Synthesis and Enantiomeric Recognition Studies of Optically Active Pyridino-Crown Ethers Containing an Anthracene Fluorophore Unit

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ABSTRACT Novel enantiopure pyridino-18-crown-6 ether-based sensor molecules containing an anthracene fluorophore unit were synthesized. Their enantiomeric recognition abilities toward the enantiomers of 1-phenylethylamine hydrogen perchlorate (PhEt), 1-(1-naphthyl)ethylamine hydrogen perchlorate (NapEt), phenylglycine methyl ester hydrogen perchlorate (PhgOMe), and phenylalanine methyl ester hydrogen perchlorate (PheOMe) were examined in acetonitrile using fluorescence spectroscopy. The sensor molecules showed appreciable enantiomeric recognition toward the enantiomers of NapEt, PhEt, and PhgOMe. The highest enantioselectivity was found in the case of crown ether containing isobutyl groups in the macroring and the enantiomers of NapEt. *Chirality 28:562–568, 2016.* © 2016 Wiley Periodicals, Inc.

KEY WORDS: fluorescent sensor molecule; chiral crown ether; complexation; enantioselectivity; anthracene

Enantiomeric recognition is an important and vital phenomenon in Nature. A great number of biologically relevant molecules are chiral, and many biological processes are based on enantioselective reactions such as the metabolism of amino acids and sugars in biosynthetic pathways. Since the individual enantiomers of a biologically active compound may have different physiological properties, the determination of the enantiomeric composition of chiral organic compounds has great importance in drug discovery, the food industry, and pesticide chemistry.

The enantioselective sensing based on fluorescence is attractive due to the selectivity, sensitivity and versatility of fluorescence spectroscopy.[1] In the past three decades many efforts have been made on the development of chiral fluorescent chemosensors.[2–11] Among them, chiral crown ethers containing different fluorophore units have also been synthesized, and their enantiomeric discrimination abilities toward the enantiomers of various optically active primary ammonium salts such as protonated primary amines, amino acid esters, and amino alcohols were investigated.[12–22]

Enantiopure pyridino-18-crown-6 ethers, among them the ones containing methyl or isobutyl groups at their stereogenic centers, are effective ligands for enantiomeric recognition.[23–32] Their abilities to differentiate the enantiomers of protonated chiral primary amines, amino acid esters, and amino alcohols were extensively studied in several solvents and solvent mixtures by titration calorimetry and nuclear magnetic resonance (NMR) spectroscopy,[23–28] solvent extraction,[29] circular dichroism (CD) spectroscopy,[30,31] and molecular modeling.[23,24,32] Furthermore, tailored enantiopure pyridino-18-crown-6 ethers were attached to ordinary and high-performance liquid chromatography (HPLC)-quality silica gels by covalent bonds, and these chiral stationary phases separated the enantiomers of protonated chiral primary amines, amino acids, and their derivatives at atmospheric[33–36] and high[37–39] pressure. It was observed in our research group that the presence of an aromatic (phenyl) group at position 4 of the pyridine ring enhanced significantly the enantiomeric separation ability of such chiral pyridino-crown ether-based stationary phases.[39]

Considering these results, we designed and synthesized novel enantiopure pyridino-18-crown-6 ethers [(*S*,*S*)-**1** and (*S*,*S*)-**2**] having methyl and isobutyl groups at their stereogenic centers, respectively, and an anthracene moiety at position 4 of the pyridine ring to provide an extended aromatic system and also to act as a fluorophore signaling unit. Studies on the enantiomeric recognition abilities of these fluorescent sensor molecules toward the enantiomers of protonated chiral primary amines and amino acid esters were performed in acetonitrile using fluorescence spectroscopy.

MATERIALS AND METHODS

General

Starting materials were purchased from Sigma–Aldrich (St. Louis, MO) unless otherwise noted. Aluminum oxide 60 F_{254} neutral type E (Merck, Darmstadt, Germany) plates were used for thin-layer chromatography (TLC). Aluminum oxide (neutral, activated, Brockman I) was used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Solvents were dried and purified according to well-established methods.[40] Evaporations were carried out under reduced pressure.

Optical rotations were taken on a Perkin–Elmer (Boston, MA) 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. IR spectra were recorded on a Bruker (Billerica, MA) Alpha-T Fourier transform infrared (FT-IR) spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were taken on a Bruker 300 Avance spectrometer. Mass spectra were recorded on an Agilent-6120 (Palo Alto, CA) Single Quadrupole liquid chromatography / mass spectroscopy (LC/MS) instrument using the electrospray ionization (ESI) method. Elemental analyses were performed at the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary.

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Received for publication 16 February 2016; Accepted 25 May 2016
DOI: 10.1002/chir.22614
Published online in Wiley Online Library (wileyonlinelibrary.com).

