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Synthesis and optical characterization of novel azacrown ethers containing an acridinone or an *N*-methylacridinone unit as potential fluorescent chemosensors

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Dedicated to Professor Károly Lempert on the occasion of his 85th birthday

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ABSTRACT

Four new achiral and four new chiral monoazacrown ethers containing an acridinone or an *N*-methylacridinone fluorescent signalling unit were prepared by reacting chloromethyl-substituted acridinone derivatives with achiral monoazacrown ethers with different cavity sizes and enantiopure monoaza-18-crown-6 ethers having two methyl and two isobutyl groups on their chiral centres, respectively. The operation of these chemosensors is based on the photoinduced electron transfer (PET) process, thus they show fluorescence enhancement in the presence of cationic guests. Their fluorescent behaviour as well as their complexation properties towards selected metal ions and the enantiomers of α-(1-naphthyl)-ethylammonium perchlorate and potassium mandelate were examined.

1. Introduction

Fluorescent chemosensors capable of selectively recognizing metal ions and organic cations as well as various anions and neutral molecules have received a great interest due to their potential application in many fields such as environmental chemistry, food industry, medical diagnosis and life sciences.[1] Fluorescence spectroscopy is an attractive tool owing to its sensitivity, selectivity, versatility and relatively simple handling.[2,3]

Using acridinone as a fluorescent signalling unit of a sensor molecule is very advantageous because of its strong fluorescence[4–6] and great photostability.[7] Acridinone[8] and its certain amide, urea or thiourea functionalized derivatives[9–11] have been proved to be efficient receptor and sensor molecules for different anions. Several crown ethers,[12–20] among them chiral ones,[17] containing an acridinone unit incorporated into their macrorings have been synthesized with the aim of studying their complexing ability towards metal and primary aralkyl ammonium ions by optical spectroscopic methods and liquid membrane transport experiments,[13,17] or using them as precursors for preparing photoswitchable macrocycles[19] and rotaxanes.[20] Furthermore, the proton-ionizable properties (acidity) of those containing electron withdrawing substituents introduced into the acridinone core have also been examined,[16,18] because these type of crown ethers may attain cation transport without the need of a counter anion across a liquid membrane or in solvent extraction.

The operation of many fluorescent chemosensors is based on either the photoinduced electron transfer (PET) or internal charge transfer (ICT) processes.[21–25] In the former case, the sensor molecules have a modular structure consisting of a fluorophore unit and a receptor unit separated by a short alkylene spacer, while in the latter case, the receptor is part of the π-electron system of the fluorophore. PET type sensor molecules exhibit a large fluorescence enhancement upon complexation with different cations compared to the free ionophores, providing by this a very sensitive response to such analytes, because in the absence of them, the sensor molecules have poor fluorescence due to an efficient quenching process (PET) in the excited state.[21–25] A number of monoazacrown ether based PET type sensor molecules,[26–46] possessing the modular structure

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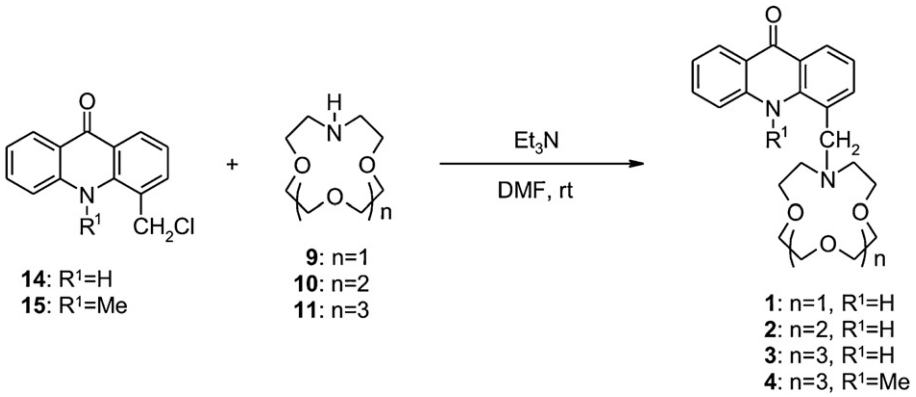


Scheme 1. Preparation of achiral fluorescent chemosensors **1**–**4**.

mentioned above, have been prepared and their selectivities for different metal ions or organic cationic guests have been studied. In the past two decades many efforts have been devoted to the development of fluorescent chiral chemosensors,[47] among them crown ether based ones containing various fluorescent units.[48–53] One of them containing an optically active binaphthyl unit incorporated into the crown ether framework, and having a PET type modular structure, showed a moderate selectivity for the enantiomers of 2-phenylglycinol.[53] Chiral ligands are usually designed and tested for enantiomeric recognition of chiral analytes such as amino acid derivatives, amino alcohols and primary amines. However, it should be noted here that the chirality of some receptor molecules may also have appreciable effect on the selectivity towards various biologically important metal ions.[54–58] This effect can be well-demonstrated as the stereostructure of chiral natural ionophores such as valinomycin, monensin, lasalocid, monactin, dinactin, salinomycin, narasin and nigericin plays an important role in the selective transport of metal cations through biomembranes.[57,58]

Herein we report the synthesis of four new achiral and four new chiral monoazacrown ethers in which an acridinone or an *N*-methylacridinone fluorescent signalling unit was attached through a methylene bridge to the nitrogen of the macrocycles. Their fluorescent behaviour as well as their PET type complexation properties towards selected metal ions (Na^+, K^+, Ag^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}) and the enantiomers of α-(1-naphthyl)ethylammonium perchlorate (NEA) and potassium mandelate were studied.

2. Results and discussion

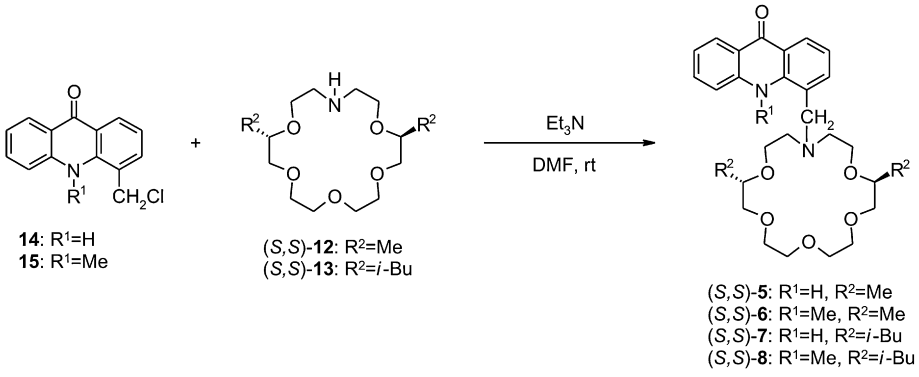
2.1. Synthesis

Achiral (Scheme 1) and chiral (Scheme 2) azacrown ether chemosensors **1**–(*S*,*S*)-**8** containing an acridinone or an *N*-methylacridinone fluorescent signalling unit were synthesized by alkylation of achiral and chiral monoazacrown ethers **9**–(*S*,*S*)-**13** with the appropriate chloromethyl-substituted acridinone derivative **14** or **15** in dry DMF in the presence of triethylamine as a base. Achiral monoazacrown ethers **9**–**11** are commercially available. Chiral monoazacrown ethers (*S*,*S*)-**12** and (*S*,*S*)-**13** were prepared according to our previously reported method.[59]

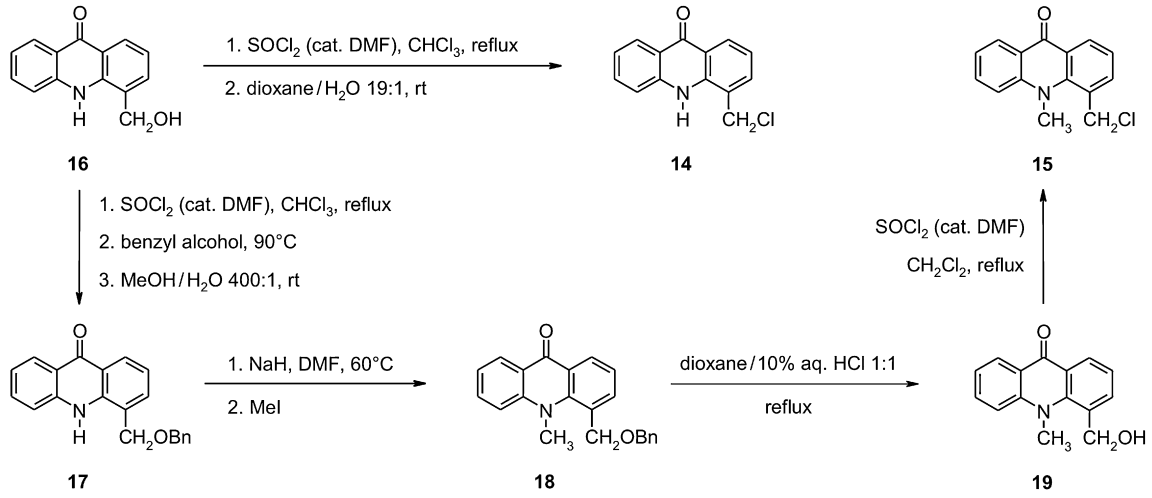
The synthesis of acridinone derivative **14** was performed with a modification of the reported procedure[60] and outlined as follows (Scheme 3). Hydroxymethyl derivative **16**[60] was treated with thionyl chloride in dry chloroform in the presence of a catalytic amount of DMF. The crude 9-chloro-4-chloromethylacridine was hydrolysed in a mixture of dioxane/water (19:1) to give chloromethyl-substituted acridinone **14**. To obtain benzyloxy derivative **17**, the aforementioned crude dichloro derivative was reacted with benzyl alcohol followed by a treatment with methanol containing a small amount of water. Benzyloxymethylacridinone **17** was deprotonated with sodium hydride in dry DMF and then was alkylated with methyl iodide to furnish *N*-methyl modified benzyloxymethylacridinone **18**. Benzyl protecting group was removed by boiling **18** in a mixture of dioxane/10% aqueous hydrochloric acid (1:1) to obtain *N*-methylated hydroxymethyl derivative **19**. In the last step, **19** was treated with thionyl chloride in dry dichloromethane in the presence of a catalytic amount of DMF to give *N*-methylated chloromethyl-substituted acridinone **15**.

