Polish J. Chem., **78**, 1785–1793 (2004)

The Synthesis, Structure and Complexing Properties of New Triazacoronands*

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(Received March 25th, 2004; revised manuscript April 26th, 2004)

Five new macrocyclic compounds of the triazacoronand type have been synthesized, starting from dimethyl iminoacetate and appropriate α,ω-diamines, in methanol as a solvent. Their complexing properties were investigated using the voltammetric method.

Key words: macrocycles, synthesis, structure, X-ray analysis, complexation, electrochemistry

The most important step of each synthesis of the macrocyclic compounds is the macrocyclization reaction. One of the possible macrocyclization variants consists in binding the ends of two linear molecules way to close the macrocycle by the newly formed bonds. The closure of the macrocycle requires the reactive bifunctional or polyfunctional substrates. One has to take into account the competitive intermolecular polycondensation reaction. The probability is that the linear, cyclic and branched oligomers are formed (Scheme 1) [1]. Unfortunately, the reaction conditions typical for organic chemistry prefer the linear polymerization reaction which is competitive to cyclization. Nevertheless, the present-day supramolecular chemistry has found several synthetic routes allowing for conducting macrocyclization in satisfactory yields.

These methods, that minimize the probability of side-reactions, are based on limitation of the frequency of molecular collisions (the high-dilution [2] and high-pressure [3] methods) or on enforcing the proper conformation of the substrates (the template method [4] as well as the methods making use of preorganization under influence of external factors [5]). One of such methods introduced by Tabushi *et al*. [6] and then modified by us [7–10] is characterized by mild reaction conditions, relatively high yields, no need for using high dilutions, and therefore no need for using ideally anhydrous solvents. This method is very versatile and enables the synthesis of macrocyclic compounds containing in their structures oxygen, nitrogen or/and sulphur atoms.

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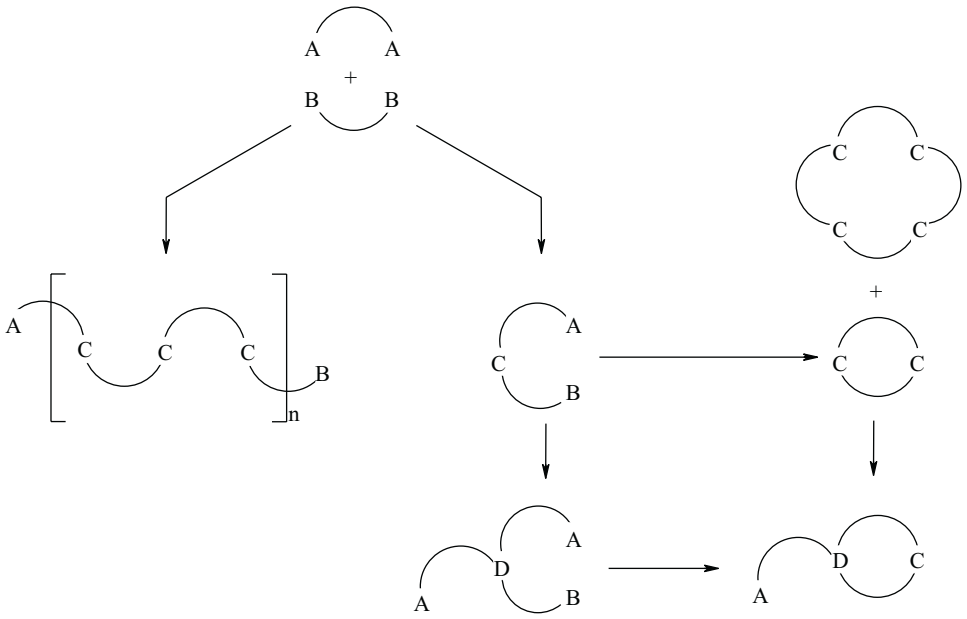
* Dedicated to Prof. Dr. Z. Galus on the occasion of his 70th birthday.



Scheme 1. Possible competitive reactions during macrocyclization process.

In this paper we would like to present the application of the above-mentioned method for the synthesis of five new triazacoronands, their structure elucidation and studies of their complexing properties towards cations of three heavy metals: cadmium, lead and thallium. The latter properties are compared with five complementary triazacoronand ligands containing the pyridine moiety.

EXPERIMENTAL

General: ^{1}H NMR spectra were recorded using a Varian Gemini (200 MHz) and/or Varian Unity Plus 500 (500 MHz) spectrometers in $CDCl_3$ or DMSO-d_6, and ^{13}C NMR spectra were recorded using also Varian Gemini (50 MHz) and/or Varian Unity Plus 500 (125 MHz) spectrometers. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm). IR spectra were obtained on a Perkin-Elmer 1640 FTIR spectrophotometer in films or KBr pellets. High-resolution mass spectrometry (HRMS) experiments were performed on an AMD-604 Intectra instrument. Column chromatography was carried out on silica gel (Merck Kieselgel-60, 200–400 mesh). Melting points were taken on a Boetius hot stage apparatus and were not corrected.