UV–vis spectra were taken on a Unicam (Cambridge, UK) UV4–100 spectrophotometer. Quartz cuvettes with path length of 1 cm were used. Fluorescence emission spectra were recorded on a Perkin–Elmer LS 50B luminescent spectrometer and were corrected by the spectrometer software. Quartz cuvettes with path length of 1 cm were used. Fluorescence quantum yields were determined relative to quinine sulfate (Φ_f = 0.53 in 0.1 M H_2SO_4).[1] Enantiomers of PhEt, NapEt, PhgOMe, and PheOMe were prepared in our laboratory.[35] The concentrations of sensor molecules (*S,S*)-**1** and (*S,S*)-**2** were 20 μM during the titrations. In order to determine the stability constants of complexes by global nonlinear regression analysis, the SPECFIT/32 software was used.

Preparation of Crown Ethers (S,S)-1, (S,S)-2, (S,S)-7, (S,S)-9, (S,S)-11, and (S,S)-13

General procedure for the synthesis of sensor molecules (*S,S*)-1 and (*S,S*)-2. A mixture of iodopyridino-crown ether (*S,S*)-**12**[39] (114 mg, 0.252 mmol) or (*S,S*)-**13** (135 mg, 0.252 mmol), anthracen-9-ylboronic acid (62 mg, 0.277 mmol), $Pd(PPh_3)_4$ (7.3 mg, 0.0063 mmol), powdered K_3PO_4 (80 mg, 0.378 mmol), and KBr (33 mg, 0.277 mmol) in dioxane–water 6:1 (4 mL) was stirred at 85 °C under Ar for a day. The solvent was evaporated, and the residue was dissolved in a mixture of CH_2Cl_2 (8 mL) and water (4 mL). The phases were mixed well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude products were purified as described below for each compound.

(*4S,14S*)-*19*-(*Anthracen-9-yl*)-*4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo*[*15.3.1*]*heneicosa-1*(*21*),*17,19-triene* [(*S,S*)-**1**]. The crude product was purified by column chromatography on alumina using first DME–hexane 1:4 then DME–toluene 1:10 mixtures as eluents to give (*S,S*)-**1** (48 mg, 38%) as a yellow oil. R_f: 0.27 (alumina TLC, DME–toluene 1:10); $[\alpha]_D^{20}$ = +25.2 (*c* = 1.0 in acetone); IR (neat): ν_{max} 3546 (br, complexed H_2O), 3079, 3049, 3028, 2969, 2866, 1601, 1554, 1444, 1378, 1363, 1347, 1334, 1271, 1106, 1016, 977, 931, 887, 863, 842, 793, 738, 681, 669, 653, 633, 615, 555, 450, 437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, *J* = 7 Hz, 6H, Me), 2.18 (br s, 1H, complexed H_2O), 3.35–3.77 (m, 12H, OCH_2), 3.85–3.96 (m, 2H, OCH), δ_A 4.97 and δ_B 4.99 (AB q, J_{AB} = 14 Hz, 4H, benzylic type CH_2), 7.36–7.42 (m, 2H, Ar-H), 7.39 (s, 2H, Py-H), 7.46–7.51 (m, 2H, Ar-H), 7.61 (d, *J* = 9 Hz, 2H, Ar-H), 8.07 (d, *J* = 9 Hz, 2H, Ar-H), 8.54 (s, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.23, 71.00, 71.19, 72.21, 74.28, 76.46, 123.09, 125.47, 126.08, 126.45, 127.52, 128.66, 129.66, 131.43, 134.51, 148.29, 159.12; MS: calcd. For $C_{31}H_{35}NO_5$, 501.3; found $[M + H]^+$, 502.3. Anal. calcd. For $C_{31}H_{35}NO_5 \cdot 0.5\ H_2O$: C 72.92, H 7.11, N 2.74; found: C 72.69, H 7.20, N 2.58.

