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Azomacrocyclic derivatives of imidazole: synthesis, structure, and metal ion complexation properties

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Abstract—New azocrown ethers comprising imidazoles in the macrocycle have been synthesized. Imidazole, 2-methyl-, 4-methyl-, and 4-phenylimidazole were incorporated to form macrocyclic units by coupling with the appropriate bis-diazonium salts. The syntheses were performed under high dilution conditions. The X-ray structure of a water adduct of the 21-membered crown ether derivative of 4-methylimidazole **8** has been solved. Metal cation binding was investigated with the use of UV–vis spectroscopy in acetonitrile, methanol, and methanol–water mixtures. The obtained chromoionophores were tested as ion-carriers in ion-selective membrane electrodes.

1. Introduction

Since Pedersen's discovery,[1] crown ethers have been intensively investigated macrocyclic compounds due to facile synthesis and almost infinite possibilities of chemical modifications. Crown ethers equipped with chromogenic residue(s) enable visual or colorimetric examination of metal cation complexation, in particular alkali metal cations, which formerly could not be determined with the use of 'classical' complexing reagents. Furthermore, in the case of macrocyclic reagents, the complexation process is controlled by the proper fit of cavity and ion radius. Previously, we presented a series of chromogenic crown ethers bearing two azo units and phenol,[2] pyrrole[3,4] or imidazole[3] residues, all forming inherent parts of the macrocycle. Macrocycles with azole residue were expected to show rather increased susceptibility to bind softer cations. In fact, the recently described pyrrole derivatives **1–4**[4] (Scheme 1a) selectively transport and bind Pb^{2+} amongst Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} cations. Lead(II) selectivity was also found for ion-selective membrane electrodes doped with the above pyrrole macrocycles.

More recently,[3] we reported the synthesis of analogous 18-membered chromogenic imidazole derivative (**5**, Scheme 1). This compound selectively binds sodium cations among alkali metal cations in acetonitrile. However, the type and location of donor atoms in the macrocycle should favor complexation of 3d block metal cations.[5,6] It is, for example, known that the imidazole residue of histidine plays a crucial role in zinc(II) and copper(II) metalloproteins, where complexes of 2:1 (ligand:metal) stoichiometry are formed.[7] In this paper, we present the synthesis of new imidazole derivatives of different macrocycle size and study their metal ion complexation.

2. Results and discussion

2.1. Synthesis

The title azocrown ethers were obtained by coupling imidazoles with the respective bis-diazonium salts (Scheme 1b and c), analogously to previously described procedures.[3] The coupling reaction was carried out in water under high dilution conditions at a pH of about 10 (NaOH). Imidazole or its derivatives substituted in position 2 or 4 were used as starting materials to obtain macrocycles with azo groups in positions 4 and 5, or in positions 2 and 5 of imidazole moiety, respectively. Consequently, compounds of different lipophilicity and with different orientation of imidazole residue versus macrocycle were obtained. By changing the length of oligooxyethylene chain in bis-diazonium salts 17-, 18-, 20-, and 21-membered chromoionophores (compounds **6–12**, **18**, and **19**) were obtained. The extracted products were purified by column chromatography. The highest yield (55%) was found for compound **6**. Macrocycles **18** and **19** with ethyl substituents in benzene rings were obtained by multistep reaction shown in Scheme 1c. The starting 3-ethylphenol was nitrated to give **13**, which in turn was alkylated with 1,5-dichloro-3-oxapentane or 1,8-dichloro-3,6-dioxaoctane to produce dinitropodands **14** or **15**, which were reduced

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Keywords: Azomacrocyclic ligands; Imidazole; Synthesis; Metal complexes; X-ray structure.

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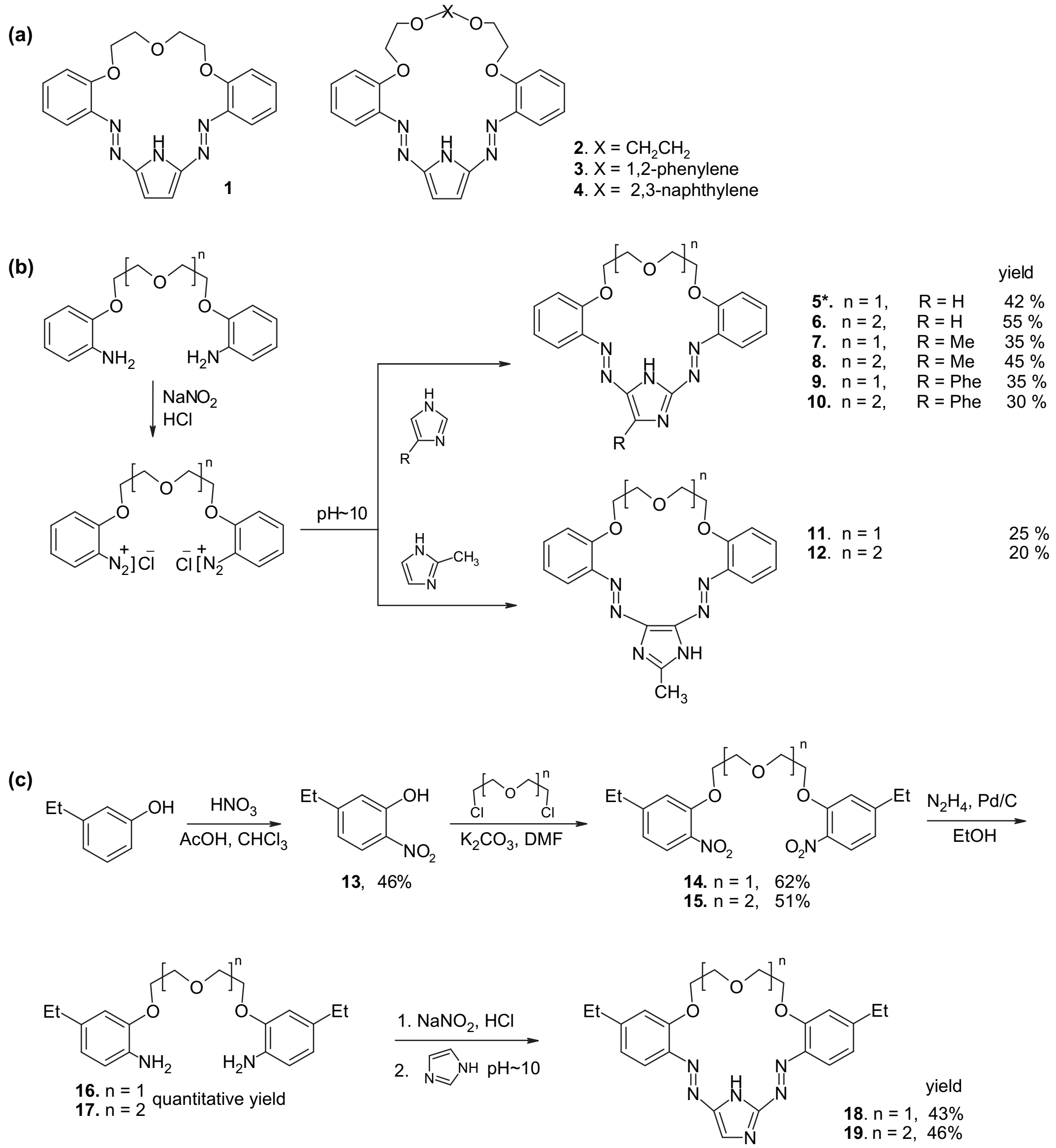


