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23. When the same chlorodisilaalkane was pyrolyzed under H_2 or H_2+Ar (1 : 2), dilution of H_2 with Ar changed the color of powder products from brown-gray to white-gray, compositions from free silicon containing SiC to SiC only. When H_2 was diluted with Ar, it was thought that scavenging of carbon by H_2 might be decreased, recombination of SiC increased (Unpublished Results).

Liquid Chromatographic Resolution of α-Arylpropionic Acids on a π-Basic Chiral Stationary Phase

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Many of nonsteroidal antiinflammatory drugs (NSAIDs) are α-arylpropionic acids. Two enantiomers of some of these drugs have been known to show different metabolic pathway and different pharmacological activity, the (S)-enantiomers being generally more active.[1] For example, the inactive (R)-(−)-enantiomer of ibuprofen (see Figure 1 for the chemical structures of NSAIDs) is known to be converted to the active (S)-(+)-enantiomer *in vivo*.[2] The decreased rate of metabolism and excretion of benoxaprofen in elderly patients exerted by the inversion of (R)-(−)-enantiomer of benoxaprofen to its (S)-(+)-enantiomer has led to the hepatotoxicity and the withdrawal from the market.[3] However, among the commercial NSAIDs, only naproxen is sold as a single enantiomer form.

Because of the biological significance of the stereochemistry of NSAIDs, the accurate and convenient means of measuring the optical purity of NSAIDs has been required and the chromatographic separation of enantiomers on chiral stationary phases (CSPs) has been the choice. Previously, several research groups have reported the chromatographic separation of the enantiomers of NSAIDs as their π-basic amide derivatives or without derivatization on the CSP derived from (R)-N-(3,5-dinitrobenzoyl)phenylglycine[4] or on the CSP based on protein or cellulose.[5] More recently, the improved CSP for the stereoselective separation of naproxen without derivatization has been developed.[6] However, the π-basic CSP which is known to be useful for the resolution of π-acidic compounds has not been fully studied for the resolution of NSAIDs.[7] In this paper, we report the resolution of various NSAIDs as their 3,5-dinitroanilide derivatives **1** on CPS **2** which has been widely used for the resolution of variety of racemates[8] and we propose the possible chiral recognition mechanism.

The stereoselective π-π interaction between CSP **2** and the analytes has been known to be essential for the chiral recognition.[8] CSP **2** has a strong π-basic functionality such as 6,7-dimethy-1-naphthyl group and, in consequence, is expected to resolve racemic NSAIDs as their π-acidic derivatives. In this study, nine kinds of NSAIDs purchased from drug stores were converted to 3,5-dinitroanilide derivatives **1** by simply treating the acid chlorides of NSAIDs with 3,5-dinitroaniline in dry methylene chloride at room temperature and then resolved on CSP **2**. As shown by the chromatographic resolution results summarized in Table 1, it was found that CSP **2** was reasonably good in resolving two enantiomers of NSAIDs as their 3,5-dinitroanilide derivatives. The elution orders for ibuprofen and naproxen shown in Table 1 were determined by chromatographing the partially resolved ibuprofen obtained by the known classical resolution method with (R)- or (S)-α-phenylethylamine[9] and the optically pure naproxen which is commercially available.

To explain the chromatographic resolution results, from the study with space filling molecular model we propose the chiral recognition model shown in Figure 2. The conformation of CSP **2** shown in Figure 2 has been thought to be heavily populated.[8] Similarly, the analyte shown in Figure 2 is presumed in the lowest energy conformation in which the methine hydrogen on the stereogenic center is eclipsed with the amide hydrogen[10] and, in consequence, approxima-

