Preparation of a New Chiral Stationary Phase Bearing Both π-Acidic and -Basic Sites from (S)-Naproxen for the Liquid Chromatographic Resolution of Enantiomers

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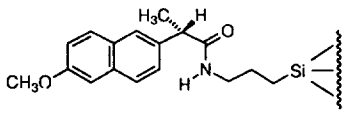
A new chiral stationary phase (CSP) for the liquid chromatographic resolution of enantiomers was prepared from (*S*)-naproxen and 3,5-dinitroaniline. The 6-alkoxy-2-naphthyl group of the CSP was presumed to act as a π-basic interaction site for resolving π-acidic racemates while the 3,5-dinitroanilide group of the CSP was presumed to play a role as a π-acidic interaction site for resolving π-basic racemates. From the chromatographic resolution trends of *N*-alkyl amide derivatives of α-arylalkylamines on the CSP prepared, the chiral recognition mode involving the intercalation of the amide alkyl chain of the less retained enantiomers between the connecting tethers of the CSP was proposed.

Introduction

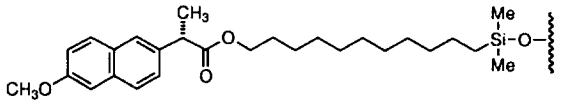
Two enantiomers of racemic drugs or pesticides often show different biological activities because living systems are chiral. Therefore, there is a certain need for methods by which each of two enantiomers can be obtained in an enantiomerically pure form and by which the enantiomeric composition of optically active compounds and the absolute configuration can be determined.[1] Among various techniques, chiral chromatography using chiral stationary phases (CSPs) has proven to be a convenient and accurate tool to solve those problems related to stereochemistry.[2]

Nowadays, the resolution of racemates by chiral liquid chromatography is quite common because various CSPs are available.[3] Among various CSPs, those named Pirkle type have been known to resolve racemates by forming energetically different two transient diastereomeric π-π complexes with two enantiomers.[4] Therefore, CSPs containing π-acidic aryl functional group have been applied for resolving π-basic racemates or their π-basic derivatives.[5] Similarly, CSPs containing π-basic aryl functional group have been used for resolving π-acidic racemates or their π-acidic derivatives.[6] CSPs bearing both π-basic and π-acidic aryl groups have also been introduced to resolve either π-acidic or π-basic racemates.[7] However, only a few CSPs bearing both π-basic and π-acidic aryl groups have been up to now reported and the use of them is limited because they are not easily available.[8]

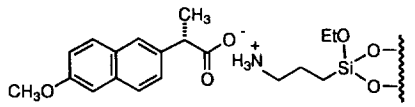
In this paper, we report the preparation of a new CSP bearing both π-basic and π-acidic aryl groups from (*S*)-naproxen and its use for resolving either π-acidic or π-basic racemates. (*S*)-Naproxen is a well known anti-inflammatory drug and readily available as an optically active form. However, previously, (*S*)-naproxen was seldom used as a chiral selector in chiral liquid chromatography. Only a few CSPs such as **1**, **2** or **3** consisting of (*S*)-naproxen immobilized on silica gel *via* an amide linkage,[9] ester linkage or ionic linkage[10] have been reported. All of these CSPs utilize the 6-methoxy-2-naphthyl group of the (*S*)-naproxen chiral selector as a π-basic aryl group to resolve π-acidic racemates. By introducing a π-acidic aryl functionality on the π-basic (*S*)-naproxen CSPs, in this study, we aimed at developing a new CSP bearing both π-acidic and π-basic interaction sites and extending the scope of application of the π-basic (*S*)-naproxen CSPs to π-basic racemates.



CSP **1**



CSP **2**



CSP **3**

Experimental

General methods. ^{1}H-NMR spectra were recorded on a Varian Gemini 300 spectrometer (300 MHz). IR spectra were measured with a Mattson Polaris FT-IR spectrometer. Melting points were taken on a Rigaku Thermal Analyzer TAS 100. Elemental analyses were performed at the OCRC center, Sogang University.