Scheme 1. Synthesis of azocrown ethers with imidazole residue. *Compound **5** was obtained previously.[3]

to diamino compounds **16** and **17**. The diamines were converted into bis-diazonium salts and coupled with imidazole as described above.

2.2. X-ray structure

A single crystal of compound **8**·H_2O was obtained by crystallization from acetone. In the solid state **8** exists in the form of an internal hydrate stabilized by hydrogen bonds. There are two independent molecules in the crystal lattice (Fig. 1, left and right structures). The molecule (right) shows disorder of one oxyethylene residue (denoted as A and B).

2.3. Metal cation complexation in solution—UV–vis spectroscopy

21-Membered 4-methylimidazole azocrown ether **8** (Scheme 1), as a representative of this class of compounds, was used for metal cation complexation studies. Binding of alkali, alkaline earth, transition, and lead(II) cations was studied spectrophotometrically in three different solvents: acetonitrile, methanol, and mixed methanol–water (4:1, v/v) system. In all systems no significant changes in absorption spectra were found in the presence of lithium, sodium, potassium, and magnesium cations.

In acetonitrile and methanol, the original orange-red color of the ligand changes to yellow on titration with Ca^{2+}, Sr^{2+} or Ba^{2+} salts, whereas titration with Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, and Pb^{2+} changes it to purple-violet. The respective spectral changes of **8** during titration are shown in Supplementary data.

The stoichiometry of the formed complexes was determined from Job's and/or molar ratio plots (not shown here) in cases where complex absorption band does not overlap bands of

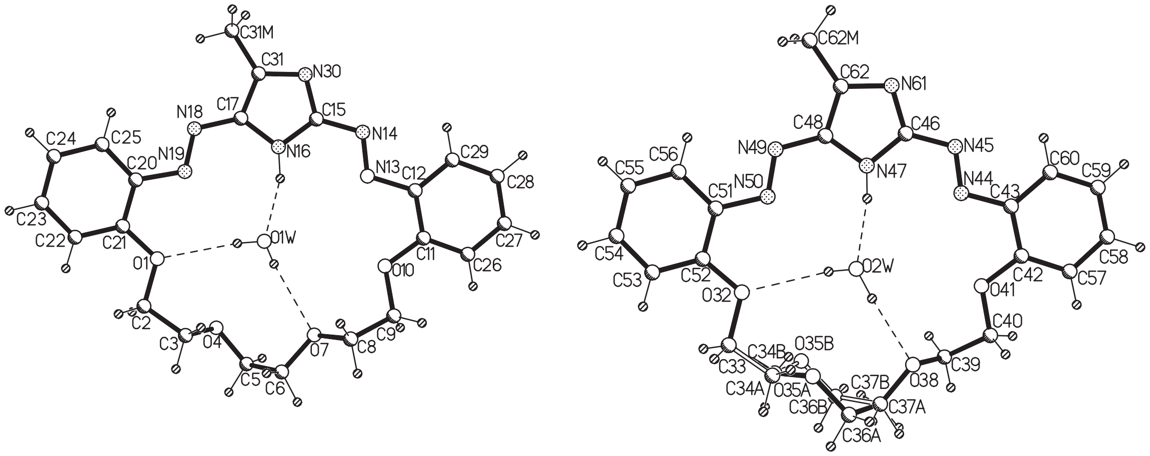


Figure 1. Structure of **8**·H_2O: non-disordered form (left) and molecule with one disordered oxyethylene residue denoted as A and B (right) with hydrogen bonds created by internal water molecule.

Table 1. Stoichiometry and values of stability constants (log β) of complexes in acetonitrile at 25±0.5 °C for **8**

Ion	Ca^{2+}	Sr^{2+}	Ba^{2+}	Zn^{2+}	Pb^{2+}	Co^{2+}	Cu^{2+}	Ni^{2+}
[L:M]	1:1	1:1	1:1	1:1	1:1		1:1	
				2:1	2:1	2:1	2:1	2:1
log β_1	4.19	4.32	4.81	5.17	5.38		6.64	
log β_2				3.80	3.87	9.02	4.55	9.31

free ligand. Stability constant values for 1:1 and 2:1 ligand: metal (L:M) complexes were calculated using Dynafit[7] program. The obtained results are listed in Table 1.

