

Synthesis of Chiral Azophenolic Pyridino-18-Crown-6 Ether and Its Enantiomeric Recognition toward Chiral Primary Amines

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The article reports the synthesis and enantiomeric recognition of a new chiral azophenolic pyridino-18-crown-6 ether, (*S,S*)-**6**, possessing diphenyl groups as chiral barriers. The association constants for the enantiomeric recognition of chiral primary amines (**7-12**) using chiral azophenolic pyridino-18-crown-6 ether, (*S,S*)-**6**, were determined by UV-visible titration method in acetonitrile at 25 °C.

Key Words : Azophenolic chiral crown ether, Pyridine-18-crown-6, Chiral recognition, Enantiomeric recognition

Introduction

Host-guest chiral recognition plays an important role in biological process, resolution of enantiomers, and asymmetric catalysis reactions.¹ Hence, the successful design, synthesis, and use of chiral macrocyclic ligands capable of the selective recognition of the guests have attracted much attention for the investigations of catalysis,^{2,3} separations,^{4,5} and enzyme mimics.⁶⁻⁸ There are numerous amines and ammonium salts which are basic building blocks of biological molecules. Enantiomeric recognition of these molecules are of considerable significance since a number of them are known to possess potent biological activities which are different from their enantiomers.⁹ Out of various types of host molecules investigated, chiral crown ethers have been quite successful for the chiral discrimination of primary amine-containing compounds. Kaneda, Naemura, Hirose, and co-workers have studied the syntheses and characterization of a number of chiral crown ethers having azophenol group capable of enantiomeric recognition toward chiral amines.¹⁰ This chiral azophenolic crown ethers displayed enantioselective color changes upon complexation with guest enantiomers.

Our interest has been focused on the enantiomeric recognition of chiral amines utilizing synthetic chiral pyridine-18-crown-6. We report herein the synthesis of chiral azophenolic pyridino-18-crown-6 ether (*S,S*)-**6** and their enantiomeric recognition of several chiral primary amines ((*R*)/(*S*)-alaninol (**7**), (*R*)/(*S*)-*sec*-butylamine (**8**), (*R*)/(*S*)-phenylglycinol (**9**), (*R*)/(*S*)-methylbenzylamine (**10**), (*R*)/(*S*)-*nat*phylethylamine (**11**), and (*R*)/(*S*)-cyclohexylethylamine (**12**)). The association constants of (*S,S*)-**6** - chiral amine complexes were determined by UV-visible titration in acetonitrile at 25 °C.