(*S*)-Naproxen, (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, was obtained from Aldrich Chemical Co. Test analytes were available from previous studies or prepared as described previously.[5b,11] Solvents for HPLC analysis were HPLC grade. All reagents were of reagent grade and were used without further purification unless otherwise indicated. All reactions were performed under an argon atomosphere.

Chromatography was performed on a HPLC system consisted of Waters model 510 pump, a Rheodyne model 7125 injector with a 20 μ sample loop, a Youngin model 710 absorbance detector with a 254 nm UV filter and a Youngin D520B

computing integrator. All chromatographic experiments were carried out at a flow rate of 2 m*l*/min. Column void volume was measured by injecting 1,3,5-tri-*tert*-butylbenzene, a presumed unretained solute.[12]

(*S*)-α-(6-Methoxy-2-naphthyl)propion-3,5-dinitroanilide (4). To a solution of 0.16 g (0.007 mole) of (*S*)-naproxen in 50 m*l* of dry benzene was added 2.18 m*l* (0.03 mole) of thionyl chloride. The stirred mixture was refluxed for 2 hrs. The mixture was evaporated to dryness using a rotary evaporator. The residue was dissolved in 40 m*l* of dry methylene chloride and then, the solution was stirred with 0.128 g (0.007 mole) of 3,5-dinitroaniline at room temperature. After stirring for 3 hrs, the reaction mixture was washed with 50 m*l* of 2N HCl solution twice and then with 50 m*l* of saturated $NaHCO_3$ solution twice. The organic solution was dried over anhydrous $MgSO_4$ and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane/methylene chloride : 1/5/1-1/3/1, v/v/v) to afford 0.132 g (48% yield) of amide **4**, as a yellow solid. HPLC analysis of **4** on a previously described CSP[6d] showed that no racemization had occurred during the course of the reaction. mp. 83-87℃ ; ^{1}H-NMR ($CDCl_3$) δ 1.67 (d, 3H), 3.89 (s, 3H), 4.12 (q, 1H), 7.07-7.08 (m, 1H), 7.12-7.15 (m, 1H), 7.36-7.39 (m, 1H), 7.64-7.67 (m, 1H), 7.67 (s, 1H), 7.71-7.74 (m, 1H), 7.97 (broad s, 1H), 8.59 (t, 1H), 8.64 (d, 2H); IR (KBr) cm^{-1} 3325, 3107, 2976, 1705, 1680.

(*S*)-α-(6-Hydroxy-2-naphthyl)propion-3,5-dinitroanilide (5). To a stirred solution of 0.79 g (0.002 mole) of (*S*)-**4** in 30 m*l* of dry methylene chloride was added dropwise a solution of 0.38 m*l* (0.004 mole) of boron tribromide in 10 m*l* of dry methylene chloride over 30 minutes at −78℃. When addition was complete, the reaction mixture was allowed to warm to room temperature over 5 hrs. The reaction mixture was cooled to 0℃ and then water was added slowly. The mixture was neutralized by adding saturated $NaHCO_3$ solution and then extracted with methylene chloride. The organic solution was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purfied by silica gel column chromatography (ethyl acetate/hexane : 1/15-1/4, v/v) to give 0.54 g (71% yield) of **5**, as a orange solid. No racemization had been found during the course of the reaction by HPLC analysis on a previously described CSP.[6d] mp. 258-260 ℃ ; ^{1}H-NMR (Acetone-D_6) δ 1.64 (d, 3H), 4.09 (q, 1H), 7.15-7.21 (m, 2H), 7.49-7.53 (m, 1H), 7.69-7.81 (m, 3H), 8.59 (t, 1H), 8.67 (s, 1H), 8.98 (d, 2H), 10.04 (broad s, 1H); IR (KBr) cm^{-1} 3358, 3099, 2982, 1685, 1637.

