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Chiral Recognition for the Two Enantiomers of Phenylalanine and Four Amino Acid Derivatives with (*S*)-Phenylethylamine Derived Nickel(II) Macrocyclic Complex

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Three organic chemists won the 2002 Nobel prize for their efforts in obtaining optically pure enantiomers through the development of good chiral catalysts for asymmetric synthesis.[1-3] Chiral chromatography was used when they checked the optical purities of some chiral compounds that were synthesized using their catalysts. Chiral chromatography is also a powerful method for obtaining optically pure enantiomers from their racemic mixtures directly.[4,5] The most important thing in chiral chromatography is the development of an effective chiral selector.[6,7] A range of organic compounds, such as cyclodextrins, proteins, celluloses, antibiotics and some small chiral molecules, were used as good chiral selectors for chiral chromatography.[8-10] An optically pure phenylethylamine-derived chiral macrocyclic metal complex (**1**, Figure 1) was recently developed and used as a good chiral selector for the chiral discrimination of racemic binaphthol.[11,12] Figure 1(a) shows the 3-dimensional structure of a monomeric precursor of (*S*)-phenylethylamine-derived chiral macrocyclic metal complex (**1**). Figure 1(b) presents the 3-dimensional structure of chiral macrocyclic metal complex (**1**) prepared from the self-assembly of the monomeric precursor with 1,3,5-benzenetricarboxylic acid.

This study attempted to use the chiral metal organic framework (MOF), **1**, as a good chiral selector candidate for the chiral discrimination of racemic phenylalanine, *N*-benzoyl-alanine, *N*-benzoyl-phenylalanine, *N*-benzoyl-methionine, *N*-CBZ-alanine. The chiral recognition ability of the chiral

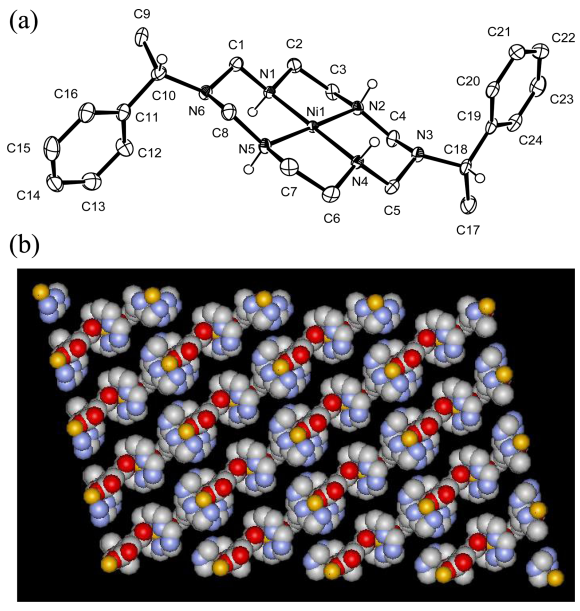

Figure 1. Structure of (*S*)-phenylethylamine derived chiral macrocyclic metal complex (**1**). 3-Dimensional structure of (a) monomeric precursor of the chiral macrocyclic metal complex (**1**), and (b) chiral macrocyclic metal complex (**1**).