2.2. Fluorescent behaviour

Ligands **1**–(*S*,*S*)-**8** have a modular (fluorophore–methylene spacer–azacrown receptor) structure, thereby PET type fluorescence response was expected upon complexation with various cations. It means that the free ligand shows reduced (near-zero) fluorescence after excitation due to a quenching process (PET) in



Scheme 2. Preparation of chiral fluorescent chemosensors (*S*,*S*)-**5**–(*S*,*S*)-**8**.



Scheme 3. Preparation of acridinone derivatives **14** and **15**.

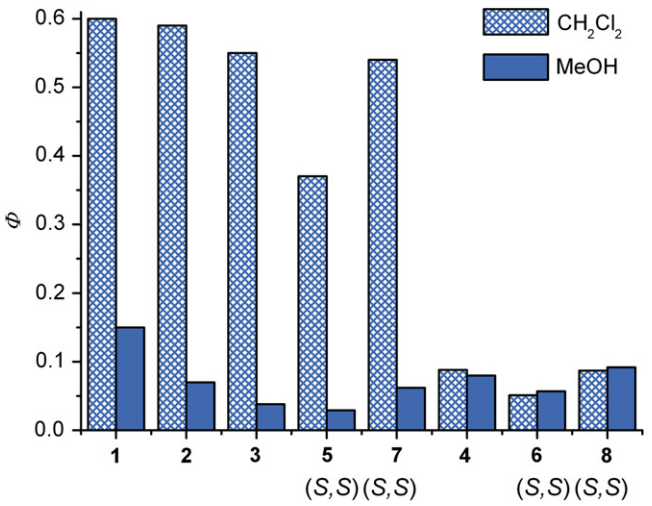


Figure 1. Solvent dependence of the fluorescence quantum yields of **1**–(*S*,*S*)-**8**.

Table 1
Fluorescence quantum yields and pK_a values of **1**–(*S*,*S*)-**8** and the parent compound acridinone

Compound	Φ_f (CH_2Cl_2)	Φ_f (MeOH)	pK_a (MeOH)[b]
Acridinone	0.35	0.74[a]	14.9[c]
1	0.60	0.15	[d]
2	0.59	0.070	16.5[e]
3	0.55	0.038	15.4
4	0.088	0.080	
(*S*,*S*)-**5**	0.37	0.029	
(*S*,*S*)-**6**	0.051	0.057	
(*S*,*S*)-**7**	0.54	0.062	
(*S*,*S*)-**8**	0.087	0.092	

[a] Acridinone is known to have extremely weak fluorescence in non-polar solvents (e.g., cyclohexane) and strong fluorescence in protic solvents.[6]
[b] The pK_a values were determined according to a reported method.[18]
[c] This value was taken from literature.[18]
[d] The pK_a of **1** could not be calculated because of the insignificant spectral changes (fluorescence intensity and absorbance) upon titration with Me_4NOH. This indicates that the deprotonation of **1** is more difficult than that of **2**.
[e] The pK_a of **2** could not be determined accurately, since the spectral signals changed continuously during the addition of Me_4NOH and its value is commeasurable with the autoprotolysis constant of MeOH (16.7).[18]

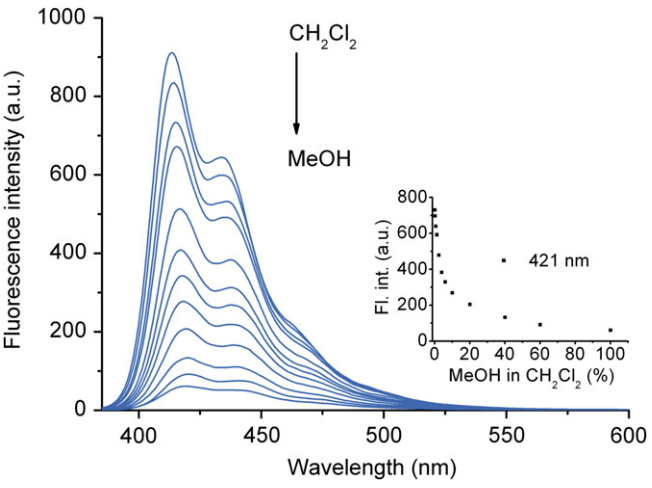


Figure 2. Fluorescence intensity changes of **3** (20 μM) as a function of solvent composition: CH_2Cl_2, 0.2%, 0.6%, 1.2%, 2.4%, 4%, 6%, 10%, 20%, 40%, 60% (v/v) MeOH in CH_2Cl_2 and MeOH, λ_{ex}=370 nm. Inset: fluorescence intensity changes at 421 nm.

the excited state directed from the donor nitrogen atom of the crown ether to the acceptor fluorophore unit. Conversely, coordination of a cation decreases the electron donating ability of the nitrogen atom, which results in a significant fluorescence enhancement without spectral shifts.

The fluorescence quantum yields of free ligands containing the acridinone unit [**1**–**3**, (*S*,*S*)-**5** and (*S*,*S*)-**7**] showed a strong solvent dependence, namely, these ligands have relatively large quantum yield values in dichloromethane and considerably (4–14.5 times) lower quantum yields in methanol (Figs. 1 and 2 and Table 1). This can be explained by the presence of a strong intramolecular H-bond formed between the acridinone NH proton and the nitrogen atom of the crown ether in dichloromethane, which inhibits the PET process leading to intense fluorescence of the free sensor molecule. In methanol, however, the intramolecular H-bonds are efficiently destroyed by the solvent molecules, thereby causing the recovery of the PET process and in accordance with this, significant reduction of the fluorescence.

It can also be seen that the strength of intramolecular H-bonds increases with the decreasing cavity size of crown ethers **1**–**3** based on the comparison of their quantum yield values determined in methanol (Fig. 1 and Table 1). Other evidence for the presence of

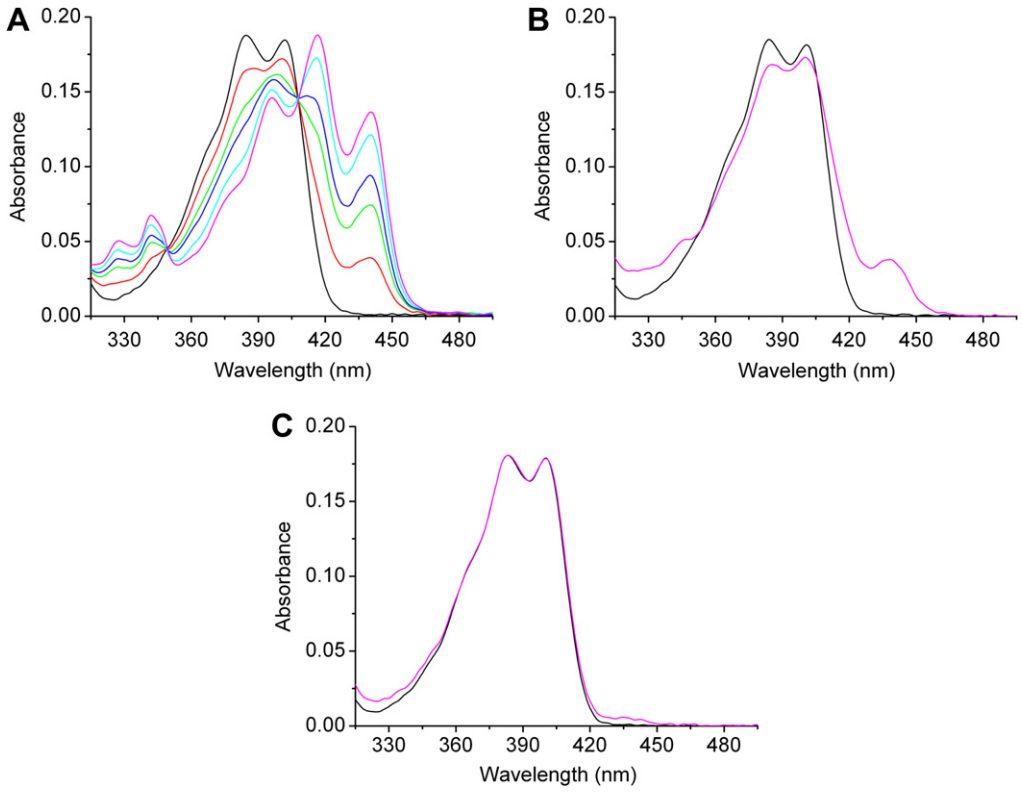


Figure 3. Absorption spectra of **1**–**3** (20 μM) in the presence of Me_4NOH in MeOH. (A) **3**, Me_4NOH: 0, 1000, 2000, 3000, 6000, 18,000 equiv (B) **2**, Me_4NOH: 0, 18,000 equiv (C) **1**, Me_4NOH: 0, 18,000 equiv.

