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Synthesis of silica gel-bound acridino-18-crown-6 ether and preliminary studies on its metal ion selectivity

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ABSTRACT

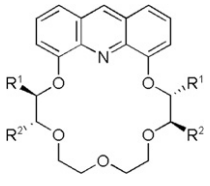
Starting from commercially available and relatively cheap chemicals a novel silica gel-bound acridino-18-crown-6 ether was prepared. Selectivity of the latter stationary phase toward different metal ions was studied. The stationary phase showed appreciable selectivity for Ag^{+}, Cu^{2+}, and Hg^{2+} ions.

1. Introduction

Selective separation and concentration of chemical species, for example, metal ions, is of great importance for many biological and industrial applications. Extraction methods using synthetic macrocycles can be applied for the selective separation of metal ions from aqueous solutions.[1–4] Commercially available macrocyclic ligands are expensive and synthesis of new derivatives is difficult, so even a small loss of them from the organic phase of the solvent extraction system must be avoided. The latter problem can be solved by using macrocycles immobilized to a solid support, such as silica gel. There are several silica gel based stationary phases containing macrocyclic ionophores for the complexation studies of metal ions reported in the literature, for example, crown ethers,[5–13] calixarenes, and calix-crown ethers,[14–16] tetrapyrazolic macrocycles,[17] Schiff base type macrocycles[18] attached covalently to silica gel and also crown ethers,[19,20] calixarenes, and calix-crown ethers[21–23] or cryptands[24] dynamically coated to silica gel.

Earlier studies on the complexation properties of crown ethers containing a pyridine subcyclic unit showed that they can selectively form complexes with heavy metal ions because of the soft nitrogen atom.[25,26] Selectivity can be improved by making the structure of the macrocycle more rigid by incorporating heterocyclic units containing a more extended aromatic system into the macroring, for example, a phenanthroline,[27] a phenazine[28] or an acridine[28,29] unit.

Up to now only a few acridino-18-crown-6 ligands have been synthetized, the achiral macrocycle **1**,[28] the enantiomerically pure ligands (*R*,*R*)-**2**,[28] (*R*,*R*)-**3**,[29] and (*R*,*R*)-**4**[29] (Fig. 1), and some 9-substituted derivatives[30] of **1** and (*R*,*R*)-**2**. It should also be noted here that the complexation properties of acridino-18-crown-6 ethers with metal ions has been reported only in one earlier paper, in which diisobutyl-substituted crown ether (*R*,*R*)-**3** and dioctyl-substituted macrocycle (*R*,*R*)-**4** were incorporated into plasticized PVC membranes and their selectivity toward metal ions was studied using a potentiometric method.[29]



1: $R^1 = R^2 = H$
(*R*,*R*)-**2**: R^1 = Me, $R^2 = H$
(*R*,*R*)-**3**: R^1 = iBu, $R^2 = H$
(*R*,*R*)-**4**: $R^1 = H$, R^2 = octyl

Fig. 1. Schematics of reported acridino-crown ethers.

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In this paper we report the synthesis of a new stationary phase containing an acridino-18-crown-6 ether covalently attached to silica gel (**SP-5**, see Fig. 2) and studies on its complexation with different metal ions.

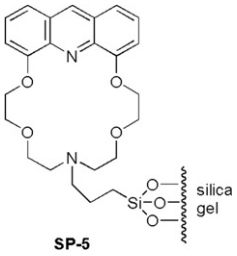


Fig. 2. New silica gel-bound acridino-18-crown-6 ether **SP-5**.

2. Results and discussion

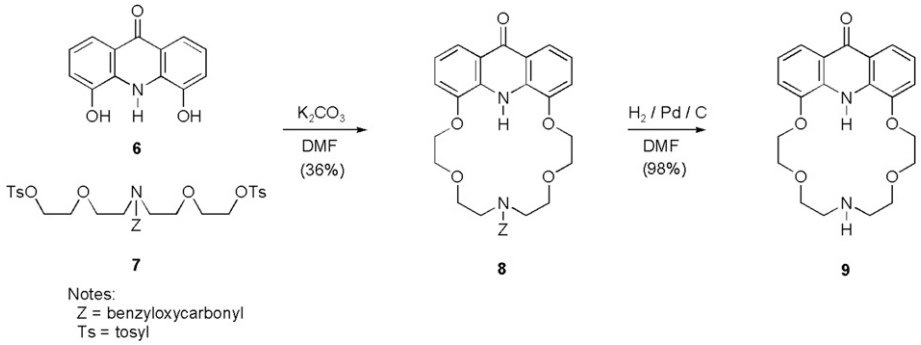
2.1. Synthesis

The synthesis of acridono-azacrown ether **9** is outlined in Scheme 1. Macrocyclization of 4,5-dihydroxyacridone **6**[31] and the protected azatetraethylene glycol ditosylate **7** in the presence of a weak base potassium carbonate using dimethylformamide as solvent rendered *N*-benzyloxycarbonyl-protected crown ether **8**. Removal of the benzyloxycarbonyl protecting group from macrocycle **8** by catalytic hydrogenation gave acridono-crown ether **9** containing a secondary amino group in the macroring.