(*4S,14S*)-*19*-(*Anthracen-9-yl*)-*4,14-diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo*[*15.3.1*]*heneicosa-1*(*21*),*17,19-triene* [(*S,S*)-**2**]. The crude product was purified by column chromatography on alumina using first DME–hexane 1:20 then DME–toluene 1:30 mixtures as eluents to give (*S,S*)-**2** (77 mg, 52%) as a yellow oil. R_f: 0.29 (alumina TLC, DME–toluene 1:30); $[\alpha]_D^{25}$ = −13.1 (*c* = 1.0 in acetone); IR (neat): ν_{max} 3326 (br, complexed H_2O), 3083, 3060, 3032, 2953, 2918, 2867, 1601, 1566, 1457, 1420, 1385, 1366, 1350, 1316, 1263, 1110, 1042, 930, 884, 871, 844, 818, 791, 777, 758, 736, 722, 685, 630, 615, 556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.81 (d, *J* = 7 Hz, 6H, iBu-CH_3), 0.82 (d, *J* = 7 Hz, 6H, iBu-CH_3), 1.17–1.24 (m, 2H, iBu-CH_2), 1.37–1.45 (m, 2H, iBu-CH_2), 1.68–1.78 (m, 2H, iBu-CH), 2.83 (br s, 1H, complexed H_2O), 3.35–3.65 (m, 12H, OCH_2), 3.79–3.85 (m, 2H, OCH), δ_A 4.90 and δ_B 5.01 (AB q, J_{AB} = 13 Hz, 4H, benzylic type CH_2), 7.41–7.45 (m, 2H, Ar-H), 7.43 (s, 2H, Py-H), 7.51–7.55 (m, 2H, Ar-H), 7.63 (dd, *J* = 9 Hz, *J* = 1 Hz, 2H, Ar-H), 8.15 (d, *J* = 9 Hz, 2H, Ar-H), 8.68 (s, 1H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.67, 23.85, 25.36, 42.26, 71.41, 71.62, 73.17, 75.80, 76.44, 123.67, 126.35, 126.91, 126.98, 128.35, 129.54, 130.36, 132.39, 135.38, 148.84, 160.18; MS: calcd. For $C_{37}H_{47}NO_5$, 585.3; found $[M + H]^+$, 586.3. Anal. calcd. For $C_{37}H_{47}NO_5 \cdot 0.5\ H_2O$: C 74.72, H 8.13, N 2.35; found: C 74.54, H 8.03, N 2.22.

(*4S,14S*)-*19-Benzyloxy-4,14-diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene* [(*S,S*)-**7**]. A suspension of NaH (417 mg, 10.4 mmol, 60% dispersion in mineral oil) in pure and dry THF (6 mL) was stirred under Ar at 0 °C. A solution of tetraethylene glycol (*S,S*)-**5**[28] (1.00 g, 3.26 mmol) in THF (14 mL) was added dropwise to the suspension. The reaction mixture was stirred at 0 °C for 10 min, at RT for 30 min, and refluxed for 3 h. The mixture was cooled to −60 °C and a solution of ditosylate **3**[41] (1.81 g, 3.26 mmol) in THF (11 mL) was added, and the reaction mixture was stirred at −60 °C for 30 min then at RT for 4 days. The solvent was evaporated and the residue was triturated with ice-water (20 mL). The mixture was washed into a separating funnel with ether (60 mL). The phases were mixed well and separated. The aqueous phase was extracted with ether (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The residue was purified by column chromatography on alumina using EtOH–toluene 1:160 mixture as an eluent to give (*S,S*)-**7** (350 mg, 21%) as a colorless oil.

R_f: 0.44 (alumina TLC, EtOH–toluene 1:90); $[\alpha]_D^{30}$ = −8.2 (*c* = 1.0 in EtOH); IR (neat): ν_{max} 3082, 3065, 3033, 2952, 2922, 2867, 1596, 1576, 1453, 1384, 1349, 1321, 1245, 1149, 1112, 1044, 991, 952, 921, 866, 846, 736, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7 Hz, 6H, iBu-CH_3), 0.93 (d, *J* = 7 Hz, 6H, iBu-CH_3), 1.16–1.24 (m, 2H, iBu-CH_2), 1.47–1.55 (m, 2H, iBu-CH_2), 1.72–1.84 (m, 2H, iBu-CH), 3.43–3.63 (m, 12H, OCH_2), 3.66–3.74 (m, 2H, OCH), δ_A 4.76 and δ_B 4.80 (AB q, J_{AB} = 13 Hz, 4H, benzylic type CH_2), 5.10–5.16 (m, 2H, benzylic type CH_2), 6.91 (s, 2H, Py-H), 7.31–7.44 (m, 5H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.51, 23.56, 24.81, 41.22, 69.93, 70.76, 71.02, 72.34, 75.29, 76.20, 107.20, 127.72, 128.45, 128.87, 136.14, 160.45, 166.16; MS: calcd. For $C_{30}H_{45}NO_6$, 515.3; found $[M + H]^+$, 516.3. Anal. calcd. For $C_{30}H_{45}NO_6$: C 69.87, H 8.80, N 2.72; found: C 69.85, H 8.95, N 2.71.

(*4S,14S*)-*4,14-Diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo*[*15.3.1*]*heneicosa-17,20-diene-19*(*21H*)-*one* [(*S,S*)-**9**]. (Benzyloxy)pyridino-crown ether (*S,S*)-**7** (700 mg, 1.36 mmol) was hydrogenated in EtOH (35 mL) in the presence of Pd/C catalyst (105 mg, 10% palladium on charcoal, activated). After the reaction was completed, the catalyst was filtered off and the solvent was evaporated to give (*S,S*)-**9** (550 mg, 95%) as a pale yellow oil which was used without purification. Macrocycle (*S,S*)-**9** prepared this way was identical in every aspect to that reported in the literature.[37]

