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Structural characterization of a sodium perchlorate−acridino-18-crown-6 ether complex

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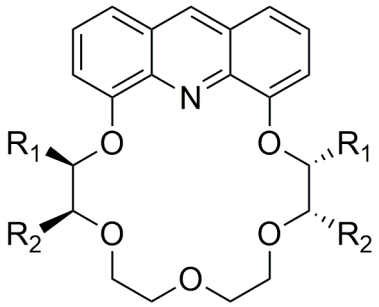
Abstract - This paper describes the X-ray crystal structure of a complex of acridino-18-crown-6 ether (*S,S*)-**2** and sodium perchlorate. The structure shows a π–π bonded homodimer in the crystal. The average distance of the two tricyclic units (3.49±0.1 Å) indicates a strong π–π interaction. Fluorescence titration was performed in order to determine the stoichiometry and stability constant (K_s) of the sodium ion-(*S,S*)-**2** complex. Based on the global fitting of the fluorescence spectra we suggest the formation of a complex with 1:1 ligand to metal ion ratio and the log*K* value determined by nonlinear regression analysis was 5.23.

Keywords: Crown ether, Acridine, Sodium complexation, X-ray analysis, π–π interaction, cation–π interaction, Fluorescence spectroscopy

Introduction

Sodium ion is essential to all living organisms. In humans, for example it regulates blood volume, blood pressure, and it helps the cells to transit nerve signals. The latter is accomplished by an active transporter molecule, Na^+/K^+-ATPase, which pumps ions against the ion gradient in the sodium/potassium channels [1]. Sensor molecules capable of selective discrimination of metal ions are of great significance due to their potential application in pharmaceutical or food industries, also in environmental chemistry [2]. During these selective interactions a generally occurring natural phenomenon called molecular recognition plays a vital role. The complexes, formed by the host and guest molecules, are held together by secondary interactions, such as hydrogen bonding, π–π [3-5] and cation–π [6-8] interactions. Receptors based on various macrocycles, such as monensin [9], bispyrrolidone [10] and crown ether derivatives [11-20], were capable of selective recognition of sodium ions.

We have studied the complexation ability of chiral dimethyl-substituted crown ether type sensor molecules containing an acridine fluorophore unit [(*R,R*)-**1** and (*S,S*)-**2**, see Figure 1] toward the enantiomers of 1-phenylethylamine hydrogen perchlorate (PEA), 1-(1-naphthyl)ethylamine hydrogen perchlorate (1-NEA), phenylglycine methyl ester hydrogen perchlorate (PGME) and phenylalanine methyl ester hydrogen perchlorate (PAME) by UV/Vis and fluorescence spectroscopies [18]. Recently, we reported the preparation and X-ray analysis of the crystalline complexes of the dimethyl-substituted acridino-18-crown-6 ether (*R,R*)-**1** and the enantiomers of 1-NEA [21]. We found that the heterochiral complex [(*R,R*)-**1**–(*S*)-1-NEA] is more stable than the homochiral one [(*R,R*)-**1**–(*R*)-1-NEA]. In the case of (*S,S*)-**2**, based on the fluorescence spectroscopic studies the macrocycle showed the highest enantiomeric discrimination toward the enantiomers of PGME [18]. In continuation of our research in this area we attempted to prepare the single crystals of (*S,S*)-**2** and the enantiomers of PGME for X-ray analysis. To our surprise, in the cases of both enantiomers of PGME complexes of (*S,S*)-**2** and sodium ions were formed. UV/Vis spectroscopic study and fluorescence titration was performed in order to determine the stoichiometry and stability constant (K_s) of the sodium ion-(*S,S*)-**2** complex. Also, to further study this complex, suitable single crystals for X-ray analysis were prepared from (*S,S*)-**2** and sodium perchlorate.



(*R,R*)-**1**: R_1=Me, R_2=H
(*S,S*)-**2**: R_1=H, R_2=Me

Figure 1. Schematics of the acridino-18-crown-6 ether host molecules.