The synthesis of acridino-crown ether **13** was carried out in three ways as outlined in Scheme 3. In the first case, acridono-crown ether **9** was reduced with amalgamated sodium by the usual method as described for the reduction of acridones[34] to give acridano-crown ether **12**. The latter was then oxidized using gaseous oxygen to obtain acridino-crown ether **13**.

In the second case, acridono-crown ether **9** was treated with sodium metal using propanol as solvent to render acridino-crown ether **13** in one step as described for the reduction of previously reported acridono-crown ethers.[29] In the third case, the reported monoaza-tetraethylene glycol **10**[32] was first treated with tosyl chloride in a mixture of dichloromethane and 40% aqueous potassium hydroxide solution to obtain tritosyl-derivative **14** in one step instead of using pyridine[35] or triethylamine in dichloromethane[36] as reported. Macrocyclization of 4,5-dihydroxyacridone **6**[31] and tritosyl-derivative **14** in the presence of potassium carbonate using dimethylformamide as solvent rendered *N*-tosyl-protected crown ether **15**. Treating the latter (**15**) with sodium metal in propanol the tosyl protecting group was removed and also the acridone unit was reduced in one step giving acridino-crown ether **13**, similarly as described earlier for the reduction of reported acridono-crown ethers.[29]

The synthesis of stationary phase **SP-5** containing an acridino-18-crown-6 ether unit is shown in Scheme 4. Acridino-crown ether **13** was first alkylated with 3-iodopropyltriethoxysilane (**16**)[37] using triethylamine as a base in dimethylformamide to give triethoxysilyl-functionalized acridino-crown ether **17**. The latter crown ether derivative **17** was then reacted with spherical silica gel to form stationary phase **SP-5** containing an acridino-crown ether.

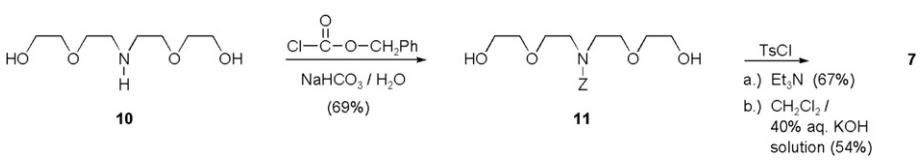


Scheme 1. Preparation of acridono-crown ether **9**.

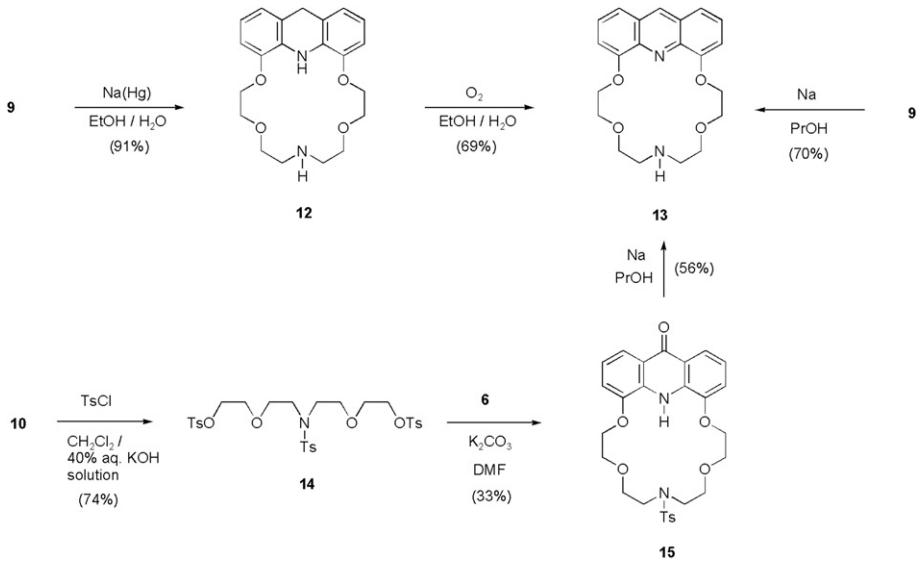
The synthesis of *N*-benzyloxycarbonyl-protected ditosylate **7** is shown in Scheme 2. The reported monoaza-tetraethylene glycol **10**[32] was treated with benzyl chloroformate in the presence of sodium hydrogen carbonate using water as solvent to obtain diol **11** in a similar way as described for the preparation of *N*-benzyloxycarbonyl-protected L-serine.[33] Diol **11** was then reacted with tosyl chloride in triethylamine or in a mixture of dichloromethane and 40% aqueous potassium hydroxide solution to give ditosylate **7** needed for the synthesis of acridono-azacrown ether **9**.