(*4S,14S*)-*4,14-Diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo*[*15.3.1*]*heneicosa-1*(*21*),*17,19-triene-19-yl trifluoromethanesulfonate* [(*S,S*)-**11**]. To a mixture of pyridino-crown ether (*S,S*)-**9** (550 mg, 1.29 mmol) and Et_3N (262 mg, 0.36 mL, 2.58 mmol) in CH_2Cl_2 (7 mL) a solution of Tf_2O (728 mg, 0.43 mL, 2.58 mmol) in CH_2Cl_2 (2 mL) was added dropwise under Ar at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 1 h. The reaction mixture was poured into ice-water (20 mL) and the pH of the mixture was adjusted to 10 with 25% aqueous NMe_4OH. The mixture was washed into a separating funnel with CH_2Cl_2 (40 mL). The phases were mixed well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The dark purple colored residue was purified by column chromatography on alumina using EtOH–toluene 1:100 mixture as an eluent to give (*S,S*)-**11** (460 mg, 64%) as a pale brown oil.

R_f: 0.78 (alumina TLC, EtOH–toluene 1:30); $[\alpha]_D^{25}$ = −16.4 (*c* = 1.0 in CH_2Cl_2); IR (neat): ν_{max} 3086, 3069, 3037, 2956, 2925, 2870, 1956, 1581, 1468, 1426, 1387, 1368, 1350, 1296, 1243, 1211, 1139, 1118, 1044, 965, 874, 819, 765, 605, 572, 516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6 Hz, 6H, iBu-CH_3), 0.92 (d, *J* = 6 Hz, 6H, iBu-CH_3), 1.10–1.30 (m, 2H, iBu-CH_2), 1.44–1.58 (m, 2H, iBu-CH_2), 1.66–1.86 (m, 2H, iBu-CH), 3.38–3.63 (m, 12H, OCH_2), 3.66–3.78 (m, 2H, OCH), δ_A 4.85 and δ_B 4.89 (AB q, J_{AB} = 14 Hz, 4H, benzylic type CH_2), 7.20 (s, 2H, Py-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.46, 23.41, 24.85, 40.96, 70.77, 71.20, 71.83, 75.68, 76.91, 112.10, 118.79 (q, *J* = 321 Hz, CF_3), 157.43, 163.12; MS: calcd. For $C_{24}H_{38}F_3NO_8S$, 557.2; found $[M + H]^+$, 558.2. Anal. calcd. For $C_{24}H_{38}F_3NO_8S$: C 51.69, H 6.87, N 2.51, S 5.75; found: C 51.50, H 7.01, N 2.39, S 5.61.

(*4S,14S*)-*19-Iodo-4,14-diisobutyl-3,6,9,12,15-pentaoxa-21-azabicyclo*[*15.3.1*]*heneicosa-1*(*21*),*17,19-triene* [(*S,S*)-**13**]. To a solution of triflate (*S,S*)-**11** (460 mg, 0.825 mmol) in toluene (9 mL) was first added NaI (619 mg, 4.13 mmol) followed by concentrated H_2SO_4 (105 mg, 58 μL, 1.07 mmol), and the resulting mixture was stirred under Ar at RT for 5 h. The solvent was evaporated, the residue was triturated with water (12 mL), and the pH of the mixture was adjusted to 10 with 1 M NaOH. The mixture was washed into a separating funnel with CH_2Cl_2 (24 mL). The phases were mixed well and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 12 mL). The combined organic phase was washed with 5% aqueous $Na_2S_2O_3$

(30 mL), 1 M NaOH (30 mL), and water (3 × 30 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The residue was purified by column chromatography on alumina using EtOH–toluene 1:300 mixture as an eluent to give (*S*,*S*)-**13** (221 mg, 50%) as a pale brown oil.

R_f: 0.52 (alumina TLC, EtOH–toluene 1:40); $[\alpha]_D^{25} = -26.8$ (c = 1.0 in CH_2Cl_2); IR (neat): ν_{max} 3083, 3066, 3034, 2953, 2921, 2867, 1560, 1446, 1385, 1366, 1350, 1332, 1263, 1114, 1042, 943, 863, 804, 747, 659, 637, 514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, J = 7 Hz, 6H, iBu-CH_3), 0.93 (d, J = 7 Hz, 6H, iBu-CH_3), 1.11–1.28 (m, 2H, iBu-CH_2), 1.45–1.58 (m, 2H, iBu-CH_2), 1.69–1.89 (m, 2H, iBu-CH), 3.36–3.63 (m, 12H, OCH_2), 3.63–3.77 (m, 2H, OCH), δ_A 4.76 and δ_B 4.79 (AB q, J_{AB} = 14 Hz, 4H, benzylic type CH_2), 7.66 (s, 2H, Py-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.49, 23.54, 24.83, 41.17, 70.82, 71.14, 71.91, 75.54, 76.59, 106.56, 129.51, 159.79; MS: calcd. For $C_{23}H_{38}INO_5$, 535.2; found $[M + H]^+$, 536.2. Anal. calcd. For $C_{23}H_{38}INO_5$: C 51.59, H 7.15, N 2.62; found: C 51.65, H 7.17, N 2.59.

