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Push or Pull for a Better Selectivity? A Study on the Electronic Effects of Substituents of the Pyridine Ring on the Enantiomeric Recognition of Chiral Pyridino-18-Crown-6 Ethers

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Abstract: Seven dimethyl-substituted optically active pyridino-18-crown-6 ethers containing various substituents at position 4 of the pyridine ring were studied with regards to the electron-donating and -withdrawing effects of substituents on enantiomeric recognition. In order to compile this set of compounds, we prepared four novel pyridino-18-crown-6 ethers, including an intermediate of a new synthetic route for a formerly reported crown ether. The discriminating ability of these pyridino-crown ethers with C_2-symmetry toward the enantiomers of protonated primary amines was examined by isothermal titration calorimetry.

Keywords: enantiomeric recognition; complexation; crown ether; pyridine derivatives; isothermal calorimetry

1. Introduction

Molecular recognition is of great importance, having found applications in drug discovery, genetics, and disease diagnostics [1]. Enantiomeric recognition, a special case of molecular recognition, is of increasing importance in the pharmaceutical industry [2]. It is often the case that only one enantiomer of biologically active compounds has a desirable effect. As the industry is working harder to exclude any adverse effects from the other enantiomer of drug molecules [2,3], demand is increasing for devices capable of detecting enantiomers of chiral compounds [4–6] or separating them [7]. Chiral crown ethers have been utilized in many instances as sensor molecules [8–12] as well as selector molecules in chiral chromatography stationary phases [7,13–18], or in transport applications [19–21].

It was found that incorporating an aromatic unit into the crown ether ring decreases the conformational mobility of the latter, hence increasing enantioselectivity. In the past, a large number of crown ethers containing various heterocyclic units were prepared [10], among them, pyridine-containing

crown ethers [14,22–29] as well. Numerous pyridino-crown ethers with different substituents at distinct positions of the macroring were synthesized. The effects of various parameters were tested: ring size, presence or absence of certain functional groups in the macroring such as ester or thioester, amide or thioamide, and the type (size) and position of the substituents at the stereogenic centers [14,22–29].

In continuation of the previous studies, this work focused on the electronic effects of the pyridine ring on the enantiomeric recognition properties of pyridino-crown ethers. For this, we prepared a series of new and reported [17,30–32] crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**7** (Figure 1) with various substituents at position 4 of the pyridine ring. The best options for electron-donating groups are dimethylamino and methoxy groups: macrocycles (*S*,*S*)-**1** and (*S*,*S*)-**2** [31] contain such substituents. On the electron-deficient side, cyano and sulfonyl groups were considered ((*S*,*S*)-**6** [32] and (*S*,*S*)-**7**). Macrocycle (*S*,*S*)-**5** [17] contains a chlorine atom, which has a negative inductive effect as well as a positive mesomeric effect, but the greater magnitude of the former makes it electron-withdrawing, which situates this ligand on the electron-deficient side. The phenyl group practically does not alter the electron density in the pyridine ring, but it does influence the π–π interaction between the host and the guest molecules, an effect we wanted to study by crown ether (*S*,*S*)-**3**.

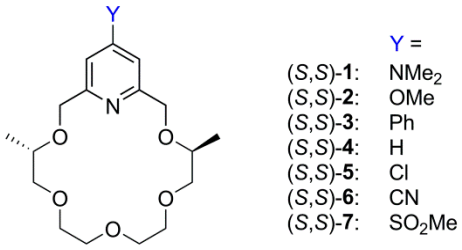
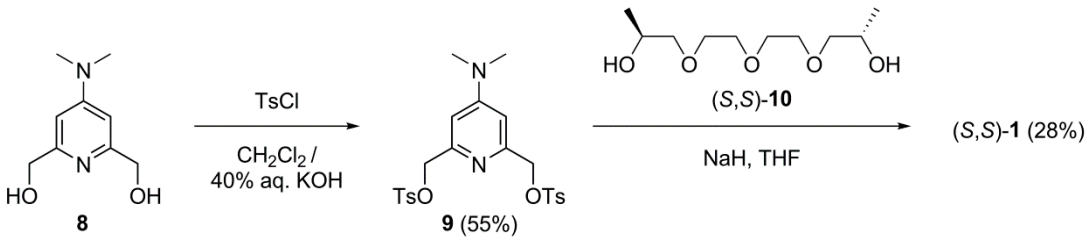


Figure 1. Enantiopure dimethyl-substituted pyridino-18-crown-6 ethers with various substituents at position 4 of the pyridine ring.