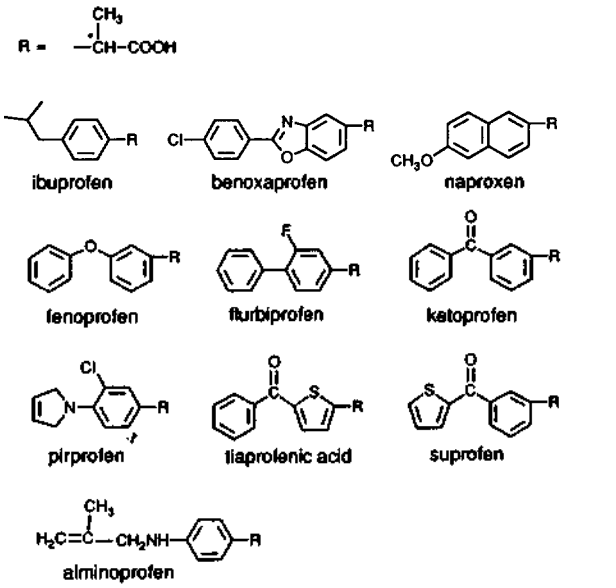

Figure 1. Chemical structures of α-arylpropionic acids (NSAIDs) mentioned in this study.

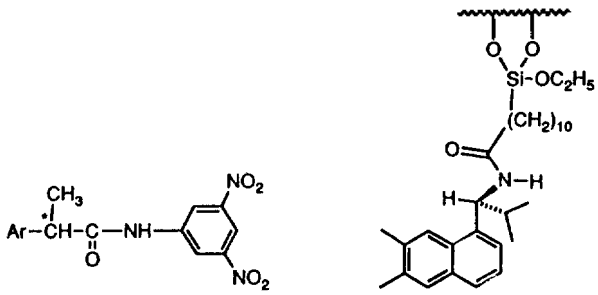

Table 1. Separation of the Enantiomers of NSAIDs as Their 3,5-Dinitroanilide Derivatives on CSP **2**[a]

NSAIDS	k_1'[b]	α[c]	conf.[d]
ibuprofen	6.83	2.16	R
naproxen	16.87	1.44	R
fenoprofen	10.83	1.61	
flurbiprofen	11.93	1.64	
ketoprofen	10.10	2.00	
pirprofen	13.72	1.86	
tiaprofenic acid	22.20	1.52	
suprofen	17.92	1.99	
alminoprofen	4.47	3.01	

[a]Chromatography was performed with Waters Model 510 pump, Waters Model U6k Liquid Chromatographic Injector, Waters Model 441 Absorbance Detector and Waters Model 740 Data Module Recorder. All data were obtained by using 10% isopropyl alcohol in hexane as mobile phase with flow rate of 2 ml/min. at 254 nm UV. [b]Capacity factor for the first eluted enantiomer. [c]Separation factor. [d]Absolute configuration for the second eluted enantiomer. For blanks, elution orders have not been determined.

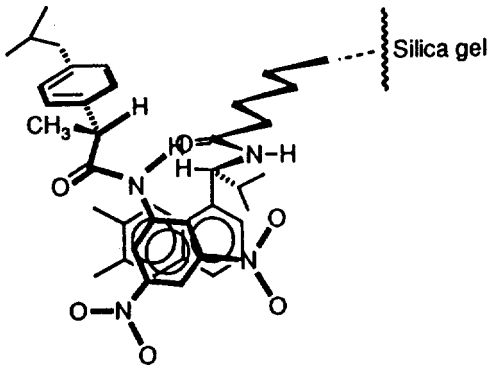

Figure 2. The proposed chiral recognition model showing the energetically more favorable diastereomeric (R,S)-complex between the 3,5-dinitroanilide derivative of (R)-ibuprofen and (S)-CSP **2**.

tely in the plane of the 3,5-dinitroanilide ring. In Figure 2, CSP **2** interacts with analyte through the face to face π-π interaction between the 3,5-dinitrophenyl ring of the analyte and the 6,7-dimethyl-1-naphthyl ring of the CSP and the hydrogen bonding between the amide N-H hydrogen of the analyte and the carbonyl oxygen of the CSP. In this interaction model, the face of the aryl substituent of the (R)-analyte is positioned at the edge of the 6,7-dimethyl-1-naphthyl ring of the CSP, invoking the face to edge π-π interaction which has received increased attention as an attractive interaction between aromatic rings in recent studies.[11] However, the aryl substituent of the (S)-analyte is directed toward the acyl connecting arm of the CSP, experiencing some degree of steric hindrance. In consequence, the (R)-enantiomer is retained longer on CSP **2**.