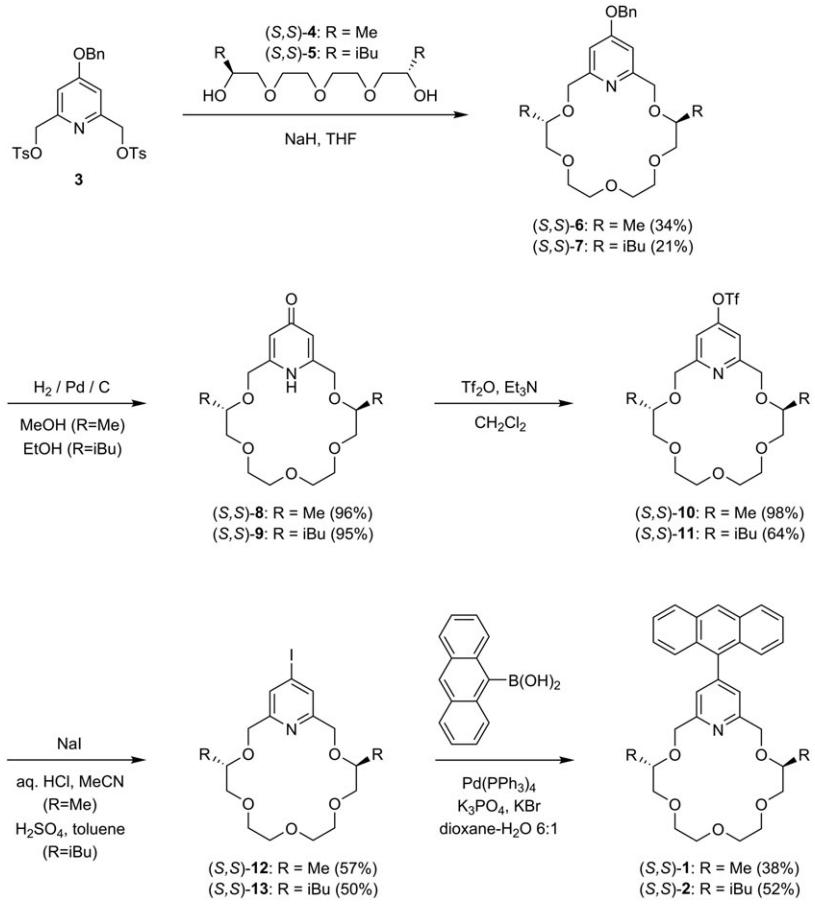
RESULTS AND DISCUSSION

Synthesis

The synthesis of pyridino-crown ethers (*S*,*S*)-**7**, (*S*,*S*)-**9**,[37] (*S*,*S*)-**11,** and (*S*,*S*)-**13** containing isobutyl groups at the stereogenic centers of their macrorings was carried out in a similar way as published for their methyl analogs (*S*,*S*)-**6**,[42] (*S*,*S*)-**8**,[42] (*S*,*S*)-**10**[39] and (*S*,*S*)-**12**[39] (Scheme 1).

(Benzyloxy)pyridino-crown ether (*S*,*S*)-**7** was prepared by a macrocyclization reaction starting from ditosylate **3**[41] and optically active tetraethylene glycol (*S*,*S*)-**5**[28] in THF using sodium hydride as a strong base. The removal of the benzyl protecting group by catalytic hydrogenation in ethanol furnished pyridono-crown ether (*S*,*S*)-**9**. Another route for the preparation of pyridono-crown ether (*S*,*S*)-**9** starting from its THP protected form (which was isolated as a crude product) has already been reported in the literature.[37] Pyridono-crown ether (*S*,*S*)-**9** was converted to triflate (*S*,*S*)-**11** by reacting the former with trifluoromethanesulfonic anhydride in dichloromethane using triethylamine as a base. Triflate (*S*,*S*)-**11** was reacted with sodium iodide in toluene in the presence of sulfuric acid to yield iodopyridino-crown ether (*S*,*S*)-**13**. Its methyl analog (*S*,*S*)-**12** was synthesized according to the literature procedure,[39] which uses sodium iodide and 30% aqueous hydrochloric acid in acetonitrile. The change of 30% aqueous hydrochloric acid to sulfuric acid in the case of iodo derivative (*S*,*S*)-**13** was made to eliminate the nucleophile water from the reaction mixture, which can provide a better yield.[43]