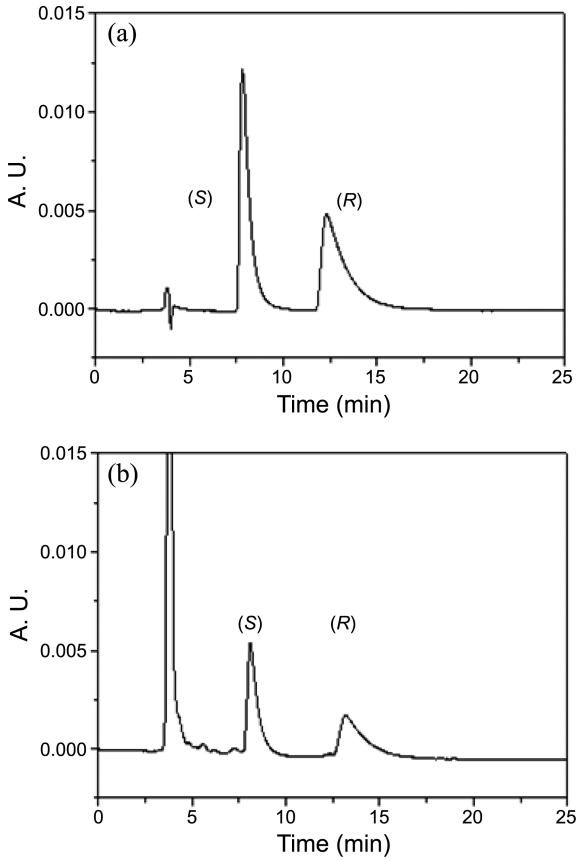

Figure 2. Chromatograms for the resolution of (a) racemic phenylalanine and (b) racemic phenylalanine treated with macromolecule complex **1** with the molar ratio of 1:5 for 2 h. Column; Chirosil column. Eluent; 20% H_2O in MeOH including 10 mM acetic acid. Flow rate; 0.5 mL/min. Detection; 254 nm UV.

Table 1. Enantiomeric excess (ee) of phenylalanine, *N*-benzoyl-alanine, *N*-benzoyl-phenylalanine, *N*-benzoyl-methionine, and *N*-CBZ-alanine by varying the molar ratio of amino acid or amino acid derivatives and the macrocyclic nickel complex (**1**)

	Phenylalanine[a]		*N*-benzoyl-alanine[b]		*N*-benzoyl-phenylalanine[b]		*N*-benzoyl-methionine[b]		*N*-CBZ-alanine[c]	
	ee (%)	RSD (%)	ee (%)	RSD (%)	ee (%)	RSD (%)	ee (%)	RSD (%)	ee (%)	RSD (%)
1:1	**2.8**	**8.7**	1.7	7.4	2.3	7.1	1.8	10.1	1.7	10.1
1:2	**5.1**	**3.7**	3.2	10.9	5.5	8.5	3.6	8.8	5.4	3.4
1:5	**11.4**	**6.7**	6.1	6.4	10.1	10.5	5.8	9.4	7.4	9.5

[a]Chirosil column, 10 mM acetic acid in 80% MeOH/H_2O. [b]Chiralhyun-LE-1 column, 0.1 M TFA in 10% IPA/hexane. [c]Chiralcel OD-H column, 0.1 M TFA in 10% IPA/hexane.

macromolecule, **1**, was examined by varying the molar ratio of the macromolecule and racemates.

Figure 2(a) shows a chromatogram of racemic phenylalanine on a Chirosil column. The ratio of the peak area between (*R*)- and (*S*)-phenylalanine was approximately 50:50. Figure 2(b) shows a chromatogram of (*R*)- and (*S*)-phenylalanine, which was placed in contact with a 5 fold excess of the chiral MOF **1** for 2 h in a methyl alcohol solution. The peak ratio of (*R*)- and (*S*)-phenylalanine contacting with the macromolecule complex **1** was approximately 44.3:55.7. Therefore, macromolecule (**1**) interacts more strongly with (*R*)-phenylalanine than the (*S*)-isomer.

The molar ratio of racemic phenylalanine and macromolecule was changed to examine the tendency of chiral recognition. As shown in the first column of Table 1, an increase in the quantity of macromolecules resulted in a larger enantiomeric excess.