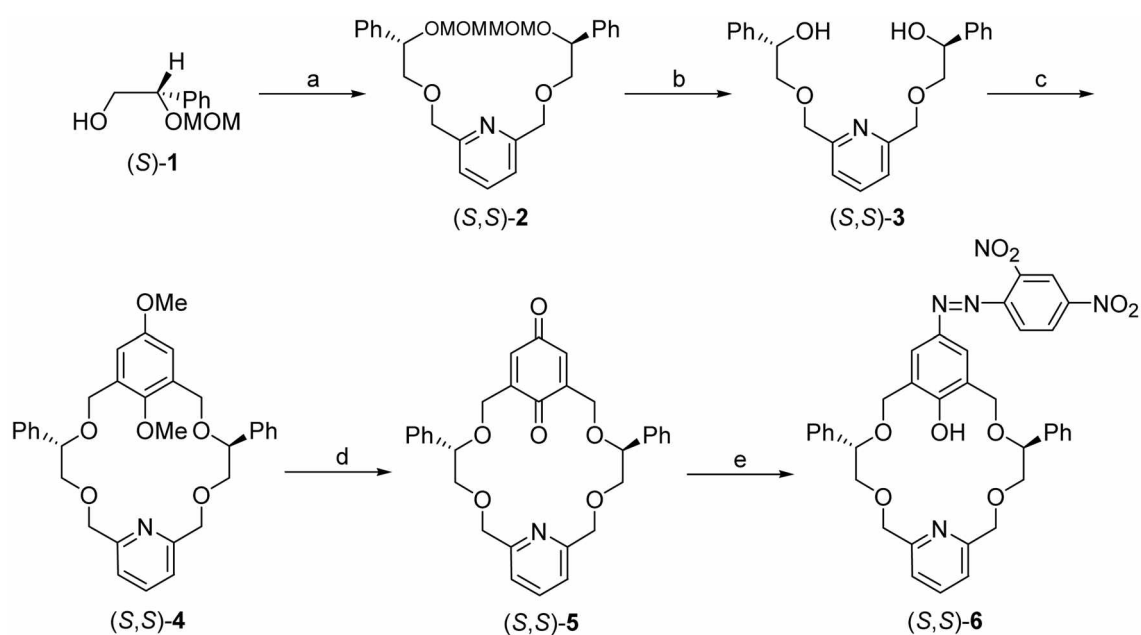
Experimental Section

General. ¹H-NMR, and ¹³C-NMR spectra were recorded

on a Varian Unity Plus 5 (500 MHz) and Varian Gemini 200 (200 MHz). Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer under fast atom bombardment (FAB) conditions with Nitrobenzyl alcohol (NBA) as the matrix in the Korea Basic Science Institute (Daegu), Korea. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040-0.063 mm). Analytical thin layer chromatography (TLC) was performed using pre-coated TLC plates with silica Gel 60 F₂₅₄ (E. Merck no. 5715-7). All reactions were carried out under argon atmosphere with dry solvent, unless otherwise noted. Tetrahydrofuran (THF), and diethyl ether were distilled from sodium/benzophenone immediately prior to use and methylene chloride (CH₂Cl₂) was dried from calcium hydride.

All chemicals were reagent grade unless otherwise specified. The (*R*)- and (*S*)-chiral amines were obtained from Aldrich Chemical Co. and used without purification. The (*2S*)-2-(methoxymethoxy)-2-phenylethanol (**2**) was prepared using our previously reported methods.¹¹ 1,3-Bis(bromomethyl)-2,5-dimethoxybenzene was synthesized according to the literature method.¹² 7-Tetraoxa-23-azatricyclo-[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaene (**4**) was synthesized using the reported analogous method.¹⁰

(5*S*,15*S*)-5,15-Diphenyl-3,6,14,17-tetraoxa-23-azatricyclo-[17.3.1.1^{8,12}]tetracos-1(23),8,11,19,21-pentaene-10,24-dione (5**).** To a stirred solution of (*S,S*)-**4** (0.42 g, 0.78 mmol) in acetonitrile (20 mL) at 50 °C under Ar was added cerium (IV) ammonium nitrate (2.55 g, 4.65 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 3 h. After cooling to 0 °C, the reaction mixture was treated with 5 mL of water. The reaction mixture was extracted with chloroform (3 × 60 mL) and the combined organic layer was washed with water, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography to give (*S,S*)-**5** (0.19 g, 48%) as a yellow oil (*R*_f 0.40, SiO₂, 2% MeOH-CH₂Cl₂). ¹H-



Scheme 1. Reaction conditions; (a) 2,6-Bis(iodomethyl)pyridine, NaH, DMF, 90 °C, 24 h; (b) 10% HCl, THF, 50 °C, 5 h; (c) 1,3-Bis(bromomethyl)-2,5-dimethoxybenzene, NaH, THF, 80 °C to 50 °C, 48 h; (d) cerium(IV) ammonium nitrate, CH₃CN, room temp., 3 h; (e) 2,4-dinitrophenylhydrazine, CH₂Cl₂, ethanol, room temp., 3 h.

NMR (200 MHz, CDCl₃) δ 3.73-3.79 (m, 4H), 3.93 (d, 2H, J = 11 Hz), 4.41 (d, 2H, J = 11 Hz), 4.50-4.70 (m, 8H), 6.67 (s, 2H), 7.11-7.48 (m, 12H), 7.72 (t, 1H, J = 6.6 Hz); ¹³C-NMR (50 MHz, CDCl₃) δ 64.8, 73.9, 75.7, 80.1, 120.6, 126.5, 128.1, 128.6, 132.6, 137.0, 138.0, 144.6, 157.7, 185.7, 187.5; HRMS (FAB, NBA) calcd 512.2073 for C₃₁H₃₀NO₆ (M + H)⁺, found 512.2073.

