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Azacrown Ethers Containing Oximic and Schiff Base Sidearms - Potential Heteronuclear Metal Ion Receptors

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Abstract: A simple synthetic pathway for the preparation of oxime- and Schiff base-containing aza- and diazacrown ethers is reported. N-Methoxymethyl-substituted aza-15-crown-5 and aza-18-crown-6 as well as N,N′-bis(methoxymethyl)-substituted diaza-18-crown-6 were treated with 5-bromosalicylaldehyde to produce the N-(2′-hydroxy-3′-carbonyl-5′-bromobenzyl)-substituted aza-15-crown-5 (**8**), aza-18-crown-6 (**9**) and N,N′-bis(2′-hydroxy-3′-carbonyl-5′-bromobenzyl)-substituted diaza-18-crown-6 (**10**) compounds. Compounds **8** and **10** were treated with hydroxylamine to give oxime-substituted ligands **12** and **13**. A series of bis-Schiff base-containing diaza-18-crown-6 ligands were prepared by reacting **10** with 2-hydroxyaniline (to form **14**), 5-nitro-2-hydroxyaniline (**15**), 2-aminopyridine (**16**), 2-hydrazinopyridine (**17**) and N-aminomorpholine (**18**). Compounds **12-18** are potential complexing agents for simultaneous binding of soft transition and hard alkali or alkaline earth metal ions in one molecule. These new oxime- and Schiff base-containing ligands interacted strongly with Na^+ and K^+ in methanol. The interaction of the aromatic portions of **9, 10,** and **12-15** with transition metal ions was shown by the UV spectra of the metal ion complexes in 50% aqueous DMF. The X-ray structure of **10** is reported.

Introduction

Earlier, we reported a modified Mannich reaction as a synthetic approach for the synthesis of phenol-containing azamacroheterocycles via coupling the N-methoxymethyl derivatives of azacrown ethers with phenolic building blocks.[3] This approach allows the combination of azacrown ether moieties with substituted phenols bearing soft donating sites in close proximity to the phenolic OH groups. We demonstrated the usefulness of such a combination with 5-chloro-8-hydroxyquinoline (CHQ) attached to a number of mono- and diazacrown ether macrocycles.[4-6] We have shown that selectivity and binding ability of both CHQ and diaza-18-crown-6 can be greatly improved by their combination into one receptor. One of the reasons for increased selectivity of CHQ derivatized ligands (see Figure 1) as compared to the parent binding fragments is that reagents **1-7** are more preorganized for interaction with particular metal ions. The size of the macrocyclic ring as well as the position of the CHQ fragments impose certain steric restrictions which are not peculiar to CHQ itself. This basic idea of combining crown ether moieties with phenol-containing chelators can be applied to a great number of crown ethers and commerically available analytical reagents such as 1-(2-pyridylazo)-2-naphthol, 4-(2-pyridylazo)resorcinol, 1-nitroso-2-naphthol and others. Thus, new families of highly specific reagents having UV and/or

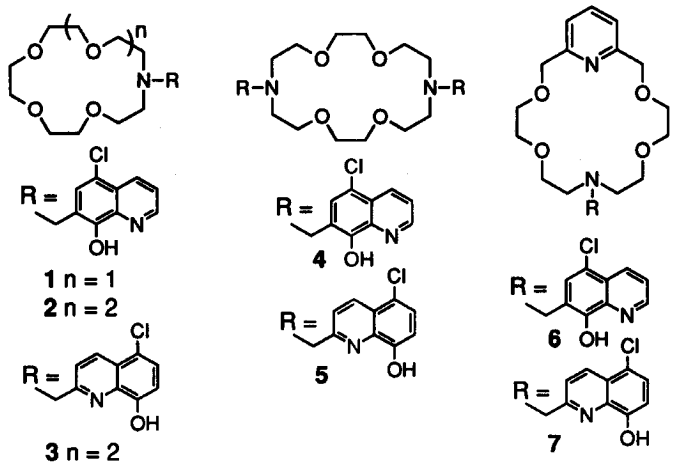


Figure 1. 5-Chloro-8-hydroxyquinoline-substituted azacrown ethers

fluorescent responding groups could be developed mostly in a one-step synthetic procedure.

Another possible application for these phenol-derivatized complexing agents prepared via Mannich condensation is their use as a heteronuclear metal ion receptor designed for simultaneous binding of soft-transition and hard-alkali or alkaline earth metal ions in one molecule or supramolecular aggregate. Heteronuclear metal ion receptors have received considerable attention[7] because bringing two metal ions together (intermetallic distance <4 Å) affects the redox properties of the complexed transition metal cation. Other areas of interest are allosteric effects, self-assembly, bimetallic activation and catalysis. In order to perform "double" coordination, the ligand should possess two sets of binding sites. One site is a multidentate ligating fragment for complexation with alkali or alkaline earth metal ions and the other is one or several soft chelating groups providing the transition metal ion with an appropriate geometry for coordination.

Here, we report a simple, general way to prepare new supramolecular receptors which can be used for heteronuclear binding with hard and soft metal ions. We also report the preliminary results on complexation of some of these receptors with a few metal cations. Complexation of these ligands with other cations and a study of their use as possible metal ion sensors will be reported when that work is done.

Results and Discussion

A number of heteronuclear metal ion receptors and their complexes have been reported.[7] Reinhoudt and co-workers elaborated approaches[8] to the synthesis of salen and salophen type complexes having polyglycol chains as multidentate binding sites for hard cations. Schiff base-substituted aromatic moieties of these ligands chelate the transition metal ions mostly in square planar coordination (Figure 2a,b). Replacement of polyglycol chains with cyclic crown ether fragments should result in enhanced affinity towards a hard cation and provide the receptor with additional rigidity. Hosseini and co-workers developed catechol-based diazacrown ether receptors[9] (Figure 2c,d) which were expected to coordinate a transition metal ion through the 1,2-dihydroxy groups of the catechol in either square planar or tetrahedral modes and bind alkali or alkaline earth metal ions by the azacrown portion. The proposed synthetic pathway

for preparation of catechol receptors required several steps as well as the protection and deprotection of the phenolic OH groups causing complications during the work up.

