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Synthesis of new optically active acridino-18-crown-6 ligands and studies of their potentiometric selectivity toward the enantiomers of protonated 1-phenylethylamine and metal ions

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ABSTRACT

Starting from commercially available and relatively inexpensive chemicals, new enantiopure diisobutyl- and dioctyl-substituted acridino-18-crown-6 ether-type ligands [(*R*,*R*)-**3**] and [(*R*,*R*)-**4**], respectively were prepared. The two lipophilic isobutyl [(*R*,*R*)-**3**] and octyl [(*R*,*R*)-**4**] groups on the stereogenic centers of these macrocycles made it possible to use them as potentiometric sensor molecules when incorporated into plasticized PVC membrane electrodes. Ligand (*R*,*R*)-**3** showed appreciable enantioselectivity toward the enantiomers of 1-phenylethylammonium chloride while macrocycle (*R*,*R*)-**4** exhibited a high selectivity toward the silver ion.

1. Introduction

Enantiomeric recognition is a generally occurring phenomenon in Nature. Examples of its action include the observation that only D-sugars and L-amino acids take part in the metabolic processes. Enantiomers can have different biological and physiological activities; frequently only one enantiomer of a drug is effective while the other might even be toxic. Therefore, the synthesis of new chiral host molecules and their use as enantioselective sensor or selector molecules is of great importance.

The role of chiral host molecules is not exclusively confined to enantioselective differentiation. Naturally occurring ionophores acting in different biosynthetic pathways are also chiral and mostly involved in chiral discrimination between enantiomeric forms of chiral molecules for example, amino acids, sugars, etc. However, among them there are examples such as valinomycin, which selectively binds an achiral guest, the potassium ion, thereby regulating its transport through the cell membrane. Moreover, it has been proven that stereochemical arrangements can play a crucial role in the formation of host–achiral guest complexes.[1] This principle was exploited to create Ag^+-specific podand-type ionophores by the proper combination of ligand geometry and stereospecific substitution.[2]

Herein, we report on the development of sensor molecules for the enantiomers of protonated primary amines and heavy metal ions such as the silver ion.

Primary amines are of great biological importance. They are formed in living systems during the degradation of amino acids, or serve as neurotransmitters. It is known that the enantiomers of biogen primary amino compounds have different biological activities; thus their enantioseparation and determination of their enantiomeric composition are essential, especially in the pharmaceutical, plant-protection, and food industries.

Silver and its compounds are used in electrical contacts and conductors, in mirrors, in the catalysis of chemical reactions, in photographic films, and as disinfectants. The traditional Ag_2S-based solid state electrode has a very high primary ion selectivity and can be used to determine Ag^+ in many applications; however Hg^{2+} causes serious interference.[3] This governs the activity of developing ionophore-based Ag^+-selective electrodes.

Sensor molecules can be built into potentiometric membrane electrodes, optodes, amperometric biosensors, and immunosensors.[4–7] Chiral crown ethers are among the most effective enantioselective sensor molecules for primary amine-containing compounds.[8] Since the 1980's several crown ethers have been used as enantioselective sensor molecules in potentiometric membrane electrodes.[9–13]

Crown ethers are also effective host molecules in Ag^+-selective potentiometric sensors and optodes.[14–16]

In connection with our present work it should be mentioned that crown ethers containing a pyridine unit have shown

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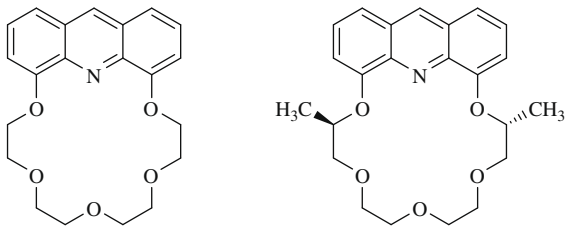
outstanding complexation properties toward heavy metal ions and protonated primary amines because of the nitrogen atom and the aromatic ring.[8,17–19] Studies on the complexes of the optically active pyridino-crown ethers and the enantiomers of chiral protonated primary aralkyl amines proved that the enantioselectivity is based on three independent interactions: tripodal hydrogen bonding, π–π stacking, and steric repulsion. To enhance the π–π interaction, we prepared macrocycles containing a more extended aromatic π-system, for example, phenanthrolino-[20], phenazino-[21], and acridino-[21]crown ethers. The relatively rigid structure of these host molecules also contributes to their improved selectivity, and as they are fluoro- and chromogenic, their complexation can be studied using sensitive photophysical methods.

Disregarding some 9-substituted derivatives,[22] up to now only two acridino-18-crown-6 ligands have been synthesized, the achiral macrocycle **1** and the enantiomerically pure ligand (*R,R*)-**2**[21] (Fig. 1). Complexes of crown ether (*R,R*)-**2** with the enantiomers of protonated primary amines have been studied by fluorescence[23] and circular dichroism[24,25] spectroscopy, and showed greater enantioselectivity[23] than its pyridino-18-crown-6 ether analog. A chiral stationary phase containing a derivative of crown ether (*R,R*)-**2** was prepared by attaching the ligand to silica gel through a spacer at the 9-position of the acridine ring and it was applied successfully for the enantioseparation of racemic protonated primary aralkyl amines.[22] It should also be noted here that the complexation properties of acridino-18-crown-6 ethers with metal ions have not yet been reported.