(*S*)-α-(6-Allyloxy-2-naphthyl)propion-3,5-dinitroanilide (6). To a solution of 1.0 g (0.0026 mole) of **5** in 40 m*l* of acetonitrile was added 0.314 g (60% dispersion in mineral oil, 0.0078 mole) of NaH. The mixture was stirred at room temperature for 2 hrs and then 0.7 m*l* (0.008 mole) of distilled allyl bromide was added. After stirring at room temperature for additional 2.5 hrs, the whole mixture was washed twice with 1N HCl and saturated $NaHCO_3$ solution. The organic solution was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was subjected to silica gel flash column chromatography (ethyl acetate/hexane : 1/20-1/5, v/v) to give 0.7 g (64% yield) of **6** as a yellow crystalline solid. After crystallization from methylene chloride/hexane, the optical purity of **6** was found to be more than 98% ee by HPLC analysis on a previously described CSP.[6d] mp. 104-107℃ ; ^{1}H-NMR ($CDCl_3$) δ 1.70 (d, 3H), 3.92 (q, 1H), 4.66-4.68 (m, 2H), 5.32-5.37 (m, 1H), 5.45-5.52 (m, 1H), 6.07-6.09 (m, 1H), 7.16 (s, 1H), 7.22-7.25 (m, 1H), 7.38-7.41 (m, 1H), 7.56 (broad s, 1H), 7.73-7.79 (m, 3H), 8.66-8.68 (m, 3H); IR (KBr) cm^{-1} 3327, 3107, 2933, 1678, 1604.

(S)-α-[6-(3-Ethoxydimethylsilylpropoxy)-2-naphthyl] propion-3,5-dinitroanilide (7). Compound **6** (2.20 g, 0.005 mole) was dissolved in 150 m*l* of dry methylene chloride. To the solution was added 40 m*l* of dimethylchlorosilane and chloroplatinic acid (about 20 mg) dissolved in 1 m*l* of dry THF. The reaction mixture was heated at reflux for 2 hrs. After checking no remaining starting material by TLC analysis, methylene chloride and excess dimethylchlorosilane were removed by simple distillation. To remove residual dimethylchlorosilane, three successive additions and distillation of small portions of methylene chloride were performed. The dark oily residue was dissolved in 30 m*l* of methylene chloride. A mixture of triethylamine and absolute enthanol (5 m*l*, 1 : 1 mixture, v/v) was then slowly added to the stirred solution, and the mixture was stirred at room temperature for 30 min. The mixture was concentrated and then purified by silica gel chromatography (ethyl acetate/hexane : 1/10-1/3, v/v) to afford **7** (1.25 g, 40% yield) as a yellow oil. Optical purity of **7** was found to be more than 98% ee by HPLC analysis on a previously described CSP.[6d] ^{1}H-NMR ($CDCl_3$) δ 0.16 (s, 6H), 0.73-0.81 (m, 2H), 1.23 (t, 3H), 1.66 (d, 3H), 1.85-1.95 (m, 2H), 3.70 (q, 2H), 3.88 (q, 1H), 4.01 (t, 2H), 7.02-7.16 (m, 2H), 7.35-7.38 (m, 1H), 7.61-7.72 (m, 3H), 8.01 (broad s, 1H), 8.58-8.59 (m, 1H), 8.64-8.66 (m, 2H), IR (KBr) cm^{-1} 3329, 3109, 2957, 1703, 1606.

Preparation of CSP 8. A flask equipped with a Dean-Stark trap and a condenser was charged with Regis Rexchrom silica gel (5 μm, 4.2 g) and toluene (100 m*l*). After heating the heterogeneous mixture at reflux until azeotropic water removal was complete, compound **7** (1.25 g) was added, and the whole mixture was heated to reflux for 72 hrs. The silica gel was filtered and washed extensively with toluene, methanol, acetone, ethyl acetate, hexane and then diethyl ether. Elemental analysis of the silica gel (C 8.06%, H 0.76%, N 1.03%) showed a loading of 0.25 mmole (based on N) or 0.28 mmole (based on C) of chiral selector per gram of stationary phase. The modified silica gel was slurried in methanol and packed into a 4.6 mm×250 mm stainless steel HPLC column using a conventional method with the Alltech HPLC Slurry Packer. The residual silanol groups of the modified silica gel were endcapped by passing a solution of 2 m*l* of hexamethyldisilazane in 50 m*l* of methylene chloride through the chiral column equilibrated in advance with methylene chloride.