N-Methoxymethylazacrown ethers interact smoothly with a variety of phenols having substituents in positions *ortho*, *meta* and *para* to the OH group.[3] A number of these substituents, particularly carbonyl groups, can be used as interacting sites for further modifications. Taking advantage of preferential attack of N-methoxymethylamines on the position *ortho* to the phenolic OH group, we have constructed a number of new heteronuclear oxime- and Schiff base-containing receptors. 5-Bromosalicylaldehyde-containing azacrown ethers **8-10** were obtained in 45-61% yields by treatment of the appropriate N-(methoxymethyl)-substituted azacrown ether with 5-bromosalicylaldehyde as shown in Scheme 1. Compound **11** was reported earlier.[3g] N-(Methoxymethyl)-substituted azacrown ethers were prepared as reported.[3] Crown ethers **8-10** are important starting materials for various subsequent transformations. The interaction of compounds **8** and **10** with hydroxylamine in aqueous ethyl alcohol gave oximes **12** and **13**, respectively, in 90 and 57% yields (Scheme 2). Lariat azacrown ethers **14-18** containing Schiff base units, were synthesized in 72-97% yields by treatment of aldehyde **10** with the appropriate aromatic amine or substituted hydrazine as shown in Scheme 3.

We have conducted a preliminary study on the complexation of synthesized receptors with a number of alkali, alkaline earth and transition metal ions. Because of the low solubility of the ligands in methanol, we could not obtain the binding constants for the whole set of compounds. The values for the equilibrium constants (log K) and enthalpy (ΔH) and entropy ($T\Delta S$) changes for the interactions of lariat ethers **8, 9, 11, 12** and **14** with Na^+ and K^+ were determined in methanol at 25 °C using a calorimetric titration technique.[10] These values are listed in Table 1. Among the lariat ethers studied, the complexes of K^+-**9**, Na^+-**14**, and K^+-**14** are the most stable (log $K > 4$). As compared with parent macrocycles aza-15-crown-5, aza-18-crown-6, and diaza-18-crown-6,[11] these new salicylaldehyde- (**8,9,11**), oximic- (**12**), and Schiff base- (**14**) containing azacrown ethers exhibit increased binding constants for Na^+ and K^+. This observation indicates a participation of the salicylaldehyde, oximic, and Schiff-base sidearms in the complexing process. Like most other lariat ethers,[12] K^+/Na^+ selectivity demonstrated by these lariat ethers is not as high as that by the cryptands. The highest K^+/Na^+ selectivity is observed for **9** which shows a K_{K+}/K_{Na+} value of 9.

The 15-membered-ring **8** forms a more stable complex with Na^+ than with K^+ while the 18-membered-ring **9** forms a more stable complex with K^+ than with Na^+, indicating that the macroring portions of **8** and **9** play a more important role in cation binding than the salicylaldehyde sidearm. The difference between **8** and **12** is that **8** has a salicylaldehyde and **12** an oxime fragment attached to the macrocyclic ring. This difference results in different cation-binding behavior

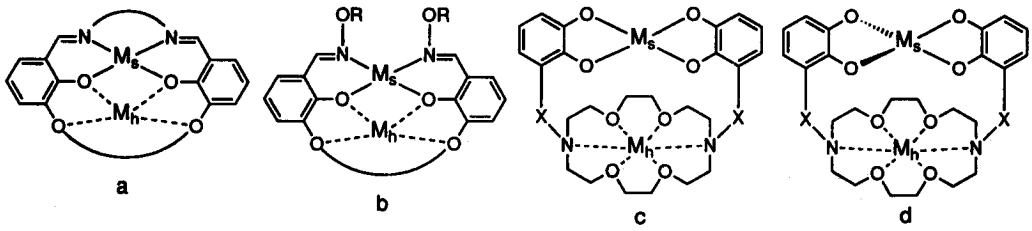
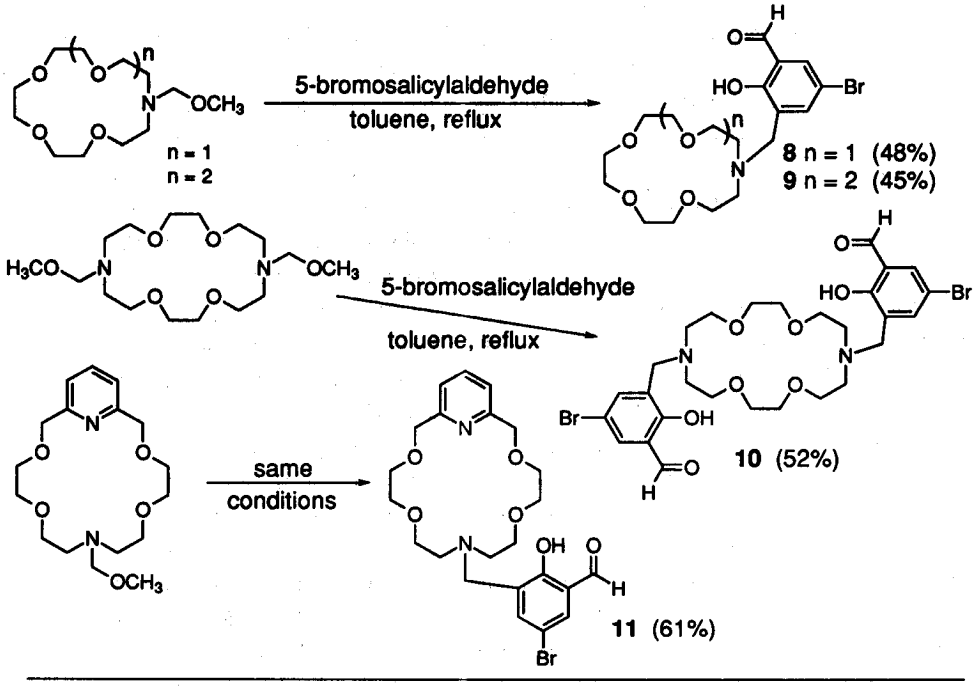
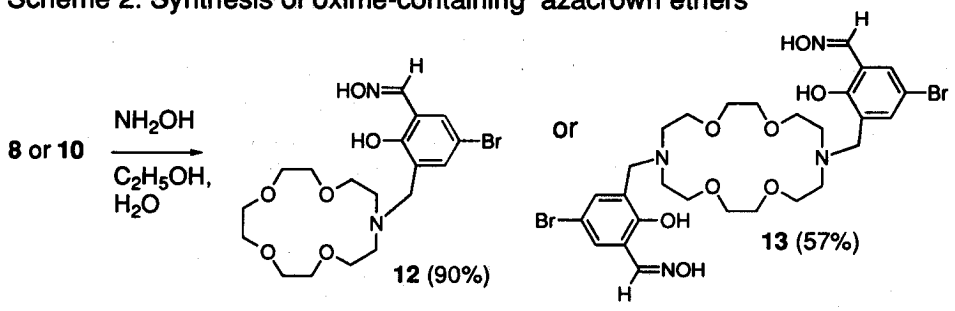


