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Synthesis and metal ion complexation of spin labeled 18-crown-6 ethers containing an acridone or an acridine fluorophore unit

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ABSTRACT

Double (spin and fluorescence) labeled pyrroline derivatives of crown ethers containing an acridone or an acridine fluorophore unit (**1** and **2**) and their diamagnetic analogues (**3** and **4**) were synthesized. Their fluorescent behavior as well as their complexation properties toward selected metal ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}) were examined.

1. Introduction

Nitroxide free radicals are efficient quenchers of the fluorescence of organic fluorophores, and they are often referred as bifunctional fluorogenic spin probes or double sensors. The fluorescence of these spin labeled fluorophores can be switched on when the paramagnetic nitroxide is converted to a diamagnetic species such as hydroxylamine or *O*-alkyl hydroxylamine, which also causes decay of the EPR signal.[1] These nitroxide–fluorophore compounds have been utilized as sensors of metal ions,[2] nitric oxide,[3–5] singlet oxygen in plants,[6] antioxidants[7,8] as well as thiyl,[9] superoxide,[10,11] and hydroxyl radicals.[12] The fluorophore–nitroxide probes also open unique opportunities to study molecular dynamics and micropolarity of the medium, which affects intramolecular fluorescence quenching, e.g., electron transfer, photoreduction, and light energy conversion.[13,14]

In the last decade a series of new donor–acceptor probes were synthesized varying both the radical moiety (nitronyl-nitroxide,[15] pyrrolidine-,[12] piperidine-nitroxide,[14] perchlorotrityl radical[11]) and the fluorophore (acridine,[16] naphthyl,[17] polyaromatics,[18] dansyl,[13] fluorescamine,[12] nile red,[8] BODIPY,[8] and CdSe quantum dots[19]). Although many spin labeled double sensors,[1–19] fluoroionophores,[20–22] and some spin labeled crown ethers[23–26] have been reported, as far as we know double sensors containing a crown ether based ionophore function have not been reported yet.

In this paper we report the synthesis of such fluorophore–ionophore–nitroxide scaffolds by modifying the recently developed acridono- and acridino-18-crown-6 ionophores[27] with a pyrroline nitroxide and also the preparation of their diamagnetic derivatives by reducing the nitroxide moiety to an amino group (Fig. 1). The fluorescent behavior and the metal ion complexing ability of these fluoroionophores were examined. The challenge of this research is to develop such multiple sensor molecules, which transduce chemical events (oxidation, reduction, pH change or metal ion binding) to fluorescence[28,29] and/or EPR signal change.

2. Results and discussion

2.1. Synthesis

Spin labeled acridono-crown ether **1**, acridino-crown ether **2** and their diamagnetic derivatives, pyrroline-substituted acridono-crown ether **3** and pyrroline-substituted acridino-crown ether **4** were synthesized as shown in Scheme 1.