2.2. Determination of the selectivity of stationary phase SP-5 toward metal ions

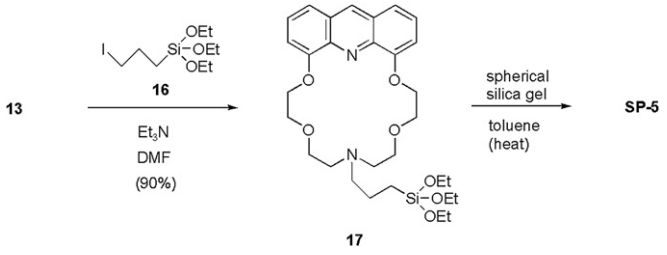
The selectivity of stationary phase **SP-5** containing an acridino-crown ether toward metal ions was determined. Stationary phase **SP-5** was equilibrated with known concentrations of metal ions in aqueous solution. After equilibration was reached, concentration of uncomplexed metal ions was determined by atomic absorption spectroscopic method. The log *K* values were then determined using the following equation:



Scheme 2. Preparation of *N*-benzyloxycarbonyl-protected monoaza-tetraethylene glycol ditosylate **7**.



Scheme 3. Preparation of acridino-crown ether **13**.



Scheme 4. Preparation of stationary phase **SP-5** by binding acridino-crown ether **17** to spherical silica gel.

$$\log K = \log \frac{n_{M^{n+}L}}{\left[M^{n+}\right] \cdot n_L}$$

where K is the equilibrium constant of the complexation, $n_{M^{n+}L}$ is the amount of the complex in mol, $[M^{n+}]$ is the concentration of uncomplexed metal ion in mol/L and n_L is the amount of free ligand in mol. In cases of the complex and the free ligand, instead of concentrations, chemical amounts were used in the determination of log K values, because concentrations of silica gel-bound complex and free ligand can not be defined clearly.

Results are shown in Table 1. These results demonstrate that complexes with Ag^+, Cu^{2+}, and Hg^{2+} ions are of similar stabilities and the other studied ions form one–two orders of magnitude weaker complexes.

After complexation experiments with each metal ion, stationary phase **SP-5** was regenerated by washing it subsequently with diluted nitric acid, water, aqueous trimethylamine solution, and water, and dried. The amounts of the stripped ions were also determined, which showed that all of the complexed ions could be removed using dilute nitric acid. The regenerated stationary phase obtained this way was used in the next experiment.

After half a year and about 10 regenerations, the determination of the log K value of the potassium-complex was repeated to demonstrate that the stationary phase did not lose its complexation properties. Repeated experiments showed a standard deviation of 0.014.

Complexation of our blank spherical silica gel used for the preparation of stationary phase **SP-5** with Mg^{2+} was also examined. In contrast to the blank silica gel used in another study,[8] our blank silica gel showed no complexation with Mg^{2+}.

Table 1
Log K values of the complexes of silica gel-bound crown with different metal ions and metal ion selectivities of **SP-5** compared to Ag^+

M^{n+}	log K	$\Delta\log K_{Ag^+,M^{n+}}$
Ag^+	2.02	
Cu^{2+}	2.01	0.01
Hg^{2+}	1.97	0.05
Ca^{2+}	1.27	0.75
Pb^{2+}	1.14	0.88
Fe^{3+}	1.10	0.92
K^+	0.88	1.14
Co^{2+}	0.63	1.39
Mg^{2+}	0.31	1.71
Na^+	0.25	1.77
Zn^{2+}	−0.18	2.20

2.3. Preliminary studies of stationary phase SP-5 for the removal of metal ions from aqueous solutions using column chromatography

Preliminary experiments were carried out for metal ion removal from dilute aqueous solutions using column chromatography. An aqueous solution containing 10 ppm Cu^{2+} and 1000 ppm Zn^{2+} was passed through a small column containing stationary phase **SP-5**. No amount of Cu^{2+} ion could be detected in the first 100 mL, then the amount increased gradually. In the first 20 mL only a small amount of Zn^{2+} can be detected, then the amount of Zn^{2+} increases reaching the maximum concentration at 40 mL. Results are shown in Fig. 3.

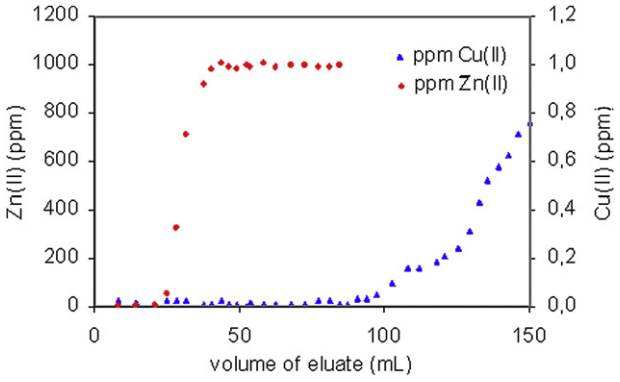


Fig. 3. Concentration of Cu^{2+} and Zn^{2+} in the eluates passed through the column containing stationary phase **SP-5**.