Figure 2. Heteronuclear metal ion receptors (M_s = soft metal ion, M_h = hard metal ion)

Scheme 1. Synthesis of 5-bromosalicylaldehyde-containing azacrown ethers



Scheme 2. Synthesis of oxime-containing azacrown ethers



between **8** and **12**. Macrocycle **8** is selective for Na^+ over K^+ by a factor of 4.1 (ratio of equilibrium constants) while **12** is selective for K^+ over Na^+ by a factor of 1.7. Macrocycle **11** differs from **9** in that a pyridine group of **11** is replaced by a $-CH_2OCH_2-$ unit in **9**. This structural change results in an increase in K^+ binding by **9** (log *K* value is increased from 3.40 for **11** to 4.07 for **9**) and a small decrease in Na^+ binding (log *K* value is decreased from 3.21 for **11** to 3.11 for **9**). Double-armed **14** shows strong interactions with both Na^+ and K^+. The phenol substituent on the imine group of **14** is probably an important factor for high Na^+ and K^+ binding constants.

Thermodynamic data in Table 1 demonstrate that complexation of Na^+ and K^+ by all the lariat ethers studied is

Scheme 3. Synthesis of Schiff base-containing azacrown ethers

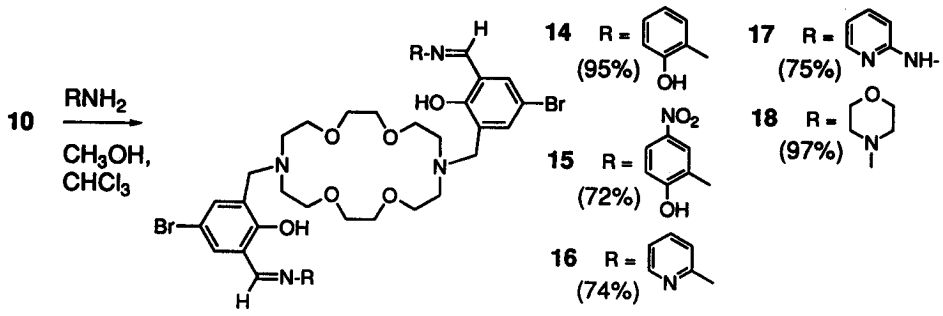


Table 1. **Log *K*, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) Values Determined by Titration Calorimetry for Interactions of Macrocyclic Ligands with Na^+ and K^+ in Methanol at 25.0 °C.**

Ligand	Cation	log *K*	ΔH	$T\Delta S$
8	Na^+	3.32 ± 0.04	-14.1 ± 0.6	4.85
	K^+	2.71 ± 0.05	-16.7 ± 0.7	-1.23
9	Na^+	3.11 ± 0.02	-29.5 ± 0.1	-11.7
	K^+	4.07 ± 0.02	-41.5 ± 0.2	-18.3
11	Na^+	3.21 ± 0.03	-19.7 ± 0.3	-1.38
	K^+	3.40 ± 0.03	-32.9 ± 0.2	-13.5
12	Na^+	2.88 ± 0.05	-20.1 ± 0.7	-3.66
	K^+	3.10 ± 0.05	-19.0 ± 0.5	-1.31
14	Na^+	4.47 ± 0.04	-33.8 ± 0.9	-8.29
	K^+	4.80 ± 0.05	-43.8 ± 0.8	-16.4

exothermic and the $T\Delta S$ values are negative except in the case of the Na^+-**8** interaction. These facts indicate that formation of complexes with these macrocyclic ligands in methanol is enthalpy driven (except the Na^+-**8** complex). Both enthalpic and entropic changes contribute to complexation of Na^+ by **8**. In each case, except for ligand **12**, K^+ interactions with the lariat ethers show more unfavorable entropy changes than do the Na^+ interactions with the same ligands, which may be caused by an extensive desolvation of the Na^+.[13]

The UV-visible spectral data for free and complexed lariat ethers **9, 10,** and **12-15** are shown in Table 2. UV spectra for free and complexed **10** and **12** are shown in Figures 3 and 4. The new functionalized diazacrown ethers **9, 10, 12** and **15** exhibit two absorption bands, while **13** and **14** exhibit three absorption bands all of which originate from their aromatic ring substituents. Crown ethers **10, 12,** and **13** have strong absorptions at 256-260 nm and 396-402 nm. The second peak is weaker than the first one. Diazacrown ether **13** shows an additional strong peak at 294 nm. Compared to **9, 10, 12,** and **13** the absorptions of diazacrown ethers **14** and **15** are much weaker (see Table 2 (a)). The maximum

Table 2. UV-Visible Spectral Data Valid in 50% DMF- 50% H_2O for Several Ligands and Their Metal Ion Complexes.