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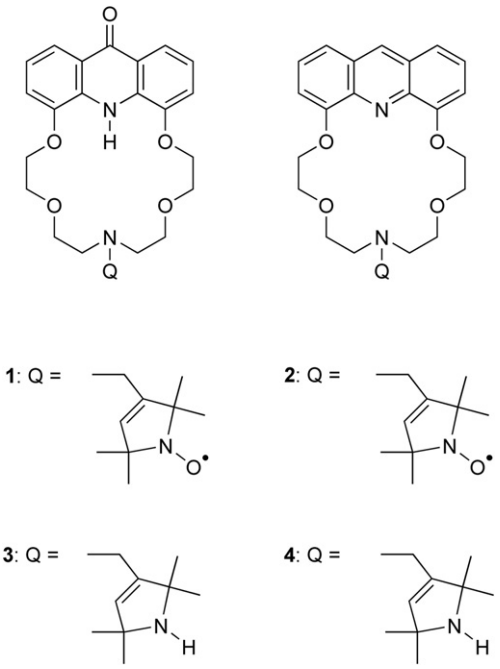
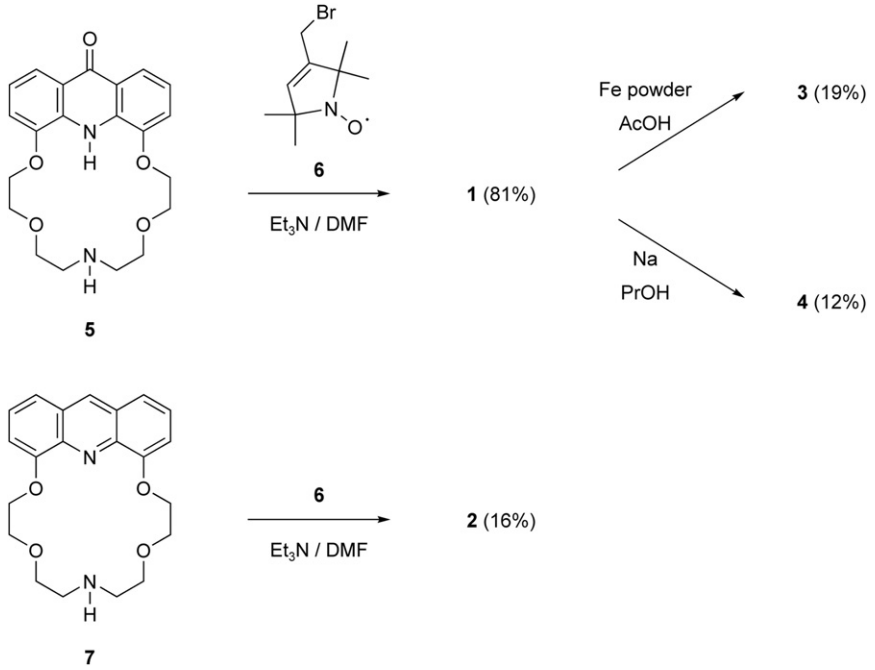


Fig. 1. Schematics of spin labeled acridono- and acridino-crown ethers **1** and **2**, and their reduced derivatives **3** and **4**.

Paramagnetic nitroxide-substituted acridono-crown ether **1** was reduced using iron powder in acetic acid to give pyrroline-substituted acridono-crown ether **3** as described in the literature[31] for the selective reduction of nitroxides to secondary amines. Pyrroline-substituted acridino-crown ether **4** was prepared also from paramagnetic nitroxide-substituted acridono-crown ether **1**, using sodium metal as a reducing agent and propanol as a solvent in this case.[32]

2.2. Fluorescent behavior

The fluorescence quantum yield and lifetime of acridono-crown ether **3** (Table 1) were similar to those of acridone, which were measured as reference values (Φ_f=0.41, τ_f=6.1 ns). However, the fluorescence data of acridino-crown ether **4** were much higher than those of acridine (Φ_f=3.5×10^{-4}, τ_f=61 ps).[33] This fluorescence enhancement could be explained by the conjugative effect induced by the oxygen atoms at positions 4 and 5 of the acridine unit.[34] The lower fluorescence quantum yields and shorter fluorescence lifetimes of the spin labeled crown ethers (**1** and **2**) compared to their reduced forms (**3** and **4**) are indicative of fast intramolecular quenching. The quenching effect of spin labeling was stronger in the case of acridono-crown ethers (**1** and **3**) than in the case of acridino-crown ethers (**2** and **4**) because of longer fluorescence lifetime and higher quantum efficiency of ligand **3** containing an acridone unit with respect to crown ether **4** having an acridine fluorophore.



Scheme 1. Preparation of the new spin labeled crown ethers and their reduced analogues containing a fluorophore unit.

Acridono-crown ether **5**[27] containing a secondary amino group in the macroring was selectively alkylated by paramagnetic bromomethyl-substituted pyrroline nitroxide **6**[30] in DMF in the presence of triethylamine to obtain spin labeled acridono-crown ether **1**.