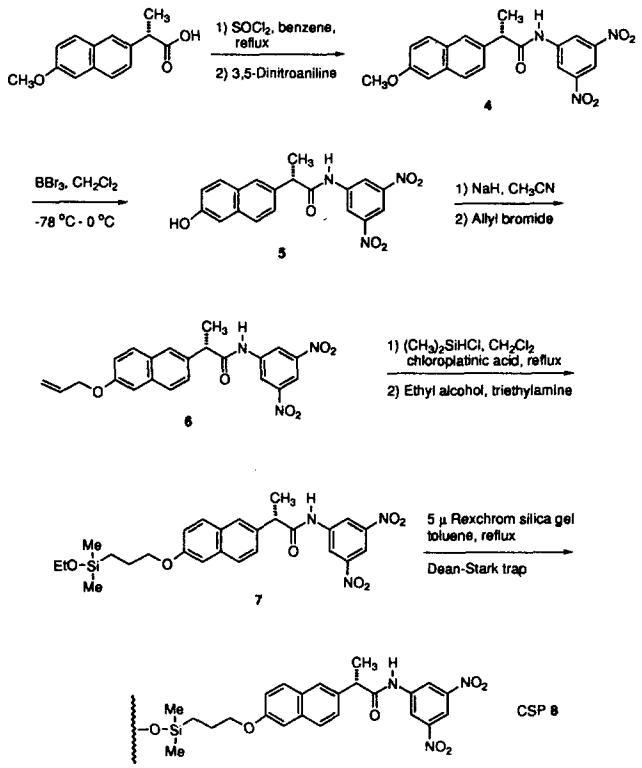
Results and Discussion

CSP **8** was prepared from (*S*)-naproxen as shown in Scheme 1. (*S*)-Naproxen was treated with thionyl chloride to afford acid chloride. When the resulting acid chloride was treated with 3,5-dinitroaniline in the presence of triethylamine, racemization was observed. Without the use of triethylamine, no racemization was detected. To improve the yield of compound **4** we tried to use excess amount of 3,5-dinitroaniline. However, there was a serious problem in separating

Table 1. Resolution of the Two Enantiomers of π-Basic Analytes on CSP **8**[a]

Anal[b]	Ar	R_1	R_2	k_1'[c]	k_2'[c]	α[d]	Conf[e]
9 a	1-Naphthyl	CH_3	CH_3	5.92	8.63	1.46	*R*
b		CH_3	CH_2CH_3	7.28	9.97	1.37	*R*
c		CH_3	$(CH_2)_2CH_3$	7.03	10.05	1.43	*R*
d		CH_3	$(CH_2)_5CH_3$	5.56	8.41	1.51	*R*
e		CH_3	$(CH_2)_{10}CH_3$	4.08	6.91	1.69	*R*
f		CH_3	$(CH_2)_{16}CH_3$	3.03	5.48	1.81	*R*
g	6,7-Dimethyl-1-naphthyl	CH_3	CH_3	9.95	14.25	1.43	*R*
h		CH_3	CH_2CH_3	11.46	15.01	1.31	*R*
i		CH_3	$(CH_2)_2CH_3$	10.78	14.50	1.35	*R*
j		CH_3	$(CH_2)_5CH_3$	8.61	12.47	1.45	*R*
k		CH_3	$(CH_2)_{10}CH_3$	6.08	9.77	1.61	*R*
l	2-Fluorenyl	$CH_2(CH_3)_2$	CH_3	6.82	8.96	1.31	
m		$CH_2(CH_3)_2$	CH_2CH_3	8.79	10.01	1.14	
n		$CH_2(CH_3)_2$	$(CH_2)_2CH_3$	8.13	9.15	1.13	
o		$CH_2(CH_3)_2$	$(CH_2)_5CH_3$	6.76	8.35	1.24	
p		$CH_2(CH_3)_2$	$(CH_2)_{10}CH_3$	4.76	6.711	1.41	
10 a	6-Methoxy-2-naphthyl	H	CH_2CH_3	10.39	11.16	1.07	
b		H	$(CH_2)_2CH_3$	9.86	10.78	1.09	
c		H	$C(CH_3)_3$	7.89	11.28	1.43	*R*
d		CH_2CH_3	CH_2CH_3	5.24	5.71	1.09	
e		$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	3.97	4.44	1.12	*R*

[a] For the chromatographic conditions, see the experimental part. Mobile phase was 20% isopropyl alcohol in hexane. [b] Racemic analytes resolved on CSP **8**. [c] Capacity factors. [d] Separation factors. [e] Absolute configuration of the second eluted enantiomers. For blanks, elution orders have not been established.