(a) Absorption Maxima (λ_{max} nm) and Molar Absorptivity Values (ϵ) of Ligands.

Ligand	λ_{max} (ϵ, $M^{-1}cm^{-1}$)	λ_{max} (ϵ, $M^{-1}cm^{-1}$)	λ_{max} (ϵ, $M^{-1}cm^{-1}$)
9	256 (1.7×10^4)		327 (6.6×10^3)
10	256 (1.3×10^4)		402 (8.4×10^3)
12	260 (2.3×10^4)		403 (1.4×10^4)
13	257 (1.6×10^4)	294 (9.4×10^3)	396 (8.2×10^3)
14	263 (2.8×10^3)	313 (2.3×10^3)	356 (2.6×10^3)
15	290 (4.0×10^3)		334 (3.5×10^3)

(b) Absorption Maxima (λ_{mzx}, nm) of the Ligand-Metal Ion Complexes.

Ligand	Na^+	K^+	Mg^{2+}	Ca^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
9	256	257	256	256	257	256	257	256
	326	326	326	329	348	352	344	334
10	256	256	256	256	256	256	256	256
	400	400	400	397	387	387	390	402
12	259	260	259	259	256	258	261	258
	399	398	396	394	375	385	317	387
							386	
13	258	256	258	257	256	256	255	256
	294	295	294	296	297	297	299	272
	395	395	394	395	380	381	386	389
14	263	267	268	267	264	268	268	262
	313	312	319	310		327	332	
	368	357		364		388	371	
15	290	290	288	287	264	292	270	263
	334	335	365	371		336	364	

absorption at the longest wavelength is more sensitive to cation complexation.

Complexation with alkali and alkaline earth metal cations (Na^+, K^+, Mg^{2+}, and Ca^{2+}) has little effect on the UV-visible spectra of **9, 10, 12,** and **13**. The same behaviour was observed for phenol- and CHQ- substituted azacrown ethers when they complexed Na^+ and K^+ in protic solvents in the absence of base.[4,5] Similar UV spectra of complexed and free

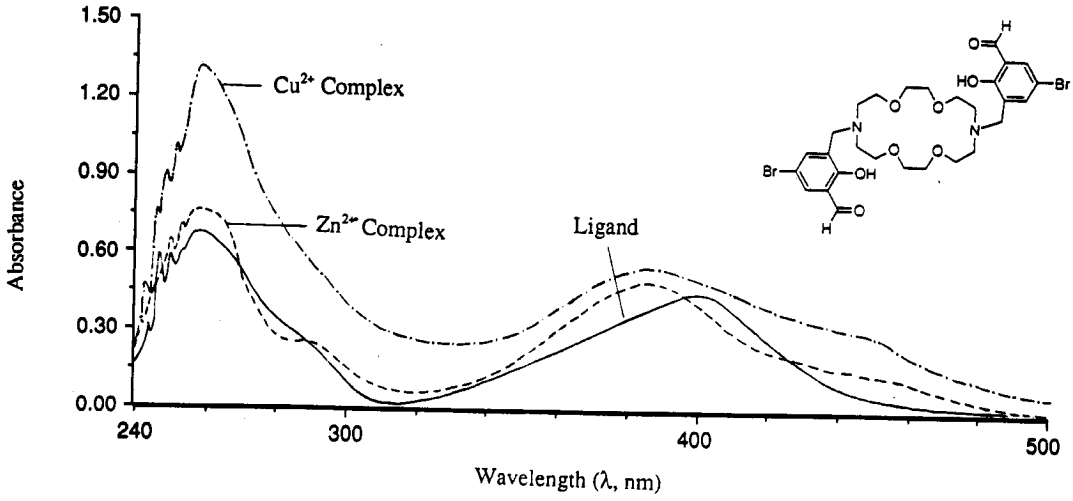


Figure 3. UV-visible spectra of free and complexed **10** in 50% DMF-50% H_2O. [**10**] = 5.04 x 10^{-5} M for Cu^{2+} (5.22 x 10^{-4} M) and Zn^{2+} (5.13 x 10^{-4} M).

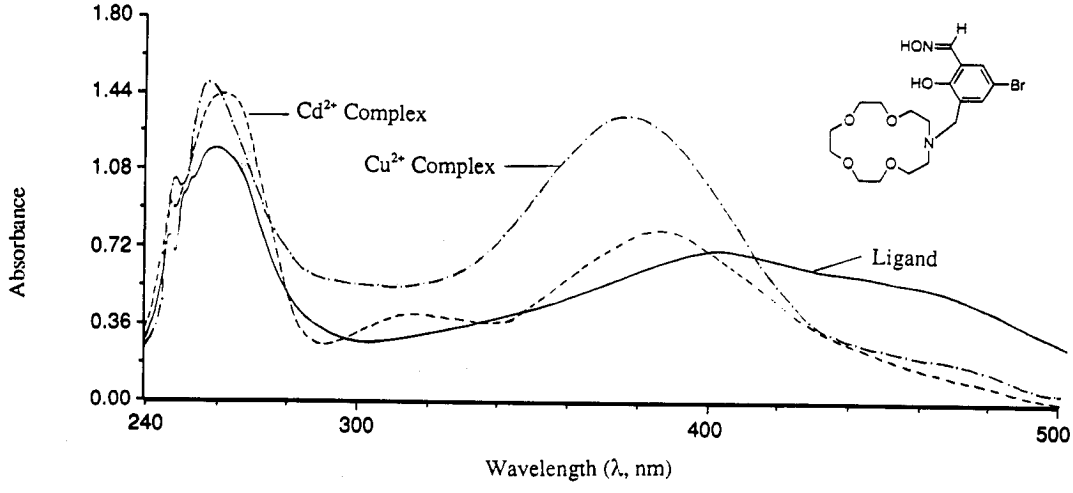


Figure 4. UV-visible spectra of free and complexed **12** in 50% DMF-50% H_2O. [**12**] = 5.11 x 10^{-5} M for Cu^{2+} (5.22 x 10^{-4} M) and Cd^{2+} (5.24 x 10^{-4} M).