2. Results and Discussion

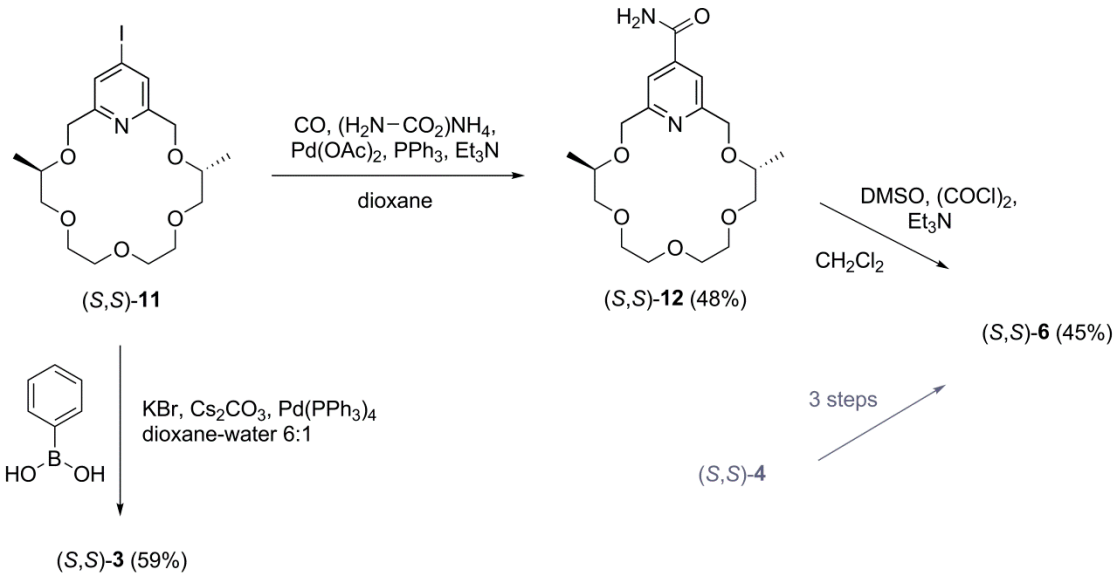
2.1. Synthesis

(Dimethylamino)pyridino-crown ether (*S*,*S*)-**1** was prepared in two steps from diol **8** [33] (Scheme 1), which was synthesized from chelidamic acid in four steps [33–35]. Diol **8** was converted to ditosylate **9** according to the procedure described in the literature for numerous analogous ditosylates [12,31,36]. Ditosylate **9** was eventually reacted with tetraethylene glycol (*S*,*S*)-**10** [37] in tetrahydrofuran (THF) using sodium hydride as a base, similarly to the reported procedures [12,31,36], to give crown ether (*S*,*S*)-**1**.



Scheme 1. Synthesis of crown ether (*S*,*S*)-**1**.

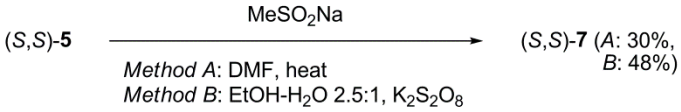
Pyridino-crown ethers (*S*,*S*)-**2** [31], (*S*,*S*)-**4** [30], and (*S*,*S*)-**5** [17] were obtained as reported. We prepared phenylpyridino-crown ether (*S*,*S*)-**3** via Suzuki coupling of iodo compound (*S*,*S*)-**11** [17] with phenylboronic acid (Scheme 2), as described for analogous compounds [11,12,17].



Scheme 2. Synthesis of crown ether (*S*,*S*)-**3** and an alternative synthetic route for the preparation of macrocycle (*S*,*S*)-**6** (the reported procedure [32] starts from crown ether (*S*,*S*)-**4**).

Cyanopyridino-crown ether (*S*,*S*)-**6** had been prepared earlier in our group, starting from crown ether (*S*,*S*)-**4** [32]; however, we followed a new synthetic route here through amide derivative (*S*,*S*)-**12** (Scheme 2). We brought iodo compound (*S*,*S*)-**11** [17] into an aminocarbonylation reaction by reacting it with ammonium carbamate and carbon monoxide in the presence of a palladium(II) catalyst. This way, we obtained amide derivative (*S*,*S*)-**12**, which was dehydrated by oxalyl chloride and DMSO in the presence of triethylamine as a base in dichloromethane to furnish carbonitrile (*S*,*S*)-**6**. This reaction was carried out under the conditions of Swern oxidation, but here actually a dehydration process took place [38].