For alkaline earth cations the best fit was found for 1:1 stoichiometry, whereas for cobalt(II) and nickel(II) the most probable stoichiometry is 2:1 (L:M). On the other hand, for lead(II), copper(II), and zinc(II) the best fit was obtained for systems where two complexes exist: 1:1 and 2:1 (L:M).

Analogous titrations of **8** with alkaline earth metal cations were performed also in methanol, however, only in the case of barium ions changes in absorption spectra were sufficient to estimate stoichiometry and the value of stability constant (Table 2). Details of these experiments are shown in Supplementary data.

Contrary to acetonitrile solutions, changes of absorption spectra in methanol are more spectacular for Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, and Pb^{2+} cations. In methanol, isosbestic points are better pronounced than in acetonitrile; they are also followed by larger spectral shifts. In most cases a bathochromic shift of about 50 nm was noticed. In methanol the largest shift, 65 nm, was found for the lead(II) complex, whereas in acetonitrile it was only about 25 nm with a less distinctive complex band (cf. Supplementary data).

Table 2. Stoichiometry and values of stability constants of complexes in methanol at 25±0.5 °C for **8**

Ion	Ca^{2+}	Sr^{2+}	Ba^{2+}	Zn^{2+}	Pb^{2+}	Co^{2+}	Cu^{2+}	Ni^{2+}
[L:M]	[a]	[a]	1:1	1:1	2:1	nd	2:1	nd
log β	—	—	4.00	5.61	7.67	nd	7.48	nd

nd, Not determined due to slow kinetics.

[a] Insufficient changes in absorption spectra do not allow determination stoichiometry and the value of stability constants.

The stoichiometry of the formed complexes and the values of their stability constant were determined as for acetonitrile solutions. The results are listed in Table 2.

The spectroscopic experiments show that in methanol the number of species under equilibrium is reduced comparing acetonitrile. In most cases only one complex is formed: 1:1 for barium and zinc, and 2:1 (L:M) for lead and copper. Cobalt and nickel ions appear not to be completely complexed within the time scale of the initial spectrophotometric titration; thus no reasonable values of stability constants could be obtained. On the other hand, complexation in acetonitrile occurs rapidly. This is in contrast with the earlier described zinc(II), cobalt(II) or nickel(II) complexation by pyrrole azocrowns.[4]

Preliminary studies of compound **8** in aqueous methanol showed increase of ligand absorption coefficient compared to solutions in pure methanol and in acetonitrile. Further titrations were performed in water–methanol system (4:1, v/v), which was found to be the most favorable (cf. Supplementary data). Table 3 compares the absorption coefficients in the above systems.

In water containing solvent system both lead(II) and copper(II) cations formed complexes of 1:1 stoichiometry with log β equal to 4.75 and 5.51, respectively. The spectral shift for the copper complex is 55 nm and for lead is 61 nm (Fig. 2).

Diversity of spectral changes upon complexation of alkaline earth cations on one, and the remaining studied cations on

Table 3. Molar absorption coefficients for compound **8** at λ_{max}=492 nm

Solvent	ε_{max} ($\times 10^4$)
Acetonitrile	1.97
Methanol	2.27
Methanol–water (4:1)	2.67

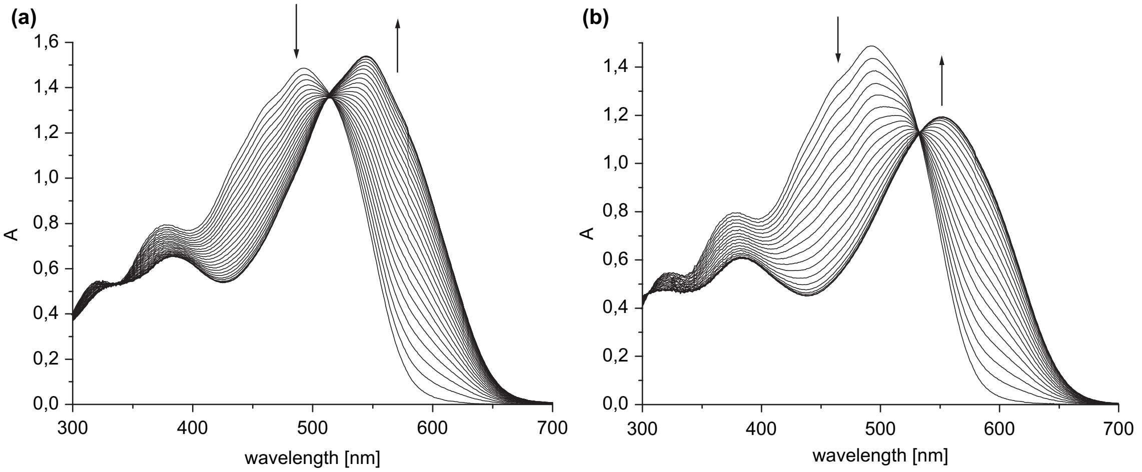


Figure 2. Changes in absorption spectra upon titration of ligand **8** with metal perchlorates: (a) copper (c_L=6.98×10^{-5} mol dm^{-3}, c_M=1.87×10^{-3} mol dm^{-3}) and (b) lead (c_L=6.98×10^{-5} mol dm^{-3}, c_M=1.42×10^{-3} mol dm^{-3}) in methanol–water (4:1). The initial spectrum is that of the starting ligand and the final corresponds to the complexed form (see Section 4).

the other side could be ascribed to the different stoichiometries of the formed compounds. However, taking into account HSBA theory, it is also possible that binding of particular ions involves different parts of ligand molecule. To distinguish between these possibilities, the complexation was studied by ^{1}H NMR spectroscopy. To better visualize the role of imidazole ring in complexation, in this experiment 21-membered azocrown **6** with an unsubstituted imidazole moiety (Scheme 1b) was used. Complexes with barium and lead(II) perchlorates were obtained using equimolar amounts of components in acetonitrile. The solvent was evaporated and the spectra were registered in *d*-acetone. Differences in chemical shifts of particular protons of ‘free’ ligand and of its respective complexes are listed in Table 4.