Acridino-crown ether **7**[27] was alkylated following the procedure mentioned above for the synthesis of acridono-macrocycle **1** to give spin labeled acridino-crown ether **2**.

Table 1
Fluorescence data of **1**–**4** in MeCN

	λ_{ex} (nm)	Φ_f	τ_f (ns)
1	408, 428	0.055	1.2
2	440	0.044	1.4
3	408, 429	0.52	7.8
4	442	0.069	2.1

2.3. Complexation studies

The complexation ability of spin labeled and reduced acridono- and acridino-crown ethers **1**–**4** (Fig. 1) was studied by fluorescence spectroscopy in acetonitrile toward some biologically important metal ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}). The absorbances of ligands **1**–**4** at the excitation wavelength (390 or 265 nm) were essentially unchanged upon complexation. The absorption spectra of the ligands are represented in Fig. 2.

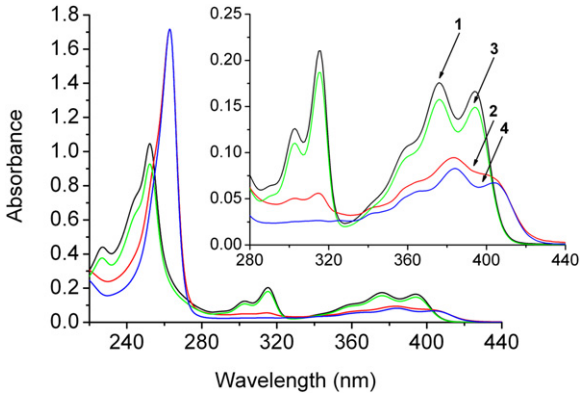


Fig. 2. Absorption spectra of **1**–**4** (20 μM) in MeCN (**1**: black, **2**: red, **3**: green, **4**: blue).

In the case of acridono-crown ethers **1** and **3**, among the studied metal ions only Ca^{2+} caused significant spectral changes, namely a bathochromic shift of the emission spectra (Figs. 3 and 4). Acridino-crown ethers **2** and **4** showed complexation ability toward Ca^{2+} and Mg^{2+}, which induced large fluorescence enhancement with a slight spectral shift (Figs. 3 and 5), and toward Zn^{2+}, which caused an appreciable bathochromic shift (50 nm) without or with a large emission increase, respectively (Fig. 3).

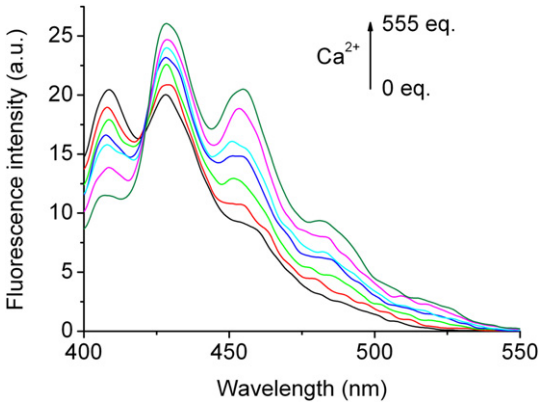


Fig. 4. Fluorescence emission series of spectra of **1** (10 μM) on increasing addition of Ca^{2+} (0, 22, 56, 111, 167, 278, 555 equiv) in MeCN, λ_{ex}=390 nm.

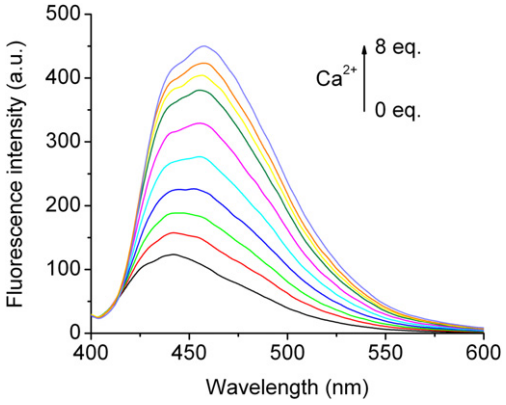


Fig. 5. Fluorescence emission series of spectra of **4** (1 μM) on increasing addition of Ca^{2+} (0.00, 0.16, 0.32, 0.48, 0.64, 0.80, 0.96, 1.12, 1.60, 8.00 equiv) in MeCN, λ_{ex}=390 nm.

