

At this stage, we do not know the details of the role of the phenyl, 3,5-dinitrophenyl or cyclohexyl group of naproxen derivatives **5**, **6** or **7** in improving their enantioselectivities on CSP **2** except that it replaces the superfluous amide N-H hydrogen of N-alkyl amide derivatives **3** of naproxen which is not critical in the chiral recognition as shown in Figure 2. However, the improved enantioselectivities of naproxen derivatives **5**, **6** or **7** on CSP **2** might be utilized in designing an improved CSP derived from a naproxen amide derivative based on the reciprocity conception of chiral recognition.[7] Previously, Pirkle *et al.* reported that a doubly tethered CSP derived from N,N-dipropyl amide of naproxen (**4b**), which was prepared by binding N,N-diallylamide of (S)-naproxen to silica gel through the two allyl group, shows greater enantioselectivities for various π-acidic racemates than a CSP derived from N-propyl amide of naproxen (**3c**).[12] The improved enantioselectivities on the doubly tethered CSP derived from N,N-dipropyl amide of naproxen (**4b**) might come from the avoidance of the presence of an amide hydrogen which often serves to increase retention, attenuate enantioselectivity and consequently diminish the efficiency of the CSP. In this context, N-phenyl N-alkyl amide derivatives **5** of naproxen seem to be excellent candidates as chiral selectors for naproxen-derived CSPs because the enantioselectivities for resolving **5** on CSP **2** are much greater than those for resolving **4** on CSP **2** and, in consequence, preparation and application of CSPs derived from N-phenyl N-alkyl amide derivatives **5** of naproxen will be the subject of our next study.

In summary, a chiral recognition model which explains the chiral resolution behavior of N-alkyl amide derivatives **3** of naproxen on CSP **1** and **2** has been proposed. Based on the proposed model, which shows that the amide N-H hydrogen of the analyte is detrimental to the enantioselectivity exerted by the CSP, various tertiary amide derivatives of racemic naproxen were prepared and resolved on CSP **2** as an effort to improve the enantioselectivities of racemic naproxen derivatives on the CSP. Finally, we found that N-alkyl N-phenyl amides **5** of naproxen are resolved best so far on CSP **2**. Based on the reciprocity conception of chiral recognition, CSPs derived from N-alkyl N-phenyl amides **5** of naproxen are expected to show excellent resolving ability for π-acidic racemic compounds.

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