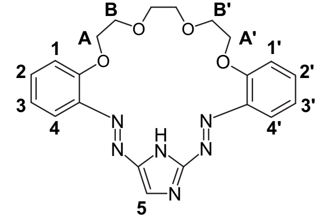
For the barium complex all OCH_2 signals are shifted more than the lead(II) complex. On the other hand, for the lead complex aromatic signals are more shifted, especially the C–H proton of the imidazole ring. These results indicate that in both cases the contribution of different parts of the ligand to the complex formation is not identical. This could explain different trends of spectral changes upon complexation of alkaline earth metal cations and other studied metal ions. Unfortunately, attempts to obtain metal complexes in form suitable for X-ray investigations that may confirm the above statement, failed.

2.4. Ion-selective electrodes

Electrodes based on pyrrole crown ethers[4] (Fig. 1a) are lead(II) selective. We carried out series of experiments to test electrodes doped with imidazole derivatives. General information on preparing electrodes and measurements are described in detail in Section 4. From preliminary studies, 60% molar amount of lipophilic salt in relation to ionophore was found to be most favorable.

Compound **5** was an inefficient ionophore as it readily leaked to the aqueous solution in the presence of Pb^{2+} ions. In general, electrodes based on smaller 17- and 18-membered ring ionophores showed very short lifetimes (less than 24 h), which makes their application limited. Better properties were found for electrodes doped with the larger, 21-membered ion-carriers. Among them, the electrode based on compound **19** possesses the best properties; however, the range of linear response is rather narrow. Parameters of constructed electrodes are listed in Table 5. The respective values of the selectivity coefficients are summarized in Figure 3.

Table 4. Shifts+Δ*δ* [ppm] in ^{1}H NMR spectra for compound **6** and for its barium or lead(II) complexes in *d*-acetone



Complex of **6** with	A,A′	B,B′	C,C′	1,1′	2,2′	3,3′	4,4′	5
Ba^{2+}	0.26	0.33	0.28	0.15	0.13	~0.09	0.00	0.44
	0.25	0.33		0.14	0.12		0.01	
Pb^{2+}	~0.2	~0.28	0.21	0.14	0.22	~0.15	0.04	0.72
				0.15	0.21	~0.12	0.06	

Table 5. Linear responses and slopes for electrodes based on compound **11**, **6**, **8**, **19**, and for blank electrode

Ionophore	11	6	8	19	Blank
Linear response range	−5.0 to −2.5	−5.0 to −3.0	−5.5 to −2.5	−4.5 to −3.0	−4.5 to −1.5
Slope [mV/dec]	30.7	37.5	35.6	25.6	21.8

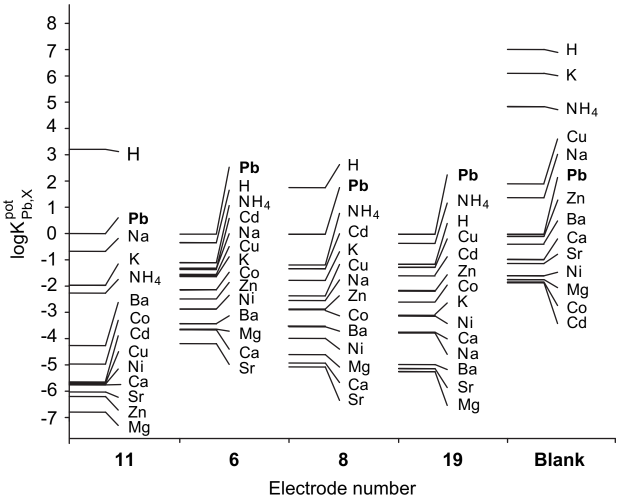


Figure 3. Selectivity coefficients ($\log K^{pot}_{Pb,X}$) for membrane electrodes doped with compound **11**, **6**, **8** or **19** and blank electrode. Number of electrode corresponds to number of ionophore (Scheme 1).

3. Conclusions

Azomacrocycles of different sizes were obtained with relatively high yield (up to 55%) by coupling imidazole with the respective bis-diazonium salts. In the solid state azocrown **8** exists in the form of an internal hydrate. The chromogenic compounds form complexes with alkaline earth metal cations and with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Pb^{2+}. The stoichiometry of the formed complexes, values of stability constants, and spectral shifts are solvent dependent. The best shape of the spectra and highest peak separations were found in methanol–water (4:1) mixtures. Due to the selectivity of complex formation, the 21-membered crown ether **8** could be used as a spectrophotometric reagent for identification and determination of Cu^{2+} and Pb^{2+} in solution. The advantage is that it may be used in water containing system, important from an analytical point of view. Electrodes with membranes doped with macrocyclic derivatives of imidazole are lead(II) selective, however, taking into account other available ionophores, often with better properties,[8] the application of the presented here crown ethers is rather limited.

4. Experimental

4.1. General

All materials and solvents were of analytical reagent grade. For TLC experiments aluminum plates covered with silica gel 60 F_{254} (Merck) were used. ^1H and ^{13}C NMR spectra (in $CDCl_3$ or *d*-acetone as indicated) were recorded on Varian instrument at 500 or 125 MHz, respectively. NMR studies of barium and lead complexes of azocrown **6** were performed in acetone. UV–vis spectra were recorded on a UNICAM UV 300 apparatus. Mass spectra were taken on AMD-604 apparatus and IR spectra were recorded on Genesis II FTIR (Mattson) instrument. The mp (°C) are uncorrected. Potentiometric measurements were done using 654 pH-meter (METROHM). As reference OP-08201 Ag/AgCl electrode (Radelkis) was used. For all solutions deionized water was used.