Synthesis: **General procedure for the synthesis of macrocyclic diamides**. An equimolar 0.01 M methanolic solution (*ca.* 2 mmol) of corresponding α,ω-diamine and dimethyl ester of iminoacetic acid (**6**), in the presence of MeONa, was left at ambient temperature for 48 hours. Then the solvent was evaporated and the residue was chromatographed on a silica gel column using 0–3% solutions of methanol in chloroform.

α,ω-Diamines **1–5** were prepared according to the literature procedures [2,4].

1,4-Dioxa-7,10,13-triaza-cyclopentadecane-8,12-dione (**7**, 75%): m.p. 120°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.54 (bs, 2H), 3.65–3.46 (m, 12H), 3.35 (bs, 4H), 1.94 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.0, 69.3, 68.5, 52.8, 38.4; IR ν_{max} (KBr)/cm^{-1}, ν = 3395, 3336, 2911, 1673,1655, 1528, 1460, 1339, 1293, 1244, 1133, 1103, 997, 828, 598, 535, 446. Anal. Calcd.: C, 48.97; H, 7.81; N, 17.13. Found: C, 48.73; H, 7.97; N, 17.19. HRMS m/z Calcd. for $C_{10}H_{19}N_3O_4$ $[M]^+$ 245.1376. Found 245.1356.

7,8,11,12,15,16-Hexahydro-6H,10H,14H-5,17-dioxa-8,11,14-triaza-benzocyclopentadecene-9,13-dione (**8**, 36%): m.p. 206–207°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42 (bs, 2H), 7.00–6.89 (m, 4H), 4.14 (t, 4H, J = 5.2 Hz), 3.76 (qw, 4H, J = 5.2 Hz), 3.40 (s, 4H), 1.79 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 148.1, 122.0, 113.7, 67.3, 53.3, 38.1; IR ν_{max} (KBr)/cm^{-1}, ν = 3393, 3340, 2945, 2885, 1681, 1648, 1539, 1507, 1260, 1215, 1120, 1041, 987, 932, 851, 742, 605. Anal. Calcd.: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.31; H, 6.49; N, 14.29. HRMS m/z Calcd. for $C_{14}H_{19}N_3O_4$ $[M]^+$ 294.1454. Found 294.1443.

1,4,7-Trioxa-10,13,16-triaza-cyclooctadecane-11,15-dione (**9**, 41%): m.p. 120–122°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (bs, 2H), 3.65–3.54 (m, 16H), 3.35 (s, 4H), 2.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 70.4, 70.2, 69.9, 53.1, 38.6; IR ν_{max} (KBr)/cm^{-1}, ν = 3354, 2912, 2878, 1677, 1663, 1554, 1527, 1446, 1349, 1256, 1096. Anal. Calcd.: C, 49.82; H, 8.01; N, 14.52. Found: C, 49.88; H, 8.02; N, 14.41. HRMS m/z Calcd. for $C_{12}H_{23}N_3O_5$ $[M+H]^+$ 290.1716. Found 290.1726.

1,15-Dioxa-5,8,11-triaza-cyclononadecane-6,10-dione (**10**, 26%): m.p. 78–80°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (bs, 2H), 3.60–3.49 (m, 12H), 3.29 (s, 4H), 2.34 (s, 1H), 1.81 (qt, 4H, J = 5.4 Hz), 1.68–1.63 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 71.0, 53.1, 38.8, 28.3, 26.2; IR ν_{max} (KBr)/cm^{-1}, ν = 3350, 2924, 2862, 1649, 1539, 1514, 1364, 1230, 1110, 1070, 558. Anal. Calcd.: C, 55.79; H, 9.03; N, 13.94. Found: C, 55.78; H, 9.26; N, 13.83. HRMS m/z Calcd. for $C_{14}H_{28}N_3O_4$ $[M]^+$ 302.2079. Found 302.2051.

1,4,7-Trioxa-11,14,17-triaza-cycloicosane-12,16-dione (**11**, 37%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11 (bs, 2H), 3.67–3.60 (m, 12H), 3.49–3.40 (q, 4H, J = 5.4 Hz), 3.30 (s, 4H), 2.52 (s, 1H), 1.83–1.78 (qt, 4H, J = 5.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 70.8, 69.9, 69.7, 52.5, 38.5, 28.3; IR ν_{max} (KBr)/cm^{-1}, ν = 3331, 2924, 2871, 1657, 1542, 1441, 1348, 1254, 1127, 992, 588. Anal. Calcd.: C, 50.14; H, 8.72; N, 12.53. Found: C, 50.28; H, 8.86; N, 12.29. HRMS m/z Calcd. for $C_{14}H_{28}N_3O_5$ $[M+H]^+$ 318.2029. Found 318.2027.

X-ray structure determinations: X-ray single-crystal diffraction experiments were carried out on a KM4CCD diffractometer. Psi-scan absorption corrections were applied for both calculations. The program used to solve structures was SHELXS86 [11]. The program used to refine the structures and to prepare materials for publication was SHELXL97 [12]. All non-H atoms were refined with anisotropic displacement parameters. H atoms were refined in isotropic approximation. All H atoms were calculated and refined as riding model.