intramolecular H-bonds and the dependence of their strength on the cavity size of the crown ethers is the decrease of acidity of acridinone NH proton in ligands **1**–**3** compared to unsubstituted acridinone (Fig. 3 and Table 1).

The presumption that the undesirable effect of the intramolecular H-bond can be eliminated by *N*-methylation of the acridinone unit seemed to be correct as the free ligands **4**, (*S*,*S*)-**6** and (*S*,*S*)-**8** showed poor fluorescence both in dichloromethane and

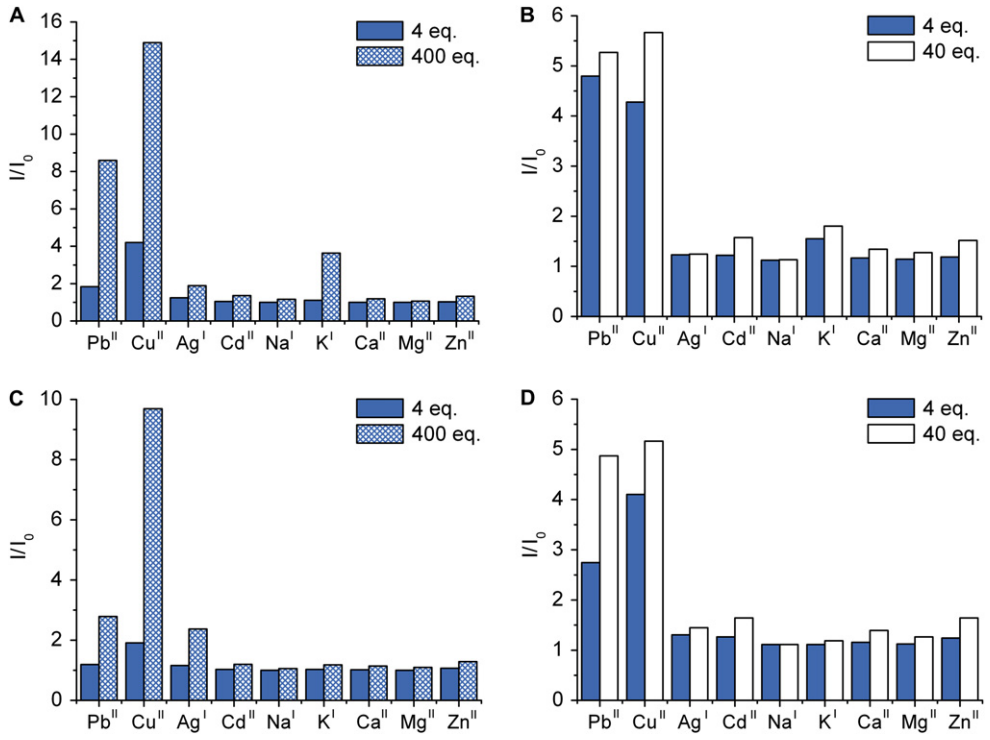


Figure 4. Fluorescence enhancement of **3** (A) and (*S*,*S*)-**7** (C) at 421 nm, **4** (B) and (*S*,*S*)-**8** (D) at 450 nm in the presence of various metal ions in MeOH (concentrations of the free ligands were 20 μM).

Table 2
Stability constants for metal ion complexes of **3**, **4**, (*S*,*S*)-**7** and (*S*,*S*)-**8** in MeOH

	log K_s			
	3	**4**	(*S*,*S*)-**7**	(*S*,*S*)-**8**
Cu^{2+}	3.47	4.87	3.59	4.88
Pb^{2+}	2.68	4.98	2.80	4.44
Ag^{+}	3.17	[a]	3.32	4.37
K^{+}	2.28	4.09	[a]	2.66

[a] The log K_s values could not be calculated because of the insignificant increase of the fluorescent signal (ca. 15–20%) upon addition of metal ions.

methanol, and also their fluorescence quantum yields are hardly influenced by solvent polarity (Fig. 1 and Table 1).

2.3. Complexation studies

We investigated the complexation properties of ligands **3**, **4**, (*S*,*S*)-**7** and (*S*,*S*)-**8** towards various metal ions (Na^{+}, K^{+}, Ag^{+}, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}) using methanol as a solvent. These ligands can really be considered as PET type sensor molecules, because they showed significant fluorescence enhancement by factors of 2–15 upon complexation with metal ions with quite small [3–6 nm in the case of **3** and (*S*,*S*)-**7**, and even smaller in the case of **4** and (*S*,*S*)-**8**] blue-shift of their emission spectra. Comparison of the fluorescence intensity changes of ligands **3**, **4**, (*S*,*S*)-**7** and (*S*,*S*)-**8** in the presence of various metal ions is represented in Figure 4, while the stability constants of the metal ion–ligand complexes are summarized in Table 2. The absorbances of ligands at the excitation wavelength used (370 nm) were essentially unchanged upon complexation with the exception of those of **3** and (*S*,*S*)-**7**, which are slightly influenced by the effect of Cu^{2+} and Pb^{2+}. The log K_s values were determined from the Benesi–Hildebrand plots[52,61] valid for 1:1 stoichiometry (Fig. 5B).

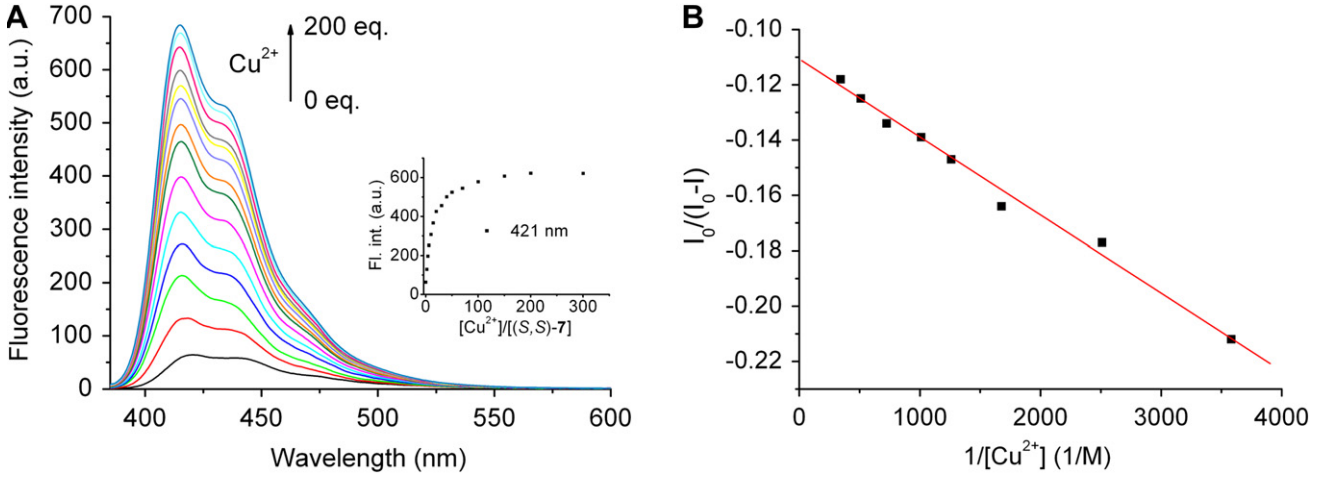


Figure 5. (A) Fluorescence emission series of spectra of (*S*,*S*)-**7** (20 μM) on increasing addition of Cu^{2+} (0–200 equiv) in MeOH, λ_{ex}=370 nm. Inset: titration curve (0–300 equiv) at 421 nm. (B) Benesi–Hildebrand plot of (*S*,*S*)-**7** (20 μM) in the presence of Cu^{2+} (14–150 equiv) at 421 nm, log K_s=3.59 (correlation coefficient: R=0.996).