4.2. Synthesis

Synthesis of macrocyclic compounds was carried out analogously to described earlier procedures.[2,3]

Two solutions were prepared:

Solution A. To a suspension of 1,5-bis-(2-aminophenoxy)-3-oxapentane, 1,8-bis-(2-aminophenoxy)-3,6-dioxaoctane,[2,9] 1,5-bis-(2-amino-5-ethylphenoxy)-3-oxapentane or 1,8-bis-(2-amino-5-ethylphenoxy)-3,6-dioxaoctane (2 mmol) in 40 cm^3 water, 1 cm^3 concd hydrochloric acid was added. The clear solution was diazotized with sodium nitrite (0.28 g, 4 mmol) dissolved in 2 cm^3 cold water.

Solution B. Imidazole, 2-methyl-, 4-methyl- or 4-phenylimidazole (2 mmol), and sodium hydroxide (0.2 g, 5 mmol) were dissolved in 40 cm^3 water. To the solution containing 4-phenylimidazole 2 cm^3 ethanol was added.

Ice-cold solutions A and B were added dropwise with the same rate during 45 min to a vigorously stirred cold (10 °C) water (600 cm^3) alkalized with NaOH to pH ~10. Then stirring was continued overnight. During the first 3 h the temperature was maintained at 10 °C, and then was kept at room temperature for 12 h. The reaction mixture was adjusted to pH ~6 with acetic acid and extracted with chloroform. The combined extracts were evaporated under reduced pressure and the respective crowns were isolated by column chromatography on silica gel using solvent mixtures of increasing polarity (methylene chloride, acetone, and methanol).

Azocrown **5**: 18-membered derivative of imidazole was described in reference.[3]

4.2.1. Azocrown 6: 21-membered derivative of imidazole.

Orange-red solid crystallized from acetone; mp 161–163 °C. TLC, R_f~0.8 (CH_2Cl_2–methanol 15:2). ^1H NMR δ_H (ppm): 8.15 (1H, s, ArH); 7.95 (1H, d, J=8.3 Hz, ArH); 7.80 (1H, d, J=7.8 Hz, ArH); 7.50–7.35 (2H, m, ArH); 7.10–7.00 (4H, m, Ar*H*); 4.35–4.25 (4H, m, $ArOCH_2$); 4.00–3.90 (4H, m, $ArOCH_2CH_2$); 3.80 (4H, s, central OCH_2CH_2O). ^{13}C NMR δ_C (ppm): 68.5; 68.6; 69.5; 69.5; 70.8; 70.8; 113.6; 113.8; 116.7; 117.0; 121.6; 132.8; 134.4; 137.0; 142.3; 142.5; 146.3; 156.0; 156.7; 157.5. IR ν_{max} (film): 3476; 1588; 1279; 1233; 1153; 1118; 1087; 1044; 756 cm^{-1}. HRMS (EI): found $[M]^+$=422.1698; $C_{21}H_{22}N_6O_4$ requires 422.1703.

^{1}H NMR of crown ether **6** and its barium and lead(II) complexes in d_6-acetone; δ_H (ppm) is as follows:

4.2.1.1. Crown 6. 8.12 (1H, s); 7.85 (1H, dd, J_1=1.5 Hz, J_2=8.3 Hz, ArH); 7.79 (1H, dd, J_1=1.5 Hz, J_2=8.3 Hz, ArH); 7.60 (1H, t, J=8.3 Hz, ArH); 7.51 (1H, t, J=8.7 Hz, ArH); 7.33 (1H, d, J=8.3 Hz, ArH); 7.28 (1H, d, J=8.7 Hz, ArH); 7.14–7.08 (2H, m); 4.41 (2H, t, J=4.4 Hz, ArOCH_2); 4.39 (2H, t, J=4.4 Hz, ArOCH_2); 3.99 (2H, t, J=4.4 Hz, ArOCH$_2$CH_2); 3.96 (2H, t, J=4.4 Hz, ArOCH$_2$CH_2); 3.82 (4H, s, central OCH_2CH_2O).

4.2.1.2. Crown 6 + Ba(ClO$_4$)$_2$. 8.56 (1H, s); 7.85 (1H, d, J=7.8 Hz, ArH); 7.80 (1H, d, J=7.8 Hz, ArH); 7.73 (1H, t, J=7.3 Hz, ArH); 7.63 (1H, t, J=7.3 Hz, ArH); 7.48 (1H, d, J=8.3 Hz, ArH); 7.42 (1H, d, J=8.3 Hz, ArH); 7.22–7.17 (2H, m, ArH); 4.67 (2H, t, J=3.9 Hz, ArOCH_2); 4.64 (2H, t, J=3.9 Hz, ArOCH_2); 4.32 (2H, t, J=3.9 Hz, ArOCH$_2$CH_2); 4.29 (2H, t, J=3.9 Hz, ArOCH$_2$CH_2); 4.10 (4H, s, central OCH_2CH_2O).

4.2.1.3. Crown 6 + Pb(ClO$_4$)$_2$. 8.82 (1H, s); 7.87 (1H, d, J=8.3 Hz, ArH); 7.83 (1H, d, J=8.3 Hz, ArH); 7.79 (1H, t, J=7.3 Hz, ArH); 7.70 (1H, t, J=8.3 Hz, ArH); 7.47–7.42 (2H, m, ArH); 7.26–7.20 (2H, m, ArH); 4.60 (4H, s, ArOCH_2); 4.25 (4H, s, ArOCH$_2$CH_2); 4.02 (4H, s, central OCH_2CH_2O).

