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Preparative Scale Separation of Enantiomers on an MPLC Chiral Column

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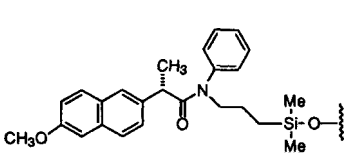
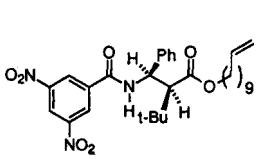
The two enantiomers of chiral drugs often show different pharmacological effects in living systems.[1] Consequently, the individual enantiomers of chiral compounds should be studied for their own pharmacological and toxicological properties during the process of drug development as required by the drug regulatory authorities.[2] In this context, the techniques of separating enantiomers and the analytical means of evaluating enantiomeric purity of chiral compounds are demanded very much. Among others, liquid chromatographic separation of enantiomers on chiral stationary phases (CSPs) have been known as the most convenient means to meet such demands because this technique can be successfully utilized in separating enantiomers and in evaluating enantiomeric purity simultaneously.[3] In addition, the technique of separating enantiomers on liquid chromatographic CSPs is very attractive in that the technique can be easily extended to the preparative scale separation of enantiomers and consequently can be employed as an alternative to preparing pure enantiomers using large chiral column packed with a suitable CSP.[4]

The successful use of liquid chromatographic CSPs for the preparative scale separation of enantiomers mostly depends on their availability in a substantial amount and their chiral recognition ability. Consequently, CSPs which have been employed in the preparative scale separation of enantiomers are limited to those usually derived from readily available chiral compounds such as amino acids,[4a,5] and cellulose derivatives.[6] In this aspect, CSP **1**, which was recently reported to be prepared from inexpensive and readily available (S)-naproxen and to show high enantioselectivity for the enantiomers of racemic compounds containing π-acidic aromatic functional groups,[7] is expected to be successfully utilized in the preparative scale separation of enantiomers.

In this study, we wish to show that an MPLC chiral column packed with CSP **1** is useful to separate enantiomers in a preparative scale (up to 2 g at one run) with an easily assembled and inexpensive MPLC system. In order to extend the use of HPLC CSP **1** to an MPLC system, CSP **1** was prepared by bonding the chiral selector, (S)-naproxen derivative, to large particle size silica gel (230-400 mesh) *via* the procedure described in the previous study.[7] CSP **1** thus prepared was dry packed into an MPLC glass column (2.5 cm ID × 60 cm length) and used for the separa-



CSP 1



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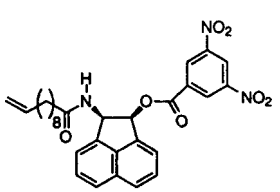

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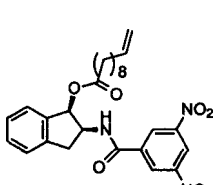

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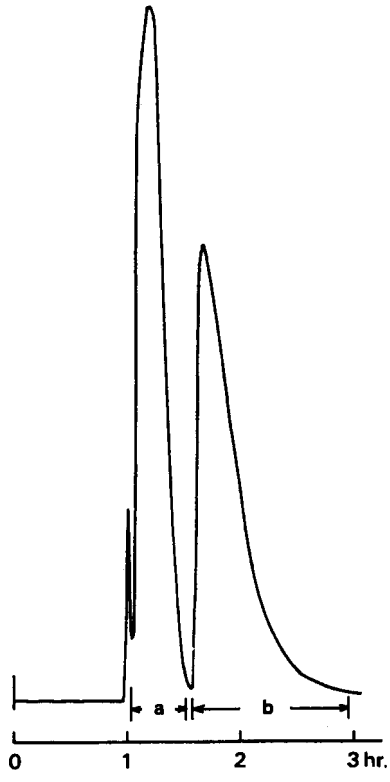

Figure 1. A representative MPLC chromatogram for separating the two enantiomers of 2.0 g of racemic compound **2** on CSP **1**. See experimental part for the chromatographic conditions. The two fractions corresponding to the two enantiomers were collected within the marked duration a and b.

tion of enantiomers.

As a representative example for the use of the MPLC chiral column packed with CSP **1** in the preparative scale separation of enantiomers, racemic compound **2** was resolved. As shown in Figure 1, the two enantiomers of 2.0 g of racemic compound **2** were separated completely within 3 hrs. The elution volume of mobile phase was only 1.8 L (the MPLC system used in this study can recycle the mobile phase and consequently reduce the elution volume very much, but mobile phase recyclization was not done in this study). The enantiomeric purity of each of the two fractions corresponding to the two enantiomers (collected at the cutting point indicated in Figure 1) was more than 99% ee by the analysis on an HPLC chiral column packed with CSP **1**.

The MPLC chiral column packed with CSP **1** was also successful in separating the enantiomers of much less resolvable racemic compound **3**. Even though the separation factor for the HPLC separation of the two enantiomers of racemic compound **3** on CSP **1** was much smaller (α=1.76) than that of racemic compound **2** (α=6.02), the two enantiomers of compound **3** were completely separated within 2 hrs on the MPLC chiral column packed with CSP **1** when the loading amount was reduced to 1.0 g.