Scheme 1.

the product from unreacted 3,5-dinitroaniline and, in consequence, one equivalent of 3,5-dinitroaniline was used. The methoxy group of 3,5-dinitroanilide compound **4** was easily converted to hydroxyl group (compound **5**) by treating with boron tribromide in methylene chloride at low temperature. 6-Hydroxy-2-naphthyl compound **5** was treated with NaH and then allyl bromide in acetonitrile to afford compound **6** which has terminal double bond needed for anchoring to silica gel. At this stage, some degree of racemization was found because of the base treatment. However, crystallization from the mixed solvent of methylene chloride and hexane improved the optical purify of compound **6** to more than 98% *ee* by HPLC analysis on previously described CSP.[6d] Finally, hydrosilylation of compound **6** and then treatment with 5 μm silica gel afforded CSP **8**. CSP **8** contains both strong π-acidic and π-basic functionalities such as 3,5-dinitroanilide and 2-naphthyl group. In consequence, various π-basic or π-acidic racements are expected to be resolved on CSP **8**.

The results for resolving π-basic racemates such as amide derivatives of α-arylalkylamines and naproxen on CSP **8** are summarized in Table 1 and the representative chromatograms are shown in Figure 1. The elution orders shown in Table 1 were determined by eluting configurationally known samples. As shown in Table 1, alkyl amide derivatives **9** of α-arylalkylamines are resolved with reasonable separation factors on CSP **8**. The resolution trends on *N*-alkyl amide derivatives of α-(1-naphthyl)ethylamide on CSP **8** are graphically shown in Figure 2.

When the α-aryl substituent is changed from 1-naphthyl to 6,7-dimethyl-1-naphthyl group (π-basicity of the α-aryl substituent increases), retention time of both enantiomers increases as shown in Table 1, indicating the occurrence of

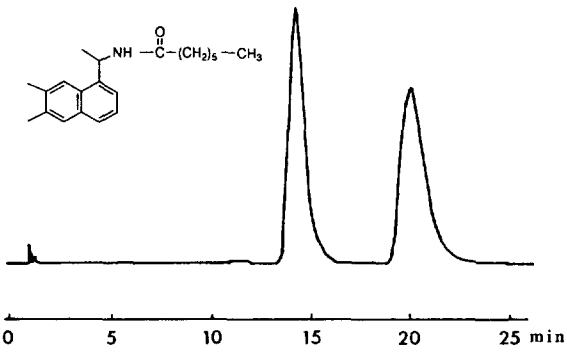


Figure 1. A representative chromatogram for resolving *N*-heptanoyl α-(6,7-dimethyl-1-naphthyl)ethylamine on CSP **8**. See the experimental part for the chromatographic conditions.

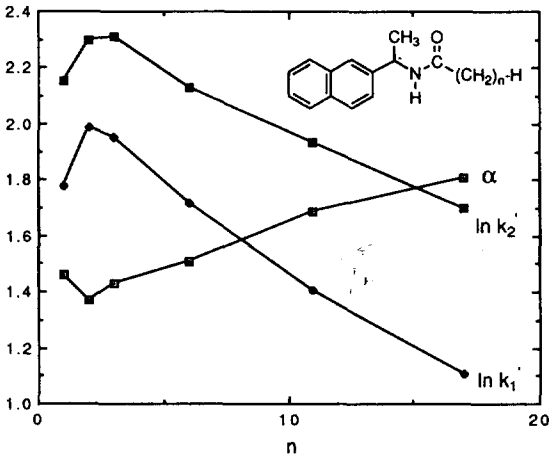
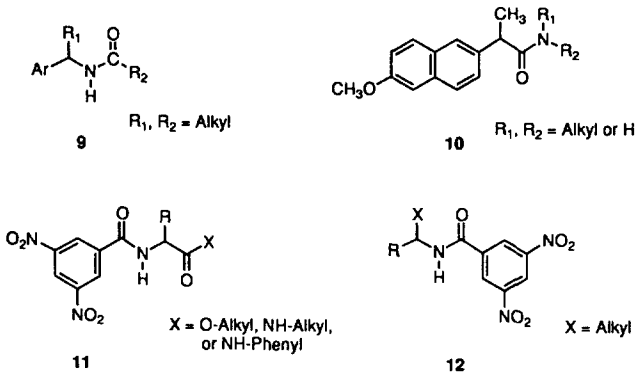