When the aryl substituent at the chiral center of the analyte is changed to the simple alkyl substituent, it is easy to imagine that there is no more attractive face to edge π-π interaction between the analyte and the CSP and instead there will be some degree of steric repulsion between the alkyl substituent of the (R)-analyte and the isopropyl group or the 6,7-dimethyl-1-naphthyl ring of the CSP. In consequence, for example, the (S)-enantiomer of the 3,5-dinitroanilide derivative of 2-methyl butanoic acid is expected to be retained longer on CPS **2**. This is indeed the case. The 3,5-dinitroanilide derivative of 2-methyl butanoic acid was resolved on CSP **2** (retention time for the first eluted enantiomer was 6.50 and the separation factor was 1.06 under the chromatographic conditions given in Table 1), the (S)-enantiomer being retained longer than the (R)-enantiomer.

Finally we want to mention that the chiral recognition model shown in Figure 2 indicates that the methyl substituent at the chiral center of the (R)-analyte is oriented alongside the acyl connecting arm of the CSP. In consequence, the long alkyl substituent instead of the methyl substituent at the chiral center of the (R)-analyte may intercalate between the connecting arm of the CSP and make the diastereomeric (R,S)-complex shown in Figure 2 more and more unfavorable as the alkyl substituent increases in length. Then, the separation factor, α value, may decrease as the alkyl substituent increases in length. Similarly, the long p-alkyl substituent at the aryl group of the (S)-analyte may intercalate between the connecting arm of the CSP. Then, the diastereomeric (S,S)-complex will be more and more unfavorable and the stability difference between the diastereomeric (R,S)-complex and the diastereomeric (S,S)-complex may increase as the p-alkyl substituent at the aryl group of the analyte increases in length. Then, the separation factor, α value, may increase as the p-alkyl substituent at the aryl group of the analyte increases in length. The efforts to prove these chromatographic behaviors expected from the chiral recognition model shown in Figure 2 are under way in our laboratory and these will be the subject of our next report.

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4-Quinolones by Unusual Cyclocondensation of *o*-Imidophenacyl Bromides and Azides

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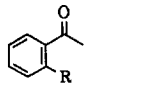
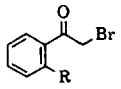
Azido functionality is very useful in the synthesis of various types of nitrogen heterocycles.[1] Recently, we reported[2] the synthesis of 5-hydroxy-1,3-benzoxazepines based on the Staudinger reaction followed by an intramolecular aza-Wittig reaction of *o*-acyloxyphenacyl azides. In this connection, we were interested in the synthesis of their nitrogen homologues, 1,3-benzodiazepines by the similar manner because it might provide a convenient route to two nitrogen containing heterocycles.[3] We describe herein unusual, useful method for the synthesis of 4-quinolones from the *o*-imidophenacyl bromides and azides.

The starting compounds, *o*-imidophenacyl bromides **2a-c**,[4] were readily obtained from the reactions of corresponding *N*-(2-acetylphenyl)imides **1a-c**[5] with copper(II) bromide in refluxing chloroform-ethyl acetate (1/1) according to King *et al.*[6] However, unexpectedly, we have found a conversion of *N*-(2-bromoacetylphenyl)maleimide (**2b**) into 4-bromo-1,5-dihydropyrrolo[1,2-a]quinoline-1,5-dione (**5**)[7] by the column chromatographic separation (silica gel, EtOAc/*n*-Hex=1/4, 68 %). On the other hand, *N*-(2-bromoacetylphenyl)phthalimide (**2a**) was converted into 6-bromo-5,11-dihydroisoindolo[2,1-a]quinoline-5,11-dione (**4a**)[8] in 62% yield in the presence of an equimolecular amount of triethylamine in dichloromethane at room temperature for 4 h, but *N*-(2-bromoacetylphenyl)succinimide (**2c**) was not participated.