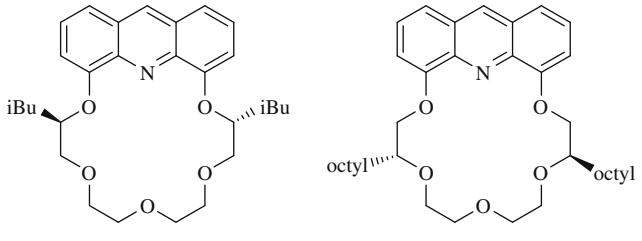
Herein, we report the synthesis of two new enantiopure acridino-18-crown-6 ethers (see Fig. 2): (*R,R*)-**3**, with isobutyl groups at the stereogenic centers exhibiting reasonable selectivity toward the enantiomers of protonated 1-phenylethylamine, and (*R,R*)-**4** containing octyl groups one carbon–carbon bond further away from the acridine unit showing selectivity for Ag^+ ions. It is remarkable to note that the latter ionophore exhibits high selectivity over Hg^{2+} ion (higher than Ag^+ ionophores offered commercially) while the selectivities over alkali, alkaline earth, and transition metal ions are also good.

The selectivity of the new crown ethers is assessed by potentiometry incorporating the ionophores into plasticized PVC membrane ion-selective electrodes (ISEs). This method is very attractive, because it is fast, requires simple instrumentation and very low amounts (typically 1 mg) of the substance.



1 (*R,R*)-**2**

Figure 1. Schematics of reported acridino-crown ethers.



(*R,R*)-**3** (*R,R*)-**4**

Figure 2. New enantiopure acridino-crown ethers.

2. Results and discussion

2.1. Synthesis

The synthesis of new enantiopure diisobutyl-substituted-acridino-18-crown-6 ligand (*R,R*)-**3** was carried out in two ways as outlined in Scheme 1. In the first case, acridinediol **5**[21] was reacted with enantiopure diisobutyl-substituted tetraethyleneglycol ditosylate (*S,S*)-**6**[26] in the presence of a weak base K_2CO_3 under similar conditions as described for the synthesis of macrocycle (*R,R*)-**2**.[21] Under these conditions, the reactions proceed by an S_N2 mechanism with total inversion of configuration in accordance with similar reactions.[21,22,26–28] In the second case the reported[27] acridono-crown ether (*R,R*)-**7** was reduced to acridino-crown ether (*R,R*)-**3** in a good yield using sodium metal in propyl alcohol by a modification of the method described[29] for the reduction of several acridones to acridines.

The new enantiopure dioctyl-substituted macrocycle (*R,R*)-**4** was prepared as shown in Scheme 2. The reported enantiopure tetraethylene glycol (*R,R*)-**8**[30] was treated with tosyl chloride in a dichloromethane–water mixture using a strong base KOH to obtain tetraethylene glycol ditosylate (*R,R*)-**9** in good yield. Dihydroxyacridone **10**[31] was then reacted with ditosylate (*R,R*)-**9** in the presence of a weak base K_2CO_3 according to the procedure described for the synthesis of the parent achiral acridono-crown ether[31] to render ligand (*R,R*)-**11** in a low yield. Acridono-crown ether (*R,R*)-**11** was then reduced with sodium metal in propyl alcohol to give acridino-crown ether (*R,R*)-**4** in an excellent yield.

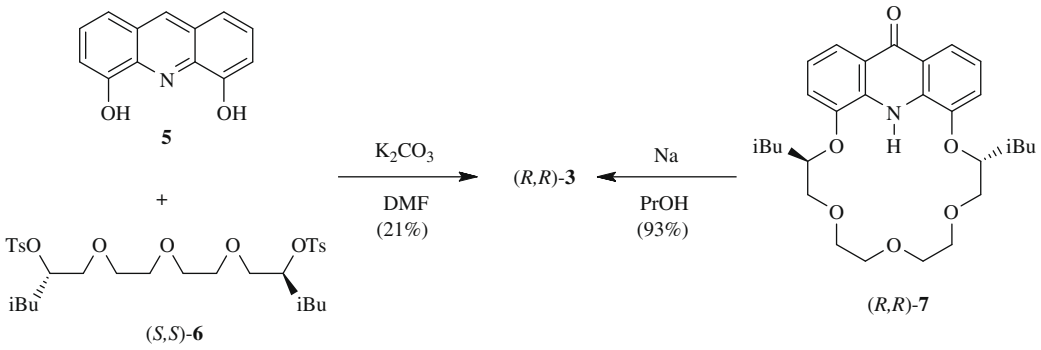
Improved procedures were used for the preparation of the reported acridine-4,5-diol **5**[21] and 4,5-dimethoxyacridine **14**[32] (Scheme 3). Reducing dihydroxyacridone **10** with sodium metal in propyl alcohol was a more efficient method than heating 4-amino-5-methoxyacridine in phosphoric acid at 180 °C as reported.[21] Strong electron-releasing groups (deprotonated phenolic hydroxyls in this case) greatly increase the tendency of acridanes to be oxidized to acridines;[33] accordingly acridane-4,5-diol could not be detected in the reaction mixture. Dimethoxyacridone **12** was reduced with sodium metal to give dimethoxyacridane **13** with a better yield than using amalgamated sodium as described in the literature.[32] Acridane **13** was then oxidized with molecular oxygen in acetic acid to give dimethoxyacridine **14** instead of using $NaNO_2$ in a mixture of concentrated sulfuric acid, acetic acid, and water as reported.[32] Dimethoxyacridine **14** was also prepared starting from dimethoxyacridone **12** without isolating the acridano-derivative **13**. Dimethoxyacridine **14** could also be converted to acridinediol **5** using 48% aqueous HBr, but only in low yield.