The largest fluorescence enhancements for ligands **3**, **4**, (*S*,*S*)-**7** and (*S*,*S*)-**8** were induced by Cu^{2+} and Pb^{2+} ions, while Ag^{+} produced minor effects. In general, ligands containing the acridinone NH proton [**3** and (*S*,*S*)-**7**] exhibited larger fluorescence enhancement upon complexation, but formed less stable complexes than their *N*-methyl analogues [**4** and (*S*,*S*)-**8**]. Furthermore, it can also be seen that the presence of isobutyl groups in ligands (*S*,*S*)-**7** and (*S*,*S*)-**8** improves the selectivity towards Cu^{2+} compared to their achiral counterparts **3** and **4**. The latter effect is much more pronounced in the case of (*S*,*S*)-**7**. In accordance with our previous observations,[59] the isobutyl groups in the crown ether ring appreciably decrease the complexing ability of ligands (*S*,*S*)-**7** and (*S*,*S*)-**8** towards K^{+} with respect to their achiral analogues **3** and **4**. This can be attributed to the conformational changes of the crown ether ring owing to the bulky isobutyl groups as we discussed earlier.[59] It should be noted that in the case of *N*-methyl modified ligands **4** and (*S*,*S*)-**8**, K^{+}, Mg^{2+}, Ca^{2+}, Zn^{2+} and Cd^{2+} ions caused 1.5–3-fold fluorescence intensity enhancement only in a large excess (400-fold) of cations, which means that they formed significantly weaker complexes than Cu^{2+} and Pb^{2+} (not shown).

It is known that Cu^{2+} can quench fluorescence upon interaction with a fluorophore due to its paramagnetic nature.[21–25] The quenching mechanism is usually attributed to the PET (photoinduced electron transfer)/EET (electronic energy transfer) processes caused by the open shell ion.[21–25] Several chemosensors for Cu^{2+} based on selective quenching of the fluorescence have been reported,[21–25,62,63] but also much research has been focused on the development of sensor molecules exploiting other effects resulting in fluorescence enhancement upon complexation with Cu^{2+} ion.[22–25,62–67] In our case, coordination of the Cu^{2+} ion to the nitrogen atom of the crown ether reduces the efficiency of the PET process, thereby causes

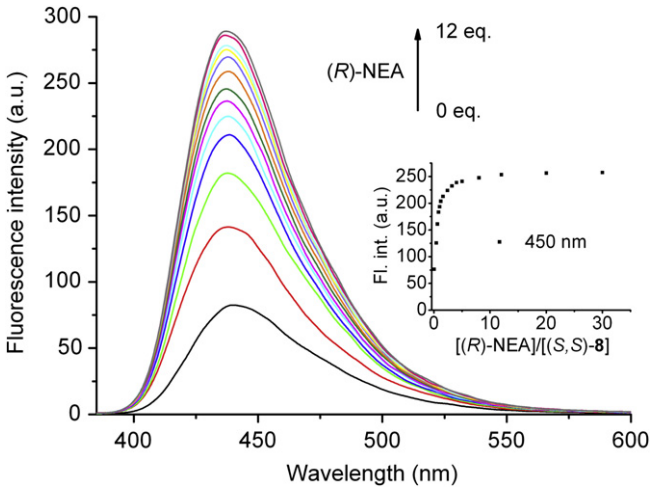


Figure 6. Fluorescence emission series of spectra of (*S*,*S*)-**8** (20 μM) on increasing addition of (*R*)-NEA (0–12 equiv) in CH_2Cl_2/MeOH (97:3), λ_{ex}=370 nm. Inset: titration curve (0–30 equiv) at 450 nm.

Table 3
Stability constants for complexes of (*S*,*S*)-**7** and (*S*,*S*)-**8** with the enantiomers of NEA and potassium mandelate in CH_2Cl_2/MeOH (97:3) and MeCN/H_2O (97.5:2.5), respectively

	log K_s	
	(*S*,*S*)-**7**	(*S*,*S*)-**8**
(*R*)-NEA	3.73±0.04	5.07±0.10
(*S*)-NEA	3.78±0.03	5.06±0.08
K (*R*)-mandelate	[a]	3.17±0.08
K (*S*)-mandelate	[a]	3.15±0.03

[a] No fluorescence enhancement upon addition of salts could be observed.

a relatively large emission increase similarly to the reported examples.[64,66,67]

Among the four ligands studied, (*S*,*S*)-**7** showed the best selectivity towards Cu^{2+} and almost 10-fold fluorescence enhancement could be measured upon titration with Cu^{2+} (Fig. 5). It is also notable that the complex **3**–Cu^{2+} fluoresced 15 times more intensely than the free ionophore **3**. Ligand (*S*,*S*)-**8** also exhibited good selectivity towards Cu^{2+} and Pb^{2+} and formed relatively stable complexes with these ions causing about 5-fold fluorescence enhancement upon complexation. Both (*S*,*S*)-**7** and (*S*,*S*)-**8** contain isobutyl groups in the crown ether ring, which increase their lipophilicity, thus it is advantageous for incorporating them into optode membranes.[68]

The complex formation of chiral ligands (*S*,*S*)-**7** and (*S*,*S*)-**8** with the enantiomers of α-(1-naphthyl)ethylammonium perchlorate (NEA) and potassium mandelate was also studied similarly to the reported examples[69,70] using dichloromethane/methanol (97:3) and acetonitrile/water (97.5:2.5), respectively. Complexation with these salts did take place causing fluorescent enhancement (1.5–3.5-fold) with a slight blue-shift (3–4 nm) in their emission spectra (Fig. 6). The Benesi–Hildebrand evaluation[52,61] was also applied for the calculation of log K_s values assuming 1:1 stoichiometry. Unfortunately, no enantiomeric recognition could be observed as the data in Table 3 show.

3. Conclusion

The synthesis and characterization of four new achiral and four new chiral monoazacrown ethers containing an acridinone and an *N*-methylacridinone fluorescent signalling units [**1**–(*S*,*S*)-**8**] and their unreported precursors have been performed. These ligands have a modular (fluorophore–methylene spacer–azacrown receptor) structure, so they exhibited PET type fluorescence response in the presence of various cations as expected. The fluorescence quantum yields of the free ligands containing the acridinone unit [**1**–**3**, (*S*,*S*)-**5** and (*S*,*S*)-**7**] showed significant solvent dependence due to intramolecular H-bonds, while those of the *N*-methyl analogues [**4**, (*S*,*S*)-**6** and (*S*,*S*)-**8**] were hardly influenced by solvent polarity. The strength of intramolecular H-bonds increased with the decreasing cavity size of crown ethers **1**–**3**. Among the four ligands [**3**, **4**, (*S*,*S*)-**7** and (*S*,*S*)-**8**] of which complexation properties were studied towards selected metal ions (Na^+, K^+, Ag^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}), ligand (*S*,*S*)-**7** had the best selectivity towards Cu^{2+} with almost 10-fold fluorescence enhancement upon complexation. The 15 times larger fluorescence quantum yield of complex **3**-Cu^{2+} with respect to the free ionophore is also notable. Ligand (*S*,*S*)-**8** also showed good selectivity towards Cu^{2+} and Pb^{2+} and formed relatively stable complexes with these ions causing about 5-fold fluorescence enhancement upon complexation. Macrocycles (*S*,*S*)-**7** and (*S*,*S*)-**8** contain lipophilic isobutyl groups at their chiral centres, so these ligands can be good candidates for the sensing unit of an optode membrane. With chiral guests (NEA or potassium mandelate), both (*S*,*S*)-**7** and (*S*,*S*)-**8** also formed complexes, but no enantiomeric recognition could be observed probably due to the too flexible conformation of these ligands. A more rigid macrocyclic framework containing an acridinone or an *N*-methylacridinone fluorescent signalling moiety is expected to show a higher degree of enantiomeric recognition. Work on this has already been started and we will report the results in due course.

4. Experimental

4.1. General

Infrared spectra were recorded on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol. NMR spectra were recorded either on a Bruker DRX-500 Avance spectrometer (at 500 MHz for ^1H and 125.8 MHz for ^{13}C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for ^1H and 75.5 MHz for ^{13}C spectra) and it is indicated in each individual case. Mass spectra were recorded on a ZQ2000 MS instrument (Waters Corp.) using ESI method. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute of Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro-melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Silica gel 60 (70–230 mesh, Merck) and aluminium oxide (neutral, activated, Brockman I) were used for column chromatography. Romil Ltd (Cambridge, UK) SuperPurity Solvent grade THF stored under argon was used as purchased. All other solvents were dried and purified according to well-established methods.[71] Evaporations were carried out under reduced pressure.