ligands (**9,10,12,** and **13**) support the fact that, in spite of the obvious participation of phenolic oxygens in binding, coordination to alkali and alkaline earth metal ions occurs without formation of the phenolates. Compounds **9, 10, 12** and **13** exhibit appreciable shifts of the second (for **9, 10,** and **12**) or the third (for **13**) band upon complexation with transition metal ions (see Figures 3 and 4 and Table 2). The second band of compound **9** shifts 7-25 nm to a longer wavelength by complexation with the transition metal ions. The second band of compound **10** shifts 15 nm to shorter wavelengths when complexed with Zn^{2+} and Cu^{2+}. The maximum absorption at the longest wavelengths of compounds

12 and **13** shift appreciably (5-28 nm) to shorter wavelengths. Upon complexation of compound **12** with Cd^{2+}, a new absorption band can be observed at 317 nm which is probably a charge transfer band (see Figure 4 and Table 2). Thus, the UV-visible spectral data indicate an appreciable interaction of the oximic and Schiff base sidearm-containing ligands with cations, especially with Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, which are able to form chelate complexes with **9, 10, 12,** and **13**. Compounds **14** and **15** also show shifts of the absorption bands. The second band of **15** has large shifts when complexed with Mg^{2+} (31 nm) and Ca^{2+} (37 nm). When **14** and **15** are complexed with Cu^{2+} and Pb^{2+}, the absorption intensity of the peak in the vicinity of 263 nm increases (for **14**, from $\epsilon = 2.8 \times 10^3\ M^{-1}\ cm^{-1}$ to $\epsilon = 1.8 \times 10^4\ M^{-1}\ cm^{-1}$; and for **15**, from $\epsilon = 4.0 \times 10^3\ M^{-1}\ cm^{-1}$ to $\epsilon = 1.0 \times 10^4\ M^{-1}\ cm^{-1}$). Since Cu^{2+} and Pb^{2+} each have absorption in that region, this increase is mainly from the Cu^{2+} and Pb^{2+} ions.

Chelating agents bearing 2-hydroxybenzyl functions attached to the azacrown moiety have common structural features - the existence of intramolecular hydrogen bonds between the phenolic OH groups and nitrogen atoms of the macrocyclic ring.[3c,4,5] In the case of bis-substituted compounds (ligand **4**, for instance), this hydrogen bonding leads to opposite side location of aromatic side arms relative to the diazacrown plane. Similar mutual position of binding fragments has been found for ligand **10** in the solid state (see Figure 5). Opposite side location of aromatic side arms is

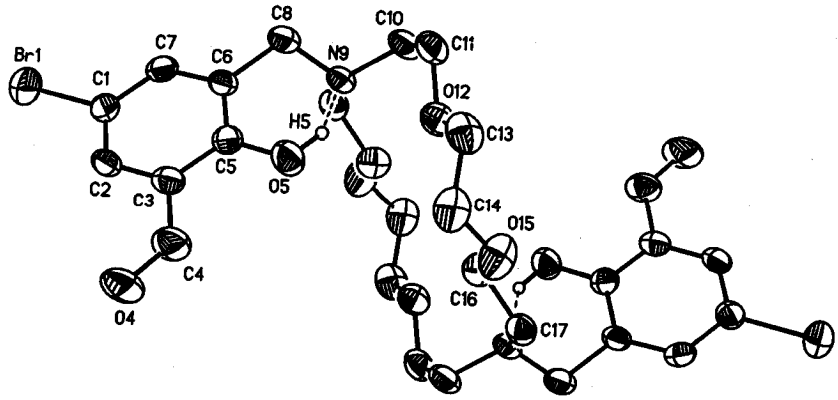


Figure 5. X-ray crystal structure of **10** with hydrogen atoms except those involved in hydrogen bonds omitted for clarity. Thermal ellipsoids were drawn at the 40% probability level.

likely present in oxime and Schiff base modified ligands **13-18** as well. However, conformational changes which bring both phenolic sidearms to one side of the macroring have been observed upon complexation.[4,5] Deprotonation should also facilitate the rotation of aromatic units[14] and promote chelation of the transition metal ions from the same side of the diazacrown plane, especially in case of cations having high deprotonating ability.

The X-ray crystal structure of **10** is shown in Figure 5.[15] The bond lengths and angles for **10** are normal. The molecule lies about a center of inversion which requires that the pendent arms of the ligand are on opposite sides of the diaza-crown ring. There are intramolecular hydrogen bonds linking the phenol oxygens of the sidearms to the nitrogen atoms of the crown ring. The hydrogen bond data are H5···N9, 1.895Å, O5···N9, 2.755Å and angle O5-H5···N9, 148.5°. The structure of **10** resembles that of the 4-chlorophenol-substituted diaza-18-crown-6 ligand.[5] That molecule also

contains a center of symmetry and intramolecular hydrogen bonds joining the side arms to nitrogen atoms of the crown ring. As mentioned above, the 4-chlorophenol- and 5-bromosalicylaldehyde-substituted ligands can undergo the conformational changes necessary to bring both side arms to the same side of the crown ring. Perhaps similar structural changes would be required to bring **13-18** into positions to form heteronuclear complexes.