2.2. Potentiometric characterization of a PVC membrane containing ionophore (*R,R*)-3

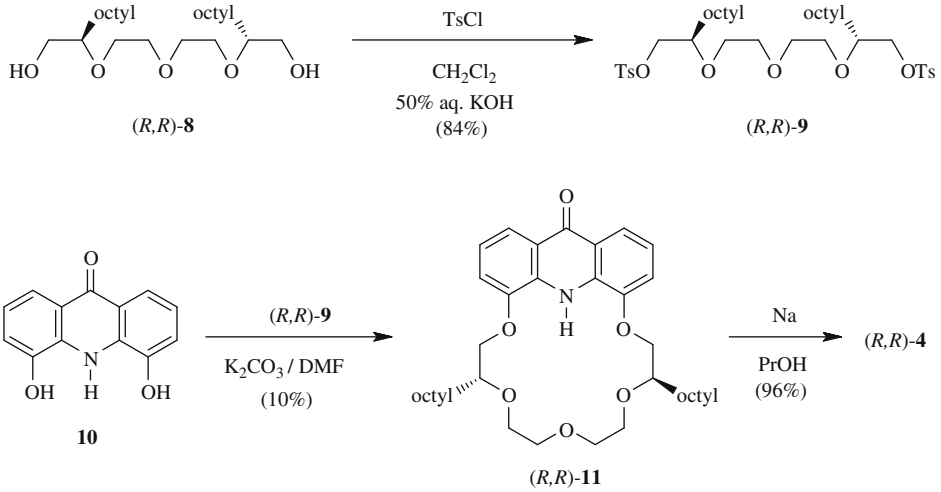
Ionophore (*R,R*)-**3** was incorporated into a plasticized PVC-based ion-selective membrane and calibrated in different concentrations of phenylethylammonium chloride ($PEAH^+Cl^-$). The calibration curve is shown in Figure 3.

The electrode, as expected, gives a near-Nernstian response to $PEAH^+$ ions with a slope of 52.9 mV/decade. The calibration curve is linear between 10^{-1} and 10^{-4} M concentrations, with a detection limit below 10^{-5} M.

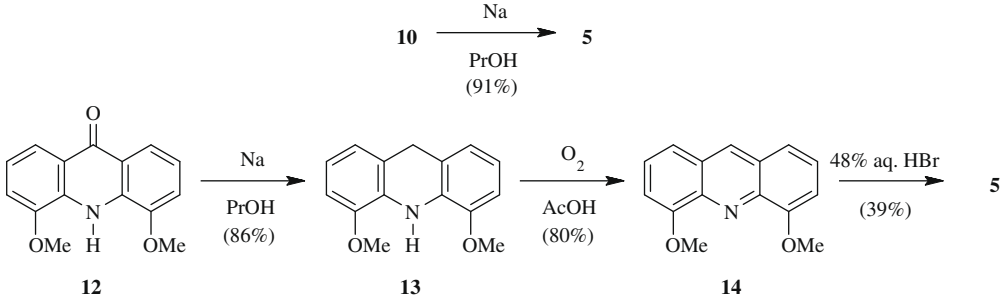
The enantioselectivity of ligand (*R,R*)-**3** for the enantiomers of $PEAH^+Cl^-$ was assessed with potentiometry, by alternatingly



Scheme 1. Synthesis of diisobutyl-substituted crown ether (*R*,*R*)-**3**.



Scheme 2. Synthesis of dioctyl-substituted crown ether (*R*,*R*)-**4**.



Scheme 3. Synthesis of acridine-4,5-diol **5** and 4,5-dimethoxyacridine **14**.

immersing the electrode into 0.1 M (*R*)- and (*S*)-phenylethylammonium chloride solutions, respectively, and recording the electromotive force (EMF) responses. The difference in the EMF values was used to calculate the potentiometric selectivity. The selectivity coefficient obtained in this way gives a good approximation of the ratio of the stability constants of the two diastereomeric complexes [(*R*,*R*)-**3**–(*S*)-$PEAH^+Cl^-$] and [(*R*,*R*)-**3**–(*R*)-$PEAH^+Cl^-$] in water[34]

That is,

$$K^{pot}_{S,R} \approx \frac{\beta^w_{RL}}{\beta^w_{SL}},$$

where

$K^{pot}_{S,R}$ is the potentiometric selectivity coefficient, β^w_{SL} is the stability constant of the complex formed by an enantiopure host molecule with a guest molecule of (*S*)-configuration in water and β^w_{SL} is the stability constant of the complex formed by an enantiopure host molecule with a guest molecule of (*R*)-configuration in water.