(5*S*,15*S*)-10-[(*E*)-(2,4-Dinitrophenyl)diazenyl]-5,15-diphenyl-3,6,14,17-tetraoxa-23-azatricyclo[17.3.1.1^{8,12}]tetracos-1(23),8(24),9,11,19,21-hexaen-24-ol (6). To a stirred solution of (*S,S*)-5 (0.18 g, 0.35 mmol) in methylene chloride (5 mL) and ethanol (5 mL) at room temperature under Ar was added 2,4-dinitrophenylhydrazine hydrogen chloride (0.41 g, 1.76 mmol) in ethanol (10 mL). After stirring at room temperature for 3 h, the reaction mixture was treated with 5 mL of water and extracted with chloroform (3 × 40 mL). The combined organic layer was washed with saturated aqueous NaHCO₃ and water, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography to give (*S,S*)-6 (0.16 g, 66%) as a red solid (R_f 0.30, SiO₂, 3% MeOH-CH₂Cl₂); [α]_D²⁴ = +58.5° (c = 0.1, CHCl₃); mp: 87-88 °C; ¹H-NMR (500 MHz, CDCl₃) δ 3.73 (dd, 2H, J = 2.5, 9.1 Hz), 3.88 (dd, 2H, J = 2.5, 9.1 Hz), 4.50 (s, 4H), 4.78 (m, 6H), 7.32-7.39 (m, 12H), 7.68 (s, 2H), 7.79 (d, 1H, J = 2.4 Hz), 8.49 (dd, 1H, J = 2.4, 8.8 Hz), 8.75 (d, 1H, J = 2.4 Hz), 9.18 (s, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 68.3, 73.2, 75.0, 81.4, 119.9, 120.0, 121.6, 125.5, 126.8, 126.9, 127.5, 128.4, 128.7, 130.7, 137.8, 145.8, 146.8, 148.9, 157.1, 161.0; HRMS (FAB, NBA) calcd 692.2356 for C₃₁H₃₀NO₆ (M + H)⁺, found 692.2355.

Results and Discussion

Synthesis and Characterization. Chiral azophenolic pyridino-18-crown-6 ether (*S,S*)-6 with diphenyl group as chiral barriers were synthesized for the enantiomeric recognition of chiral primary amines. The synthesis of the designed chiral azophenolic pyridino-18-crown-6 ether (*S,S*)-6 is summarized in Scheme 1. The chiral subunit alcohol (*S*)-1 was prepared from (*S*)-(+)-mandelic acid using our previously reported route.¹¹ The alcohol (*S*)-1 was coupled with the 2,6-bis(iodomethyl)pyridine by using sodium hydride to generate (*S,S*)-2 in 51% yield. The MOM-protecting group of (*S,S*)-2 was removed by using 10% HCl to afford the diol (*S,S*)-3, the southern part of the macrocycle, in 81% yield. The generated compound (*S,S*)-3 was coupled with the 1,3-bis(bromomethyl)-2,5-dimethoxybenzene,¹² the northern part of the macrocycle, by using sodium hydride in THF under high dilution conditions to afford the macrocycle (*S,S*)-4 in 42% yield. The oxidation¹³ of (*S,S*)-4 with cerium(IV) ammonium nitrate in acetonitrile generated (*S,S*)-5 in 48% yield, which was immediately treated with 2,4-dinitrophenylhydrazine in methylene chloride and ethanol to obtain chiral azophenolic pyridino-18-crown-6 ether (*S,S*)-6 as a red solid in 66% yield.