The results for the preparative scale separation of enantiomers using the MPLC chiral column packed with CSP **1** are summarized in Table 1. Especially the separation of the two enantiomers of compound **4** (entry 3 in Table 1) is quite interesting in that the separation experiment was done

Table 1. Preparative Scale Separation of enantiomers on an MPLC chiral column packed with CSP **1**

Entry	Compound	α Value on analytical CSP **1**	Sample size	Mobile phase[a]	Mobile phase needed for a complete run
1	**2**	6.02	2.0 g	A	1.8 L
2	**3**	1.76	1.0 g	A	1.2 L
3	**4**[b]	2.40	1.5 g	B	2.4 L

[a] Mobile phase A is 50% methylene chloride in hexane. Mobile phase B is 40% methylene chloride in hexane. [b] Optically enriched compound: 73% ee.

with optically enriched compound (73% ee). After chromatography with 1.50 g of optically enriched compound, 1.29 g of the first eluted enantiomer (more than 99% ee by the HPLC analysis on CSP **1**) of compound **4** was obtained. This example shows that the preparative scale separation of enantiomers can be easily applicable to the purification of optically enriched compounds which are difficult in other ways to improve the optical purity.

In conclusion, CSP **1** prepared from commercially available (S)-naproxen was found to be readily applicable to the preparative scale separation of enantiomers. In this study, we have shown that the two enantiomers of even 2.0 g of a racemic compound can be completely separated. From these results we expect that the feasibility of separating enantiomers up to more than 100 g scale by chromatography on CSP **1** can be easily established by simply enlarging the size of the chiral column.

Experimental

The MPLC system used in this study was assembled with a FMI Lab Pump Model QSY, a Yamazen Prep UV 254 UV-detector and a Fisher Recordall series 5000 recorder. Mobile phase was 50% or 40% methylene chloride in n-hexane. Flow rate was 9.8 mL/min. CSP **1** was prepared by bonding covalently (S)-naproxen derivative, N-phenyl-N-(2-propenyl)-(S)-α-(6-methoxy-2-naphthyl)propionamide, to silica gel (Merck, grade 9385, 230-400 mesh, 60 angstrom) as described in the previous study.[7] Elemental analysis of CSP **1** (C 11.53, H 1.65, N 0.54%: performed at the Organic Chemistry Research Center, Sogang University, Seoul, Korea) showed a loading 0.38 mmole (based on both C and N) of chiral selector per gram of stationery phase. CSP **1** thus prepared was dry packed into a ACE Glass chromatography column (2.5 cm ID $\times$ 60 cm length). Compound **2** was prepared by the known method.[8] Preparation of compound **3** and **4** will be reported elsewhere.

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Kinetics of Site Selective Deuterium Exchange in the Substituted Pyrroles and Synthesis of Partially Deuterated Porphyrins Therefrom

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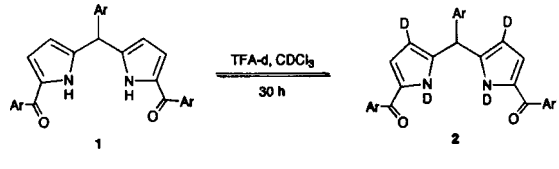
Isotopically labeled porphyrins have been important in various biological applications including interpretation of isotropic nmr shifts in heme proteins. Especially deuterated porphyrins are essential in obtaining ^2H NMR spectra of paramagnetic metal complexes,[3] ESR study of paramagnetic metalloporphyrin complexes,[3] peak assignment of various hemoproteins[3] and assignment of vibrational modes in the molecule.[4] The interpretation of resonance Raman spectra of hemes and hemoproteins also aided by the use of isotopically labeled porphyrin derivatives. Simple *meso*-tetraarylporphyrin with β-pyrrolic deuterium enrichment is readily available by simple condensation of arylaldehydes with pyrrole-d_5 or by treating *meso*-tetraphenylporphyrin (TPP) with TFA-d.[5] However these methods can not be applied in the synthesis of partial labeling of isotope at specific β-pyrrolic positions. The major obstacle in creating sophisticated models of porphyrins is the limited availability of the building subunits in most occasions. Existing synthetic routes are mainly the condensation of an aldehydes with deuterated pyrroles or pyrromethanes with aldehydes.[6,7] Thus, only symmetrically deuterated porphyrins would be available accordingly. The synthesis of porphyrins with partial labeling of deuterium at β-pyrrolic position is dependent on availability of the building subunits which can afford desired porphyrins after self-condensation. Difficulties in the synthesis of asymmetric porphyrins are also associated with construction of the dipyrromethane components bearing deuterium at specified positions. With our current studies, we report the kinetics of regioselective deuterium exchange in substituted pyrroles and the results obtained during the attempted synthesis of partially deuterated porphyrins. We also report the substituents effect on the rate of site selective deuterium exchange in the substituted pyrroles. The methods reported here will have great potentials in the synthesis of various biochemical systems and may provide an efficient synthetic method of partially deuterated porphyrins.[7]

The site selective protium-deuterium exchange in the 1,9-bisacyldipyrromethane (**1**) has been observed previously.[8] The involvement of the extended iminol-type intermediate has been proposed in the selective deuterium exchange in compound (**1**). Current studies indicate that in fact these types of exchange are very common in the acyl-substituted pyrroles. Pyrrole generally undergoes electrophilic substitution easily. The positional nucleophilicity of pyrrole is greatly influenced by substituents. For example, an α-substituted pyrrole can be electrophilically acylated at the α'-position as far as the α-substituent is not electron-withdrawing. But if electron withdrawing substituents is placed at α-position, electrophilic acylation takes place at 4-position.[9] In order to access the exchange rate and effect of substituents to the rates, we synthesized various N-substituted pyrroles and 2 or 3-substituted pyrroles.

As shown in Scheme 2, selective introduction of acyl group at 1,14-position of 16-oxatripyrrane (**3**) was possible by utilizing the reaction of pyrrole-Grignard and acid chlorides.[10] 16-Oxatripyrrane (**3**) was treated with 2.2 equivalents of ethyl magnesium bromide in THF at room temperature and resulting tripyrromethane-Grignard reagent was



Scheme 1.