The results are shown in Table 1. The electrode containing (*R*,*R*)-**3** shows a marked and very reproducible difference in the potential response toward the two enantiomers. It favors the (*S*)-form of $PEAH^+Cl^-$ over the (*R*)-form by a factor of almost 2.

Potentiometric selectivity of ligand (*R*,*R*)-**3** toward other ions such as alkali and alkaline earth metal ions, transition metal ions, H^+, and ammonium ion was also determined. The selectivity coefficients are shown in Table 2.

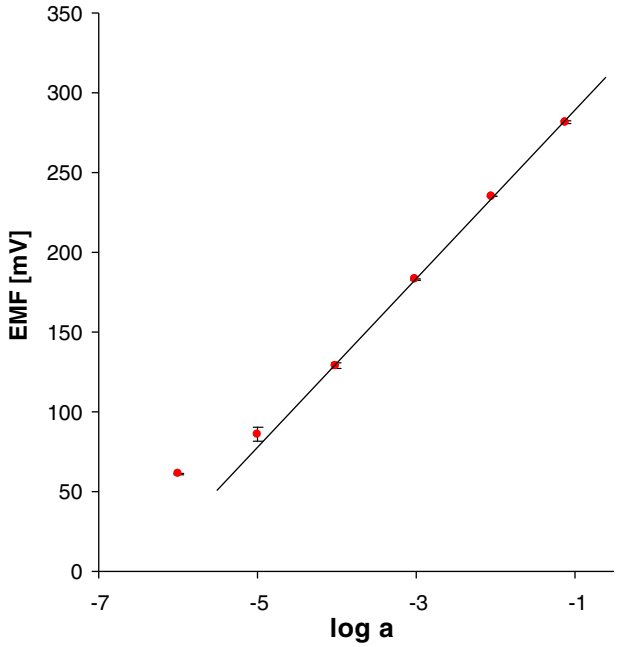


Figure 3. Calibration curve of the membrane electrode containing crown ether (*R*,*R*)-**3** as ionophore with racemic 1-phenylethylammonium ion.

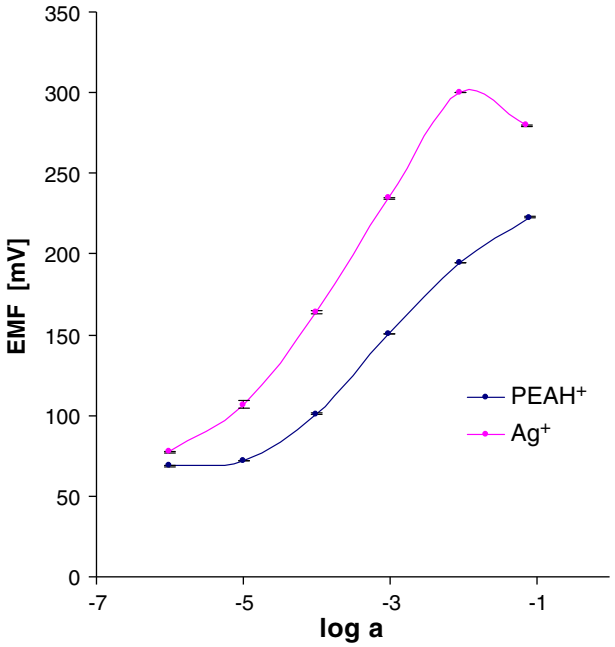


Figure 4. Calibration curve of the membrane electrode containing crown ether (*R*,*R*)-**4** as ionophore with silver ion and racemic 1-phenylethylammonium ion.

Table 1
Selectivity of ligand (*R*,*R*)-**3** for the enantiomers of $PEAH^+Cl^-$ expressed as the EMF difference in 0.1 M $PEAH^+Cl^-$ solutions and the corresponding potentiometric and enantioselectivity factors obtained by 11 measurements

$\Delta\Delta EMF = \Delta EMF_S - \Delta EMF_R$ (mV)	Potentiometric selectivity $K^{pot}_{S,R}$	Enantioselectivity $\frac{\beta^w_{SL}}{\beta^w_{RL}}$
13.40 ± 0.45	0.558 ± 0.011	1.79 ± 0.035

Table 2
Potentiometric selectivity of the PVC membrane electrode containing ligand (*R*,*R*)-**3** for different metal ions, NH_4^+ and H^+ in comparison to $PEAH^+$

M^{n+}	$\log K^{pot}_{PEAH^+,M^{n+}}$
Ag^+	−0.66
H^+	−0.82
K^+	−1.40
NH_4^+	−2.33
Na^+	−2.61
Fe^{2+}	−2.88
Fe^{3+}	−2.95
Cu^{2+}	−3.17
Li^+	−4.03
Cd^{2+}	−4.44
Ca^{2+}	−4.57
Mg^{2+}	−4.58
Zn^{2+}	−4.61

The electrode shows high selectivity toward $PEAH^+$ against almost all ions studied. The selectivity against Ag^+ ion and H^+ are not as good.

2.3. Potentiometric characterization of a PVC membrane containing ionophore (*R*,*R*)-4

Ligand (*R*,*R*)-**4** was also incorporated into a plasticized PVC membrane electrode and calibrated in the solutions of $AgNO_3$ and racemic $PEAH^+Cl^-$. Calibration curves are shown in Figure 4.