(Methanesulfonyl)pyridino-crown ether (*S*,*S*)-**7** was successfully prepared in a single step by modification of the reported methods [39,40], from chloro compound (*S*,*S*)-**5** [17], by reacting it with a large excess of sodium methanesulfinate in *N*,*N*-dimethylformamide (DMF) (Scheme 3). We also tried ethanol/water 2.5:1 instead of DMF and adding potassium peroxodisulfate as an initiator, thereby using an alternative method described in the literature [41]. The latter procedure was carried out at room temperature instead of refluxing DMF, which gave a cleaner crude product, but some of the starting chloro compound (*S*,*S*)-**5** remained unreacted and was recovered.



Scheme 3. Synthesis of crown ether (*S*,*S*)-**7**.

2.2. Enantiomeric Recognition Studies

The complexation properties and enantiomeric differentiation abilities of macrocycles (*S*,*S*)-**1**–(*S*,*S*)-**7** were studied with the enantiomers of 1-phenylethylammonium perchlorate (PEA) and 1-(1-naphthyl)ethylammonium perchlorate (NEA) in acetonitrile (Figure 2). The method of choice was isothermal calorimetric titration, as it allows the determination the enthalpy and entropy changes of complexation and the equilibrium constant simultaneously [42]. Furthermore, it enables a more precise determination of the latter parameter than NMR titration [26].

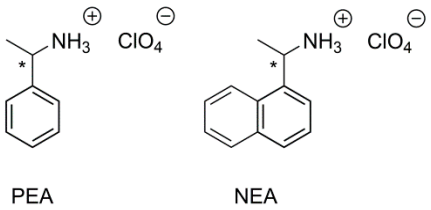


Figure 2. Chiral ammonium salts used as guests for enantiomeric recognition studies.

In the case of (dimethylamino)pyridino-crown ether (*S*,*S*)-**1**, we could not determine complex stability constants because the titration curves showed anomalous tendencies, presumably due to protonation of the ligand by the enantiomers of PEA and NEA. This can be supported by the pK_a (MeCN) values of protonated forms of analogous compounds 4-(dimethylamino)pyridine (17.95) and benzylamine (16.91) [43]. Henceforth, ligand (*S*,*S*)-**2** was the most electron-rich compound investigated. The results of the isothermal calorimetric measurements (Table 1) showed several general tendencies, which are discussed below.

Table 1. Equilibrium constants (log *K* values), enthalpy and entropy changes, and enantioselectivities (Δ log *K* values) for complexation of crown ethers (*S*,*S*)-**2**–(*S*,*S*)-**7** with the enantiomers of 1-phenylethylammonium perchlorate (PEA) and 1-(1-naphthyl)ethylammonium perchlorate (NEA) in MeCN.

Ligand	Substituent (Y)	σ_p [a]	Guest	log *K* [b] (*K* in M^{-1})	Δ log *K* (*K* in M^{-1})	Δ*H* [c] (kJ mol^{-1})	Δ*S* [d] (J mol^{-1} K^{-1})
(*S*,*S*)-**2**	MeO	−0.27	(*R*)-PEA	5.84	0.23	−46.0	−42.2
			(*S*)-PEA	5.61		−40.8	−29.0
			(*R*)-NEA	5.95	0.25	−48.9	−50.0
			(*S*)-NEA	5.70		−39.5	−23.5
(*S*,*S*)-**3**	Ph	−0.01	(*R*)-PEA	5.59	0.23	−43.0	−37.3
			(*S*)-PEA	5.36		−41.8	−37.6
			(*R*)-NEA	5.72	0.32	−48.1	−51.8
			(*S*)-NEA	5.40		−41.9	−37.3
(*S*,*S*)-**4**	H	0.00	(*R*)-PEA	5.56	0.24	−44.6	−43.3
			(*S*)-PEA	5.32		−39.8	−31.7
			(*R*)-NEA	5.62	0.30	−45.8	−46.0
			(*S*)-NEA	5.32		−39.8	−31.7
(*S*,*S*)-**5**	Cl	0.23	(*R*)-PEA	4.83	0.19	−43.7	−54.3
			(*S*)-PEA	4.64		−40.7	−47.7
			(*R*)-NEA	5.00	0.25	−44.5	−53.7
			(*S*)-NEA	4.75		−40.2	−44.0
(*S*,*S*)-**6**	CN	0.66	(*R*)-PEA	4.49	0.17	−40.2	−48.9
			(*S*)-PEA	4.32		−37.1	−41.7
			(*R*)-NEA	4.73	0.32	−44.1	−57.4
			(*S*)-NEA	4.41		−38.4	−44.3
(*S*,*S*)-**7**	SO_2Me	0.72	(*R*)-PEA	4.43	0.15	−39.2	−46.7
			(*S*)-PEA	4.28		−33.9	−31.8
			(*R*)-NEA	4.78	0.37	−42.0	−49.5
			(*S*)-NEA	4.41		−36.1	−36.6