Experimental

Infrared spectrum was obtained on a Bruker Alpha-T FT-IR spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were taken on a Bruker DRX-500 Avance spectrometer. Optical rotation was taken on a Perkin-Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. Elemental analysis was performed on a Vario EL III instrument (Elementanalyze Corporation) in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting point was taken on a Boetius micro melting point apparatus and was uncorrected. Reagents were purchased from Sigma–Aldrich Corporation. All chemicals were of analytical grade, $NaClO_4 \cdot H_2O$ was used in the complexation study. UV/Vis spectra were taken on a Multiskan Spectrum Microplate Spectrophotometer controlled by SkanIt Software for Multiscan version 2.1. Fluorescence spectra were recorded on a BMG Labtech CLARIOstar spectrophotometer. Spectrophotometric titrations were carried out according to the literature [22]. The stability constants of the complexes were determined by global nonlinear regression analysis using the ReactLab^{TM} Equilibria spectral analyses suite (Jplus Consulting, www.jplusconsulting.com). The concentrations of the solutions of sensor (*S,S*)-**2** were 100 μM for the UV/Vis measurements and 20 μM for the fluorescence titrations.

Synthesis of the crystalline (*S,S*)-2-Na^+ complex

Crown ether (*S,S*)-**2** [(8*S*,16*S*)-8,16-dimethyl-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] was prepared

according to the literature [18]. Crown ether (*S,S*)-**2** (70 mg, 0.18 mmol) was added to the solution of $NaClO_4 \cdot H_2O$ (22 mg, 0.18 mmol) in ethanol (8 mL). The mixture was refluxed for 10 mins and filtered hot. Suitable single crystals for X-ray crystallographic studies were obtained from the almost saturated solution which was allowed to stand at room temperature in a glass ampoule. This way 35 mg (37%) of bright red plates were obtained.

Mp 139–142°C; $[\alpha]_D^{25}$ = +14 (c 0.14, EtOH); IR (KBr) ν_{max} 3427, 3099, 3089, 3029, 2977, 2938, 2884, 1631, 1594, 1567, 1509, 1492, 1467, 1422, 1413, 1364, 1326, 1292, 1199, 1130, 1095, 1078, 956, 890, 790, 759, 721, 624 cm^{-1}; ^{1}H-NMR (CD_3CN, 500 MHz) δ 1.37 (broad s, 6H), 3.55–3.91 (m, 8H, OCH_2), 4.15–4.37 (m, 4H, OCH_2), 4,43 (d, *J* = 8Hz, 2H, OCH_2), 7.13–7.35 (m, 1H, Ar-H), 7.41–7.61 (m, 2H, Ar-H), 7.62–7.95 (m, 3H, Ar-H), 8.89 (s, 1H, Ar-H) ^{13}C-NMR (CD_3CN, 125 MHz) δ 15.80, 64.81, 68.90, 70.62, 70.66, 71.37, 73.08, 74.07, 74.41, 109.78, 121.80, 122.04, 127.46, 128.71, 129.57, 138.00, 140.92, 149.11, 150.01, 153.66; Anal Calcd for $C_{23}H_{27}ClNNaO_9$: C 53.14; H 5.23; N 2.69. Found: C 52.85; H 5.51; N 2.62.

Crystal structure determination

A suitable crystal was selected and the X-ray dataset has been collected at 102 K on a single source micro-focus Cu X-ray sealed tube SuperNova diffractometer (Agilent Technologies) with monochromated Cu-*K*α radiation (λ = 1.5418 Å) and Eos CCD detector. The data reduction was performed with program package CrysAlisPro SXRED [23]. The space group determination was performed via GRAL module by applying the Laue symmetry. The structures were solved by direct methods using Olex2 [24] and refined using fullmatrix least-squares. All calculations were performed using Olex2[24] and SHELXL97 [25] programs. The crystal data and refinement parameters are presented in Table 1. The data (CCDC 1548555) can be obtained at www.ccdc.cam.ac.uk/conts/retrieving.html.