The plasticized PVC electrode containing ligand (*R*,*R*)-**4** exhibits a potentiometric response to both silver and phenylethylammonium ions, but has a preference for silver ions.

The slope of the calibration curve for Ag^+ is 69.7 mV/decade in the 10^{-2}–10^{-4} M concentration range, (somewhat higher than the theoretical Nernstian response) with a detection limit of $<10^{-5}$ M. At concentrations higher than 10^{-2} M, the calibration line has a negative slope, which is caused[35] by the co-extraction of the relatively lipophilic NO_3^- ion into the electrode membrane material.

The highest slope of the calibration curve in racemic $PEAH^+Cl^-$ is 49.7 mV/decade between 10^{-3} and 10^{-4} M. The detection limit is approximately 5×10^{-5} M. Above a 10^{-3} M concentration, we observed a decreased slope.

Potentiometric ion-selectivity values with respect to Ag^+ ion ($\log K^{pot}_{Ag,M}$) were determined by the separate solution method (Table 3). It can be seen that the electrode measures silver ions with a high selectivity over many alkali, alkaline earth, and transition

Table 3
Potentiometric selectivity of the PVC membrane electrode containing ligand (*R*,*R*)-**4** for different metal ions, H^+, and $PEAH^+$ in comparison to Ag^+ ion

M^{n+}	$\log K^{pot}_{Ag^+,M^{n+}}$
H^+	−1.19
$PEAH^+$	−1.79
K^+	−3.29
Fe^{3+}	−3.39
Na^+	−3.54
NH_4^+	−3.79
Cr^{3+}	−3.99
Fe^{2+}	−4.25
Cu^{2+}	−4.50
Hg^{2+}	−4.63
Li^+	−4.96
Cd^{2+}	−5.23
Zn^{2+}	−5.75
Co^{2+}	−5.93
Ca^{2+}	−5.95
Mg^{2+}	−6.02

Table 4
Selectivity of ligand (*R,R*)-**4** for the enantiomers of $PEAH^+Cl^-$ expressed as the EMF difference in 0.1 M $PEAH^+Cl^-$ solutions and the corresponding potentiometric selectivity and enantioselectivity coefficients obtained by 10 measurements

$\Delta\Delta EMF = \Delta EMF_S - \Delta EMF_R$ (mV)	Potentiometric selectivity $K_{S,R}^{pot}$	Enantioselectivity $\frac{\beta_{SL}^{w}}{\beta_{RL}^{w}}$
−1.95 ± 0.18	1.17 ± 0.017	0.853 ± 0.013

metal cations. Even mercury(II) which is always a problematic interfering ion for Ag^+ ionophores, shows surprisingly little interference. Some interference is observed in the presence of H^+. This is due to the basic character of the N atom in the acridino group which is easily protonated.

The enantioselectivity of ligand (*R,R*)-**4** for $PEAH^+Cl^-$ was also assessed with potentiometry in the same way, as described for ligand (*R,R*)-**3**.

The electrode showed very little, but reproducible EMF difference for the solutions of the two enantiomers of $PEAH^+Cl^-$ resulting in a low enantioselectivity (see Table 4). Unlike ligand (*R,R*)-**3**, the ionophore (*R,R*)-**4** has a preference for (*R*)-1-phenylethylammonium ion over the other enantiomer.

3. Conclusion

The synthesis of new chiral crown ethers (*R,R*)-**3** and (*R,R*)-**4** containing an acridine unit have been achieved. New efficient procedures were used for the preparation of acridine-4,5-diol **5** and dimethoxyacridine **14**.

We have demonstrated that diisobutyl-substituted ligand (*R,R*)-**3** and dioctyl-substituted ligand (*R,R*)-**4** could be used as sensor molecules built in potentiometric membrane electrodes. Ligand (*R,R*)-**3** showed high enantioselectivity toward 1-phenylethylammonium ion and most of the metal ions studied do not interfere. Ligand (*R,R*)-**4** exhibited poor enantioselectivity toward 1-phenylethylammonium ion, but it showed high selectivity toward silver ion even in the presence of Hg^{2+}. These results are in accordance with previous investigations on pyridine-crown ether analogs which showed the effect of the alkyl groups at the stereogenic centers on enantioselectivity.[36] Experiments are currently in progress to apply the electrode-containing enantiopure ligand (*R,R*)-**3** for the enantiomeric discrimination toward other protonated primary amines, amino acids and their derivatives.

4. Experimental

4.1. General

Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained on a Bruker Avance 300 spectrometer. Mass spectra were recorded on a Finningan-MAT 95 XP MS instrument (reference compound: heptacosafluorotributylamine) using EI (70 eV) method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus and were corrected. Starting materials were purchased from Sigma–Aldrich Corporation unless otherwise noted. Silica Gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminum oxide (neutral, activated, Brockman I) and Silica Gel 60 (70–230 mesh, Merck) 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[37] methods. Evaporations were carried out under reduced pressure unless otherwise stated.