[a] Hammett substituent constants were taken from [44]. [b] Estimated error ± 0.05. [c] Estimated error ± 1 kJ mol^{-1}. [d] Estimated error ± 3.4 J mol^{-1} K^{-1}.

It can be seen that ligands (*S*,*S*)-**2**–(*S*,*S*)-**7** formed more stable complexes with (*R*)-NEA than (*R*)-PEA, and (*S*)-NEA than (*S*)-PEA. The discrimination between the enantiomers was also greater in the case of NEA than PEA. These can be attributed to the more extended π system of NEA in comparison to PEA, making the π–π stacking with the pyridine ring stronger, which is one of the

three intermolecular interactions in the complexes besides tripodal hydrogen bonding and steric repulsion [26]. A heterochiral preference was experienced in all cases, namely, (*R*)-enantiomers of both NEA and PEA exhibited a higher affinity toward the crown ethers than the (*S*)-enantiomers. These observations are in accordance with the previous results for crown ether (*S*,*S*)-**4** [26,29] and in general, for its analogues with other groups at the chiral centers or/and at position 4 of the pyridine ring [11,12,26].

The complex stability constants of macrocycles (*S*,*S*)-**2**–(*S*,*S*)-**7** decreased for both PEA and NEA as the Hammett substituent constant increased (Table 1, Figure 3A). This was caused by the weaker hydrogen bonds between the guests and the pyridine nitrogen of the hosts having a more electron-deficient pyridine ring. It can be noted here that a methoxy group (instead of a hydrogen atom) also increased the complex stability constants with these guests in the case of the pyridine-2,6-diester type crown ether analogue of (*S*,*S*)-**2** [26].

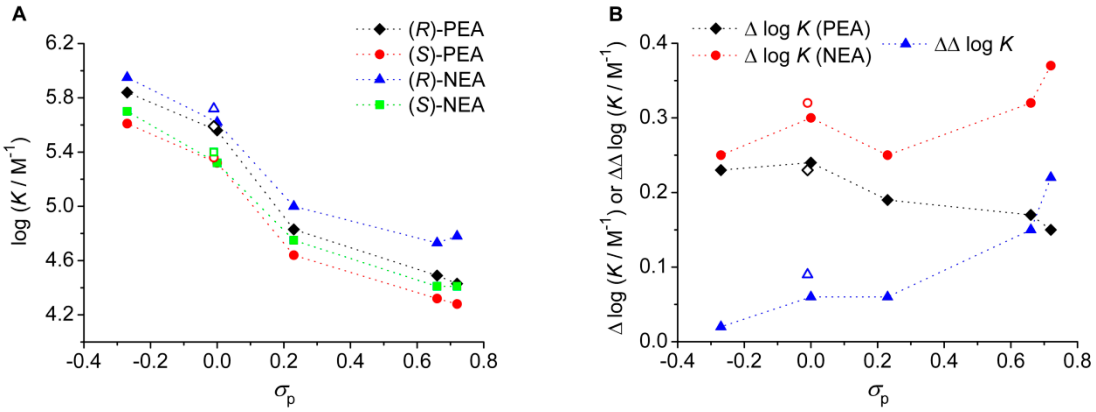


Figure 3. log *K* values (**A**) and Δ log *K* values and their difference (ΔΔ log *K* = Δ log *K* (NEA) − Δ log *K* (PEA)) (**B**) as a function of the Hammett parameter for ligands (*S*,*S*)-**2**–(*S*,*S*)-**7** and PEA and NEA in MeCN. The corresponding values for ligand (*S*,*S*)-**3** are indicated with hollow symbols. The dashed lines are shown as a guide for the eye.