4.2.2. Azocrown 7: 18-membered derivative of 4-methylimidazole. Deep red solid; mp 185–187 °C. TLC, R_f ~0.6 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 8.00–7.80 (2H, m, ArH); 7.55–7.35 (2H, m, ArH); 7.20–7.05 (4H, m, ArH); 4.35–4.30 (4H, m, ArOCH_2); 4.10–3.95 (4H, m, ArOCH$_2$CH_2); 2.75 (3H, s, CH_3). ^{13}C NMR δ_C (ppm): 12.7; 71.1; 71.3; 116.1; 116.5; 117.9; 123.0; 123.1; 133.2; 135.5, 142.7; 142.9; 157.3; 158.4. IR ν_{max} (film): 3442; 1591; 1547; 1264; 1134; 1055; 1012; 754; 616 cm^{-1}. HRMS (EI): found [M]$^+$=392.1587; $C_{20}H_{20}N_6O_3$ requires 392.1597.

4.2.3. Azocrown 8: 21-membered derivative of 4-methylimidazole. Dark red solid crystallized from acetone; mp 162–166 °C. TLC, R_f ~0.75 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 7.95 (1H, d, J=8.3 Hz, ArH); 7.84 (1H, d, J=7.8 Hz, ArH); 7.44 (1H, t, J=7.3 Hz, ArH); 7.35 (1H, t, J=7.4 Hz, ArH); 7.06–7.00 (4H, m, ArH); 4.38–4.28 (4H, m, ArOCH_2); 4.00–3.90 (4H, m, ArOCH$_2$CH_2); 3.79 (4H, s, central OCH_2CH_2O); 2.80 (3H, s CH_3). ^{13}C NMR δ_C (ppm): 13.2; 68.7; 68.7; 69.6; 69.7; 70.8; 70.9; 113.7; 113.9; 116.7; 117.0; 121.6; 121.7; 132.0; 134.1; 142.5; 142.7; 143.0; 147.6; 155.1; 156.4; 157.5. IR ν_{max} (film): 3478, 1584, 1538, 1350, 1304, 1275, 1242, 1221, 1197, 1156, 1105, 954, 757 cm^{-1}. HRMS (ESI): found [M]$^+$=436.1956; $C_{22}H_{25}N_6O_4$ requires 436.1956.

4.2.4. Azocrown 9: 18-membered derivative of 4-phenylimidazole. Dark red-violet solid; mp 186–190 °C. TLC, R_f ~0.6 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 8.58–8.55 (2H, m, ArH); 8.10 (1H, dd, J_1=6.4 Hz, J_2=1.5 Hz, ArH); 7.94–7.90 (1H, dd, J_1=6.8Hz, J_2=1.5Hz, ArH); 7.58–7.50 (3H, m, ArH); 7.49–7.42 (2H, m, ArH); 7.20–7.10 (4H, m, ArH); 4.50–4.48 (4H, m, ArOCH_2); 4.15–4.00 (4H, m, ArOCH$_2$CH_2). ^{13}C NMR δ_C (ppm): 70.2; 71.0; 71.2; 116.3; 116.5; 116.6; 116.7; 122.6; 128.5; 128.9; 129.0; 133.0; 133.4; 135.3; 142.2; 142.8; 143.6; 154.7; 157.4; 158.3. IR ν_{max} (film): 3554; 3502; 1587; 1300; 1274; 2222; 1158; 1062; 936; 758 cm^{-1}. HRMS (EI): found [M]$^+$=454.1749; $C_{25}H_{22}N_6O_3$ requires 454.1753.

4.2.5. Azocrown 10: 21-membered derivative of 4-phenylimidazole. Dark brownish-red solid from methylene chloride–acetone, magenta dilute solution in acetone; mp 193–195 °C. TLC, R_f ~0.85 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 8.56–8.48 (2H, m, ArH); 8.10 (1H, d, J=7.8 Hz, ArH); 7.84 (1H, d, J=7.8 Hz, ArH); 7.56–7.50 (2H, m, ArH); 7.49–7.36 (3H, m, ArH); 7.18–7.10 (4H, m, ArH); 4.35–4.32 (4H, m, ArOCH_2); 4.00–3.90 (4H, m, ArOCH$_2$CH_2); 3.75 (4H, s, central OCH_2CH_2O). ^{13}C NMR δ_C (ppm): 29.6; 68.5; 68.5; 69.5; 70.8; 70.8; 113.6; 113.7; 117.2; 117.3; 121.7; 121.7; 128.7; 128.9; 129.2; 132.6; 134.6; 142.3; 142.5; 143.1; 156.7; 157.6. IR ν_{max} (film): 3603; 1586; 1492; 1447; 1276; 1227; 1164; 1132; 1105; 1062; 940; 759 cm^{-1}. HRMS (EI): found [M]$^+$=498.2017; $C_{20}H_{22}N_6O_3$ requires 498.2016.

4.2.6. Azocrown 11: 17-membered derivative of 2-methylimidazole. Brownish-red solid; mp 193–195 °C. TLC, R_f ~0.45 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 7.82 (2H, d, J=7.8 Hz, ArH); 7.32–7.27 (2H, t, J=7.3 Hz, ArH); 7.12–7.08 (2H, t, J=7.3 Hz, ArH); 6.99 (2H, d, J=8.3 Hz, ArH); 4.25–4.15 (4H, m, ArOCH_2); 4.00–3.85 (4H, m, ArOCH$_2$CH_2); 2.60 (3H, s, CH_3). ^{13}C NMR δ_C (ppm): 15.0; 69.2; 70.0; 114.2; 121.4; 131.2; 131.6; 143.2; 147.5; 149.7. IR ν_{max} (film): 3152; 1593; 1529; 1280; 1250; 1160; 1141; 1119; 1064; 940; 755 cm^{-1}. HRMS (ESI): found [M+H]$^+$=393.1691; $C_{20}H_{20}N_6O_3$ requires 392.1691.