3. Conclusion

The synthesis of new acridino-crown ether **13** containing a secondary amino group in the macroring has been achieved in three different ways. Using the latter acridino-macrocycle, preparation of the new silica gel-bound 18-crown-6 ether **SP-5** was accomplished.

Selectivity of the latter stationary phase **SP-5** toward different metal ions was determined. The results show that the silica gel-bound macrocycle **SP-5** forms strongest complexes with Ag^{+}, Cu^{2+}, and Hg^{2+} ions among the studied metal ions. This can be due to the soft nitrogen atoms of the macroring. The similarity of log *K* values for these three ions is not surprising, many reported ionophores, which are selective for one of these three ions show large interference of the other two ions.[38] Our earlier results showed that alkyl groups on the macroring of enantiopure acridino-crown ethers can enhance selectivity.[29] A similar acridino-macrocycle bound to silica gel containing alkyl groups on the macroring may also show higher selectivity.

Preliminary column chromatographic studies on stationary phase **SP-5** showed that removal of Cu^{2+} ions in the presence of 100-fold excess of Zn^{2+} ions in aqueous solution can be achieved. Further experiments are needed to examine the applicability of silica gel-bound acridino-macrocycle **SP-5** for the removal of ppb amounts of Cu^{2+}, Ag^{+} or Hg^{2+} ions from aqueous solutions in the presence of different metal ions.

4. Experimental section

4.1. General

Starting materials were purchased from Sigma–Aldrich Corporation unless otherwise noted. Silica gel PharmPrep® 60 CC (40–63 μm, spherical, Merck) was used for the preparation of stationary phase **SP-5**. 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.[39] Evaporations were carried out under reduced pressure unless otherwise stated.

Infrared spectra were recorded on a Bruker Alpha-T 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 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 uncorrected.

For the determination of log *K* values, nitrate salts of metal ions were used with the exception of Hg^{2+}, where chloride was applied. All metal ion salts were purchased from Sigma–Aldrich Corporation and were of analytical grade. Water used in the experiments was deionized and then purified by ultrafiltration.

In studies of selectivity, concentrations of metal ions (Ag^{+}, Ca^{2+}, Co^{2+}, Cu^{2+}, Fe^{3+}, Mg^{2+}, Pb^{2+}, Zn^{2+}) were determined by flame atomic absorption method in air-acetylene flame using a Varian Techtron AA6 atomic absorption spectrometer combined with PC data station. However K^{+} and Na^{+} were determined by flame optical emission method using the same instrument. The range of calibration was 0.1–10 mg/L for these metal ions.

Concentration of Hg^{2+} was determined by cold vapor mercury method. The mixed, micro reactor type cold vapor instrument with 7 cm long gas cuvette was attached to a Unicam SP-9 atomic absorption spectrometer combined with PC data station. Sample volume of 3.00 mL and the $SnCl_2$ reduction agent was used. The calibration covered the range of 0.01–0.4 mg/mL for the Hg^{2+} ions.

4.2. Equilibration experiments

A slurry of stationary phase **SP-5** (4.0 g, 0.648 mmol free ligand) and different metal nitrates (1 mmol) in water (100 mL) was stirred mechanically at rt for 1 h. The mixture was filtered, diluted and the metal concentration of the filtrate was determined using atomic absorption spectroscopic method. The residue was washed sequentially with 0.01 M aqueous nitric acid (8×10 mL), water (3×20 mL), 0.01 M aqueous Me_3N (2×20 mL), water (3×20 mL) and dried at 65 °C for 24 h. The amount of the stripped ions was also determined using atomic absorption spectroscopic method.

In the case of Hg^{2+} ions instead of nitrate salt, $HgCl_2$ (0.25 mmol) was used with 1 g of stationary phase **SP-5** in water (250 mL).

Complexation studies of the blank spherical silica gel with Mg^{2+} was carried out using 4 g of silica gel, in the same way as described above for the complexation studies of stationary phase **SP-5**, with other metal ions.

4.3. Experiments for removal of Cu^{2+} ions from an aqueous solution

A 2.5 cm diameter column filled with stationary phase **SP-5** (3.4 g, 0.554 mmol free ligand) was conditioned by elution with water, then an aqueous solution containing 10.0 ppm Cu^{2+} and 1000 ppm Zn^{2+} (150 mL) was passed through it, while 3–8 mL samples were taken. Concentrations of the samples were determined using atomic absorption spectroscopy.