4.2. Potentiometric measurements

To incorporate the ligands into the potentiometric sensor, the following membrane composition was prepared: 1 mg ionophore, 33 mg PVC powder, and 66 mg dioctyl sebacate (DOS) plasticizer were dissolved in 2 ml THF. The solution was cast into a 20 mm diameter teflon ring. After evaporation of the solvent a 7 mm disk cut from the membrane was incorporated into a Philips IS-561 (Glasblaserei Moller, Zurich, Switzerland) electrode body using 10^{-3} M racemic $PEAH^+Cl^-$ inner filling solution. The indicator electrode was used with an Ag/AgCl double-junction reference electrode (Metrohm, Herisau, Switzerland) in a Radelkis OP-208/1 precision pH-meter (Radelkis Ltd, Budapest, Hungary). Potentiometric selectivity coefficients were determined by the separate solution method from the EMF data measured in $PEAH^+Cl^-$, metal chloride or nitrate salts. Activity coefficients were calculated using the Debye–Hückel equation, EMF data were corrected for the diffusion potentials estimated with the Henderson equation.[38]

4.3. (7*R*,17*R*)-7,17-Bis(2-methylpropyl)-6,9,12,15,18-pentaoxa-25-azatetracyclo[21.3.1.$0^{5,26}$.$0^{19,24}$]heptacosa-1(26),2,4,19,21,23(27),24-heptaene (*R,R*)-3

4.3.1. Starting from acridine-4,5-diol 5

A mixture of acridine-4,5-diol **5** (698 mg, 3.31 mmol), diisobutyl-substituted tetraethylene glycol ditosylate (*S,S*)-**6** (2.24 g, 3.65 mmol), finely powdered anhydrous K_2CO_3 (4.58 g, 33.14 mmol), and dry DMF (56 mL) were stirred vigorously under Ar at rt for 10 min, then at 50 °C for 7 days.

The solvent was removed and the residue was taken up in a mixture of ice-water (75 mL) and EtOAc (150 mL). The phases were shaken well and separated. The aqueous phase was extracted with EtOAc (3 × 75 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified by chromatography on alumina using ethanol–toluene (1:200) mixture as an eluent to give (*R,R*)-**3** (577 mg, 36%) as a yellow solid. After recrystallization from hexane, 339 mg (21%) of pale yellow crystals were obtained.

Mp: 113–116 °C (hexane); R_f: 0.18 (alumina TLC, MeOH–CH_2Cl_2 1:60); $[\alpha]_D^{27} = -35.5$, $[\alpha]_{578}^{27} = -37.7$, $[\alpha]_{546}^{27} = -45.5$, $[\alpha]_{436}^{27} = -133$ (*c* 0.52, CH_2Cl_2); IR (KBr) ν_{max} 3056, 2951, 2894, 2863, 1622, 1557, 1454, 1359, 1250, 1116, 988, 941, 876, 757, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 6 Hz, 6H), 0.98 (d, J = 6 Hz, 6H), 1.59 (broad s, half mol of complexed H_2O, 1H), 1.67–1.75 (m, 2H), 1.82–1.94 (m, 4H), 3.69–3.79 (m, 6H), 3.85–4.00 (m, 4H), 4.28–4.35 (m, 2H), 5.26–5.34 (m, 2H), 7.15 (d, J = 7 Hz, 2H), 7.41 (t, J = 6.5 Hz, 2H), 7.57 (d, J = 6 Hz, 2H), 8.66 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.11, 23.32, 25.11, 39.97, 71.57, 71.79, 73.41, 78.11, 112.84, 120.62, 126.21, 128.31, 135.46, 142.19, 154.72; MS Calcd for $C_{29}H_{39}NO_5$: 481.2828, Found: 481.2823; Anal. Calcd for $C_{29}H_{39}NO_5 \cdot 0.5H_2O$: C, 70.99; H, 8.22; N, 2.85. Found: C, 70.83; H, 8.27; N, 2.57.

4.3.2. Starting from acridono-crown ether (*R,R*)-7

To a boiling solution of acridono-crown ether (*R,R*)-**7** (58 mg, 0.117 mmol) in propanol (6 mL) was added sodium (80.4 mg, 3.50 mmol) in 5 portions under Ar, and the mixture was refluxed for 1 h. Water (10 mL) was added to the cooled reaction mixture, and the pH was adjusted to 7 with 30% aqueous HCl solution.

The solvent was removed, and the residue was taken up in a mixture of water (50 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (4 × 20 mL) and the combined organic phase was shaken with saturated brine (2 × 50 mL), dried over $MgSO_4$, filtered, and the solvent was removed.

The crude product was purified by chromatography on alumina using ethanol–toluene (1:200) mixture as an eluent to give yellow crystals (52 mg, 93%).

Mp: 115–118 °C; $[\alpha]_D^{25} = -35.1$ (*c* 0.50, CH_2Cl_2). Compound (*R*,*R*)-**3** had the same IR and NMR spectra as the one prepared above from acridinediol **5** and ditosylate *(S,S)*-**6**.