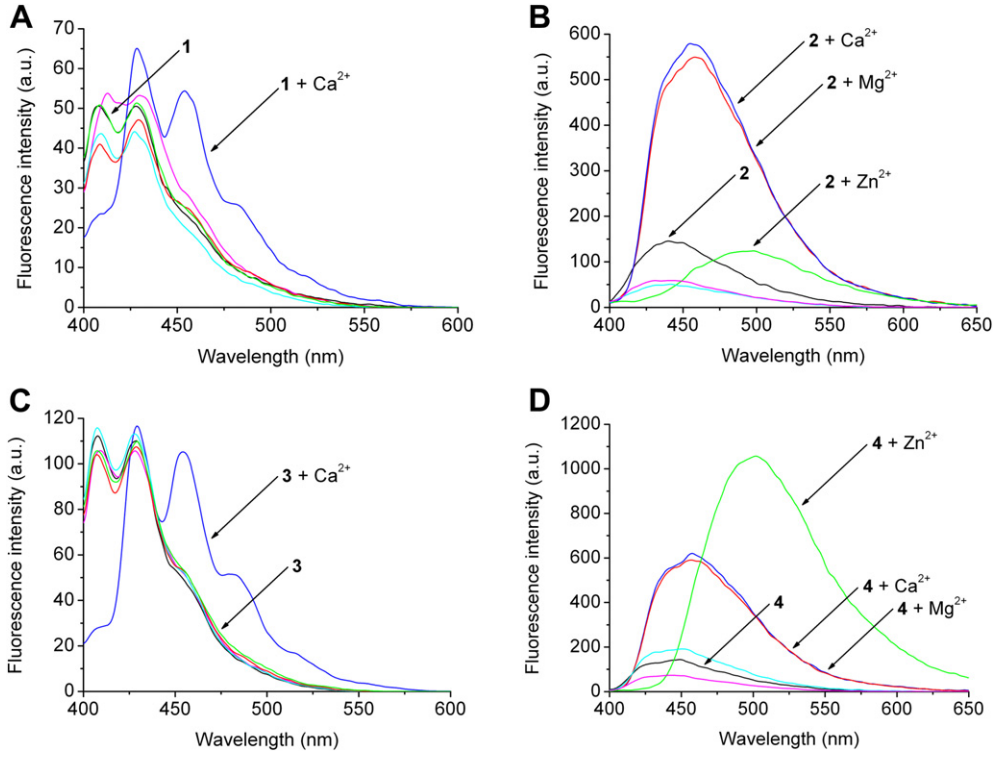


Fig. 3. Fluorescence emission spectral changes of **1**–**4** (A: **1**, B: **2**, C: **3**, D: **4**; 10 μM, black) upon addition of metal ions (1000 equiv; Na^+: cyan, K^+: magenta, Mg^{2+}: red, Ca^{2+}: blue, Zn^{2+}: green) in MeCN, λ_{ex}=390 nm (A, C) or 265 nm (B, D).

Ca^{2+} formed much more stable complexes with the ligands containing an acridine unit (**2** and **4**) than with the ones having an acridone moiety (**1** and **3**) as seen in Table 2. The complex formation of the spin labeled (**1** and **2**) and reduced forms (**3** and **4**) with Ca^{2+} essentially did not show differences. Mg^{2+} and Zn^{2+} caused changes only in the emission spectra of the ligands containing an acridine unit (**2** and **4**) (Fig. 3). However, in the case of Mg^{2+} and Zn^{2+} there was a difference between the complexation of the spin labeled (**2**) and reduced (**4**) forms, since ligand **4** formed a more stable complex with Mg^{2+} (Table 2), and showed much more significant spectral changes upon addition of Zn^{2+} (Fig. 3).