Results and Discussion

The enantiomeric discrimination ability of the dimethyl-substituted acridino-18-crown-6 ether (*S,S*)-**2** toward the enantiomers of the perchlorate salts of primary aralkylamines and α-amino acid esters was studied by *Kertész et al*. The fluorescence spectroscopic studies demonstrated that in the case of (*S,S*)-**2**, the highest enantiomeric discrimination was observed for the enantiomers of PGME [18]. In order to better understand the secondary interactions governing

the enantiomeric recognition of crown ether based sensor and selector molecules containing an acridine moiety our aim was to prepare suitable single crystals for X-ray analysis from (*S,S*)-**2** and the enantiomers of PGME. However, instead of the diastereomeric complexes, the complexes of macrocycle (*S,S*)-**2** and sodium ions were obtained in both cases. The presence of sodium ions can be explained by the fact that the last step of the preparation of (*S,S*)-**2** [18] is a *Bouveault–Blanc* reduction [26], which employs sodium metal as a reducing agent, and during the reduction the oxidation of the metal takes place and sodium ions are formed. Presumably, crown ether (*S,S*)-**2** formed strong secondary interactions with sodium ions, and this complex withstood the purification of the crude product. It can also be assumed that crown ether (*S,S*)-**2** forms a complex with sodium ions with a higher stability constant (K_s) than with the enantiomers of PGME. In order to prove this assumption and to determine the stoichiometry and stability constant (K_s) of the sodium ion-(*S,S*)-**2** complex, UV/Vis spectroscopic study and fluorescence titration were performed. Also, the single crystals of (*S,S*)-**2** and sodium perchlorate were prepared and studied by X-ray analysis.

UV/Vis and fluorescence spectroscopic studies

The complexation ability of (*S,S*)-**2** was first studied by UV/Vis spectroscopy in acetonitrile. Figure 2. shows that no changes could be observed in the absorbance spectra even upon addition of a twenty-five-fold excess of sodium ions. However, the binding of sodium ions by (*S,S*)-**2** was associated with significant fluorescence enhancement upon addition of these ions (Figure 3), thus fluorescence titration was performed. The fluorescence spectra were measured at 15 different cation to (*S,S*)-**2** ratios (Figure 3). The latter fluorescence changes were used to determine the stability constant and stoichiometry of the complex. Upon being treated with sodium ions the fluorescence enhancement of the sensor molecule (*S,S*)-**2** followed the *Benesi-Hildebrand* equation [22, 27], therefore we could assume the formation of a complex with 1:1 ligand to metal ion ratio. The changes in the spectra were further analyzed using nonlinear regression analysis and global fitting of the fluorescence spectra, which also suggested the 1:1 stoichiometry. The log*K* value determined by ReactLab^{TM} Equilibria program suite was 5.23. *Kertész et al.* determined the log*K* values for the complexation of (*S,S*)-**2** with the enantiomers of PGME, in the same solvent (MeCN) [18]. Macrocycle (*S,S*)-**2** formed a more stable complex with (*S*)-

PGME (log*K* 4.87) than with (*R*)-PGME (log*K* 4.61). It means that ligand (*S,S*)-**2** is 2.3-fold more selective toward sodium ions than toward the (*S*) enantiomer of PGME.