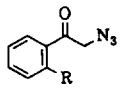
The reactions of *o*-imidophenacyl bromides **2a** and **2c** with sodium azide were carried out in acetone-water at room temperature and gave *o*-imidophenacyl azides **3a** (76%) and **3c** (92%), respectively.[9] Interestingly again, the crude *N*-(2-bromoacetylphenyl)phthalimide (**3a**) was cyclized directly to 6-azido-5,11-dihydroisoindolo[2,1-a]quinoline-5,11-dione (**4b**)[10] by the column chromatographic purification (silica gel, CH_2Cl_2, 70%). But, in case of **3c** was cyclized to 4-azido-1,2,3,5-tetrahydropyrrolo[1,2-a]quinoline-1,5-dione (**6a**)[11] only in the presence of an equimolecular amount of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in chloroform at 0℃ within 5 min (40% yield). The reaction of the crude *N*-(2-bromoacetylphenyl) maleimide (**2b**) with sodium azide was unsuccessful under various reaction conditions, and only gave complex mixture.



1a-c

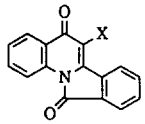


2a-c

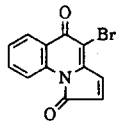


3a-c

a, R=phthalimide **b**, R=maleimide **c**, R=succinimide



4a, X=Br
4b, X=N_3
4c, X=N=PPh_3
4d, X=NH_2
4e, X=H



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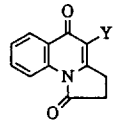

6a, Y=N_3
6b, Y=N=PPh_3
6c, Y=H

Treatment of *N*-(2-azidoacetylphenyl)phthalimide (**3b**) with an equimolecular amount of triphenylphosphine in chloroform at reflux temperature for 1 h gave anormalous 6-[(triphenylphosphoranylidene)amino]-5,11-dihydroisoindolo[2,1-a]quinoline-5,11-dione (**4c**, 41%) and 6-amino-5,11-dihydroisoindolo[2,1-a]quinoline-5,11-dione (**4d**, 29%).[12] Alternatively, the same compounds, **4c** (90%) and **4d** (8%) could also be obtained from the reaction of 3-azidoquinoline-4-one (**4b**) with triphenylphosphine for 4 h at room temperature, and **4d** (62%) from the pyrolysis of **4b** in refluxing toluene for 15 min, respectively. Similarly, treatment of *N*-(2-azidoacetylphenyl)-succinimide (**3c**) with triphenylphosphine resulted in only low yield of 6-[(triphenylphosphoranylidene)amino]-1,2,3,5-tetrahydropyrrolo[1,2-a]quinoline-1,5-dione (**6b**, 38%).[13]

Finally, the reaction of *N*-(2-bromoacetylphenyl)phthalimide (**2a**) with triphenylphosphine and triethylamine in acetonitrile at room temperature for 2 h yielded 3-bromoquinoline-4-one (**4a**, 63%) and the Wittig reaction product **4e** (34%),[14] and *N*-(2-bromoacetylphenyl)succinimide (**2c**) gave only the known 1,2,3,5-tetrahydropyrrolo[1,2-a]quinoline-1,5-dione (**6c**)[15] in 77 % yield at reflux temperature for 6 h.

Further studies on the preparation of 5-hydroxy-1,3-benzodiazepines by other intramolecular condensation reaction method and some remaining mechanistic problems are underway.

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