The enantiomeric recognition abilities for PEA decreased with increasing Hammett substituent constant (when $\sigma_p \geq 0.00$) (Table 1, Figure 3B). However, the Δ log K values for NEA increased when the Y group (Figure 1) was changed from electron-donating methoxy to strong electron-withdrawing cyano then sulfonyl. An explanation for this may be that the role of π–π interaction in enantiomeric differentiation is greater for NEA than PEA, and the π–π interaction gets stronger as the substituent becomes more electron-withdrawing. Nonetheless, the increase in enantiomeric recognition seems to be related to the decreasing mesomeric effect of the substituent rather than the Hammett parameter itself, because the Δ log K values were smaller for both methoxy- and chloro-substituted ligands ((*S*,*S*)-**2** and (*S*,*S*)-**5**) compared to the unsubstituted ligand ((*S*,*S*)-**4**). As a result of the two tendencies for NEA and PEA, the differences between the Δ log K values for NEA and PEA (ΔΔ log K) increased with increasing Hammett substituent constant (Figure 3B).

However, phenyl-substituted ligand (*S*,*S*)-**3** slightly fell off the latter trend because of its slightly higher ΔΔ log *K* value (0.09) compared to unsubstituted crown ether (*S*,*S*)-**4** (0.06). The log *K* values for NEA were also slightly higher for ligand (*S*,*S*)-**3** than for macrocycle (*S*,*S*)-**4** (Table 1, Figure 3A). Since the Hammett substituent constants are almost the same for the Y groups of the two ligands, these were probably due to other factors such as the extended π system of host (*S*,*S*)-**3**; however, this effect seems to be very small.

Complexation processes were exothermic (enthalpy changes were negative) and the entropy changes were also negative (unfavorable) in all cases, similarly to previous studies [26]. This means that a variation in substitution did not reverse any of these trends. Looking at the thermodynamic parameters of complexation, we could identify the fact that the enthalpy–entropy correlation was

significantly different for ligands with substituents having small or large Hammett parameters (Figure 4).

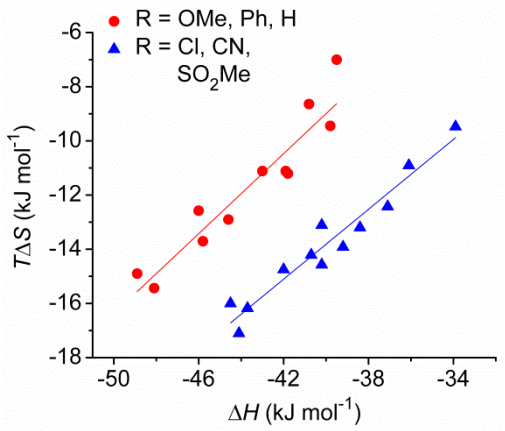


Figure 4. Correlation between the enthalpic and entropic contribution to the binding affinity of ligands (*S*,*S*)-**2**–(*S*,*S*)-**4** (R = OMe, Ph, H) and (*S*,*S*)-**5**–(*S*,*S*)-**7** (R = Cl, CN, SO_2Me) toward the enantiomers of PEA and NEA in MeCN.

3. Materials and Methods

3.1. General Information

Starting materials were purchased from Sigma-Aldrich, Merck, and Alfa Aesar. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for thin-layer chromatography. Silica gel 60 (70–230 mesh, Merck) and aluminium oxide (neutral, activated, Brockman I) were 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 [45]. Evaporations were carried out under reduced pressure.

Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. IR spectra were recorded on a Bruker Alpha-T Fourier transform infrared (FTIR) spectrometer. For (*S*,*S*)-**12**, we recorded ^{1}H (500 MHz) and ^{13}C (125.7 MHz) NMR spectra on a Bruker Avance III 500 spectrometer. In the other cases, ^{1}H NMR (500 MHz) spectrum was obtained on a Bruker DRX-500 Avance spectrometer, and ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were taken on a Bruker 300 Avance spectrometer. HRMS analyses were performed on a Waters Q-TOF Premier mass spectrometer in positive electrospray ionization (ESI) mode.

Enantiomers of PEA and NEA were prepared as previously reported [15]. Isothermal titration calorimetry experiments were performed with a MicroCal VP-ITC instrument in MeCN (VWR HiPerSolv Chromanorm for LC–MS) at 298 K. PEA or NEA solutions (1.5–15 mM) were injected from the computer-controlled microsyringe at an interval of 120 s into solutions of (*S*,*S*)-**1**–(*S*,*S*)-**7** (0.12–1.2 mM) while stirring at 300 rpm. The solutions were degassed prior to titration. The small dilution heat, measured by adding PEA or NEA solutions into MeCN under the same conditions as in the titration of (*S*,*S*)-**1**–(*S*,*S*)-**7**, was always subtracted. The enthalpograms were analyzed by one-site binding model using Microcal ORIGIN software.