Experimental Section

The ^{1}H NMR spectra were recorded at 200 MHz. CI and low voltage ionization were used to record the mass spectra. Starting materials and solvents were purchased from commercial sources where available. The N-(methoxymethyl)-substituted azacrown ethers were synthesized as described.[3a,3b]

N-(2′-Hydroxy-3′-carbonyl-5′-bromobenzyl)-1-aza-4,7,10,13-tetraoxacyclopentadecane (8) (Scheme 1). To a solution of 1.35 g (45 mmol) of paraformaldehyde in 50 mL of CH_3OH was added 7.42 g (33.8 mmol) of aza-15-crown-5. After standing for 30 min., CH_3OH was removed and to the residue was added 8.04 g (40 mmol) of 5-bromosalicylaldehyde and 150 mL of toluene. The mixture was stirred under reflux for 24 h. Toluene was evaporated and the residue was dissolved in a saturated solution of tartaric acid in water and extracted 3 times with 20-mL portions of EtOAc. The water phase was neutralized with Na_2CO_3 and brought to pH 8 with $NaHCO_3$. The crude product was extracted 4 times with 25-mL portions of $CHCl_3$. After removal of $CHCl_3$, the product was isolated by column chromatography on silica gel using THF as eluant to give 7 g (48%) of **8** as an oil; ^{1}H NMR ($CDCl_3$) δ: 2.80 (t, 4 H), 3.65 (m, 16 H), 3.84 (s, 2 H), 7.53 (m, 2 H), 9.50 (br, 1 H), 10.40 (s, 1 H); MS, m/z 433 $[M + 1]^+$. Anal. Calcd for $C_{18}H_{26}BrNO_6$: C, 50.01; H, 6.06. Found: C, 50.28; H, 6.10.

N-(2′-Hydroxy-3′-carbonyl-5′-bromobenzyl)-1-aza-4,7,10,13,16-pentaoxacyclooctadecane (9) (Scheme 1). Compound **9** was obtained in the same manner as above for **8** from 1.35 g (45 mmol) of paraformaldehyde, 10.53 g (40 mmol) of aza-18-crown-6 and 8.04 g (40 mmol) of 5-bromosalicylaldehyde. Ligand **9** (8.57 g, 45%) was isolated after column chromatography as an oil; ^{1}H NMR ($CDCl_3$) δ: 2.75 (t, 4 H), 3.66 (m, 20 H), 3.86 (s, 2 H), 7.55 (m, 2 H), 9.45 (br, 1 H), 10.41 (s, 1 H); MS, m/z 477 $[M + 1]^+$. Anal. Calcd for $C_{20}H_{30}BrNO_7$: C, 50.43; H, 6.35. Found: C, 50.50; H, 6.39.

N,N′-Bis(2′-hydroxy-3′-carbonyl-5′-bromobenzyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (10) (Scheme 1). Compound **10** was synthesized in the same manner as above for **9** from 0.93 g (31 mmol) of paraformaldehyde, 4 g (15 mmol) of diaza-18-crown-6 and 6.03 g (30 mmol) of 5-bromosalicylaldehyde. Ligand **10** (5.37 g, 52%) was isolated after column chromatography as a solid; mp 154-157 °C; ^{1}H NMR ($CDCl_3$) δ: 2.84 (t, 8 H), 3.60 (s, 8 H), 3.67 (t, 8 H), 3.86 (s, 4 H), 7.70 (m, 4 H), 9.40 (br, 2 H), 10.38 (s, 2 H); MS, m/z 689 $[M + 1]^+$. Anal. Calcd for $C_{28}H_{36}Br_2N_2O_8$: C, 48.85; H, 5.27. Found: C, 49.01; H, 5.31.

N-(2′-Hydroxy-3′-aldoximino-5′-bromobenzyl)-1-aza-4,7,10,13-tetraoxacyclopentadecane (12) (Scheme 2). A mixture of 0.6 g (1.4 mmol) of aldehyde **8**, 4 mL of a 1.4 mol/L solution of hydroxylamine in water and 10 mL of CH_3OH was refluxed for 0.5 h and stirred for 0.5 h at rt. CH_3OH was evaporated and 20 mL of water was added. The

product was extracted two times with 20-mL portions of $CHCl_3$. The combined organic layers were dried and the solvent was evaporated to give **12** (0.6 g, 90%) as an oil; ^1H NMR ($CDCl_3$) δ: 2.75 (t, 4 H), 3.65 (m, 16 H), 3.79 (s, 2 H), 7.40 (m, 2 H), 8.40 (s, 1 H), 9.10 (br, 1 H); MS, m/z 448 $[M + 1]^+$. Anal. Calcd for $C_{18}H_{27}BrN_2O_6$: C, 48.33; H, 6.08. Found: C, 48.17; H, 6.14.

N,N′-Bis(2′-hydroxy-3′-aldoximino-5′-bromobenzyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (13) (Scheme 2). A mixture of 1.14 g (1.7 mmol) of aldehyde **10**, 5 mL of an aqueous solution of hydroxylamine (1.4 mol/L) and 20 mL of CH_3OH was refluxed for 1 h and stirred at rt for 15 h. CH_3OH was removed under reduced pressure, 50 mL of H_2O was added and the product was extracted 5 times with 50-mL portions of $CHCl_3$. The organic phase was dried and evaporated. The residue was washed with 5 mL of $CHCl_3$ and the product was filtered and washed with ether to give **13** (0.7 g, 57%) as a solid; mp 104-106 °C (dec.); ^1H NMR (DMSO-d_6) δ: 2.78 (m, 8 H), 3.55 (m, 16 H), 3.82 (s, 4 H), 7.45 (m, 4 H), 8.25 (s, 2 H), 11.40 (br, 2 H); MS, m/z 719 $[M + 1]^+$. Anal. Calcd for $C_{28}H_{38}Br_2N_4O_8$: C, 46.81; H, 5.33. Found: C, 46.83; H, 5.31.