4.4. Stationary phase SP-5 (see Scheme 4)

A slurry of spherical silica gel [PharmPrep® 60 CC (40–63 μm), Merck] (12.0 g) and 3-triethoxysilylpropyl-functionalized acridino-crown ether **17** (1.18 g, 2.05 mmol) in dry and pure toluene (125 mL) was heated with mechanical stirring at reflux temperature under Ar for 2 days. The mixture was cooled down to rt and the modified silica gel was collected by filtration, washed sequentially with toluene (60 mL), CH_2Cl_2 containing 1% Et_3N (60 mL), MeOH (60 mL), a mixture of MeOH–water 2:1 (60 mL), MeOH (60 mL) and dried at 65 °C for 24 h. A sample of blank silica gel was dried in the same way and it gave a combustion analysis of C, 0.31; H, 1.25; N, 0.00. The combustion analysis of modified silica gel **SP-5** gave C, 4.86; H, 1.67; N, 0.46. This result shows that each gram of modified silica gel **SP-5** contained 0.16 mmol (by C%), 0.14 mmol (by H%), and 0.16 mmol (by N%) of the appropriate acridino-crown ether derivative.

4.5. [(Benzyloxycarbonyl)azanediyl]bis[(ethane-2,1-diyloxy) ethane-2,1-diyl] bis(4-methylbenzenesulfonate) (7) (see Scheme 2)

4.5.1. Using triethylamine as a solvent. A mixture of *N*-benzyloxy carbonyl-protected diol **11** (2.2 g, 6.72 mmol), tosyl chloride (3.1 g, 16.13 mmol), and triethylamine (100 mL) was stirred under Ar at rt for 24 h. After the reaction was completed, the solvent was evaporated and the residue was taken up in water (600 mL) and CH_2Cl_2 (200 mL). The aqueous phase was extracted with CH_2Cl_2 (4×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The crude product was purified by column chromatography on silica gel using

EtOH–EtOAc–hexane (1:1:8) mixture as eluent to give **7** (2.84 g, 67%) as a colorless oil.

R$_f$: 0.73 (silica gel TLC, EtOH–EtOAc–hexane 0.5:3:2); IR (neat) ν_{max} 3080, 3060, 2952, 2870, 1740, 1720, 1704, 1600, 1464, 1416, 1360, 1236, 1176, 1168, 1132, 1056, 924, 816, 768, 700, 664 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.36 (s, 6H), 3.35 (t, *J*=6 Hz, 4H), 3.41–3.55 (m, 8H), 4.01–4.06 (m, 4H), 5.03 (s, 2H), 7.23–7.29 (m, 9H), 7.71 (d, *J*=8 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 21.84, 47.92, 48.40, 67.35, 68.56, 68.65, 69.37, 69.89, 70.20, 128.07, 128.13, 128.23, 128.72, 130.07, 133.19, 136.87, 145.06, 156.23; MS calcd for $C_{30}H_{37}NO_{10}S_2$: 635.2. Found $(M+1)^+$: 636.1. Anal. Calcd for $C_{30}H_{37}NO_{10}S_2$: C, 56.68; H, 5.87; N, 2.20; S, 10.09. Found: C, 56.46; H, 5.86; N, 2.09; S, 9.80.

4.5.2. Applying a mixture of CH_2Cl_2 and 40% aqueous KOH solution. To a vigorously stirred mixture of *N*-benzyloxycarbonyl-protected diol **11** (0.49 g, 1.53 mmol), CH_2Cl_2 (16 mL) and 40% aqueous KOH solution (20 mL), was added tosyl chloride (0.70 g, 3.67 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and then at rt for 4 h. After the reaction was completed, CH_2Cl_2 (40 mL) and water (20 mL) were added. The phases were shaken 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 removed. The crude product was purified by column chromatography on silica gel using EtOH–EtOAc–hexane (1:1:8) mixture as eluent to give **7** (0.53 g, 54%) as a colorless oil.

Compound **7** had the same IR and NMR spectra as the one prepared above using triethylamine as solvent.

4.6. Benzyl 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-carboxylate (8) (see Scheme 1)

A mixture of 4,5-dihydroxyacridine-9(10*H*)-one[31] (**6**) (1.97 g, 8.68 mmol), *N*-benzyloxycarbonyl-protected ditosylate **7** (6.07 g, 9.55 mmol), finely powdered anhydrous K_2CO_3 (12.00 g, 86.8 mmol), and dry DMF (200 mL) was stirred vigorously under Ar at 50 °C for 3 days. The solvent was removed at 25 °C (bath temperature) and the residue was taken up in a mixture of water (600 mL) and EtOAc (400 mL). The aqueous phase was extracted with EtOAc (3×200 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The crude product was purified by column chromatography on silica gel using acetone–hexane (1:2) mixture as eluent. The yellow solid (2.11g, 47%) was recrystallized from 1,2-dichloroethane to give the protected acridono-crown ether **8** (1.62g, 36%) as pale yellow crystals.