*3.2. Preparation of Compounds (S,S)-***1***, (S,S)-***3***, (S,S)-***6***, (S,S)-***7***, ***9***, and (S,S)-***12***

3.2.1. (4S,14S)-19-Dimethylamino-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo [15.3.1]heneicosa-1(21),17,19-triene ((*S*,*S*)-**1**)

Tetraethylene glycol (*S*,*S*)-**10** [37] (680 mg, 3.06 mmol) dissolved in THF (10 mL) was slowly added to a suspension of NaH (343 mg, 8.57 mmol) in THF (3.6 mL) under Ar. The mixture was

refluxed for 4 h, then it was cooled to −75 °C, and ditosylate **9** (1.50 g, 3.06 mmol) in THF (54 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 3 days. The solvent was removed, and the residue was taken up in a mixture of ice water (80 g) and diethyl ether (50 mL). The phases were shaken well and separated. The aqueous phase was further extracted with diethyl ether (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on alumina using ethanol–trimethylamine–hexane 1:1:20 mixture as an eluent to give (*S*,*S*)-**1** (315 mg, 28%) as a yellow oil.

R_f: 0.39 (alumina TLC, EtOH–toluene 1:10); $[\alpha]_D^{25}$ = +28.5 (c = 1.06, EtOH); IR (neat) $\widetilde{\nu}_{max}$ (cm^{-1}) 2966, 2867, 1646, 1602, 1550, 1507, 1444, 1403, 1370, 1351, 1296, 1254, 1220, 1102, 1032, 982, 925, 878, 835; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.18 (d, J = 6 Hz, 6H), 3.03 (s, 6H), 3.40–3.70 (m, 12H), 3.79–3.91 (m, 2H), the diastereotopic benzylic type –CH_2– protons give an AB quartet: δ_A 4.64 and δ_B 4.73 (J_{AB} = 13 Hz, 4H), 6.53 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 17.24, 39.34, 70.59, 70.72, 72.16, 73.48, 75.66, 103.85, 155.65, 157.91; HRMS m/z $(M+H)^+$ found 369.2382, $C_{19}H_{33}N_2O_5^+$ requires 369.2384.

3.2.2. (4S,14S)-19-Phenyl-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1.(21),17,19-triene ((*S*,*S*)-**3**)

A mixture of iodopyridino-crown ether (*S*,*S*)-**11** [17] (130 mg, 0.288 mmol), phenylboronic acid (39.4 mg, 0.323 mmol), Cs_2CO_3 (214 mg, 0.646 mmol), KBr (38.4 mg, 0.323 mmol), and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) in peroxide-free 1,4-dioxane (6 mL) and water (1 mL) was stirred at 90 °C under Ar for a day. The solvent was removed, and the residue was dissolved in a mixture of ethyl acetate (10 mL) and water (10 mL). The phases were shaken well and separated. The aqueous phase was further extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on alumina using ethanol–toluene 1:80 mixture as an eluent to give (*S*,*S*)-**3** (68 mg, 59%) as a pale yellow oil.

R_f: 0.34 (alumina TLC, EtOH–toluene 1:40); $[\alpha]_D^{25}$ = +2.7 (c = 1.00, acetone); IR (neat) $\widetilde{\nu}_{max}$ (cm^{-1}) 3061, 3002, 2968, 2929, 2864, 1605, 1555, 1499, 1450, 1411, 1371, 1350, 1255, 1106, 1002, 989, 925, 880, 844, 764, 696, 615, 594, 532, 497; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.19 (d, J = 6 Hz, 6H), 3.42–3.67 (m, 12H), 3.80–3.92 (m, 2H), 4.81–4.93 (m, 4H), 7.36–7.52 (m, 3H), 7.48 (s, 2H), 7.61–7.69 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 17.30, 70.80, 70.99, 72.12, 73.99, 76.15, 118.63, 127.27, 129.01, 129.14, 138.80, 149.43, 159.14; HRMS m/z $(M+H)^+$ found 402.2272, $C_{23}H_{32}NO_5^+$ requires 402.2275.