N,N′-Bis[2′-hydroxy-3′-N-(2′′-hydroxyphenyl)aldimino-5′-bromobenzyl]-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (14) (Scheme 3). A mixture of 0.5 g (0.7 mmol) of **10**, 0.158 g (1.4 mmol) of 2-aminophenol, 15 mL of $CHCl_3$ and 15 mL of CH_3OH was stirred under reflux for 24 h. After cooling to rt the product was filtered, washed with ether and dried to give **14** (0.6 g, 95%) as a solid; mp 102-110 °C(dec.); ^1H NMR (DMSO-d_6) δ: 2.75 (t, 8 H), 3.60 (m, 16 H), 3.75 (s, 4 H), 7.30 (m, 12 H), 8.32 (s, 2 H), 8.95 (s, 2 H), 9.75 (br, 2 H); MS, m/z 871 $[M + 1]^+$. Anal. Calcd for $C_{40}H_{46}Br_2N_4O_8$: C, 55.18; H, 5.33. Found: C, 55.16; H, 5.34.

N,N′-Bis[2′-hydroxy-3′-N-(2′′-hydroxy-5′′-nitrophenyl)aldimino-5′-bromobenzyl]-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (15) (Scheme 3). A mixture of 0.5 g (0.7 mmol) of **10**, 0.224 g (1.45 mmol) of 2-amino-4-nitrophenol and 15 mL of $CHCl_3$ was refluxed for 1 h and stirred at rt for 15 h. The mixture was filtered and $CHCl_3$ was evaporated to give 0.5 g (72 %) of **15** as a solid; mp 130-140 °C (dec.); ^1H NMR ($CDCl_3$) δ: 2.90 (t, 8 H), 3.70 (s, 8 H), 3.79 (t, 8 H), 3.85 (s, 4 H), 7.50 (m, 10 H), 9.10 (s, 2 H); MS, m/z 961 $[M + 1]^+$. Anal. Calcd for $C_{40}H_{44}Br_2N_6O_{12}$: C, 50.01; H, 4.62. Found: C, 50.04; H, 4.71.

N,N′-Bis[2′-hydroxy-3′-N-(2′′-pyridyl)aldimino-5′-bromobenzyl]-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (16) (Scheme 3). A mixture of 0.5 g (0.7 mmol) of **10**, 0.137 g (1.4 mmol) of 2-aminopyridine, 10 mL of $CHCl_3$ and 10 mL of CH_3OH was stirred under reflux for 1 h. After removing the solvents, 15-mL of ether was added and product was filtered and dried to give **16** (0.45 g, 74 %) as a solid; mp 165-170 °C (dec.); ^1H NMR ($CDCl_3$) δ: 2.88 (t, 8 H), 3.65 (m, 16 H), 3.81 (s, 4 H), 7.72 (m, 12 H), 9.40 (s, 2 H); MS, m/z 841 $[M + 1]^+$. Anal. Calcd for $C_{38}H_{44}Br_2N_6O_6$: C, 54.30; H, 5.28. Found: C, 54.21; H, 5.39.

N,N′-Bis[2′-hydroxy-3′-N-(2′′-aminopyridyl)aldimino-5′-bromobenzyl]-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (17) (Scheme 3). To a solution of 0.5 g (0.7 mmol) of **10** in 15 mL of $CHCl_3$ was added 0.159 g (1.45 mmol) of 2-hydrazinopyridine and the mixture was refluxed for 15 min and stirred at rt for 15 h. The product was filtered, washed with $CHCl_3$ and ether and dried to give **17** (0.5 g, 75%) as a solid; mp 218-223 °C (dec.); ^1H NMR

(DMSO-d_6) δ: 2.89 (m, 8 H), 3.56 (m, 16 H), 3.85 (s, 4 H), 7.42 (m, 12 H), 8.25 (s, 2 H); MS, m/z 871 $[M + 1]^+$. Anal. Calcd for $C_{38}H_{46}Br_2N_8O_6$: C, 52.42; H, 5.33. Found: C, 52.38; H, 5.50.

N,N′-Bis[2′-hydroxy-3′-N-(N-morpholyl)aldimino-5′-bromobenzyl]-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (18) (Scheme 3). Compound **18** was obtained in the same manner as above for **16** from 0.5 g (0.7 mmol) of **10** and 0.15 g (1.4 mmol) of N-aminomorpholine. Ligand **18** (0.6 g, 97%) was isolated as a solid; mp 145-149 °C (dec.); ^{1}H NMR ($CDCl_3$) δ: 2.82 (t, 8 H), 3.15 (t, 8 H), 3.62 (s, 8 H), 3.69 (t, 8 H), 3.75 (s, 4 H), 3.85 (t, 8 H), 7.39 (m, 4 H), 7.80 (s, 2 H); MS, m/z 857 $[M + 1]^+$. Anal. Calcd for $C_{36}H_{52}Br_2N_6O_8$: C, 50.47; H, 6.12. Found: C, 50.53; H, 6.23.

Determination of Thermodynamic Quantitites. Log *K*, Δ*H*, and TΔ*S* values were determined as described earlier[10] in MeOH at 25.0 ± 0.1 °C by titration calorimetry using a Tronac Model 450 calorimeter equipped with a 20-mL reaction vessel. The metal ion solutions were titrated into the macrocyclic ligand solutions and the titrations were carried out to a two-fold excess of the metal ions. The titration experiments showed that all interactions studied had a 1:1 cation-ligand ratio. The method used to process the calorimetric data and to calculate the log *K* and Δ*H* values has been described.[16]

UV-visible Spectral Measurements. UV-visible spectra were recorded at 23 ± 1 °C in a 1-cm quartz cell by using a Hewlett-Packard 8452A Diode Array spectrophotometer. 50% DMF-50% H_2O (v:v) was used as the solvent. Concentrations were 10^{-4}-10^{-5}M for ligands and 10 times the ligand concentrations for the metal ions.

X-ray Determination. Crystal and intensity data were obtained using a Siemens R3m/V automated diffractometer which utilized MoKα radiation. The intensity data were collected to a 2θ maximum of 50° using a 2θ-θ scanning technique. Three standard reflections measured every 97 reflections indicated that the crystal and electronics were stable.