Figure 2. The chromatographic resolution trends of a series of *N*-alkyl amide derivatives **9** of α-(1-naphthyl)ethylamine on CSP **8**. See the experimental part of the chromatographic conditions.



the π-π interaction between the 3,5-dinitroanilide group of the CSP and the α-aryl groups of analytes **9**. However, the increase in the π-basicity of the α-aryl substituent does not influence the separation factors significantly. The increase in the lipophilicity of analytes is known to usually diminish the retention of analytes on the column because of the increased mobile phase-solute interaction or the diminished stationary phase-solute interaction in the normal phase chromatography. This is indeed the case. As shown in Table 1 and Figure 2, the retention (or the capacity factors) of

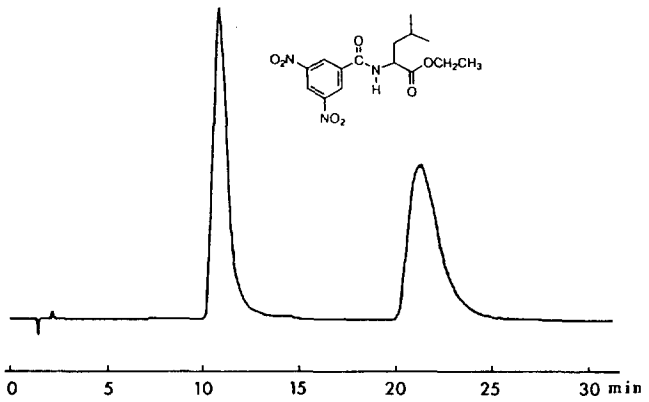


Figure 3. A representative chromatogram for resolving *N*-(3,5-dinitrobenzoyl)leucine ethyl ester on CSP **8**. See the experimental part for the chromatographic conditions.

both enantiomers of analytes **9** is diminished except the initial increase as the amide alkyl chain (R_2) of analytes **9** increases in length. The initial increase in the capacity factors may be a consequence of conformational factors.[13] As the amide alkyl changes from methyl to ethyl, there is a significant change in steric bulk and, consequently, in the extent of solvation around the amide functionality. This could influence the conformational perferences of analyte and enhance the CSP-solute interaction. A further lengthening of amide alkyl is of little impact on the conformational perferences, since the ethyl group is bulky enough to effectively change the extent of solvation around the amide functionality. Even though the retention of both enantiomers is diminished as the amide alkyl chain of analytes **9** increases in length, the capacity factors of the first eluted enantiomers decrease more rapidly than those of the second eluted enantiomers and, in consequence, the separation factors (α) increase as the alkyl amide chain of analytes **9** increases in length as shown in Figure 2. From these results, it might be assumed that the amide alkyl chain of the first eluted enantiomers intercalates between the connecting tethers of the CSP.[13]

Naproxen itself has also been resolved on CSP **8** as its alkyl amide derivatives **10**. The best resolution of naproxen derivatives **10** was obtained when the amide alkyl is *t*-butyl. The resolution of dialkyl amide derivatives of naproxen is not quite different from that of monoalkyl amide derivatives of naproxen as shown in Table 1. From this, it can be assumed that the amide N-H hydrogen does not play any important role in the chiral recognition.