Sensor molecules (*S*,*S*)-**1** and (*S*,*S*)-**2** were prepared from iodopyridino-crown ethers (*S*,*S*)-**12** and (*S*,*S*)-**13**, which were reacted with anthracen-9-ylboronic acid in Suzuki–Miyaura cross-coupling reactions (Scheme 1). First, we used dioxane as a solvent for the synthesis of ligand (*S*,*S*)-**1** according to an analogous procedure[39] described for the reaction of iodo derivative (*S*,*S*)-**12** and 4-(methoxycarbonyl) phenylboronic acid, but in our case the total consumption of iodo derivative (*S*,*S*)-**12** could not be achieved according to the TLC analysis. It is known that the yields of Suzuki–Miyaura reactions carried out with sterically hindered boronic acids can be improved by adding water as a cosolvent



Scheme 1. Synthesis of sensor molecules (*S*,*S*)-**1** and (*S*,*S*)-**2**.

to the reaction mixture.[44] In our case the change of dioxane to a dioxane–water 6:1 mixture resulted in the total conversion of iodopyridino-crown ether (*S*,*S*)-**12** and the formation of only one main product according to the TLC analysis, thus we carried out the synthesis of both sensor molecules [(*S*,*S*)-**1** and (*S*,*S*)-**2**] applying the latter solvent mixture.

Enantiomeric Recognition Studies

The enantiomeric recognition abilities of pyridino-crown ethers (*S*,*S*)-**1** and (*S*,*S*)-**2** toward the enantiomers of 1-phenylethylamine hydrogen perchlorate (PhEt), 1-(1-naphthyl) ethylamine hydrogen perchlorate (NapEt), phenylglycine methyl ester hydrogen perchlorate (PhgOMe), and phenylalanine methyl ester hydrogen perchlorate (PheOMe) (Fig. 1) were studied in acetonitrile by UV–vis and fluorescence spectroscopies.

The absorption spectra of crown ethers (*S*,*S*)-**1** and (*S*,*S*)-**2** showed no (in the cases of the enantiomers of PhEt and NapEt) or small (in the cases of the enantiomers of PhgOMe and PheOMe) spectral changes upon addition of the various optically active primary ammonium salts (Fig. 2).

However, the addition of these protonated aralkyl amines and amino acid esters to sensor molecules (*S*,*S*)-**1** and (*S*,*S*)-**2** having fluorescence quantum yields of 0.60 and 0.58, respectively in acetonitrile, caused significant fluorescence quenching with 93.5–99.4% decreases of emission intensities during the titrations (Fig. 3A–C). All the fluorescence spectral changes were evaluated using global nonlinear regression analysis. The titration series of spectra could be fitted satisfactorily by assuming 1:1 complex formation, and the stability constants were calculated (Table 1).

Based on these results, it can be seen that the stabilities of complexes are lower in the case of crown ether (*S*,*S*)-**2** because of the steric effect of the bulky isobutyl groups attached to the macroring. However, the trends for the enantiomeric recognition abilities of macrocycles (*S*,*S*)-**1** and (*S*,*S*)-**2** are similar. Namely, the highest enantioselectivities were found with NapEt, which contains a more extended aromatic system relative to a phenyl group, and smaller degrees of enantiomeric recognition were observed in the cases of PhEt and PhgOMe containing a phenyl group at their stereogenic centers. The presence of a methoxycarbonyl group in PhgOMe had an adverse effect on the enantiomeric recognition relative to the methyl group in PhEt. The enantioselectivity preferences in these cases [(*R*)-enantiomer for NapEt and PhEt, and (*S*)-enantiomer for PhgOMe] are the same considering the spatial arrangements of the amino group, the aromatic moiety (naphthyl or phenyl), and the third group (methyl or methoxycarbonyl), which are similar in (*R*)-NapEt, (*R*)-PhEt, and (*S*)-PhgOMe. In the case of PheOMe containing a phenyl group attached by a methylene spacer to its stereogenic center, none of the sensor molecules showed enantiomeric discrimination.

The largest degree of enantiomeric recognition was experienced in the case of pyridino-crown ether (*S*,*S*)-**2** and NapEt (Table 1, Fig. 3). This can be explained by the presence of the extended aromatic system in the chiral ammonium salt and the bulky isobutyl groups at the stereogenic centers of the macrocycle. It seems to be that a stronger π–π interaction in the complex is needed for the bulkiness of the substituents in the macroring to play an important role in enantiomeric discrimination.

Since the complexation with the chiral ammonium salts has a fluorescence quenching effect, the Stern–Volmer equation (Eq. 1)[1] can be applied for the titration processes (Fig. 3D).

$$I_0/I = 1 + K_{SV}\,[Q] \tag{1}$$

where I_0 and I are the fluorescence intensities of the sensor molecule in the absence and the presence of a quencher (which is a chiral ammonium salt in our case), respectively, [Q] is the concentration of the quencher, and K_{SV} is the Stern–Volmer constant. In the case of the highest enantioselectivity observed [(*S*,*S*)-**2** and NapEt] we recorded the fluorescence intensity versus the enantiomeric composition of added chiral salt.