3.2.3. (4S,14S)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19- triene-19-carbonitrile ((*S*,*S*)-**6**)

To a flame-dried, round-bottom flask equipped with a septum, an Ar inlet, and a stirring bar, we added a solution of amide derivative (*S*,*S*)-**12** (70 mg, 0.19 mmol) in dry dichloromethane (0.8 mL). Then, pure and dry DMSO (27 µL, 29 mg, 0.38 mmol) was added via a syringe. The reaction vessel was cooled to −78 °C, while carefully maintaining the Ar stream, and a solution of oxalyl chloride (23 µL, 34 mg, 0.27 mmol) in dry dichloromethane (0.2 mL) was added via a syringe. The mixture solidified at this point. After 15 min, triethylamine (80 µL, 58 mg, 0.57 mmol) was added via a syringe, upon which the mixture could be stirred again. After stirring for 1 h at −78 °C, the reaction mixture was quenched by adding water (2 mL), and it was allowed to warm to room temperature. TLC analysis showed approximately 50% conversion of the starting amide (*S*,*S*)-**12**. Ethyl acetate (20 mL) and water (20 mL) were added to the mixture, and the phases were shaken well and separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on alumina using ethanol–toluene 1:100 mixture as an eluent to give nitrile (*S*,*S*)-**6** (30 mg, 45%) as a white crystalline solid and starting amide (*S*,*S*)-**12** (21 mg, 30%).

All physical and spectroscopic properties of (*S*,*S*)-**6** were identical to those reported in the literature [32].

3.2.4. (4S,14S)-19-Methanesulfonyl-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1] heneicosa-1(21),17,19-triene ((*S*,*S*)-**7**)

Method A

Chloropyridino-crown ether (*S*,*S*)-**5** [17] (520 mg, 1.45 mmol) was dissolved in dry DMF (5 mL), and sodium methanesulfinate (1.10 g, 9.31 mmol) was added. The mixture was stirred at 100 °C for 2 days. The solvent was removed, and the residue was dissolved in a mixture of dichloromethane (30 mL) and water (30 mL). The phases were shaken well and separated. The aqueous phase was further extracted with dichloromethane (3 × 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography first on alumina using ethanol–trimethylamine–hexane 1:1:20 mixture as an eluent, then on silica gel using methanol–dichloromethane mixture 1:20 as an eluent to give (*S*,*S*)-**7** (174 mg, 30%) as a yellow oil.

R_f: 0.39 (alumina TLC, EtOH–toluene 1:40); $[\alpha]_D^{25}$ = +29.0 (c = 1.07, ethanol); IR (neat) $\widetilde{\nu}_{max}$ (cm^{-1}) 3067, 2969, 2922, 2870, 1571, 1453, 1408, 1374, 1351, 1311, 1141, 1109, 1090, 987, 962, 925, 882, 760, 733, 576, 530, 462; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.15 (d, J = 6 Hz, 6H), 3.06 (s, 3H), 3.43–3.58 (m, 12H), 3.80 (m, 2H), the diastereotopic benzylic type –CH_2– protons give an AB quartet: δ_A 4.87 and δ_B 4.93 (J_{AB} = 14 Hz, 4H), 7.70 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 16.94, 43.83, 70.62, 70.88, 71.30, 74.36, 76.29, 116.58, 149.09, 161.40; HRMS m/z $(M+H)^+$ found 404.1740, $C_{18}H_{30}NO_7S^+$ requires 404.1737.

Method B

Chloro compound (*S*,*S*)-**5** [17] (100 mg, 0.278 mmol) and sodium methanesulfinate (69 mg, 0.656 mmol) were placed in a round-bottom flask, followed by ethanol (2.2 mL) and water (0.9 mL). Finally, $K_2S_2O_8$ (15 mg, 0.055 mmol) was added, and the mixture was stirred at room temperature for 2 days. TLC analysis showed that about half of the starting material ((*S*,*S*)-**5**) was consumed, and a new spot for the product appeared. (The reaction did not proceed any further than this, despite of the repeated addition of large amounts of sodium methanesulfinate.) The volatile components were evaporated, and the residue was dissolved in a mixture of dichloromethane (25 mL) and water (25 mL). The phases were shaken well and separated. The aqueous phase was further extracted with dichloromethane (2 × 25 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude product was purified as described above for *Method A* to afford (*S*,*S*)-**7** (54 mg, 48%) and (*S*,*S*)-**5** (23 mg, 23%).

All properties of (*S*,*S*)-**7** prepared this way were identical to the one prepared by *Method A*.