4.2.7. Azocrown 12: 20-membered derivative of 2-methylimidazole. Dark brownish-red solid; mp 135–138 °C. TLC, R_f ~0.5 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 7.53 (2H, d, J=7.3 Hz, ArH); 7.34 (2H, t, J=8.3 Hz, ArH); 7.06 (2H, d, J=8.3 Hz, ArH); 7.01 (2H, t, J=7.8 Hz, ArH); 4.34–4.26 (4H, m, ArOCH_2); 3.64–3.58 (4H, m, ArOCH$_2$CH_2); 3.32 (4H, s, central OCH_2CH_2O); 2.6 (3H, s, CH_3). ^{13}C NMR δ_C (ppm): 14.9; 70.5; 71.2; 117.5; 120.0; 122.0; 132.0; 145.2; 146.9; 155.5. IR ν_{max} (film): 3466; 1589; 1504; 1283; 1244; 1227; 1111; 1042; 941; 754 cm^{-1}. HRMS (ESI): found [M+H]$^+$=437.1962; $C_{22}H_{24}N_6O_4$ requires 436.1962.

4.2.8. 5-Ethyl-2-nitro-phenol (13). To a solution of 3-ethylphenol (7.32 g, 60 mmol) in a mixture of 500 cm^3 chloroform and 80 cm^3 glacial acetic acid, concd nitric acid (4.60 cm^3) in acetic acid (80 cm^3) was added dropwise with stirring at room temperature. Stirring was continued for 4 h. The mixture was diluted with water. The organic layer was separated and washed with sodium bicarbonate solution and evaporated. The residue was chromatographed on column using methylene chloride–petroleum ether (1:2) mixture as an eluent. The first fraction contains yellow oily product. ^{1}H NMR δ_H (ppm): 10.7 (1H, s, ArOH); 8.02 (1H, d, J=8.7 Hz, ArH); 7.02 (1H, d, J=1.9 Hz, ArH); 6.86 (1H, dd, J=1.9 Hz, J=8.7 Hz, ArH); 2.70 (2H, q, J=7.6 Hz, ArCH_2); 1.30 (3H, t, J=7.5 Hz, ArCH$_2$CH_3). MS (EI): found [M]$^+$=167; $C_8H_9NO_3$ requires 167.

4.2.9. 1,5-Bis-(5-ethyl-2-nitrophenoxy)-3-oxapentane (14). A mixture of 5-ethyl-2-nitrophenol **13** (6.1 g, 40 mmol), anhydrous potassium bicarbonate (7.2 g, 52 mmol), and 1,5-dichloro-3-oxapentane (1.42 cm^3) in DMF (26 cm^3) was heated at 140 °C for 8 h. To the cooled mixture, water was added and the product was extracted with chloroform and purified on a short column using methylene chloride–petroleum ether (1:1) mixture as an eluent. Yield of yellow oily product is 62%.

^{1}H NMR δ_H (ppm): 7.92–7.80 (2H, d, J=1.7 Hz, ArH); 7.62–7.48 (2H, dd, J=1.7 Hz, J=8.3 Hz, ArH); 7.34–7.10 (2H, d, J=8.3 Hz, ArH); 4.36–4.28 (4H, m, ArOCH_2); 4.10–3.98 (4H, m, ArOCH$_2$CH_2); 2.73 (4H, q, J=7.6 Hz, ArCH_2); 1.28 (6H, t, J=7.5 Hz, ArCH$_2$CH_3). IR ν_{max} (film): 2968; 2939; 2876; 1606; 1589; 1551; 1425; 1348; 1282; 1262; 1178; 1138; 1092; 1046; 946; 878; 838 cm^{-1}. HRMS (EI): found [M]$^+$=404.1589; $C_{20}H_{24}N_2O_7$ requires 404.1584.

4.2.10. 1,8-Bis-(5-ethyl-2-nitrophenoxy)-3,6-dioxaoctane (15). This compound was obtained analogously to compound (**14**) using 1,8-dichloro-3,6-dioxaoctane instead of 1,5-dichloro-3-oxapentane. Yield of yellow solid is 51%; mp 78–80 °C. ^{1}H NMR δ_H (ppm): 7.80–7.72 (2H, d, J=1.8 Hz, ArH); 7.50–7.42 (2H, dd, J=1.9 Hz, J=7.9 Hz, ArH); 7.28–7.14 (2H, d, J=8.1 Hz, ArH); 4.32–4.24 (4H, m, ArOCH_2); 4.00–3.92 (4H, m, ArOCH$_2$CH_2); 3.82–3.74 (4H, m, central OCH_2CH_2O); 2.69 (4H, q, J=7.6 Hz, ArCH_2); 1.26 (6H, t, J=6.6 Hz, ArCH$_2$CH_3). IR ν_{max} (film): 2967; 2934; 2875; 1606; 1590; 1529; 1515; 1454; 1426; 1351; 1282; 1263; 1178; 1128; 1092; 1047; 949; 878; 838 cm^{-1}. HRMS (EI): found [M]$^+$=448.4289; $C_{22}H_{28}N_2O_8$ requires 448.4286.

4.2.11. Reduction of dinitro compounds 14 and 15 to amines 16 and 17. To a solution of the respective dinitro compound (2 mmol) in methanol, Pd–C was added as catalyst. To the warm (50 °C) reaction mixture first portion of 80% hydrazine (0.5 cm^3) was added. After 1 h hydrazine was added in next three portions of 0.5 cm^3 each in 1 h intervals. Reduction progress was monitored by TLC (methylene chloride–acetone 20:1). After about 5 h (no substrate in reaction mixture), the catalyst was filtered off and the filtrate was evaporated under reduced pressure until first amine crystals appear. Products were allowed to crystallize overnight at 5 °C. Pure products were obtained with 97–99% yield.