4.4. (8*R*,16*R*)-8,16-Dioctyl-6,9,12,15,18-pentaoxa-25-azatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23(27),24-heptaene (*R*,*R*)-4

Macrocycle (*R*,*R*)-**4** was prepared as described above for (*R*,*R*)-**3** (see entry 4.3.2.) starting from acridono-crown ether (*R*,*R*)-**11** (58 mg, 0.0952 mmol), sodium (65.6 mg, 2.85 mmol), and propanol (6 mL). Chromatography on alumina using ethanol–toluene (1:250) mixture as an eluent gave a dark yellow oil (54 mg, 96%).R_f: 0.52 (alumina TLC, ethanol–toluene 1:15); $[\alpha]_D^{20} = +1.2$, $[\alpha]_{578}^{20} = +1.0$, $[\alpha]_{546}^{20} = +1.7$ (*c* 0.58, CH_2Cl_2); IR (neat) ν_{max} 2922, 2853, 1625, 1561, 1463, 1405, 1320, 1273, 1260, 1188, 1129, 1106, 802, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.90 (t, *J* = 7 Hz, 6H), 1.28–1.71 (m, 28H), 2.05 (broad s, half mol of complexed H_2O, 1H), 3.77–3.87 (m, 6H), 4.01–4.11 (m, 4H), 4.31–4.39 (m, 4H), 6.94 (d, *J* = 7.5 Hz, 2H); 7.44 (t, *J* = 8 Hz, 2H); 7.56 (d, *J* = 8.5 Hz, 2H) 8.68 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 14.32, 22.88, 25.87, 29.50, 29.78, 29.90, 29.94, 32.09, 70.72, 71.54, 73.19, 78.45, 107.16, 119.74, 126.23, 128.25, 135.37, 141.39, 154.86; MS Calcd for $C_{37}H_{55}NO_5$: 593.4080, Found: 593.4063; Anal. Calcd for $C_{37}H_{55}NO_5 \cdot 0.5H_2O$: C, 73.72; H, 9.36; N, 2.32. Found: C, 73.34; H, 9.21; N, 2.05.

4.5. Acridine-4,5-diol 5

4.5.1. Starting from 4,5-dihydroxyacridone 10

Acridinediol **5** was prepared as described above for (*R*,*R*)-**3** (see entry 4.3.2.) starting from dihydroxyacridone **10** (300 mg, 1.32 mmol), sodium (900 mg in 6 portions, 39.15 mmol), and propanol (12 mL). The work-up was modified as follows: 20 mL water was added to the cooled reaction mixture, and the pH was adjusted to 7 with 30% aqueous HCl solution. The volatile compounds were removed, and the residue was taken up in a mixture of water (50 mL) and dichloromethane (50 mL). The aqueous phase was extracted with dichloromethane (4 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed.

The crude product was recrystallized from aqueous ethanol to give acridinediol **5** as yellow crystals (255 mg, 91%). Acridinediol **5** had the same physical properties and spectroscopic data as reported.[21]

4.5.2. Starting from 4,5-dimethoxyacridine 14

A mixture of dimethoxyacridine **14** (184 mg, 0.769 mmol) and 48% aqueous HBr (4 mL) was stirred vigorously under Ar at reflux temperature for 2 days. The reaction mixture was filtered to give the hydrogen bromide salt of **14** as maroon crystals (129 mg, 57%). Mp: 253–254.5 °C; R_f: 0.35 (silica gel TLC, MeOH–CH_2Cl_2 1:20); IR (KBr) ν_{max} 3383, 3328, 2965, 1627, 1590, 1507, 1474, 1466, 1419, 1328, 1119, 800, 789, 743, 712, 576, 555, 530, 402 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.17 (broad s, 2OH, NH^+, absorbed H_2O), 7.15 (d, *J* = 7 Hz, 2H), 7.47 (t, *J* = 8 Hz, 2H), 7.59 (d, *J* = 9 Hz, 2H), 9.07 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 111.90, 119.18, 127.69, 128.34, 137.17, 139.45, 151.57.

The hydrogen bromide salt (129 mg, 0.441 mmol) was suspended in water (4 mL), the pH was adjusted to 8 with $NaHCO_3$, and the crystals were filtered and washed with water. The greenish yellow solid was recrystallized from aqueous ethanol to give acridinediol **5** (63 mg, 68%) which was identical in every respect to the reported one.[21]

4.6. (2*R*,2′*R*)-2,2′-Oxybis[(ethane-2,1-diyloxy)decane-2,1-diyl] bis(4-methylbenzenesulfonate) (*R*,*R*)-9

To a vigorously stirred solution of diol (*R*,*R*)-**8** (4.19 g, 10 mmol) in CH_2Cl_2 (80 mL) were added successively tosyl chloride (4.2 g, 22 mmol) and 50% (w/w) aqueous KOH (12 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 5 min then at rt for 4 h. After 4 h tosyl chloride (3.0 g, 16 mmol) and 50% (w/w) aqueous KOH (8 mL) were added to the reaction mixture and stirring was continued for 24 h. After that time, TLC analysis showed the total consumption of diol (*R*,*R*)-**8** and tosyl chloride and also the formation of a new compound (*R*,*R*)-**9**. Water (80 mL) and CH_2Cl_2 (50 mL) were added to the mixture and the phases were shaken thoroughly. The phases were separated, and the organic phase was shaken with water (2 × 30 mL), dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified by chromatography on silica gel using toluene then toluene–EtOAc mixture (20:1) as eluents to give ditosylate (*R*,*R*)-**9** (6.1 g, 84%) as a pale yellow oil. R_f: 0.75 (silica gel TLC, toluene–EtOAc = 9:2); $[\alpha]_{365}^{18} = +15.7$ (*c* 1.12, $CHCl_3$); IR (neat) ν_{max} 2928, 2856, 1600, 1450, 1354, 1192, 1184, 1176, 1096, 976, 816, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 6H), 1.20–1.50 (m, 28H), 2.44 (s, 6H), 3.46–3.65 (m, 10H), 3.94–4.04 (m, 4H), 7.34 (d, *J* = 8 Hz, 4H), 7.79 (d, *J* = 8 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.06, 21.59, 22.62, 25.06, 29.21, 29.44, 29.54, 31.39, 31.83, 69.71, 70.71, 71.57, 77.73, 127.93, 129.82, 133.07, 144.75; Anal. Calcd for $C_{38}H_{62}O_9S_2$: C, 62.78; H, 8.60; S, 8.82. Found: C, 62.64; H, 8.71; S, 8.77.