UV–vis spectra were taken on a UNICAM UV4-100 spectrophotometer controlled by VISION 3.4 software (ATI UNICAM, Cambridge, UK). Fluorescence spectra were recorded on a Perkin–Elmer LS 50B luminescent spectrometer supplied with an FL WinLab 3.0™ software (Perkin–Elmer Corp., USA). 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=0.546 in 0.5 M H_2SO_4).[2] Spectrophotometric titrations were carried out according to the literature.[18,59] Determination of the pK_a values were performed by titration with 1.0 M solution of Me_4NOH in MeOH. Absorption spectra of ligands **1**–**3** (20 μM) in the presence of large excess (6000 and 18,000 equiv) of Me_4NOH were corrected with the spectrum of the latter compound, because its absorbance is not entirely negligible in those concentrations. Perchlorate salts of the metal cations were used in general with the exception of $AgNO_3$ and KSCN. All of metal ion salts were of analytical grade. Enantiomers of NEA[72] and potassium mandelate[73] were prepared in our laboratory. Ratios of solvents are given in volumes (v/v) in all cases.

4.2. General procedure for the synthesis of crown ethers 1–(*S*,*S*)-8

A solution of the appropriate monoazacrown ether **9**–(*S*,*S*)-**13** (0.41 mmol), acridinone derivative **14** (100 mg, 0.41 mmol) or **15** (106 mg, 0.41 mmol) and triethylamine (114 μL, 0.82 mmol) in dry DMF (1.5 mL) was stirred under Ar at rt for a day. The volatile compounds were evaporated at 40 °C and the residue was dissolved in a mixture of CH_2Cl_2 (4 mL) and water (4 mL). The pH of the aqueous phase was adjusted to 9 by addition of 5% aqueous Me_4NOH solution and the phases were mixed well and separated.

The aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The crude products were purified as described below for each compound.

*4.2.1. 4-(1,4,7-Trioxa-10-azacyclododecan-10-ylmethyl)acridin-9(10H)-one (**1**).* The crude product was purified by recrystallization from MeOH to give **1** (89 mg, 57%) as yellow crystals. Mp: 170–172 °C; R_f=0.37 (silica gel TLC, 1:2 acetone/hexane); IR (KBr) ν_{max} 3432, 3256, 2936, 2880, 2840, 1620, 1608, 1596, 1528, 1484, 1440, 1344, 1288, 1254, 1152, 1100, 1052, 992, 920, 840, 760, 692, 616, 564, 544 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.85 (br s, 0.5 mol of complexed H_2O, 1H), 2.86 (br s, 4H), 3.58–3.77 (m, 12H), 4.00 (s, 2H), 7.15 (t, *J*=8 Hz, 1H), 7.25 (t, *J*=8 Hz, 1H), 7.43 (d, *J*=8 Hz, 1H), 7.65 (t, *J*=8 Hz, 1H), 7.87 (d, *J*=8 Hz, 1H), 8.45 (d, *J*=8 Hz, 1H), 8.46 (d, *J*=8 Hz, 1H), 12.03 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 55.34, 60.49, 70.13, 70.71, 70.90, 119.42, 120.62, 121.66, 121.86, 122.25, 124.45, 126.85, 127.02, 133.26, 133.36, 141.22, 141.58, 178.93; MS: 383 $(M+1)^+$. Anal. Calcd for $C_{22}H_{26}N_2O_4\cdot 0.5H_2O$: C, 67.50; H, 6.95; N, 7.16. Found: C, 67.34; H, 6.96; N, 7.03.

*4.2.2. 4-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-ylmethyl)acridin-9(10H)-one (**2**).* The crude product was purified by recrystallization from EtOH/hexane to give **2** (93 mg, 53%) as yellow crystals. Mp: 95–97 °C; R_f=0.28 (silica gel TLC, 1:2 acetone/hexane); IR (KBr) ν_{max} 3288, 2932, 2885, 2856, 2810, 1616, 1608, 1596, 1540, 1526, 1440, 1344, 1120, 1108, 1096, 1048, 936, 760, 696, 616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.87 (br s, 0.5 mol of complexed H_2O, 1H), 2.87 (t, *J*=6 Hz, 4H), 3.61–3.74 (m, 16H), 4.05 (s, 2H), 7.15 (t, *J*=8 Hz, 1H), 7.25 (t, *J*=8 Hz, 1H), 7.43 (d, *J*=8 Hz, 1H), 7.64 (t, *J*=8 Hz, 1H), 7.71 (d, *J*=8 Hz, 1H), 8.44 (d, *J*=8 Hz, 1H), 8.47 (d, *J*=8 Hz, 1H), 12.18 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 54.80, 60.26, 69.14, 70.37, 70.65, 71.04, 118.71, 120.28, 121.18, 121.46, 121.78, 123.92, 126.55, 126.68, 132.86, 132.96, 140.77, 141.21, 178.51; MS: 427 $(M+1)^+$. Anal. Calcd for $C_{24}H_{30}N_2O_5\cdot 0.5H_2O$: C, 66.19; H, 7.17; N, 6.43. Found: C, 66.02; H, 7.09; N, 6.28.

*4.2.3. 4-(1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-ylmethyl)-acridin-9(10H)-one (**3**).* The crude product was purified by recrystallization from MeOH to give **3** (87 mg, 45%) as yellow crystals. Mp: 72–74 °C; R_f=0.15 (silica gel TLC, 1:2 acetone/hexane); IR (KBr) ν_{max} 3534, 3512, 2952, 2888, 2872, 1620, 1608, 1596, 1528, 1440, 1344, 1112, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.43 (br s, 1 mol of complexed H_2O, 2H), 2.87 (br s, 4H), 3.55–3.77 (m, 20H), 4.06 (s, 2H), 7.10–7.18 (m, 1H), 7.20–7.28 (m, 1H), 7.41–7.46 (m, 1H), 7.63–7.74 (m, 2H), 8.44 (d, *J*=8 Hz, 1H), 8.47 (d, *J*=8 Hz, 1H), 12.25 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 54.07, 59.08, 69.29, 70.85, 71.27, 71.29, 71.42, 119.05, 120.60, 121.48, 121.76, 122.09, 124.44, 126.81, 127.00, 133.34, 133.67, 141.20, 141.46, 178.89; MS: 471 $(M+1)^+$. Anal. Calcd for $C_{26}H_{34}N_2O_6\cdot H_2O$: C, 63.92; H, 7.43; N, 5.73. Found: C, 63.72; H, 7.32; N, 5.59.

*4.2.4. 10-Methyl-4-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-ylmethyl)acridin-9(10H)-one (**4**).* The crude product was purified by column chromatography first on alumina using 1:110 EtOH/toluene as an eluent then on silica gel using 1:10 MeOH/acetone as an eluent to give **4** (107 mg, 54%) as a yellow oil. R_f=0.18 (silica gel TLC, 1:2:0.03 acetone/hexane/triethylamine); IR (neat) ν_{max} 2952, 2888, 2872, 1636, 1608, 1600, 1592, 1496, 1460, 1440, 1416, 1356, 1280, 1192, 1120, 948, 760, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.71 (br s, 4H), 2.71 (br s, 0.5 mol of complexed H_2O, 1H), 3.42–3.62 (m, 20H), 3.95 (s, 3H), 3.98 (s, 2H), 7.14–7.23 (m, 2H), 7.43 (d, *J*=8 Hz, 1H), 7.63 (t, *J*=8 Hz, 1H), 7.83 (br s, 1H), 8.34 (d, *J*=8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 42.51, 53.72, 59.89, 69.66, 70.14, 70.59, 70.64, 70.76, 116.68, 121.36, 121.70, 122.81, 125.03, 126.40, 126.92, 127.89, 133.58, 137.60, 145.47, 146.03, 178.77; MS: 485 $(M+1)^+$. Anal. Calcd for $C_{27}H_{36}N_2O_6\cdot 0.5H_2O$: C, 65.70; H, 7.56; N, 5.68. Found: C, 65.61; H, 7.28; N, 5.67.

*4.2.5. 4-[(2S,12S)-2,12-Dimethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-ylmethyl]acridin-9(10H)-one [(S,S)-**5**].* The crude product was purified by column chromatography on alumina using 1:140 EtOH/toluene as an eluent to give (*S,S*)-**5** (78 mg, 38%) as a yellow oil. R_f=0.32 (silica gel TLC, 1:2 acetone/hexane); $[\alpha]_D^{25}$ −6.7 (*c* 0.93, acetone); IR (neat) ν_{max} 3080, 2952, 2888, 2872, 1616, 1608, 1600, 1528, 1448, 1344, 1260, 1112, 1000, 952, 824, 760, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J*=6 Hz, 6H), 2.38 (br s, 0.5 mol of complexed H_2O, 1H), 2.73–3.04 (m, 4H), 3.42–3.52 (m, 4H), 3.60–3.85 (m, 14H), the benzylic –CH_2– gives an AB quartet, δ_A 3.93, δ_B 4.28 (J_{AB}=14 Hz, 2H), 7.15 (t, *J*=8 Hz, 1H), 7.22–7.27 (m, 1H), 7.44 (d, *J*=8 Hz, 1H), 7.61–7.68 (m, 2H), 8.43 (d, *J*=8 Hz, 1H), 8.48 (d, *J*=8 Hz, 1H), 12.23 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 16.90, 53.98, 58.93, 67.83, 70.87, 70.93, 74.98, 75.87, 118.30, 120.16, 121.00, 121.30, 121.58, 124.25, 126.22, 126.66, 132.86, 132.96, 140.60, 141.06, 178.53; MS: 499 $(M+1)^+$. Anal. Calcd for $C_{28}H_{38}N_2O_6\cdot 0.5H_2O$: C, 66.25; H, 7.74; N, 5.52. Found: C, 66.45; H, 7.76; N, 5.32.