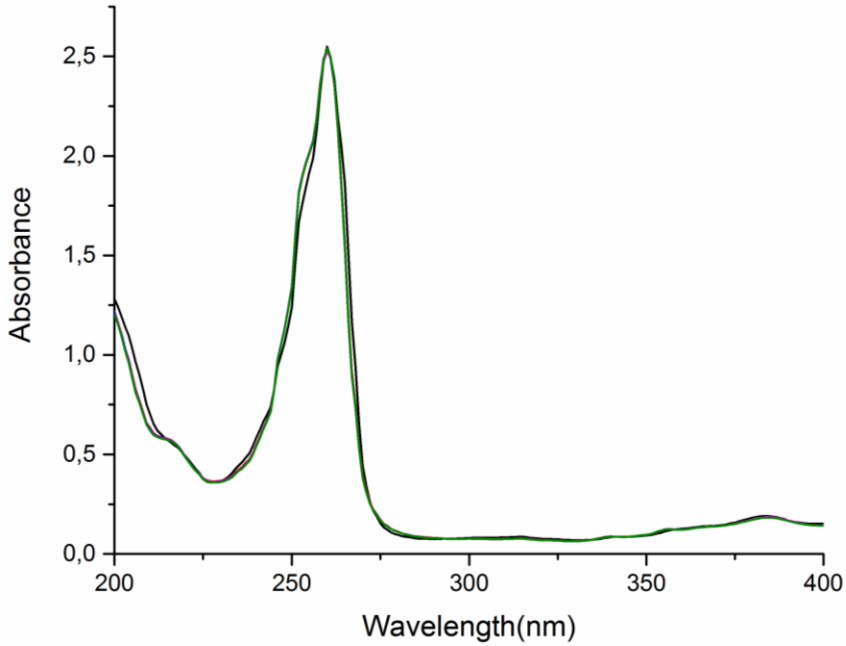


Figure 2. UV/Vis spectra of (*S,S*)-**2** (100 μM) in the presence of 0, 1, 5, 10, and 25 equiv. of sodium ions.

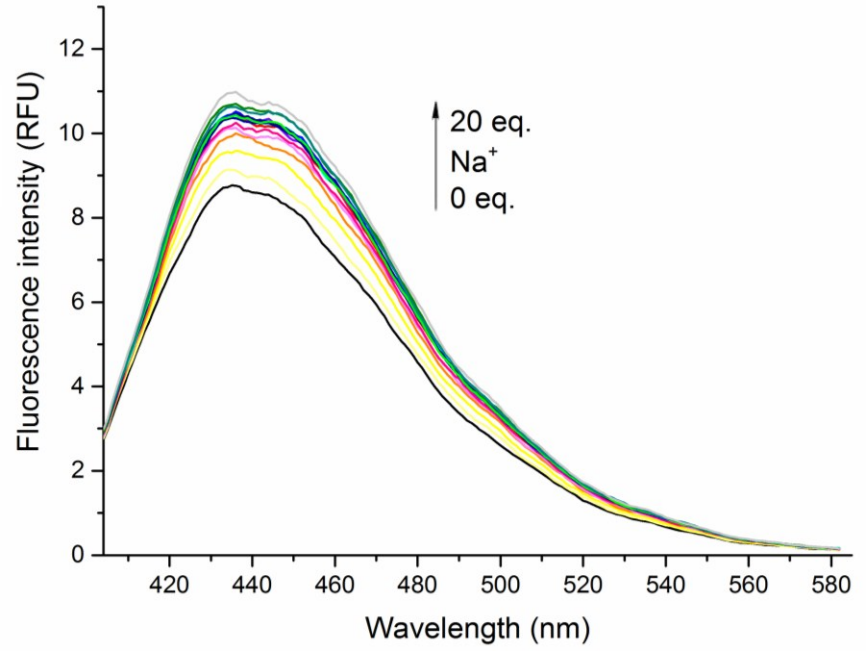


Figure 3. Fluorescence emission series of spectra upon titration of (*S,S*)-**2** (20 μM) with sodium ions (0–20 equiv.) in MeCN, λ_{ex} = 380 nm.

Crystal structure of the sodium-crown ether complex

In the crystal, the complex is found as a homodimer (Figure 4) consisting of two acridino-crown ethers and two sodium ions. The complex crystallized in the orthorhombic crystal system (Table 1). The distances of the two acridine rings of the monomers (3.41–3.59 Å) indicates a strong π–π interaction. The X-ray studies also suggest the existence of cation–π interaction, at a distance of 3.96–4.85 Å, between the sodium ions and the electron rich acridine moieties (Table 2).