3.2.5. [4-(Dimethylamino)pyridine-2,6-diyl]bis(methylene) bis(4-methylbenzenesulfonate) (**9**)

A mixture of diol **8** [33] (2.55 g, 14.1 mmol), dichloromethane (25 mL), and 40% aqueous KOH solution (25 mL) was vigorously stirred at 0 °C, and 4-toluenesulfonyl chloride (6.30 g, 33.0 mmol) was added to it. The reaction mixture was stirred at room temperature for 3 days, then it was washed to a separatory funnel with dichloromethane (150 mL) and water (150 mL). The phases were mixed well and separated. The aqueous phase was further extracted with dichloromethane (3 × 100 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was recrystallized from a dichloromethane–methanol mixture to give ditosylate **9** (3.84 g, 55%) as a white crystalline solid.

R_f: 0.77 (silica gel TLC, AcOH–iPrOH–toluene 1:6:16); mp: 90–91 °C; IR (KBr) $\widetilde{\nu}_{max}$ (cm^{-1}) 3068, 2998, 2943, 2881, 2843, 2810, 2588, 2526, 2269, 1932, 1819, 1609, 1548, 1518, 1492, 1450, 1405, 1360, 1308, 1292, 1223, 1190, 1175, 1032, 980, 932, 879, 854, 840, 829, 816, 735, 706, 663, 637, 606, 551; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.44 (s, 6H), 2.99 (s, 6H), 4.94 (s, 4H), 6.48 (s, 2H), 7.32 (d, J = 8 Hz, 4H), 7.80 (d, J = 8 Hz, 4H); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ (ppm) 21.75, 39.41, 72.16, 103.86, 128.17, 129.98, 133.02, 145.09, 153.47, 155.70; HRMS m/z $(M+H)^+$ found 491.1309, $C_{23}H_{27}N_2O_6S_2^+$ requires 491.1305.

3.2.6. (4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-19-carboxamide ((*S*,*S*)-**12**)

In a typical experiment, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.050 mmol), ammonium carbamate (40.6 mg, 0.52 mmol), and iodopyridino-crown ether (*S*,*S*)-**11** [17] (226 mg, 0.50 mmol) were dissolved in dry 1,4-dioxane (5 mL) under Ar in a 100 mL stainless steel autoclave. Triethylamine (0.1 mL, 0.72 mmol) was added into the autoclave, and then the atmosphere was changed to carbon monoxide, and the autoclave was pressurized to 20 bar of carbon monoxide. (Caution: High pressure carbon monoxide should only be used with adequate ventilation (hood) using CO sensors as well.) The reaction was conducted for 20 h upon stirring at 100 °C. After 20 h, the reaction mixture was cooled to room temperature, and the autoclave was carefully depressurized in a well-ventilated hood. The mixture was then filtered and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and shaken with distilled water (2 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on alumina using a chloroform–ethanol 98:2 mixture as an eluent to give (*S*,*S*)-**12** (88 mg, 48%) as a yellow waxy solid.

R_f: 0.41 (alumina TLC, $CHCl_3$–EtOH 98:2); mp: 92–94 °C; $[\alpha]_D^{25} = +17.1$ (c = 1.00, MeOH); IR (KBr) $\widetilde{\nu}_{max}$ (cm^{-1}) 3435, 3363, 3326, 3271, 3211, 3084, 2971, 2877, 2752, 1683, 1604, 1567, 1471, 1452, 1405, 1379, 1350, 1302, 1275, 1262, 1117, 1034, 998, 949, 918, 893, 859, 847, 815, 773, 623, 589, 530, 483; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.21 (d, J = 6 Hz, 6H), 3.50–3.74 (m, 12H), 3.77–3.86 (m, 2H), the diastereotopic benzylic type –CH_2– protons give an AB quartet: δ_A 4.68 and δ_B 4.94 (J_{AB} = 12 Hz, 4H), 7.10 and 7.13 (br s, 2H, overlapping two NH protons), 7.56 (s, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm) 16.74, 70.45, 70.53, 71.83, 73.97, 76.05, 119.40, 142.27, 158.36, 166.41; HRMS m/z $(M+H)^+$ found 369.2026, $C_{18}H_{29}N_2O_6^+$ requires 369.2020.

4. Conclusions

We prepared seven pyridino-18-crown-6 ethers containing substituents with different Hammett parameters for enantiomeric recognition studies, among them three novel macrocycles, and we elaborated a new synthetic route for one that already reported. Isothermal calorimetric titrations were performed with the enantiomers of primary ammonium salts (PEA and NEA). The results showed several tendencies: the change of the Hammett substituent constant influenced the complex stability constant, the degree of enantioselectivity for PEA and NEA, the difference between the enantioselectivity for PEA and NEA, and the enthalpy–entropy correlation of binding affinity.

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