UV-visible Titration Studies. The chiral azophenolic crown ether (*S,S*)-6 is a red indicator that can generate a new blue anionic ligand (*S,S*)-6⁻ by deprotonation. To investigate the enantiomeric recognition, chiral azophenolic crown ether (*S,S*)-6 was treated with chiral primary amines ((*R*)/(*S*)-alaninol (7), (*R*)/(*S*)-*sec*-butylamine (8), (*R*)/(*S*)-phenylglycinol (9), (*R*)/(*S*)-methylbenzylamine (10), (*R*)/(*S*)-natphyl-

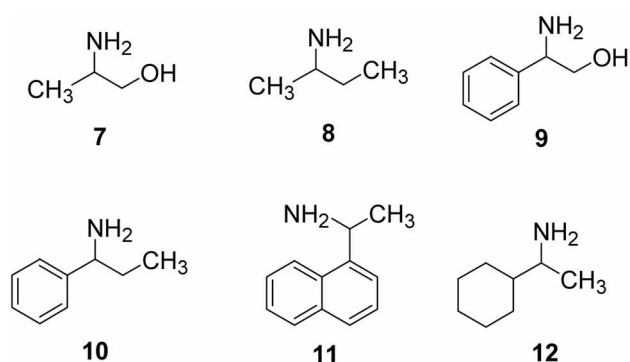


Figure 1. The chemical structure of chiral primary amines (7-12) used in experiments.

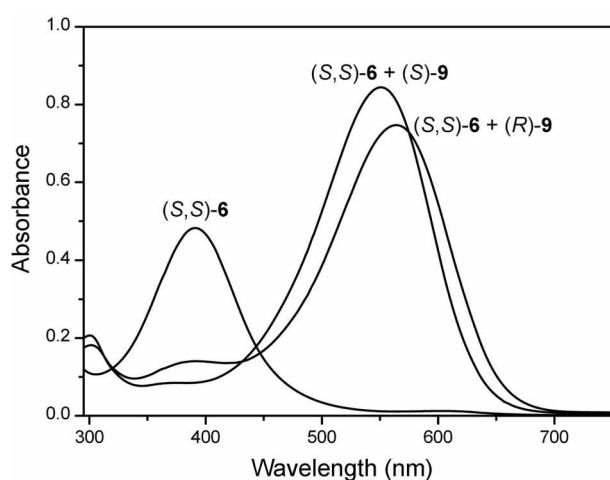


Figure 2. UV-visible spectra changes of chiral azophenolic crown ether (*S,S*)-6 (0.02 mM) in the presence of (*R*)-, and (*S*)-phenylglycinol (**9**) (4.0 mM) in acetonitrile at 25 °C.

ethylamine (**11**), and (*R*)/(*S*)-cyclohexylethanamine (**12**) as shown in Figure 1.

The titration experiments for the complexation of the host (*S,S*)-6 with chiral amine (*R*)-8 are described here as an example for the determination of the association constants by UV-visible spectroscopy. A solution of (*S,S*)-6 in acetonitrile was prepared and an initial UV spectrum of this solution was recorded. Separately, a solution of (*R*)-8 in acetonitrile was prepared. Samples were made by adding the guest solution to the host solution and dilution with acetonitrile to make the total volume of 4.0 mL, so that the concentration of the guest in each samples were 0.0, 2.0, 4.0, 8.0, 14, and 20 mM, respectively. The concentration of the host was kept constant at 0.02 mM in each sample. Then, the spectra of these twelve different solutions were recorded. The binding constants were calculated from the absorption intensity of the complexes at absorption maximum based on the Rose-Drago method.¹⁴ The spectrophotometric behavior of (*S,S*)-6 with colorless chiral amines such as **7-12** was examined in acetonitrile at 25 °C. (*S,S*)-6 itself has absorption maxima at 397 nm. As the chiral amine was added to (*S,S*)-6, the new absorption band was developed at long wavelength and its absorbance was increased in proportion

Table 1. Association constants (K_a /mol) of chiral azophenolic crown ether (*S,S*)-6 with chiral primary amines (**7-12**) in acetonitrile at 25 °C