4.7. (8*R*,16*R*)-8,16-Dioctyl-6,9,12,15,18-pentaoxa-25-azatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23-hexaene-27-one (*R*,*R*)-11

A mixture of acridonediol monohydrate **10** (490 mg, 2 mmol), ditosylate (*R*,*R*)-**9** (1.6 g, 2.2 mmol), finely powdered anhydrous K_2CO_3 (2.76 g, 20 mmol) was stirred in dry and pure DMF (45 mL) vigorously under Ar at rt for 10 min then at 50 °C for 6 days. The solvent was removed and the residue was taken up in a mixture of water (150 mL) and EtOAc (150 mL). The phases were shaken well and separated. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was shaken with water (2 × 50 mL), dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified by chromatography on silica gel using CH_2Cl_2–EtOAc mixture (20:1) as an eluent to give macrocycle (*R*,*R*)-**11** (130 mg, 10 %) as a semihydrate. Mp: 72–73 °C; R_f: 0.36 (silica gel TLC, toluene–*i*PrOH 10:1); $[\alpha]_D^{23} = -28.9$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3424, 2928, 2856, 1624, 1600, 1560, 1532, 1454, 1272, 1224, 1136, 1128, 1112, 1104, 1084, 746, 592 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 6H), 1.24–1.53 (m, 24 H), 1.59–1.66 (m, 2H), 1.69–1.75 (m, 2H), 2.03 (broad s, half mol of complexed water, 1H), 3.70–3.84 (m, 8H), 3.87–3.90 (m, 2H), 4.19–4.28 (m, 4H), 7.05 (d, *J* = 8 Hz, 2H), 7.16 (t, *J* = 8 Hz, 2H), 8.05 (d, *J* = 8 Hz, 2H), 9.29 (broad s , NH, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.24, 22.78, 25.67, 29.33, 29.65, 29.89, 31.61, 31.97, 70.18, 71.00, 71.93, 77.81, 111.84, 118.28, 120.50, 121.93, 131.17, 146.35, 177.60; MS Calcd for $C_{37}H_{55}NO_6$: 609.4024. Found: 609.4012; Anal. Calcd for $C_{37}H_{55}NO_6 \cdot 0.5H_2O$: C, 71.81; H, 8.96; N, 2.26. Found: C, 71.70; H, 9.18; N, 2.06.

4.8. 4,5-Dimethoxy-9,10-dihydroacridine 13

Compound **13** was prepared as described above for (*R,R*)-**3** (see entry 4.3.2.) starting from dimethoxyacridone **12** (0.5 g, 1.96 mmol), sodium (1.5 g in 6 portions, 65.2 mmol), and propanol (20 mL). The work-up was modified as follows: 30 mL water was added to the cooled reaction mixture, and the pH was adjusted to 7 with acetic acid. The volatile compounds were removed and the crude product was filtered and dried over KOH in a desiccator under reduced pressure to give **13** as yellow crystals (0.407 g, 86%). We should note here that every step of the preparation was carried out under an inert atmosphere. The crude product was used without further purification. A small amount of crude product was recrystallized from ethanol to give an analytical sample as pale yellow crystals.

Mp: 80–80.5 °C (ethanol) (lit.[32] mp: 91–92.5 °C (ethanol)); R_f: 0.88 (silica gel TLC, MeOH–CH_2Cl_2 1:60); IR (KBr) ν_{max} 3424, 3055, 3001, 2958, 2933, 2852, 2833, 1613, 1576, 1510, 1492, 1478, 1449, 1408, 1335, 1268, 1253, 1105, 1074, 925, 759, 727, 697, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.93 (s, 6H), 4.13 (s, 2H), 6.73 (d, J = 8 Hz, 2H); 6.76 (d, J = 8 Hz, 2H); 6.82 (t, J = 8 Hz, 2H) 6.97 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 31.06, 55.58, 107.98, 119.59, 119.80, 120.60, 129.75, 145.98.

4.9. 4,5-Dimethoxyacridine 14

Dimethoxyacridane **13** (0.448 g, 1.86 mmol) in acetic acid (20 mL) was stirred under oxygen atmosphere at reflux temperature for 5 h. The solvent was removed and the brown solid was triturated with water, filtered, and washed with water. The pH of the aqueous phase was adjusted to 9 with 25% aqueous Me_3N solution and shaken with dichloromethane (4×10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed.

The combined crude product (the filtered solid and the crystals obtained from the organic phase) was recrystallized from methanol to give **14** (0.357 g, 80%) as yellow crystals.

Dimethoxyacridine **14** had the same physical properties and spectral data as reported.[31]

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