Table 2
Stability constants for 1:1 stoichiometric complexes of **1**–**4** with Mg^{2+}, Ca^{2+}, and Zn^{2+} in MeCN

	log K		
	Mg^{2+}	Ca^{2+}	Zn^{2+}
1	—	2.74	—
2	1.67	6.73	6.92
3	—	2.88	—
4	3.84	6.80	6.32

Acridino-crown ethers **2** and **4** formed the most stable complexes with Ca^{2+} and Zn^{2+} (Table 2), but in the case of spin labeled acridino-crown ether **2** there was a more significant difference between the spectral changes caused by the two latter ions, namely Ca^{2+} induced large fluorescence enhancement, while Zn^{2+} caused a significant bathochromic shift without intensity increase (Fig. 3).

The complexation properties of spin labeled acridono- and acridino-crown ethers **1** and **2** were also examined by EPR spectroscopy in methanol. However, the EPR spectra of the ligands (100 μM) were unchanged after addition of the metal ions (100 equiv).

3. Conclusion

The synthesis of new spin labeled macrocycles (acridono- and acridino-crown ether pyrroline nitroxides **1** and **2**) and also their diamagnetic derivatives (**3** and **4**) has been achieved.

Fluorescence spectroscopic study of ligands **1**–**4** showed that in the case of paramagnetic derivatives (**1** and **2**) fluorescence quenching occurred. The complexation properties of fluoroionophores **1**–**4** were examined toward selected metal ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}) by fluorescence spectroscopy. Spin labeled acridino-crown ether **2** formed the most stable complexes with Ca^{2+} and Zn^{2+}, and complexation with Ca^{2+} caused large fluorescence enhancement. However, there was no change in the EPR spectra on binding.

4. Experimental

4.1. General

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. Silica gel 60 (70–230 mesh, Merck) and aluminum 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.[35] Evaporations were carried out under reduced pressure unless otherwise stated.

Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. ^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 300 Avance spectrometer. Mass spectra were recorded on an Automass Multi instrument in EI mode (70 eV, direct inlet) or on a BioTOF II instrument (Bruker Daltonics, Billerica, MA) in ESI mode, and it is indicated in each individual case. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. EPR spectra were obtained from 100 μM solutions in MeOH using a Miniscope MS200 (Magnettech GmBH) type spectrometer.

UV–vis spectra were taken on an HP 8452A diode array spectrophotometer. Fluorescence spectra were recorded on a Perkin Elmer LS 50B luminescence spectrometer. Both the emission and excitation spectra 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).[36] Fluorescence decay curves were measured on an Edinburgh Instruments FLS920 fluorescence lifetime spectrometer using an EPL-375 diode laser for excitation (378 nm, pulse duration: 100 ps at FWHM) and a Hamamatsu R3809U-50 microchannel plate photomultiplier for detection. Data were analyzed by a nonlinear least-squares deconvolution method using Edinburgh F900 software. The samples were deoxygenated by bubbling with high-purity (99.996%) nitrogen. Acridone was purchased from Sigma–Aldrich Corporation for the determination of its fluorescence quantum yield and lifetime. Analytical grade metal perchlorate salts were used. The stability constants of complexes were determined by global nonlinear regression analysis using SPECFIT/32™ program.