CSP **8** was also effective in resolving π-acidic analytes such as 3,5-dinitrobenzoyl derivatives **11** of amino acid esters or amides. The chromatographic results for resolving π-acidic analytes on CSP **8** are summarized in Table 2 and the representative chromatogram is shown in Figure 3. As shown in Table 2, 3,5-dinitrobenzoyl derivatives of amino acid esters are resolved quite well on CSP **8**. Lengthening the ester alkyl chain diminishes the capacity factors of the two enantiomers of 3,5-dinitrobenzoyl derivatives of leucine esters. However, the separation factors are not influenced quite much by lengthening the ester alkyl chain as shown in Table 2. When CSP **8** resolves 3,5-dinitrobenzoyl derivatives of

Table 2. Resolution of the Two Enantiomers of π-Acidic Analytes on CSP **8**[a]

Anal[b]	*R*	*X*	k_1'[c]	k_2'[c]	α[d]	Conf[e]
11 a	CH_3	OCH_2CH_3	8.29	14.29	1.72	*R*
b	$CH(CH_3)_2$	OCH_2CH_3	7.40	13.25	1.79	*R*
c	$CH_2CH(CH_3)_2$	OCH_3	9.15	19.76	2.16	*R*
d		OCH_2CH_3	7.22	15.16	2.10	*R*
e		$O(CH_2)_2CH_3$	6.19	12.78	2.06	*R*
f		$O(CH_2)_3CH_3$	5.65	11.82	2.09	*R*
g		$O(CH_2)_5CH_3$	5.56	12.23	2.20	*R*
h		$O(CH_2)_7CH_3$	5.25	11.64	2.22	*R*
i	$CH_2CH(CH_3)_2$	$NH\text{-}(CH_2)_2CH_3$	1.33	1.83	1.38	*R*
j	Phenyl	OCH_2CH_3	12.00	13.56	1.13	*R*
k	Phenyl	$NH\text{-}(CH_2)_2CH_3$	4.00	4.75	1.19	*S*
l	CH_3	NH-2,6-DiMephenyl	5.81	9.27	1.60	
m	Allyl	NH-3,5-DiMephenyl	3.45	3.96	1.15	
12 a	3,5-Dimethoxyphenyl	CH_3	26.40	28.84	1.09	
b	4-Methoxyphenyl	$(CH_2)_2CH_3$	20.40	20.40	1.00	
c		$(CH_2)_3CH_3$	20.47	20.47	1.00	
d		$(CH_2)_4CH_3$	17.18	17.94	1.04	
e		$(CH_2)_5CH_3$	16.01	16.91	1.06	
f		$(CH_2)_6CH_3$	15.45	16.43	1.06	
g		$(CH_2)_7CH_3$	14.83	15.94	1.07	
h		$(CH_2)_8CH_3$	14.19	15.20	1.07	
i		$(CH_2)_9CH_3$	13.47	14.64	1.09	
j		$(CH_2)_{10}CH_3$	13.13	14.45	1.10	
k		$(CH_2)_{12}CH_3$	12.93	14.42	1.12	
l		$(CH_2)_{16}CH_3$	11.28	12.89	1.14	

[a] For the chromatographic conditions, see the expeimental part. Mobile phase was 20% isopropyl alcohol in hexane. [b] Racemic analytes resolved on CSP **8**. [c] Capacity factors. [d] Separation factors. [e] Absolute configuration of the second eluted enantiomers. For blanks, elution orders have not been established.

amino esters, the face to face π-π interaction between the 6-alkoxy-2-naphthyl group of the CSP and the 3,5-dinitrobenzoyl group of analytes is maintained and the additional attractive interactions seem to occur between the amide or ester functionality of the CSP and the analytes. In this instance, the ester alkyl chain of analytes is directed toward the 3,5-dinitroanilide group of the CSP and there is no chance of the intercalation of the ester alkyl chain of analytes beteen the connecting tethers of the CSP and the separation factors should not be influenced by the ester alkyl chain length.