*4.2.6. 10-Methyl-4-[(2S,12S)-2,12-dimethyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-ylmethyl]acridin-9(10H)-one [(S,S)-**6**].* The crude product was purified by column chromatography on alumina using first 1:140 EtOH/toluene then CH_2Cl_2 as eluents to give (*S,S*)-**6** (78 mg, 37%) as a yellow oil. R_f=0.30 (silica gel TLC, 1:2:0.03 acetone/hexane/triethylamine); $[\alpha]_D^{25}$ +7.3 (*c* 1.26, acetone); IR (neat) ν_{max} 2962, 2908, 2864, 1636, 1608, 1600, 1592, 1496, 1460, 1440, 1416, 1356, 1276, 1192, 1124, 996, 892, 760, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, *J*=6 Hz, 6H), 2.62–2.75 (m, 4H), 2.69 (br s, 0.5 mol of complexed H_2O, 1H), 3.31–3.40 (m, 4H), 3.44–3.63 (m, 14H), the benzylic –CH_2– gives an AB quartet, δ_A 3.95, δ_B 4.07 (J_{AB}=14 Hz, 2H), 3.96 (s, 3H), 7.15–7.21 (m, 2H), 7.42 (d, *J*=8 Hz, 1H), 7.63 (t, *J*=8 Hz, 1H), 7.83 (d, *J*=8 Hz, 1H), 8.33–8.37 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.25, 42.61, 54.13, 60.42, 67.96, 71.09 (very high, probably two carbon 13 signals together), 74.95, 76.06, 116.84, 121.54, 121.87, 123.06, 125.28, 126.58, 127.20, 128.39, 133.76, 137.87, 145.69, 146.27, 179.06; MS: 513 $(M+1)^+$. Anal. Calcd for $C_{29}H_{40}N_2O_6\cdot 0.5H_2O$: C, 66.77; H, 7.92; N, 5.37. Found: C, 66.74; H, 7.87; N, 5.30.

*4.2.7. 4-[(2S,12S)-2,12-Diisobutyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-ylmethyl]acridin-9(10H)-one [(S,S)-**7**].* The crude product was purified by column chromatography on alumina using 1:200 EtOH/toluene as an eluent to give (*S,S*)-**7** (79 mg, 33%) as a yellow oil. R_f=0.50 (silica gel TLC, 1:2 acetone/hexane); $[\alpha]_D^{25}$ −25.6 (*c* 2.04, acetone); IR (neat) ν_{max} 3080, 2952, 2888, 2872, 1620, 1608, 1600, 1528, 1448, 1352, 1264, 1112, 1000, 948, 824, 760, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.66 (d, *J*=7 Hz, 6H), 0.69 (d, *J*=7 Hz, 6H), 0.91–0.99 (m, 2H), 1.16–1.24 (m, 2H), 1.41–1.53 (m, 2H), 1.95 (br s, 0.5 mol of complexed H_2O, 1H), 2.68–2.88 (m, 4H), 3.32–3.46 (m, 6H), 3.52–3.70 (m, 10H), 3.88–3.95 (m, 2H), the benzylic –CH_2– gives an AB quartet, δ_A 3.95, δ_B 4.16 (J_{AB}=14 Hz, 2H), 7.06 (t, *J*=8 Hz, 1H), 7.15 (t, *J*=8 Hz, 1H), 7.35 (d, *J*=8 Hz, 1H), 7.52 (d, *J*=8 Hz, 1H), 7.55 (t, *J*=8 Hz, 1H), 8.34 (d, *J*=8 Hz, 1H), 8.39 (d, *J*=8 Hz, 1H), 12.18 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.35, 23.30, 24.70, 41.03, 54.28, 59.71, 68.90, 71.16, 71.28, 75.53, 77.89, 118.63, 120.38, 121.22, 121.58, 121.81, 124.49, 126.47, 126.95, 133.03, 133.14, 140.87, 141.41, 178.80; MS: 583 $(M+1)^+$. Anal. Calcd for $C_{34}H_{50}N_2O_6\cdot 0.5H_2O$: C, 69.01; H, 8.69; N, 4.73. Found: C, 68.78; H, 8.76; N, 4.57.

*4.2.8. 10-Methyl-4-[(2S,12S)-2,12-diisobutyl-1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-ylmethyl]acridin-9(10H)-one [(S,S)-**8**].* The crude product was purified by column chromatography on alumina using first 1:200 EtOH/toluene then 2:1 CH_2Cl_2/hexane as eluents

to give (*S*,*S*)-**8** (78 mg, 32%) as a yellow oil. R_f=0.49 (silica gel TLC, 2:1:0.03 EtOAc/hexane/triethylamine); $[\alpha]_D^{25}$ −10.2 (*c* 2.24, acetone); IR (neat) ν_{max} 2952, 2888, 2872, 1636, 1608, 1600, 1592, 1496, 1416, 1356, 1256, 1192, 1112, 948, 824, 760, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J*=7 Hz, 6H), 0.85 (d, *J*=7 Hz, 6H), 1.01–1.09 (m, 2H), 1.23–1.31 (m, 2H), 1.56–1.70 (m, 2H), 2.66–2.82 (m, 4H), 2.75 (br s, 0.5 mol of complexed H_2O, 1H), 3.34–3.85 (m, 18H), the benzylic $-CH_2-$ gives an AB quartet, δ_A 4.02, δ_B 4.16 (J_{AB}=14 Hz, 2H), 4.04 (s, 3H), 7.24 (t, *J*=8 Hz, 1H), 7.28 (d, *J*=8 Hz, 1H), 7.50 (d, *J*=8 Hz, 1H), 7.71 (t, *J*=8 Hz, 1H), 7.89 (d, *J*=8 Hz, 1H), 8.42 (d, *J*=8 Hz, 1H), 8.44 (d, *J*=8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.48, 23.47, 24.76, 41.25, 42.55, 54.40, 60.84, 68.92, 71.16, 71.22, 75.65, 77.53, 116.83, 121.55, 121.87, 123.11, 125.33, 126.65, 127.26, 128.38, 133.77, 137.90, 145.71, 146.29, 179.11; MS: 597 $(M+1)^+$. Anal. Calcd for $C_{35}H_{52}N_2O_6 \cdot 0.5H_2O$: C, 69.39; H, 8.82; N, 4.62. Found: C, 69.27; H, 8.78; N, 4.57.

4.3. 4-Chloromethylacridin-9(10*H*)-one (14)

A mixture of **16**[60] (1.44 g, 6.4 mmol), thionyl chloride (14 mL, 0.19 mol), dry DMF (0.2 mL) and dry $CHCl_3$ (70 mL) was stirred at reflux temperature until the TLC analysis showed that the reaction was completed (approximately 6 h). The volatile compounds were evaporated at 40 °C and the residue was stirred in a mixture of dioxane/water (19:1, 140 mL) at rt for a day. The reaction mixture was condensed to third of its original volume by evaporation of the volatile components and the deposited crystals were filtered off. The mother liquor was stirred at rt for a day and a second crop was collected by filtration. The two crops were combined to give **14** (1.17 g, 75%) as pale orange crystals. Mp: >360 °C [lit.[60] mp: >360 °C (EtOH)]; R_f=0.39 (silica gel TLC, 1:1:20 EtOH/AcOH/toluene); IR (KBr) ν_{max} 3280, 3208, 3144, 1624, 1608, 1592, 1576, 1528, 1496, 1484, 1464, 1448, 1344, 1256, 1192, 1152, 1000, 920, 824, 752, 696, 654, 632, 586, 572, 536 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 5.28 (s, 2H), 7.26 (t, *J*=8 Hz, 1H), 7.30 (t, *J*=8 Hz, 1H), 7.77 (t, *J*=8 Hz, 1H), 7.87 (d, *J*=8 Hz, 1H), 7.89 (d, *J*=8 Hz, 1H), 8.23 (d, *J*=8 Hz, 1H), 8.29 (d, *J*=8 Hz, 1H), 10.88 (s, 1H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 43.00, 117.81, 120.13, 120.56, 121.05, 121.48, 124.69, 125.55, 127.10, 133.41, 135.29, 138.39, 140.60, 176.35.