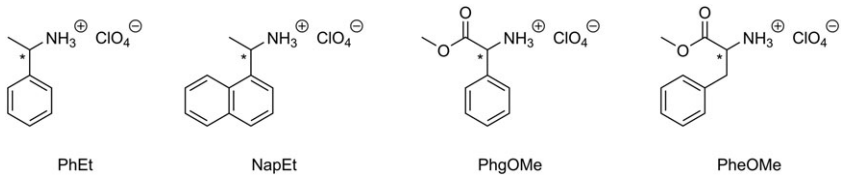


Fig. 1. Optically active primary ammonium salts used in the enantiomeric recognition studies.

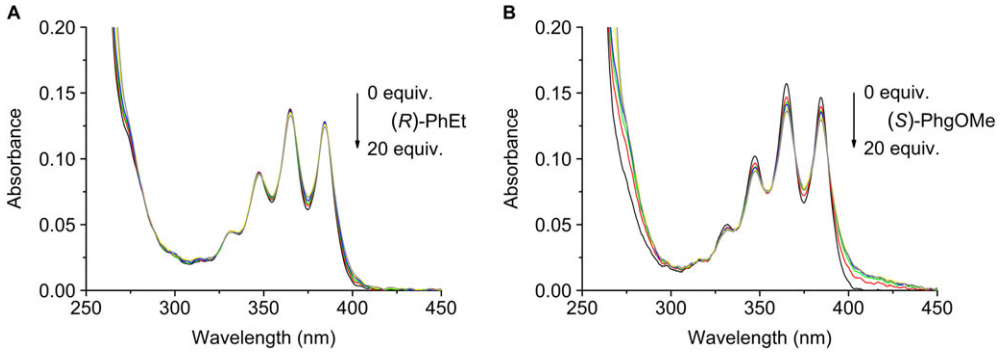


Fig. 2. Series of absorption spectra upon titration of (*S*,*S*)-**2** (20 μM) with (*R*)-PhEt (0, 0.5, 1, 2, 10, 20 equiv.) (**A**) and (*S*,*S*)-**1** (20 μM) with (*S*)-PhgOMe (0, 0.5, 1, 2, 10, 20 equiv.) (**B**) in MeCN.

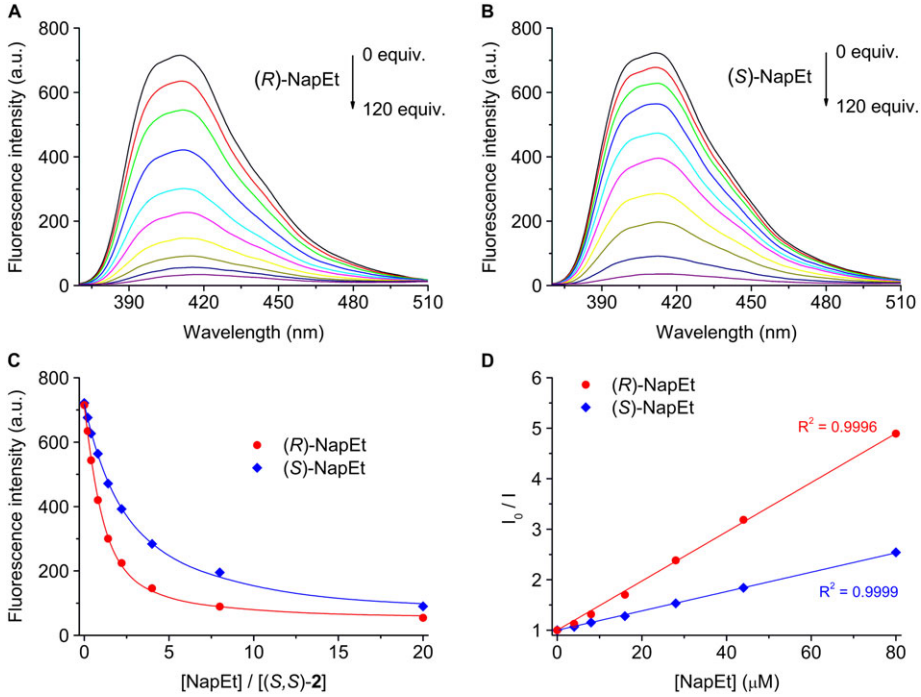


Fig. 3. Series of fluorescence emission spectra upon titration of (*S*,*S*)-**2** (20 μM) with (*R*)-NapEt (**A**) and (*S*)-NapEt (**B**) (0, 0.2, 0.4, 0.8, 1.4, 2.2, 4, 8, 20, 120 equiv.) in MeCN, λ_{ex} = 337 nm. Titration curves (0–20 equiv., solid lines: fitted curves) (**C**) and Stern–Volmer plots (0–4 equiv., 0–80 μM) (**D**) at 410 nm for the titrations with (*R*)-NapEt and (*S*)-NapEt.