Entry	Amine	K_a	$\alpha[K_a(R)/K_a(S)]^a$
1	(<i>R</i>)-7	$12.6(\pm 0.7) \times 10^3$	1.07
2	(<i>S</i>)-7	$11.7(\pm 0.7) \times 10^3$	
3	(<i>R</i>)-8	$104(\pm 0.7) \times 10^3$	1.55
4	(<i>S</i>)-8	$67.4(\pm 0.7) \times 10^3$	
5	(<i>R</i>)-9	$8.19(\pm 0.7) \times 10^3$	1.16
6	(<i>S</i>)-9	$7.05(\pm 0.7) \times 10^3$	
7	(<i>R</i>)-10	$11.3(\pm 0.7) \times 10^3$	0.85
8	(<i>S</i>)-10	$13.3(\pm 0.7) \times 10^3$	
9	(<i>R</i>)-11	$6.72(\pm 0.7) \times 10^3$	0.85
10	(<i>S</i>)-11	$7.94(\pm 0.7) \times 10^3$	
11	(<i>R</i>)-12	$93.8(\pm 0.7) \times 10^3$	1.06
12	(<i>S</i>)-12	$87.9(\pm 0.7) \times 10^3$	

^a $K_a(R)$ for the complex with (*R*)-amine and $K_a(S)$ for the complex with (*S*)-amine.

to the concentration of chiral amine. The observed absorption maxima of the complexes in acetonitrile appeared in the wavelength region of 563-590 nm. For example, as shown in the Figure 2, when (*R*)-9 and (*S*)-9 were added to (*S,S*)-6, a new absorption maxima for the (*S,S*)-6:(*R*)-9 complex and (*S,S*)-6:(*S*)-9 complex were observed at 568 nm and 563 nm, respectively.

The association constants (K_a) for (*S,S*)-6 with chiral amines **7-12** were determined by the Rose-Drago method¹⁴ on the basis of the UV-visible titration of complexes in acetonitrile at 25 °C. The chiral amines causing higher association constants gave rise to larger blue-shift, although the (*S,S*)-6 : chiral amine **7-12** system does not exhibit a clear proportional relationship. The association constants and the ratio of association constants $K_a(R)/K_a(S)$ are summarized in Table 1. Among them, the association constants of (*S,S*)-6 with the (*R*)/(*S*)-enantiomer of *sec*-butylamine (**8**) were found to be $104 (\pm 0.7) \times 10^3 \text{ M}^{-1}$ and $67.4 (\pm 0.7) \times 10^3 \text{ M}^{-1}$, respectively. The ratio of association constants $K_a(R)/K_a(S)$ of *sec*-butylamine was 1.55. The chiral macrocycle (*S,S*)-6 exhibits good recognition for **8**, and show a little for **9**, **10**, and **11**, but no enantiomeric recognition for **7**, and **12**. Even though it is quite difficult to extract any clear reason of this trend, the hydrogen bonding of the ammonium salt of the guest with the oxygens and nitrogen of the macrocycle, and the steric effects of the diphenyl group of the macrocycle could play important roles in enantiomeric recognition. Out of the factors mentioned above, the hydrogen bonding between the host and the guests may lead to the formation of the complex, while steric interaction contributes to enantiomeric recognition.

Conclusion

In conclusion, the synthesis and enantiomeric recognition of a new chiral azophenolic pyridino-18-crown-6 ether (*S,S*)-6 possessing diphenyl groups as chiral barriers are reported. The association constants for the enantiomeric

recognition of chiral primary amines (**7-12**) using chiral azophenolic pyridino-18-crown-6 ether, (*S,S*)-**6**, were determined by UV-visible titration method in acetonitrile at 25 °C. The chiral macrocycle (*S,S*)-**6** exhibits good recognition for **8**, and show a little for **9**, **10**, and **11**, but no enantiomeric recognition for **7**, and **12**.

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Supporting Information: The spectroscopic data and experimental procedures for the syntheses of compound **2-4** are available via the internet at <http://www.kcsnet.or.kr/bkcs>.

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