Mp: 165.5–166.5 °C (1,2-dichloroethane); *R*$_f$: 0.54 (silica gel TLC, MeOH–CH_2Cl_2 1:15); IR (KBr) ν_{max} 3424, 3080, 3060, 2928, 2880, 1708, 1628, 1616, 1596, 1536, 1488, 1424, 1272, 1224, 1152, 1136, 1080, 996, 752, 688, 592 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.52–3.57 (m, 4H), 3.64–3.71 (m, 4H), 3.79–3.84 (m, 4H), 3.96 (s, br half mol of complexed H_2O, 1H), 4.19–4.24 (m, 4H), 5.01 (s, 2H), 6.99–7.03 (m, 2H), 7.09 (t, *J*=7 Hz, 2H), 7.16–7.21 (m, 5H), 8.00 (d, *J*=8 Hz, 2H), 9.19 (s, NH, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 48.52, 49.01, 67.38, 69.04, 69.21, 69.45, 70.05, 70.57, 113.32, 113.52, 119.16, 120.90, 120.98, 122.25, 128.00, 128.17, 128.61, 131.85, 136.79, 146.68, 156.36, 178.06; MS calcd for $C_{29}H_{30}N_2O_7$: 518.2. Found $(M+1)^+$: 519.2. Anal. Calcd for $C_{29}H_{30}N_2O_7 \cdot 0.5H_2O$: C, 66.02; H, 5.92; N, 5.31. Found: C, 66.01; H, 5.71; N, 5.23.

4.7. 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 (9) (see Scheme 1)

N-Benzyloxycarbonyl-protected acridono-crown ether **8** (163 mg, 0.314 mmol) was dissolved in DMF (25 mL) and hydrogenated in the presence of Pd/C catalyst (33 mg, palladium on charcoal; activated, 10% Pd). After the reaction was completed, the catalyst was filtered off and the solvent evaporated at 25 °C (bath temperature) to give acridono-crown ether **9** (119 mg, 98%) as an off-white solid. This product was used without further purification.

Mp: 196–197 °C; *R*$_f$: 0.71 (alumina TLC, EtOH–toluene 1:2); IR (KBr) ν_{max} 3460, 3416, 2928, 1624, 1616, 1592, 1536, 1488, 1448, 1276, 1224, 1124, 1084, 752, 608 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.94 (s, br, NH, disappears shaken with D_2O, 1H), 2.88 (t, *J*=5 Hz, 4H), 3.75 (t, *J*=5 Hz, 4H), 3.94 (t, *J*=4 Hz, 4H), 4.39 (t, *J*=4 Hz, 4H), 7.08 (d, *J*=7 Hz, 2H), 7.17 (d, *J*=8 Hz, 2H), 8.07 (d, *J*=8 Hz, 2H), 9.21 (s, NH, disappears shaken with D_2O, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 49.24, 68.38, 69.08, 71.07, 112.20, 118.81, 120.86, 122.36, 131.53, 146.64, 178.16; MS calcd for $C_{21}H_{24}N_2O_5$: 384.2. Found $(M+1)^+$: 385.2. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.50; H, 6.27; N, 7.29.

4.8. 2,2′-{[(Benzyloxycarbonyl)azanediyl]bis(ethane-2,1-diyloxy)}diethanol (11) (see Scheme 2)

N-Benzyloxycarbonyl-protected diol **11** was prepared with minor modification as described for *N*-benzyloxycarbonyl-protected L-serine.[33]

To a solution of monoaza-tetraethylene glycol **10**[32] (7.0 g, 36.2 mmol) and $NaHCO_3$ (21.6 g, 257.1 mmol) in water (255 mL) was added dropwise benzyl chloroformate (11.5 g, 67.41 mmol) at room temperature (rt). The reaction mixture was stirred at rt for 6 h. After the reaction was completed the reaction mixture was extracted with EtOAc (4×200 mL). The combined organic phase was shaken with saturated brine (2×200 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography on silica gel using EtOH–EtOAc–hexane (1:6:4) mixture as eluent to give **11** (8.23 g, 69%) as a colorless oil.

R$_f$: 0.16 (silica gel TLC, EtOH–EtOAc–hexane 1:6:4); IR (neat) ν_{max} 3416, 3080, 3040, 2960, 2872, 1688, 1615, 1596, 1540, 1476, 1448, 1420, 1368, 1232, 1128, 1096, 1064, 888, 768, 740, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.02 (s, br, OH, 2H), 3.46–3.61 (m, 16H), 5.06 (s, 2H), 7.22–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 48.09, 48.68, 61.75, 67.39, 69.51, 69.86, 72.55, 128.05, 128.21, 128.65, 136.73, 156.54; MS calcd for $C_{16}H_{25}NO_6$: 327.2. Found $(M+1)^+$: 328.3. Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.43; H, 7.64; N, 4.02.

4.9. 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) (see Scheme 3)

Acridano-crown ether **12** was prepared by the usual method as described for the reduction of acridones.[34] To a suspension of acridono-crown ether **9** (200 mg, 0.52 mmol) in ethanol (20 mL) and water (1 mL) was added finely powdered sodium amalgam (10 g of 2%, 8.70 mmol Na) under Ar at rt. After addition of the sodium amalgam, the mixture was stirred for 2 h at 70 °C. The reaction mixture was removed from the mercury by decantation. The suspension was filtered and the solvent was removed. The crude product was purified by triturating it thoroughly with water. The precipitate was filtered and dried over KOH in a vacuum desiccator to give off-white crystals of acridano-crown ether **12** (175 mg, 91%). It should be noted here that every step of the preparation was carried out under inert atmosphere. The product was used without further purification.