TABLE 1. Stability constants for complexes of (*S*,*S*)-1 and (*S*,*S*)-2 with the enantiomers of optically active primary ammonium salts and the degrees of enantiomeric recognition in MeCN

	(*S*,*S*)-**1**		(*S*,*S*)-**2**	
	log *K*	Δ log *K*	log *K*	Δ log *K*
(*R*)-PhEt	5.29 ± 0.02	0.26	4.60 ± 0.02	0.26
(*S*)-PhEt	5.03 ± 0.02		4.34 ± 0.02	
(*R*)-NapEt	5.55 ± 0.03	0.38	5.08 ± 0.02	0.60
(*S*)-NapEt	5.17 ± 0.03		4.48 ± 0.02	
(*R*)-PhgOMe	5.38 ± 0.04	−0.18	5.02 ± 0.04	−0.17
(*S*)-PhgOMe	5.56 ± 0.04		5.19 ± 0.03	
(*R*)-PheOMe	5.09 ± 0.04	0.04	4.66 ± 0.04	0.05
(*S*)-PheOMe	5.05 ± 0.03		4.61 ± 0.04	

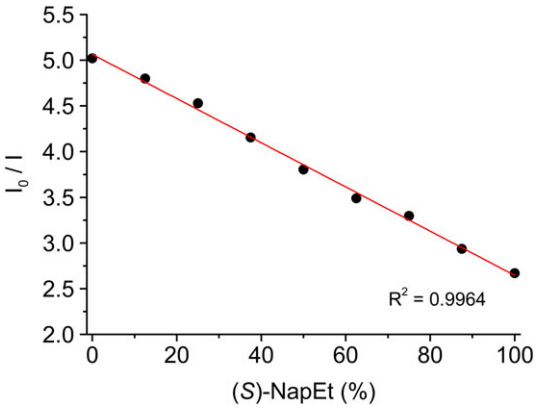


Fig. 4. Stern–Volmer calibration curve for (*S*,*S*)-**2** (20 μM) and different enantiomeric compositions of NapEt (4 equiv.) in MeCN.

Because of the good linearity of the Stern–Volmer plots for both enantiomers of NapEt (Fig. 3D), the Stern–Volmer equation can be used in the following form (Eq. 2).[1,45]

$$I_0/I = 1 + K_{SV,(R)}\,[(R)\text{-NapEt}] + K_{SV,(S)}\,[(S)\text{-NapEt}] = 1 + \left[K_{SV(R)} + \left(K_{SV,(S)} - K_{SV(R)}\right) x_{(S)}\right][\text{NapEt}] \quad (2)$$

where [NapEt] is the sum of concentrations of (*R*)- and (*S*)-NapEt, $x_{(S)}$ is the molar fraction of (*S*)-NapEt, $K_{SV,(R)}$ and $K_{SV,(S)}$ are the Stern–Volmer constants for the quenching processes with (*R*)- and (*S*)-NapEt, respectively. Since the NapEt concentration was kept constant (4 equiv.) during the experiment, I_0/I varied linearly with $x_{(S)}$ giving a calibration curve (Fig. 4), which can provide an opportunity[45–49] for the determination of the enantiomeric composition of NapEt.

CONCLUSION

Novel enantiopure pyridino-crown ether-based fluorescent sensor molecules [(*S*,*S*)-**1** and (*S*,*S*)-**2**] containing an anthracene unit were synthesized, and their enantiomeric recognition abilities toward various primary ammonium salts in acetonitrile were investigated by fluorescence spectroscopy. The sensor molecules showed a remarkable "turn-off" fluorescence response upon addition of the ammonium salts, with an almost total quenching of the fluorescence during the titrations. The largest degree of enantiomeric recognition (Δ log *K* = 0.60) was observed in the case of pyridino-crown ether (*S*,*S*)-**2** containing isobutyl groups in the macroring and the enantiomers of 1-(1-naphthyl)ethylamine hydrogen perchlorate (NapEt). It can be explained by the presence of both the bulky substituents in the macroring and the extended aromatic system in the ammonium salt. Based on the Stern–Volmer equation a linear relationship was found as a function of the enantiomeric composition of NapEt, providing an opportunity for the determination of the latter.

Because of the significant role of the bulkiness of the substituent at the stereogenic centers in enantiomeric

recognition,[25,26] we plan to synthesize the analogous fluorescent pyridino-crown ether containing *tert*-butyl groups at those places to achieve higher enantioselectivity.

ACKNOWLEDGMENTS

Financial support of the Hungarian Scientific Research Fund / National Research, Development and Innovation Office (OTKA / NKFIH No. K 112289 and PD 104618), the New Széchenyi Development Plan (TÁMOP-4.2.1/B-09/1/KMR-2010-0002), and the Zsuzsanna Szabó Research Fellowship are gratefully acknowledged. The authors thank Dr. György Tibor Balogh and Dr. Eszter Riethmüller for taking mass spectra.

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