The complexation environment of both sodium ions is well defined: among the six coordination partners, one nitrogen and five oxygen atoms are provided from the acridine unit and the macroring of the appropriate crown ethers, additionally two perchlorate ions are also present (Figures 4 and 5, Table 3). The strength of the π–π and cation–π interactions overcompensated the electrostatic repulsion between the sodium ions, thus the ions are drawn together (Figure 4).

In accordance with the XRD measurements the fluorescence titration suggested the formation of a complex with 1:1 ligand to metal ion ratio, which was also confirmed by elemental analysis (see Experimental Section). Due to the coordination the more flexible parts of the macroring (O3, O7, O11 or O17, O29, O34 of the appropriate monomer) are drawn toward the complexed sodium ions (Figure 5, Table 3).

NMR spectra

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in CD_3CN due to the poor solubility of the complex in CD_3OD. The signals doubled in the ^{13}C spectrum of the complex comparing to the spectrum of free ligand (*S,S*)-**2** [18], which also suggests the complexation of sodium ions.

Table 1.: Crystallographic data for (*S,S*)-**2**-sodium complex

Compound	**(*S,S*)-2-sodium complex**
Empirical formula	$C_{46}H_{54}Cl_2N_2Na_2O_{18}$
Formula weight	1039.79
Crystal system	orthorhombic
Space group	$P\,2_12_12_1$
Unit cell dimensions *a,* Å	13.77(19)
b, Å	15.90(2)
c, Å	22.33(3)

α,°	90
β,°	90
γ,°	90
Volume, Å^3	4886.41(11)
Z	4
Density (calculated), g/cm^3	1.413
T, K	102
F(000)	2176.0
θ–max for data collection. °	70.998
Index ranges (h,k,l max)	h ≤ 16, k ≤ 19, l ≤ 27
Reflections collected	9454
Goodness-of-fit on F^2	0.999
Final *R* indices [$I>2\sigma(I)$]	0.0569
w_R^2 indices (all data)	0.1638

Table 2.: Distances of the appropriate atoms that may indicate the presence of π–π and cation–π interactions.

π–π interaction		cation–π interaction	
C· · ·*C*	*C*· · ·*C* (Å)	*Na*· · ·*C/N*	*Na*· · ·*C/N* (Å)
C33 · · ·C38	3.49	Na8 · · ·N18	4.05
C23 · · ·C51	3.59	Na8 · · ·C15	4.76
C14 · · ·C19	3.48	Na8 · · ·C19	4.85
C15 · · ·C22	3.41	Na8 · · ·C26	4.76
C21 · · ·C43	3.43	Na8 · · ·C27	4.54
C19 · · ·C28	3.54	Na3 · · ·C2	4.37
		Na3 · · ·N12	3.96
		Na3 · · ·C6	4.43
		Na3 · · ·C25	4.65
		Na3 · · ·C5	4.70

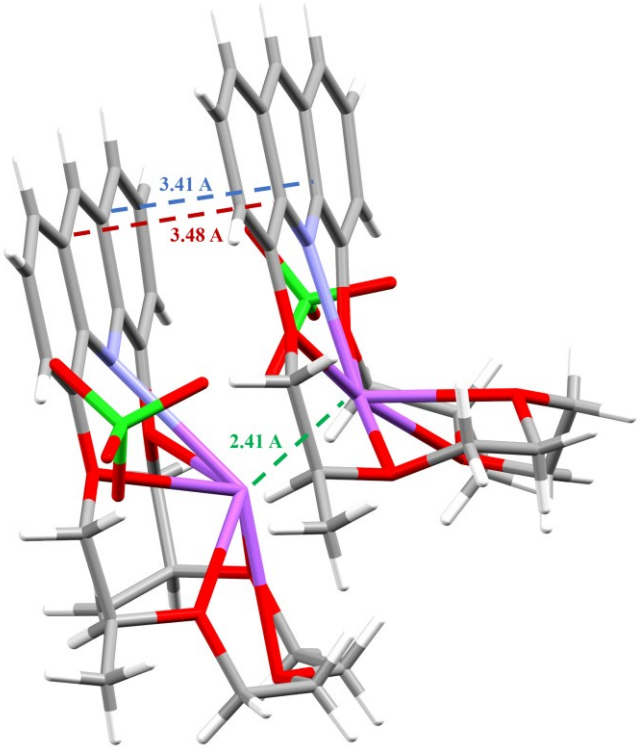


Figure 4. Structure of the dimer containing two monomers. Other species (two perchlorate ions) are also shown. Atomic coloring is as follows: C: grey, O: red, N: blue, Cl: green, Na: lilac, H: white.