Mp: 149–151 °C; *R*$_f$: 0.88 (alumina TLC, EtOH–toluene 1:2); IR (KBr) ν_{max} 3408, 3319, 3080, 2936, 2920, 2902, 2860, 1612, 1592, 1580, 1552, 1496, 1488, 1448, 1360, 1336, 1260, 1136, 1100, 1048, 960, 920, 888, 824, 764, 720, 684, 616 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.13 (s, br, NH+H_2O, disappears shaken with D_2O, 3H), 2.87 (t, *J*=5 Hz, 4H), 3.72 (t, *J*=5 Hz, 4H), 3.85–3.87 (m, 4H),

4.09 (s, 2H), 4.22–4.24 (m, 4H), 6.66 (d, *J*=8 Hz, 2H), 6.72–6.78 (m, 4H), 7.05 (s, NH, disappears shaken with D_2O, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 31.47, 49.19, 68.04, 69.43, 70.86, 109.01, 119.71, 120.23, 120.99, 130.19, 145.16; MS calcd for $C_{21}H_{26}N_2O_4$: 370.2. Found $(M+1)^+$: 371.2. Anal. Calcd for $C_{21}H_{26}N_2O_4 \cdot H_2O$: C, 64.93; H, 7.26; N, 7.21. Found: C, 64.95; H, 6.99; N, 6.97.

4.10. 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 (13) (see Scheme 3)

*4.10.1. Starting from acridano-crown ether **12**.* Acridano-crown ether **12** (175 mg, 0.47 mmol) was dissolved in ethanol (50 mL) and stirred under O_2 at 60 °C for 1 h. The solvent was evaporated and the residue was taken up in water (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (4×20 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The crude product was recrystallized from acetone to give acridino-crown ether **13** (121 mg, 69%) as yellow crystals.

Mp: 152–154 °C (acetone); *Rf*: 0.16 (alumina TLC, EtOH–toluene 1:2); IR (KBr) ν_{max} 3456, 3305, 3080, 2958, 2920, 2890, 2872, 1624, 1568, 1468, 1424, 1404, 1360, 1320, 1272, 1124, 968, 904, 824, 744, 608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.91 (t, *J*=5 Hz, 4H), 3.20 (s, br, NH+H_2O, disappears shaken with D_2O, 3H), 3.86 (t, *J*=5 Hz, 4H) 4.09–4.12 (m, 4H), 4.37–4.40 (m, 4H), 6.97 (d, *J*=7 Hz, 2H), 7.41 (t, *J*=8 Hz, 2H), 7.53 (d, *J*=8 Hz, 2H), 8.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 49.28, 68.42, 69.13, 71.58, 107.06, 120.00, 126.17, 128.11, 135.66, 141.08, 155.04; MS calcd for $C_{21}H_{24}N_2O_4$: 368.3. Found $(M+1)^+$: 369.3. Anal. Calcd for $C_{21}H_{24}N_2O_4 \cdot H_2O$: C, 65.27; H, 6.78; N, 7.25. Found: C, 64.99; H, 6.62; N, 7.16.

*4.10.2. Starting from acridono-crown ether **9**.* To a boiling solution of acridono-crown ether **9** (113 mg, 0.29 mmol) in propanol (4.5 mL) was added sodium (350 mg, 15.2 mmol) in six portions under Ar, and then the mixture was refluxed for 1 h. Water (10 mL) was added to the cooled reaction mixture, and the pH of it 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 recrystallized from acetone to give acridino-crown ether **13** (76 mg, 70%) as yellow crystals.

Mp: 152–154 °C (acetone); compound **13** had the same IR and NMR spectra as the one prepared above from acridano-crown ether **12**.

*4.10.3. Starting from N-tosyl-acridono-crown ether **15**.* Acridino-crown ether **13** was also prepared starting from *N*-tosyl-acridono-crown ether **15** in a similar manner as described above starting from acridono-crown ether **9** (procedure in Section 4.10.2) using *N*-tosyl-acridono-crown ether **15** (0.975 g, 1.81 mmol), sodium (1.46 g, 63.4 mmol), and propanol (40 mL).

The work-up was modified as follows: after pH adjustment the solvent was removed, and the residue was taken up in a mixture of water (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (4×50 mL) and the combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed.

The crude product was purified by column chromatography on alumina using EtOH–toluene (1:10) mixture as eluent. The yellow solid was recrystallized from EtOH–water mixture to give acridino-crown ether **13** (373 mg, 56%) as yellow crystals.

Mp: 150–152 °C (EtOH–water); compound **13** had the same IR and NMR spectra as the one prepared above from acridano-crown ether **12**.