Similar chiral discrimination studies with racemic *N*-benzoyl-alanine, *N*-benzoyl-phenylalanine, *N*-benzoyl-methionine and *N*-CBZ-alanine were performed to check the chiral recognition ability of the chiral macromolecule by varying the macromolecule to racemate ratio. As shown in Table 1, phenylalanine and *N*-benzoyl-phenylalanine showed better enatiomeric excess than the others. The tests were carried out more than three times for each sample under the same conditions, and the reproducibility of the data was relatively good (Average relative standard deviation was approximately 7-8%). From the results, phenylalanine and *N*-benzoyl-phenylalanine showed good chiral recognition on the (*S*)-phenylethylamine-derived nickel(II) macrocyclic MOF (**1**).

The potency of new chiral selector candidate was assessed by this simple chiral discrimination test. This experiment showed that the macrocyclic molecule (**1**) can be a powerful candidate as a chiral selector to obtain optically pure amino acid or amino acid derivatives, particularly phenylalanine and *N*-benzoyl-phenylalanine enantiomers from racemic mixtures.

Experimental

Instruments and Materials. High performance liquid chromatography (HPLC) was performed on a JASCO HPLC system, consisting a JASCO PU-2080 Plus Intelligent Pump, a Rheodyne Model 7125 injector with a 20 μM sample loop, and a JASCO UV-2075 Plus Intelligent UV/VIS detector from JASCO (Tokyo, Japan). A Waters HPLC system (WATERS, Milford, USA), which consists of a Waters 2690 Separation Module and a Waters 996 Photodiode Array Detector, was also used to confirm the optical purities of the chiral samples studied. Methanol (MeOH), *n*-hexane and 2-propanol (IPA) of HPLC grade were obtained from J. T. Baker (USA). All racemic analytes tested in this study were purchased from Sigma-Aldrich (USA).

All HPLC solvents were supplied by Merck Korea (Seoul, Korea). The chiral columns and mobile phase conditions for each chiral sample were as follows: (1) phenylalanine; column, Chirosil (RStech, Korea); eluent, 10 mM acetic acid in an 80% methyl alcohol aq. solution; flow rate, 0.5 mL/min; and detection at 254 nm UV. (2) *N*-Benzoyl-alanine, *N*-benzoyl-phenylalanine, *N*-benzoyl-methionine; column, Chiralhyun-LE(*S*)-1 (K-mac, Korea); eluent, 0.1% TFA in a 10% IPA in hexane; flow rate, 1.0 mL/min; and detection at 254 nm UV. (3) *N*-CBZ-alanine; column, Chiralcel OD-H (Daicel, Japan); eluent, 0.1% TFA in a 10% IPA in hexane; flow rate, 1.0 mL/min; and detection at 254 nm UV. The HPLC injection volume was 5 mL. The shaking incubator used to mix the chiral selector and racemic mixture was purchased from DAIHAN Scientific KMC-8480SF Model (Seoul, Korea). The chiral macrocyclic complex (**1**) used in this study was prepared using the same procedure with previous work.[11,12]

Chiral Discrimination. Put 200 mg of the racemic samples into 200 mL of methyl alcohol (1000 mg/L sample solution). The racemic sample and macromolecule **1** were mixed at various molar ratios of 1:1, 1:2 and 1:5. [18 mg (1:1), 36 mg (1:2), 90 mg (1:5) of the macromolecule **1** was placed separately into three vials containing 1.62 mL of the 1000 mg/L racemic phenylalanine solution.] 1.90 mL of the 1000 mg/L *N*-benzoylalanine solution, 2.65 mL of the 1000 mg/L *N*-benzoylphenylalanine solution, 2.49 mL of the 1000 mg/L *N*-benzoylmethionine solution, and 2.19 mL of the 1000 mg/L *N*-CBZ-alanine solution were used instead of 1.62 mL of the 1000 mg/L of racemic phenylalanine solution. The mixed solution was shaken for two hours using a shaking incubator. After removing the solid particles by passing a silica micro column or filter paper, chiral HPLC was performed three times with the filtrate for each sample. The enatiomeric purity was measured by calculating the peak area for each peak of the (*R*)- and (*S*)-isomer from the chromatograms of racemic samples on each CSP.

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