4.4. 4-Chloromethyl-10-methylacridin-9(10*H*)-one (15)

A mixture of **19** (1.32 g, 5.5 mmol), thionyl chloride (0.8 mL, 11 mmol), dry DMF (10 μL) and dry CH_2Cl_2 (26 mL) was stirred at reflux temperature for 1 h. The volatile compounds were evaporated. The residue and triethylamine (0.85 mL, 6.1 mmol) were stirred in THF (66 mL) at rt for 15 h. The precipitate was filtered off, washed with THF (identified as triethylamine hydrochloride by comparison of its IR spectrum to that of an authentic sample) and the solvent was removed to give **15** (1.36 g, 96%) as pale orange crystals. Mp: 166–168 °C; R_f=0.51 (silica gel TLC, 1:2 acetone/hexane); IR (KBr) ν_{max} 1632, 1616, 1608, 1600, 1592, 1500, 1448, 1416, 1364, 1280, 1260, 1080, 984, 804, 752, 652, 584 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.85 (s, 2H), 7.18–7.25 (m, 2H), 7.40 (d, *J*=8 Hz, 1H), 7.66 (t, *J*=8 Hz, 1H), 7.69 (d, *J*=8 Hz, 1H), 8.34 (d, *J*=8 Hz, 1H), 8.41 (d, *J*=8 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 42.83, 45.76, 116.82, 122.19, 122.40, 123.21, 125.75, 126.03, 127.35, 128.66, 134.25, 138.81, 144.98, 146.16, 178.67. Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; Cl, 13.76; N, 5.43. Found: C, 69.78; H, 4.82; Cl, 13.71; N, 5.28.

4.5. 4-Benzyloxymethylacridin-9(10*H*)-one (17)

A mixture of **16**[60] (4.96 g, 22 mmol), thionyl chloride (48 mL, 0.66 mol), dry DMF (0.7 mL) and dry $CHCl_3$ (250 mL) was stirred at reflux temperature until the reaction was completed (approximately 6 h). The volatile compounds were evaporated at 40 °C and the residue was stirred in benzyl alcohol (40 mL) at 90 °C for 3 h. The reaction mixture was cooled down to rt and stirred with a mixture of MeOH/H_2O (400:1, 401 mL) for 30 min. The precipitate was filtered off and dried. The crude product was recrystallized from DMF to give **17** (3.47 g, 50%) as pale orange crystals. Mp: 228–230 °C; R_f=0.46 (silica gel TLC, 1:1:20 EtOH/AcOH/toluene); IR (KBr) ν_{max} 3280, 3208, 2896, 2856, 1624, 1612, 1600, 1592, 1576, 1528, 1496, 1448, 1352, 1264, 1088, 1064, 1000, 912, 824, 752, 728, 688, 616, 552, 464 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.64 (s, 2H), 5.00 (s, 2H), 7.24–7.41 (m, 7H), 7.74 (t, *J*=8 Hz, 1H), 7.77 (d, *J*=8 Hz, 1H), 7.86 (d, *J*=8 Hz, 1H), 8.23 (d, *J*=8 Hz, 1H), 8.25 (d, *J*=8 Hz, 1H), 10.59 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 68.21, 71.33, 118.04, 120.38, 120.50, 120.96, 121.38, 125.24, 125.72, 125.97, 127.49, 127.60, 128.24, 133.33, 133.37, 138.16, 138.84, 140.79, 176.81. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.81; H, 5.64; N, 4.28.

4.6. 4-Benzyloxymethyl-10-methylacridin-9(10*H*)-one (18)

In a three neck flask equipped with a reflux condenser, Ar inlet and a dropping funnel was stirred a suspension of **17** (1.39 g, 4.4 mmol) and NaH (2.64 g, 66 mmol, 60% dispersion in mineral oil) in dry DMF (28 mL) under Ar at 60 °C for 2 h. Methyl iodide (5.5 mL, 88 mmol) was added dropwise to the reaction mixture at 60 °C and stirring was continued at this temperature for a day. The volatile compounds were evaporated and the residue was taken up in a mixture of CH_2Cl_2 (50 mL) and ice-cold water (50 mL). The phases were mixed well and separated. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue was purified by column chromatography on silica gel using 1:6 dioxane/hexane (dioxane was freshly distilled prior to use) as an eluent to give **18** (0.58 g, 40%) as yellow crystals. Mp: 90–91 °C; R_f=0.33 (silica gel TLC, 1:4 dioxane/hexane); IR (KBr) ν_{max} 3104, 2848, 1636, 1616, 1608, 1600, 1592, 1500, 1464, 1448, 1424, 1352, 1284, 1264, 1192, 1064, 1000, 904, 864, 816, 752, 696, 672, 664, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.64 (s, 2H), 4.80 (s, 2H), 7.27–7.40 (m, 7H), 7.45 (d, *J*=8 Hz, 1H), 7.72 (t, *J*=8 Hz, 1H), 7.76 (d, *J*=8 Hz, 1H), 8.47 (d, *J*=8 Hz, 1H), 8.52 (d, *J*=8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.00, 71.09, 72.95, 116.66, 121.79, 121.95, 122.93, 125.19, 126.08, 127.26, 127.88, 128.15, 128.23, 128.70, 133.97, 137.63, 138.46, 145.20, 145.81, 178.77. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.17; H, 5.92; N, 4.23.

4.7. 4-Hydroxymethyl-10-methylacridin-9(10*H*)-one (19)

A solution of **18** (1.38 g, 4.2 mmol) in a mixture of freshly distilled dioxane/10% aqueous HCl solution (1:1, 140 mL) was stirred at reflux temperature for 3 h. The reaction mixture was cooled down to 0 °C and kept at this temperature while its pH was adjusted to 8 by addition of 20% aqueous NaOH solution. The mixture was saturated with solid NaCl and EtOAc (60 mL) was added to it. The phases were mixed well and separated. The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed. The residue was purified by column chromatography on silica gel using 1:3 EtOAc/toluene as an eluent to give **19** (0.44 g, 44%) as yellow crystals. Mp: 170–172 °C; R_f=0.29 (silica gel TLC, 1:2 acetone/hexane); IR (KBr) ν_{max} 3384, 1608, 1600, 1588, 1504, 1488, 1480, 1440, 1416, 1360, 1280, 1264, 1192, 1160, 1136, 1008, 952, 896, 760, 704, 648, 616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.23 (br s, OH and 1 mol of complexed H_2O together, 3H), 4.01 (s, 3H), 5.00 (s, 2H), 7.01 (t, *J*=8 Hz, 1H), 7.29 (t, *J*=8 Hz, 1H), 7.44 (d, *J*=8 Hz, 1H), 7.68 (d, *J*=8 Hz, 1H), 7.71 (t, *J*=8 Hz, 1H), 8.22 (d, *J*=8 Hz, 1H), 8.39 (d, *J*=8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 42.29, 64.56, 116.76, 121.89, 121.96,

122.76, 124.62, 127.23, 127.24, 129.55, 134.16, 136.90, 144.48, 145.79, 178.83. Anal. Calcd for $C_{15}H_{13}NO_2 \cdot H_2O$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.10; H, 5.77; N, 5.34.