4.11. [(4-Methylbenzenesulfonyl)azanediyl]bis[(ethane-2,1-diyloxy)ethane-2,1-diyl] bis(4-methylbenzenesulfonate) (14) (see Scheme 3)

To a vigorously stirred mixture of monoaza-tetraethylene glycol **10**[32] (1.0 g, 5.18 mmol), CH_2Cl_2 (32 mL), and 40% aqueous KOH solution (40 mL) was added tosyl chloride (3.55 g, 18.62 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and then at rt for 4 h. After the reaction was completed CH_2Cl_2 (100 mL) and water (100 mL) were added. The phases were shaken well and separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give **14** (2.52 g, 74%) as a colorless oil.

Compound **14** had the same physical properties and spectroscopic data as reported.[35]

4.12. 12-(4-Methylbenzenesulfonyl)-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 (15) (see Scheme 3)

A mixture of 4,5-dihydroxyacridine-9(10*H*)-one[31] (**6**) (337 mg, 1.48 mmol), tritosyl-derivative **14** (1.07 g, 1.63 mmol), finely powdered anhydrous K_2CO_3 (2.05 g, 14.8 mmol), and dry DMF (30 mL) was stirred vigorously under Ar at 50 °C for 3 days. The solvent was removed at 25 °C (bath temperature) and the residue was taken up in a mixture of water (250 mL) and CH_2Cl_2 (250 mL). The aqueous phase was extracted with CH_2Cl_2 (3×125 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The crude product was purified by column chromatography on silica gel using EtOAc–hexane (3:1) mixture as eluent. The yellow solid (440 mg, 55%) was triturated with MeOH to give protected acridono-crown ether **15** (264 mg, 33%) as pale yellow crystals.

Mp: 212–212.5 °C (MeOH); *Rf*: 0.39 (silica gel TLC, EtOAc–hexane 3:1); IR (KBr) ν_{max} 3424, 3136, 2962, 2928, 2882, 2821, 1624, 1616, 1600, 1532, 1488, 1468, 1448, 1360, 1340, 1272, 1224, 1164, 1084, 1024, 752, 736, 712, 656, 576, 552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.31 (s, 3H), 3.47 (t, *J*=5 Hz, 4H), 3.82 (t, *J*=5 Hz, 4H), 3.90–3.96 (m, 4H), 4.26–4.31 (m, 4H), 7.07 (d, *J*=8 Hz, 2H), 7.16–7.19 (m, 4H), 7.67 (d, *J*=8 Hz, 2H), 8.07 (d, *J*=8 Hz, 2H), 9.19 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 21.35, 49.41, 68.90, 69.32, 70.90, 112.61, 118.75, 120.69, 121.96, 127.14, 129.52, 131.37, 136.27, 143.31, 146.45, 177.80; MS calcd for $C_{28}H_{30}N_2O_7S$: 538.2. Found $(M+1)^+$: 539.1. Anal. Calcd for $C_{28}H_{30}N_2O_7S$: C, 62.44; H, 5.61; N, 5.20; S, 5.95. Found: C, 62.25; H, 5.45; N, 5.17; S, 5.90.

4.13. 12-[3-(Triethoxysilyl)propyl]-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 (17) (see Scheme 4)

A mixture of acridino-crown ether **13** (110 mg, 0.3 mmol), 3-iodopropyltriethoxysilane[37] (**16**) (120 mg, 0.36 mmol), triethylamine (45 mg, 0.45 mmol), and dry DMF (1 mL) was stirred vigorously under Ar at rt for 12 h. The solvent was removed and the residue taken up in a mixture of water (25 mL) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (6×12.5 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed. The crude product was triturated with hexane to give *N*-alkylated crown ether **17** (154 mg, 90%) as pale yellow crystals.

Mp: 132–135 °C (hexane); *Rf*: 0.39 (alumina TLC, EtOH–toluene 1:2); IR (KBr) ν_{max} 2965, 2925, 2884, 1626, 1563, 1475, 1466, 1450, 1406, 1389, 1363, 1320, 1260, 1189, 1164, 1070, 1016, 956, 903, 864, 794, 749, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.51 (t, *J*=8 Hz, 2H), 1.11 (t, *J*=7 Hz, 9H), 1.88–1.95 (m, 2H), 3.27 (t, *J*=8 Hz, 2H), 3.64–3.75 (m, 10H), 4.14–4.48 (m, 14H, including 1 mol of complexed

H_2O), 7.04 (d, J=8 Hz, 2H), 7.48 (t, J=8 Hz, 2H), 7.62 (d, J=8 Hz, 2H), 8.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 7.54, 17.69, 18.42, 54.64, 57.98, 58.68, 66.59, 68.63, 69.47, 107.76, 107.96, 120.64, 126.40, 128.15, 140.61, 154.26; MS calcd for $C_{30}H_{44}N_2O_7Si$: 572.3. Found $(M+1)^+$: 573.2. Anal. Calcd for $C_{30}H_{44}N_2O_7Si \cdot H_2O$: C, 60.99; H, 7.85; N, 4.74; Si, 4.75. Found: C, 60.70; H, 7.65; N, 4.58; Si, 4.73.

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