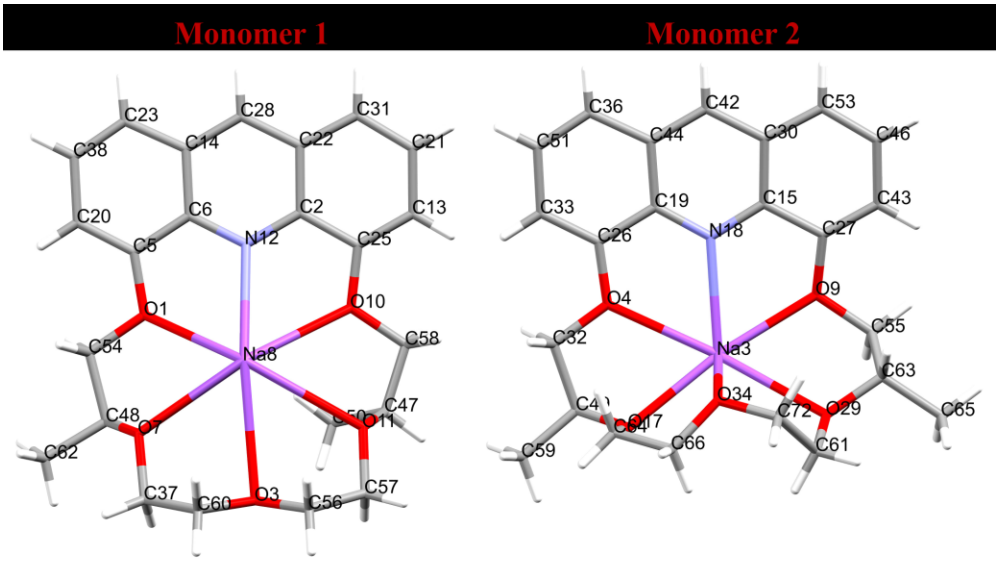


Figure 5. Separate representation of the two monomers. Note the differences in the lower parts of the macrorings of the appropriate crown ethers. Atomic coloring is as follows: C: grey, O: red, N: blue, Na: lilac, H: white.

Table 3.: Geometry of the complexed sodium ions.

Monomer	*O/N· · ·Na*	*O/N· · ·Na* (Å)	*O/N· · ·Na3· · ·O34* (°)
Monomer 1	O3 · · ·Na8	3.0	
	O11 · · ·Na8	3.0	
	O10 · · ·Na8	3.0	
	O1 · · ·Na8	3.0	
	O7 · · ·Na8	2.9	
	N12 · · ·Na8	2.9	
Monomer 2	O4 · · ·Na3	2.6	101.2
	O17 · · ·Na3	2.5	66.8
	O34 · · ·Na3	2.5	-
	O29 · · ·Na3	2.7	66.1
	O9 · · ·Na3	2.5	107.3
	N18 · · ·Na3	2.5	107.3
Monomer 1 and 2	Na8 · · ·Na3	2.4	

Conclusions and further aims

We succeeded in preparing suitable crystals for X-ray analysis from the sodium complex of acridino-18-crown-6 ligand (*S,S*)-**2**. Macrocycle (*S,S*)-**2** forms a π–π bonded dimer in the crystal. Fluorescence titration was also performed in order to determine the stoichiometry and stability constant (K_s) of the sodium ion-(*S,S*)-**2** complex: global fitting of the fluorescence spectra and elemental analysis indicated 1:1 stoichiometry.

Acknowledgements

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