4.2. {2,2,5,5-Tetramethyl-3-[(27-oxo-6,9,15,18-tetraoxa-12,25-diazatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23-hexaene-12-yl)methyl]-2,5-dihydropyrrol-1-yl}oxidanyl (1)

A mixture of acridono-crown ether **5**[27] (138 mg, 0.359 mmol), paramagnetic bromomethyl-substituted pyrroline nitroxide **6**[30] (209 mg, 0.898 mmol), triethylamine (273 mg, 2.643 mmol), and dry DMF (50 mL) was stirred vigorously under Ar at rt for 3 h. The solvent was removed at 30 °C (bath temperature), and the crude product was purified by triturating with boiling acetone to give spin labeled acridono-crown ether **1** (157 mg, 81%) as pale yellow crystals.

Mp: 208–209 °C; R_f: 0.86 (alumina TLC, EtOH–toluene 1:2); IR (KBr) ν_{max} 3480, 3440, 3424, 2976, 2960, 2936, 2744, 2680, 2488, 1720, 1628, 1592, 1536, 1472, 1432, 1400, 1272, 1224, 1168, 1132, 1084, 1036, 804, 744, 592 cm^{-1}; MS calcd for $C_{30}H_{38}N_3O_6$: 536.3. Found (ESI) $(M+1)^+$: 537.3. Anal. Calcd for $C_{30}H_{38}N_3O_6 \cdot H_2O$: C, 64.96; H, 7.27; N, 7.58. Found: C, 64.70; H, 6.98; N, 7.36. EPR: triplet, a_N=15.1 G.

4.3. {2,2,5,5-Tetramethyl-3-[(6,9,15,18-tetraoxa-12,25-diazatetracyclo[21.3.1.0^{5,26}.0^{19,24}]heptacosa-1(26),2,4,19,21,23(27),24-heptaene-12-yl)methyl]-2,5-dihydropyrrol-1-yl}oxidanyl (2)

A mixture of acridino-crown ether **7**[27] (80 mg, 0.216 mmol), paramagnetic bromomethyl-substituted pyrroline nitroxide **6**[30] (126 mg, 0.54 mmol), triethylamine (219 mg, 2.16 mmol), and dry DMF (16 mL) was stirred vigorously under Ar at rt for 4 h. The solvent was removed at 30 °C (bath temperature), and the crude product was recrystallized from EtOH to give spin labeled acridino-crown ether **2** (18 mg, 16%) as pale yellow crystals.

Mp: 157–158 °C (EtOH); R_f: 0.76 (alumina TLC, EtOH–toluene 1:2); IR (KBr) ν_{max} 3080, 2968, 2952, 2928, 2896, 2872, 1624, 1592,

1564, 1520, 1452, 1424, 1408, 1360, 1320, 1280, 1240, 1128, 1056, 1024, 936, 904, 744, 728 cm^{-1}; MS calcd for $C_{30}H_{38}N_3O_5$: 520.3. Found (ESI) $(M+1)^+$: 521.4. Anal. Calcd for $C_{30}H_{38}N_3O_5 \cdot H_2O$: C, 66.89; H, 7.48; N, 7.80. Found: C, 66.63; H, 7.26; N, 7.52. EPR: triplet, a_N=15.1 G.

4.4. 12-[(2,2,5,5-Tetramethyl-2,5-dihydropyrrol-3-yl)methyl]-6,9,15,18-tetraoxa-12,25-diazatetracyclo[21.3.1.0^{5,26}.0^{19,24}] heptacosa-1(26),2,4,19,21,23-hexaene-27-one (3)

A mixture of paramagnetic nitroxide-substituted acridono-crown ether **1** (110 mg, 0.205 mmol), iron powder (110 mg, 1.97 mmol), and glacial acetic acid (8 mL) was stirred under Ar at 50 °C for 15 h. After the reaction was completed the solvent was removed, water (10 mL) was added and the pH was adjusted to 7 with tetramethylammonium hydroxide. The mixture was extracted with EtOAc (4×10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent removed. The crude product was purified by preparative thin layer chromatography on alumina using EtOH–toluene mixture (1:7) as an eluent. The resulting solid (46 mg, 43%) was recrystallized from EtOH to give pyrroline-substituted acridono-crown ether **3** (21 mg, 19%) as off-white crystals.