4.2.12. 1,5-Bis-(2-amino-5-ethylphenoxy)-3-oxapentane (16). ^{1}H NMR δ_H (ppm): 6.98 (2H, d, J=7.6 Hz, ArH); 6.68 (2H, d, J=6.2 Hz, ArH); 6.44 (2H, d, J=8.3 Hz, ArH); 4.30–4.20 (4H, m, ArOCH_2); 4.08–3.96 (4H, m, ArOCH$_2$CH_2); 3.70 (4H, s, ArNH_2); 2.70 (4H, q, J=7.6 Hz, ArCH_2); 1.25 (6H, t, J=6.6 Hz, ArCH$_2$CH_3). HRMS (EI): found [M]$^+$=334.4379; $C_{20}H_{28}N_2O_3$ requires 334.4366.

4.2.13. 1,8-Bis-(2-amino-5-ethylphenoxy)-3,6-dioxaoctane (17). ^{1}H NMR δ_H (ppm): 6.94 (2H, d, J=7.8 Hz, ArH); 6.76–6.54 (4H, m, ArH); 4.30–4.20 (4H, m, ArOCH_2); 4.00–3.94 (4H, m, ArOCH$_2$CH_2); 3.84–3.76 (4H, m, central OCH_2CH_2O); 3.73 (4H, s, ArNH_2); 2.70 (4H, q, J=7.6 Hz, ArCH_2); 1.25 (6H, t, J=6.6 Hz, ArCH$_2$CH_3). HRMS (EI): found [M]$^+$=388.4850; $C_{22}H_{32}N_2O_4$ requires 388.4842.

4.2.14. Azocrown 18: 18-membered derivative of imidazole. Pale-red solid; mp 220–222 °C. TLC, R_f ~0.7 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 8.02 (1H, s, ArH); 7.88 (1H, d, J=7.8 Hz, ArH); 7.74 (1H, d, J=8.3 Hz, ArH); 7.35 (1H, d, J_1=8.3 Hz, ArH); 6.98–6.84 (3H, m, ArH); 4.45–4.35 (4H, m, ArOCH_2); 4.05–3.95 (4H, m, ArOCH$_2$CH_2); 2.75–2.62 (4H, m, ArCH_2); 1.32–1.28 (4H, m, ArCH$_2$CH_3). IR ν_{max} (film): 2965; 2929; 2873; 1598; 1454; 1435; 1238; 1162; 1116; 1059; 952; 856; 753 cm^{-1}. HRMS (EI): found [M]$^+$=434.2057; $C_{23}H_{26}N_6O_3$ requires 434.2066.

4.2.15. Azocrown 19: 21-membered derivative of imidazole. Red solid; mp 164–165 °C. TLC, R_f ~0.8 (CH$_2$Cl$_2$–methanol 15:2). ^{1}H NMR δ_H (ppm): 8.14 (1H, s ArH); 7.97 (1H, d, J=8.3 Hz, ArH); 7.73 (1H, d, J=7.8 Hz, ArH); 6.92–6.84 (4H, m, ArH); 4.40–4.28 (4H, m, ArOCH_2); 4.00–3.90 (4H, m, ArOCH$_2$CH_2); 3.84–3.76 (4H, s, central OCH_2CH_2O); 2.75–2.62 (4H, m, ArCH_2); 1.32–1.28 (6H, m, ArCH$_2$CH_3). IR ν_{max} (film): 2963; 2927; 2899; 1598; 1576; 1454; 1431; 1280; 1246; 1233; 1168; 1116; 1103; 1055; 955; 848; 836 cm^{-1}. HRMS (EI): found [M]$^+$=478.2336; $C_{21}H_{22}N_6O_4$ requires 478.2329.

4.3. X-ray studies

All measurements were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs.

The structure was solved by direct methods[10] and refined using SHELXL.[11] The refinement was based on F^2 for all reflections with exception of those with very negative F^2. The $F_0^2 > 2\sigma(F_0^2)$ criterion was used only for calculation of R factors. Some hydrogen atoms were located from a differential map and refined isotropically. The remaining hydrogen atoms were located in idealized averaged geometrical positions, allowed to ride at the heavy atoms. Additionally, disorder in the polyether linker in one of the macrocyclic molecules with occupation factors, 0.645(1) and 0.355(1), was solved.

4.4. UV–vis spectroscopy

The complexation studies were performed using UV–vis spectroscopy in acetonitrile, methanol, and methanol–water (4:1, v/v) solvent mixture. In all titration experiments ligand concentration was about 10^{-5} mol dm^{-3}. Starting volume of titrated ligand: 3 cm^3. All metal perchlorates were used at concentration of about 10^{-2} mol dm^{-3}. Titration step: 0.01 cm^3. The values of appropriate stability constants were calculated using Dynafit[7] program. For systems where complex absorption band do not overlap ligand band the stoichiometry of formed compounds was additionally estimated using molar ratio and/or continuous variation methods.[12]

4.5. Membrane electrodes and potentiometric measurements

The preparation of membrane for ion-selective electrodes was described earlier in details.[13] In 1 cm^3 of freshly distilled THF 2 mg of ionophore, 50 mg PCV, 0.1 cm^3 of 2-nitrophenyl-octyl ether, and potassium tetrakis(4-chlorophenyl)borate were dissolved. The following amounts of lipophilic salts (% mol in relation to the ionophore): 100, 80, 70, 60, and 50 were used for membrane preparation. Membranes were incorporated onto Ag/AgCl electrode bodies with 5×10^{-3} mol dm^{-3} $PbCl_2$ as an internal electrolyte. The selectivity coefficients were determined using the separate solution method[14] employing metal nitrate solutions of 10^{-2} activity at pH 5.0±0.1 (adjusted with HNO_3).

Electrodes were conditioned in 10^{-2} mol dm^{-3} $Pb(NO_3)_2$ solution for 24 h, then soaked for 1 h in water (pH 5.0 from HNO_3) before taking measurements.

Supplementary data: It is deposited with the Cambridge Crystallographic Data Centre with supplementary publication number CCDC 623703 (CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Electronic supplementary material associated with this article contains additional X-ray data, absorption spectra, and spectroscopic titration experiments with metal perchlorates in different solvents. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.095.

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