Analytes containing both π-acidic and π-basic functionalities may act either π-basic or π-acidic analytes. In this case, the interaction between CSP **8** and the analytes may be quite complicated. For example, the face to face π-π interaction may be possible between the 6-alkoxy-2-naphthyl group of CSP **8** and the π-acidic group of analyte or between the 3,5-dinitroanilide group of CSP **8** and the π-basic group of analyte and, in consequence, two modes of chiral recognition are possible. If the two modes of chiral recognition are in the opposite sense, the resolution of analytes containing both π-acidic and π-basic functionalities on CSP **8** may be quite inefficient. The resolution of 3,5-dinitrobenzoyl derivative **11**j of phenylglycine ethyl ester and 3,5-dinitrobenzoyl derivatives **12** of α-arylakylamines shown in Table 2 seems to be the case.

In conclusion, CSP **8** prepared from commercially available (*S*)-naproxen contains both π-basic and π-acidic functionalities and, in consequence, has been successfully utilized in resolving racemates containing either π-acidic or π-basic functional group. From the chromatographic resolution trends for the resolution of *N*-alkyl amide derivatives **9** of α-alylalkylamines on CSP **8**, the chiral recognition mode involving the intercalation of the amide alkyl chain of the less retained enantiomers between the connecting tethers of the CSP was presumed. In resolving π-acidic racemates on CSP **8**, the 6-alkoxy-2-naphthyl group of the CSP seems to play a role as a π-basic interaction site. However, more chromatographic, spectroscopic and/or X-ray crystallographic experimental results are needed to propose the more convincing chiral recognition model. The efforts to elucidate more appropriate chiral recognition model are underway in our laboratory.

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Kinetic Studies on the Aminolysis of 2-Phenyl-1-propyl Arenesulfonates in Methanol

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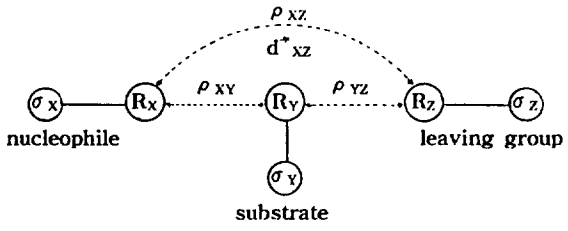
The results of kinetic studies on the reactions of 2-phenyl-1-propyl arenesulfonates with anilines and benzylamines in methanol at 55.0℃ are reported. The transition state variation with the substituents in the nucleophile (*X*) and leaving group (*Z*) is in accord with that expected from a negative ρ_{XZ} value : A stronger nucleophile and nucleofuge lead to a greater extent of bond-making and -breaking. Somewhat greater magnitude of ρ_{XZ} compared to the nearly constant value for the similar processes at a primary carbon atom has been interpreted to result from a partial contribution of the concurrent frontal displacement path.

Introduction

The cross-interaction constants, ρ_{ij} in Eq. (1) where *i* and *j* represent substituents in the nucleophile (*X*), substrate (*Y*) or leaving group (*Z*) in Scheme 1, are useful as a mechanistic tool for organic reactions in solution.[1]

$$\log(k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \quad (1)$$

We have shown for nucleophilic substitution reactions that: (i) The magnitudes of ρ_{XY} and ρ_{YZ} are directly proportional to the extent of bond-making and -breaking respectively in the transition state (TS), provided the fall-off of $|\rho_{ij}|$ (by *ca.* 2.8) due to an intervening nonconjugative group. *e.g.* CH_2 or CO, between the substituent and the reaction center is accounted for.[2] (ii) A positive [negative] ρ_{XZ}, which can be alternatively given as Eq. (2), leads to an earlier [later] TS along the



Scheme 1.

$$\rho_{XZ} = \frac{\partial\rho_z}{\partial\sigma_X} = \frac{\partial\rho_x}{\partial\sigma_z} \quad (2)$$

reaction coordinate for a stronger nucleophile ($\delta\sigma_X<0$) and/or a stronger nucleofuge, *i.e.*, a better leaving group ($\delta\sigma_Z>0$).[1] (iii) The magnitude of ρ_{XZ}, is a measure of the TS tightness; the greater the $|\rho_{XZ}|$, the tighter is the TS (the shorter is the d^*_{XZ} in Scheme 1).[1,3]