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References and notes

1. *Chemosensors of Ion and Molecule Recognition*; Desvergne, J. P., Czarnik, A. W., Eds.; NATO ASI Series C; Kluwer: Dordrecht, The Netherlands, 1997; Vol. 492.
2. Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*, 2nd ed.; Kluwer: New York, NY, 1999.
3. Valeur, B. *Molecular Fluorescence: Principles and Applications*; Wiley-VCH: Weinheim, Germany, 2002.
4. Albert, A. *The Acridines*, 2nd ed.; Edward Arnold: London, UK, 1966.
5. Acheson, R. M. In *The Chemistry of Heterocyclic Compounds*, 2nd ed.; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, NY, 1973; Vol. 9.
6. Siegmund, M.; Bendig, J. *Ber. Bunsenges. Phys. Chem.* **1978**, *82*, 1061–1068.
7. Rothman, J. H.; Still, W. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 509–512.
8. Miyaji, H.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 154–157.
9. Blázquez, M. T.; Muniz, F. M.; Sáez, S.; Simón, L. M.; Alonso, Á.; Raposo, C.; Lithgow, A.; Alcázar, V.; Morán, J. R. *Heterocycles* **2006**, *69*, 73–81.
10. García-Garrido, S. E.; Caltagirone, C.; Light, M. E.; Gale, P. A. *Chem. Commun.* **2007**, 1450–1452.
11. Lin, C.; Simov, V.; Drueckhammer, D. G. *J. Org. Chem.* **2007**, *72*, 1742–1746.
12. Vichet, A.; Galy, J.-P.; Baldy, A.; Barbe, J. *Acta Cryst. C* **1991**, *47*, 2508–2510.
13. Vichet, A.; Patellis, A.-M.; Galy, J.-P.; Galy, A.-M.; Barbe, J.; Elguero, J. *J. Org. Chem.* **1994**, *59*, 5156–5161.
14. Huszthy, P.; Köntös, Z.; Vermes, B.; Pintér, Á. *Tetrahedron* **2001**, *57*, 4967–4975.
15. Santini, V.; Boyer, G.; Galy, J.-P. *Heterocycl. Commun.* **2003**, *9*, 265–270.
16. Huszthy, P.; Vermes, B.; Báthori, N.; Czugler, M. *Tetrahedron* **2003**, *59*, 9371–9377.
17. Szalay, L.; Farkas, V.; Vass, E.; Hollósi, M.; Móczár, I.; Pintér, Á.; Huszthy, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1487–1493.
18. Kádár, M.; Biró, A.; Tóth, K.; Vermes, B.; Huszthy, P. *Spectrochim. Acta, Part A* **2005**, *62*, 1032–1038.
19. Orda-Zgadzaj, M.; Abraham, W. *Synthesis* **2007**, 3345–3356.
20. Orda-Zgadzaj, M.; Abraham, W. *Tetrahedron* **2008**, *64*, 2669–2676.
21. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
22. Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3–40.
23. de Silva, A. P.; McClean, G. D.; Moody, T. S.; Weir, S. M. In *Handbook of Photochemistry and Photobiology*; Nalwa, H. S., Ed.; American Scientific: Stevenson Ranch, CA, 2003; Vol. 3, Chapter 5.
24. Montalti, M.; Prodi, L.; Zaccheroni, N. In *Handbook of Photochemistry and Photobiology*; Nalwa, H. S., Ed.; American Scientific: Stevenson Ranch, CA, 2003; Vol. 3, Chapter 6.
25. Callan, J. F.; de Silva, A. P.; Magri, D. C. *Tetrahedron* **2005**, *61*, 8551–8588.
26. de Silva, A. P.; de Silva, S. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1709–1710.
27. Alihodžić, S.; Žinić, M.; Klaić, B.; Kiralj, R.; Kojić-Prodić, B.; Herceg, M.; Cimerman, Z. *Tetrahedron Lett.* **1993**, *34*, 8345–8348.
28. de Silva, A. P.; Gunaratne, H. Q. N.; McVeigh, C.; Maguire, G. E. M.; Maxwell, P. R. S.; O'Hanlon, E. *Chem. Commun.* **1996**, 2191–2192.
29. Kubo, K.; Kato, N.; Sakurai, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3041–3046.
30. Kubo, K.; Ishige, R.; Kubo, J.; Sakurai, T. *Talanta* **1999**, *48*, 181–187.
31. Chang, J. H.; Kim, H. J.; Park, J. H.; Shin, Y.-K.; Chung, Y. *Bull. Korean Chem. Soc.* **1999**, *20*, 796–800.
32. Cooper, C. R.; James, T. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 963–969.
33. Kele, P.; Orbulescu, J.; Calhoun, T. L.; Gawley, R. E.; Leblanc, R. M. *Tetrahedron Lett.* **2002**, *43*, 4413–4416.
34. Gawley, R. E.; Pinet, S.; Cardona, C. M.; Datta, P. K.; Ren, T.; Guida, W. C.; Nydick, J.; Leblanc, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 13448–13453.
35. Clapham, B.; Sutherland, A. J. *Chem. Commun.* **2003**, 84–85.
36. Geue, J. P.; Head, N. J.; Ward, A. D.; Lincoln, S. F. *Dalton Trans.* **2003**, 521–526.
37. Jia, L. H.; Guo, X. F.; Liu, Y. Y.; Qian, X. H. *Chin. Chem. Lett.* **2004**, *15*, 118–120.
38. Roy, M. B.; Samanta, S.; Chattopadhyay, G.; Ghosh, S. *J. Lumin.* **2004**, *106*, 141–152.
39. Gawley, R. E.; Shanmugasundaram, M.; Thorne, J. B.; Tarkka, R. M. *Toxicon* **2005**, *45*, 783–787.
40. Mao, H.; Thorne, J. B.; Pharr, J. S.; Gawley, R. E. *Can. J. Chem.* **2006**, *84*, 1273–1279.
41. Kele, P.; Orbulescu, J.; Gawley, R. E.; Leblanc, R. M. *Chem. Commun.* **2006**, 1494–1496.
42. Kele, P.; Nagy, K.; Kotschy, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2565–2567.
43. Kálai, T.; Hideg, K. *Tetrahedron* **2006**, *62*, 10352–10360.
44. Gawley, R. E.; Mao, H.; Haque, M. M.; Thorne, J. B.; Pharr, J. S. *J. Org. Chem.* **2007**, *72*, 2187–2191.
45. Mashraqui, S. H.; Sundaram, S.; Khan, T.; Bhasikuttan, A. C. *Tetrahedron* **2007**, *63*, 11093–11100.
46. Tsukanov, A. V.; Dubonosov, A. D.; Bren, V. A.; Minkin, V. I. *Chem. Heterocycl. Comp.* **2008**, *44*, 899–923.
47. Pu, L. *Chem. Rev.* **2004**, *104*, 1687–1716.
48. Prodi, L.; Bolletta, F.; Montalti, M.; Zaccheroni, N.; Huszthy, P.; Samu, E.; Vermes, B. *New J. Chem.* **2000**, *24*, 781–785.
49. Wong, W.-L.; Huang, K.-H.; Teng, P.-F.; Lee, C.-S.; Kwong, H.-L. *Chem. Commun.* **2004**, 384–385.
50. Dolci, L. S.; Huszthy, P.; Samu, E.; Montalti, M.; Prodi, L.; Zaccheroni, N. *Collect. Czech. Chem. Commun.* **2004**, *69*, 885–896.
51. Gunnlaugsson, T.; Bichell, B.; Nolan, C. *Tetrahedron* **2004**, *60*, 5799–5806.
52. Upadhyay, S. P.; Pissurlenkar, R. R. S.; Coutinho, E. C.; Karnik, A. V. *J. Org. Chem.* **2007**, *72*, 5709–5714.
53. Kim, K. S.; Jun, E. J.; Kim, S. K.; Choi, H. J.; Yoo, J.; Lee, C.-H.; Hyun, M. H.; Yoon, J. *Tetrahedron Lett.* **2007**, *48*, 2481–2484.
54. Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *31*, 4243–4256.
55. Sasaki, S.; Naito, H.; Maruta, K.; Kawahara, E.; Maeda, M. *Tetrahedron Lett.* **1994**, *35*, 3337–3340.
56. Shibutani, Y.; Mino, S.; Long, S. S.; Moriuchi-Kawakami, T.; Yakabe, K.; Shono, T. *Chem. Lett.* **1997**, *26*, 49–50.
57. Tsukube, H.; Yamada, T.; Shinoda, S. *Ind. Eng. Chem. Res.* **2000**, *39*, 3412–3418.
58. Gokel, G. W.; Nakano, A. In *Crown Compounds: Toward Future Applications*; Cooper, S. R., Ed.; VCH: New York, NY, 1992; Chapter 1.
59. Móczár, I.; Huszthy, P.; Maidics, Z.; Kádár, M.; Tóth, K. *Tetrahedron* **2009**, *65*, 8250–8258.
60. Kavadias, G. *Chim. Chron., New Ser.* **1994**, *23*, 79–95.
61. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
62. Ballesteros, E.; Moreno, D.; Gómez, T.; Rodríguez, T.; Rojo, J.; García-Valverde, M.; Torroba, T. *Org. Lett.* **2009**, *11*, 1269–1272 and references cited therein.
63. Swamy, K. M. K.; Ko, S.-K.; Kwon, S. K.; Lee, H. N.; Mao, C.; Kim, J.-M.; Lee, K.-H.; Kim, J.; Shin, I.; Yoon, J. *Chem. Commun.* **2008**, 5915–5917.
64. Csokai, V.; Kádár, M.; Ha Mai, D. L.; Varga, O.; Tóth, K.; Kubinyi, M.; Grün, A.; Bitter, I. *Tetrahedron* **2008**, *64*, 1058–1063.
65. Jun, E. J.; Won, H. N.; Kim, J. S.; Lee, K.-H.; Yoon, J. *Tetrahedron Lett.* **2006**, *47*, 4577–4580.
66. Qi, X.; Jun, E. J.; Xu, L.; Kim, S.-J.; Hong, J. S. J.; Yoon, Y. J.; Yoon, J. *J. Org. Chem.* **2006**, *71*, 2881–2884.
67. Kaur, S.; Kumar, S. *Chem. Commun.* **2002**, 2840–2841.
68. Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593–1687.
69. Turgut, Y.; Şahin, E.; Toğrul, M.; Hoşgören, H. *Tetrahedron: Asymmetry* **2004**, *15*, 1583–1588.
70. Toğrul, M.; Askin, M.; Hoşgören, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2771–2777.
71. Riddick, J. A.; Bunger, W. B.; Sakano, T. K. In *Techniques of Chemistry*, 4th ed.; Weissberger, A., Ed.; Wiley-Interscience: New York, NY, 1986; Vol. 2.
72. Izatt, R. M.; Wang, T.; Hathaway, J. K.; Zhang, X. X.; Curtis, J. C.; Bradshaw, J. S.; Zhu, C. Y.; Huszthy, P. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 157–175.
73. Schmidt, M.; Schier, A.; Schmidbaur, H. *Z. Naturforsch. B* **1998**, *53*, 1098–1102.