Mp: 181–182 °C (EtOH); R_f: 0.32 (alumina TLC, EtOH–toluene 1:7); IR (KBr) ν_{max} 3414, 3326, 2960, 2926, 2880, 1819, 1624, 1609, 1597, 1532, 1489, 1449, 1358, 1276, 1224, 1134, 1079, 915, 750, 612 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 6H), 1.22 (s, 6H), 1.98 (br s, NH+H_2O, 3H), 2.85 (t, J=5 Hz, 4H), 3.14 (s, 2H), 3.78 (t, J=5 Hz, 4H), 3.98 (t, J=5 Hz, 4H), 4.34 (t, J=5 Hz, 4H), 5.48 (s, 1H), 7.08 (d, J=8 Hz, 2H), 7.17 (t, J=8 Hz, 2H), 8.06 (d, J=8 Hz, 2H), 9.26 (s, NH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.92, 31.00, 54.19, 54.93, 63.36, 66.60, 69.45, 69.64, 71.93, 112.39, 118.84, 120.92, 122.28, 131.52, 133.76, 144.60, 146.89, 179.23. MS calcd for $C_{30}H_{39}N_3O_5$: 521. Found (EI) $(M)^+$: 521. Anal. Calcd for $C_{30}H_{39}N_3O_5 \cdot H_2O$: C, 66.77; H, 7.66; N, 7.79. Found: C, 66.56; H, 7.42; N, 7.59.

4.5. 12-[(2,2,5,5-Tetramethyl-2,5-dihydropyrrol-3-yl)methyl]-6,9,15,18-tetraoxa-12,25-diazatetracyclo[21.3.1.0^{5,26}.0^{19,24}] heptacosa-1(26),2,4,19,21,23(27),24-heptaene (4)

To a boiling solution of paramagnetic nitroxide-substituted acridono-crown ether **1** (180 mg, 0.335 mmol) in propanol (9 mL) was added sodium (430 mg, 18.7 mmol) in six 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 7.5 with 10% aqueous HCl solution. The solvent was removed, and the residue was taken up in a mixture of water (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (4×20 mL) and 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 EtOH–MeCN–toluene (1:2:5) mixture as an eluent. The resulting dark yellow oil (98 mg, 58%) was triturated with hexane, the product was filtered and then recrystallized from EtOH to give pyrroline-substituted acridino-crown ether **4** (20 mg, 12%) as dark yellow crystals.

Mp: 175–178 °C (EtOH); R_f: 0.28 (alumina TLC, EtOH–MeCN–toluene 1:2:5); IR (KBr) ν_{max} 3423, 3056, 2961, 2922, 2863, 2805, 1625, 1565, 1476, 1468, 1452, 1424, 1409, 1359, 1323, 1281, 1237, 1193, 1141, 1120, 1085, 938, 906, 850, 748, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 6H), 1.40 (s, 6H), 2.09 (br s, NH+H_2O, 3H), 2.89 (s, 4H), 3.34 (s, 2H), 3.97 (t, J=5 Hz, 4H), 4.15 (s, 4H), 4.38 (t, J=5 Hz, 4H), 5.47 (s, 1H), 6.98 (d, J=8 Hz, 2H), 7.45 (t, J=8 Hz, 2H), 7.56 (d, J=8 Hz, 2H), 8.68 (s, NH, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.92, 31.00, 54.19, 54.93, 63.36, 66.60, 69.45, 69.64, 71.93, 112.39, 118.84, 120.92, 122.28, 131.52, 133.76, 144.60, 146.89, 179.23. MS calcd for $C_{30}H_{39}N_3O_4$: 505. Found (EI) $(M)^+$: 505. Anal. Calcd for $C_{30}H_{39}N_3O_4 \cdot H_2O$: C, 68.81; H, 7.89; N, 8.02. Found: C, 68.79; H, 7.81; N, 7.88.

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