The structure was solved using a combination of heavy atom and direct methods. Since the molecule is located about a center of symmetry, the asymmetric unit is one-half of the molecule. Positions of the hydrogen atoms bonded to the phenol oxygen atom, O5, and the carbonyl carbon atom, C4, were located in a difference map. Positions for the remaining hydrogen atoms were calculated. All hydrogen atoms were allowed to ride on their neighboring heavy atom and were assigned isotropic thermal parameters which were not refined. All the non-hydrogen atoms were refined anisotiopically. Unit weights were used in the full-matrix least-squares refinement of the structure. The programs used in solving, refining and displaying the structure of **10** are contained in the program package SHELXTL-PLUS.[17]

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References

1. Present address of A.V.B.; Chem. Eng. 210-41; California Institute of Technology; Pasadena, CA 91125.
2. Present address of V.N.P.; A.V. Bogatsky Physico Chemical Institute; National Academy of Sciences of Ukraine; Odessa 270080, UKRAINE.
3. (a) Bogatsky, A.V.; Lukyanenko, N.G.; Pastushok, V.N.; Kostyanovsky, R.G. *Synthesis* **1983**, 992. (b) Lukyanenko, N.G.; Pastushok, V.N.; Bordunov, A.V. *Synthesis,* **1991**, 241. (c) Bordunov, A.V.; Lukyanenko, N.G.; Pastushok, V.N.; Krakowiak, K.E.; Bradshaw, J.S.; Dalley, N.K.; Kou, X. *J. Org. Chem.* **1995**, *60*, 4912. (d) Lukyanenko, N.G.; Pastushok, V.N.; Bordunov, A.V.; Vetrogon, V.I.; Vetrogon, N.I.; Bradshaw, J.S. *J.*

Chem. Soc., Perkin Trans. **1994**, 1489. (e) Bordunov, A.V.; Bradshaw, J.S.; Pastushok, V.N.; Izatt, R.M. *SynLett*, **1996**, 933. (f) Pastushok, V.N.; Bradshaw, J.S.; Bordunov, A.V.; Izatt, R.M., *J. Org. Chem.* **1996**, *61*, 6888-6892. (g) Bordunov, A.V.; Hellier, P.C.; Bradshaw, J.S.; Dalley, N.K.; Kou, X.; Zhang, X.X.; Izatt, R.M. *J. Org. Chem.* **1995**, *60*, 6097.

4. Zhang, X.X.; Bordunov, A.V.; Bradshaw, J.S.; Dalley, N.K.; Kou, X.; Izatt, R.M. *J. Am. Chem. Soc.* **1995**, *117*, 11507.
5. Bordunov, A.V.; Bradshaw, J.S.; Zhang, X.X.; Dalley, N.K.; Kou, X.; Izatt, R.M. *Inorg. Chem.*, **1996**, *35*, 7229.
6. Zhang, X.X.; Bradshaw, J.S.; Bordunov, A.V.; Izatt, R.M. *J. Incl. Phenom.* **1997**, in press.
7. van Vergel, F.C.J.M.; Verboom, W.; Reinhoudt, D.N. *Chem. Rev.* **1994**, *94*, 279.
8. (a) van Staveren, C.J.; van Eerden, J.; van Veggel, F.C.J.M.; Harkema, S.; Reinhoudt, D.N. *J. Am. Chem. Soc.* **1988**, *110*, 4994. (b) van Staveren, C.J.; Reinhoudt, D.N.; van Eerden, J.; Harkema, S. *J. Chem. Soc., Chem. Commun.* **1987**, 974. (c) van Veggel, F.C.J.M.; Harkema, S.; Bos, M.; Verboom, W.; Klein Woolthuis, G.; Reinhoudt, D.N. *J. Org. Chem.* **1989**, *54*, 2351. (d) van Veggel, F.C.J.M.; Bos, M.; Harkema, S.; Verboom, W.; Reinhoudt, D.N. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 746.
9. Graf, E.; Hosseini, M.W.; Ruppert, R. *Tetrahedron Lett.* **1994**, *35*, 7779.
10. (a) Oscarson, J.L.; Izatt, R.M. In *Physical Methods of Chemistry Vol. VI: Determination of Thermodynamic Properties*; Rossiter, B.W.; Baetzold, R.C. (Eds.) John Wiley & Sons: New York, 1992; Chapter 7. (b) Izatt, R.M.; Wu, G. *Thermochim. Acta* **1989**, *154*, 161.
11. (a) Izatt, R.M.; Pawlak, K.; Bradshaw, J.S.; Bruening, R.L. *Chem. Rev.* **1991**, *91*, 1721. (b) Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J.; Sen, D. *Chem. Rev.* **1985**, *85*, 271.
12. (a) Gokel, G.W.; Trafton, J.E. In *Cation Binding by Macrocycles*; Inoue, Y.; Gokel, G.W. (Eds.) Marcel Dekker: New York, 1990; Chapeter 6. (b) Arnold, K.A.; Hernandez, J.C.; Li, C.; Mallen, J.V.; Nakano, A.; Schall, O.F.; Trafton, J.E.; Tsesarskaja, M.; White, B.D.; Gokel, G.W. *Supramol. Chem.* **1995**, *5*, 45.
13. Izatt, R.M.; Zhang, X.X.; An, H.-Y.; Zhu, C.-Y.; Bradshaw, J.S. *Inorg. Chem.* **1994**, *33*, 1007.
14. Bordunov, A.V.; Dalley, N.K.; Kou, X.; Bradshaw, J.S.; Pastushok, V.N. *J. Heterocyclic Chem.***1996**, *33*, 933.
15. Tables of positional and thermal parameters and crystal data and experimental conditions for **10** have been deposited in the Cambridge Crystallographic Data Center. These data can be obtained from the Director, Cambridge Crystallographic Center, 12 Union Road, Cambridge, CB2IEZ, UK.
16. Eatough, D.J.; Christensen, J.J.; Izatt, R.M *Thermochim. Acta.* **1972**, *3*, 219.
17. Sheldrich, G.M. "SHELXTL-PLUS™," Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, 1990.

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