Electrochemical measurements: Reagents and apparatus. Voltammetric experiments were carried out at hanging mercury drop electrode (Metrohm VA 663) using Autolab PGSTAT12 potentiostat. Double-junction silver/silver chloride reference electrode filled with 0.1 M tetraethylammonium chloride solution in methanol was used in all experiments. Platinum foil served as the counterelectrode. Oxygen was removed by purging the solution with argon. All measurements were carried out in ambient temperature. 0.1 M tetrabutylammonium perchlorate in acetonitrile was used as supporting electrolyte. Metal macrocyclic ligands and metal cations were introduced into the cell by adding the appropriate volumes of concentrated stock solutions. Stock solution of Pb^{2+} ions was prepared from $Pb(ClO_4)_2$, Cd^{2+} from $Cd(NO_3)_2$ and Tl^+ – from CF_3COOTl. In a typical measurement the concentration of the metal cation was kept constant at 10^{-4} M level, while the macrocycle concentration was varied.

Voltammograms in the potential range appropriate for the observation of cation reduction were measured at scan rates of 0.05, 0.1 and 0.2 V/s. Every voltammogram was recorded at least twice and the averaged voltammograms were used for further analysis. Peak potentials and peak heights were measured using the standard option in Autolab software. For analysis of semiderivative data the standard voltammograms were numerically semi-differentiated using the Autolab software option.

Electrochemical experiments. Upon the increase of the concentration of ligands **12–16** both the cathodic and the anodic voltammetric peak of Tl^{+}, Pb^{2+} and Cd^{2+} show a shift toward negative potentials. A similar effect is observed for ligands **7–11** and thallium cation peak. Unlike them, the addition of ligand **7–11** to the solution of lead or cadmium ions causes the decrease of both cathodic and anodic peaks of these cations. In the case of lead ions, the peak of uncomplexed Pb^{2+} decreases faster than predicted under assumption that the whole ligand is bound in 1:1 inert complex. In parallel, two new cathodic and two new anodic peaks appear and grow (see Fig. 1). Except of ligand **8**, the two new signals are usually poorly resolved, giving rise to the formation of a broad anodic and cathodic peaks. The semiderivative voltammograms (Fig. 1) show that the reduction of Pb^{2+} ions is a diffusion-controlled process, because the first cathodic signal has a form of a symmetric peak. Only when 0.75 or more of molar equivalent of the macrocycle is added, the slower decay of the semiderivative after reaching Pb^{2+} reduction potential suggests that a chemical process preceding the electron transfer step starts to play a role.

The stability constants of labile complexes of said ligands with cations were determined using a method similar to POLAG [13], that is based on DeFord-Hume approach [14]. The experimentally measured potential shifts and the current ratios were used in the equation

$$\left(I_P^L / I_P\right)\exp\left[(nF/RT)\left(E_p - E_P^L\right)\right] = \sum_{i=0}^{n}\beta_i[L]^i$$

(where I_P^L, I_P are peak current in respectively the presence and absence of the ligand, E_P^L and E_P are the corresponding peak potentials) employed to fit the values of β_i. The fitting procedure used nonlinear least squares method according to Marquardt [15]. The actual concentration of the ligand, [*L*], used in the fitting equation, was computed in every iteration step using the procedure described by Bos and Meershoek [16]. Thanks to this approach, the simplification $[L] = c_L$, used in original DeFord-Hume method, is no longer necessary and the concentration of the ligand need not to be significantly higher than the concentration of the metal cation.

The potentials used for calculations were taken as averages between the cathodic and anodic voltammetric peak. Alternatively, the voltammograms were semi-differentiated [17] and average values of cathodic and anodic semi-derivative peaks were used in calculations to minimize the impact of small changes of peak potentials caused by the addition of ligands. The results of both approaches were very similar and the $\log\beta$ values obtained in both ways were practically the same. The stability constants for inert complex with lead cation were determined from the decrease of the peak height of free metal ions upon addition of the ligand. The data were fitted to the models for ML, ML_2 and M_2L complex formation, and only the models giving non-negative values for stability constants were taken into consideration.

RESULTS AND DISCUSSION

In order to accomplish the first aim, we decided to use the reaction of five α,ω-diamines **1–5** with dimethyl ester of iminoacetic acid (**6**), carried out in methanol as a solvent, in the presence of MeONa, at ambient temperature, during 48 hours. The results of the preparations are shown in Table 1. During our investigations of the reaction of dicarboxylate **6** with diamines **1–5** we found that in all the cases only macrocyclic diamides **7–11** are formed. Conformational lability of diamines, which increases together with the lengths of chain, influences the yield of the macrocyclization reactions. The only exception concerns the reaction of **6** with the relative rigid diamine **2**; in this case the low yield is probably caused by a not very good fitting of the preferred conformation of dicarboxylate **6** into a distance of between amino groups in molecule of completely rigid diamine **2**.

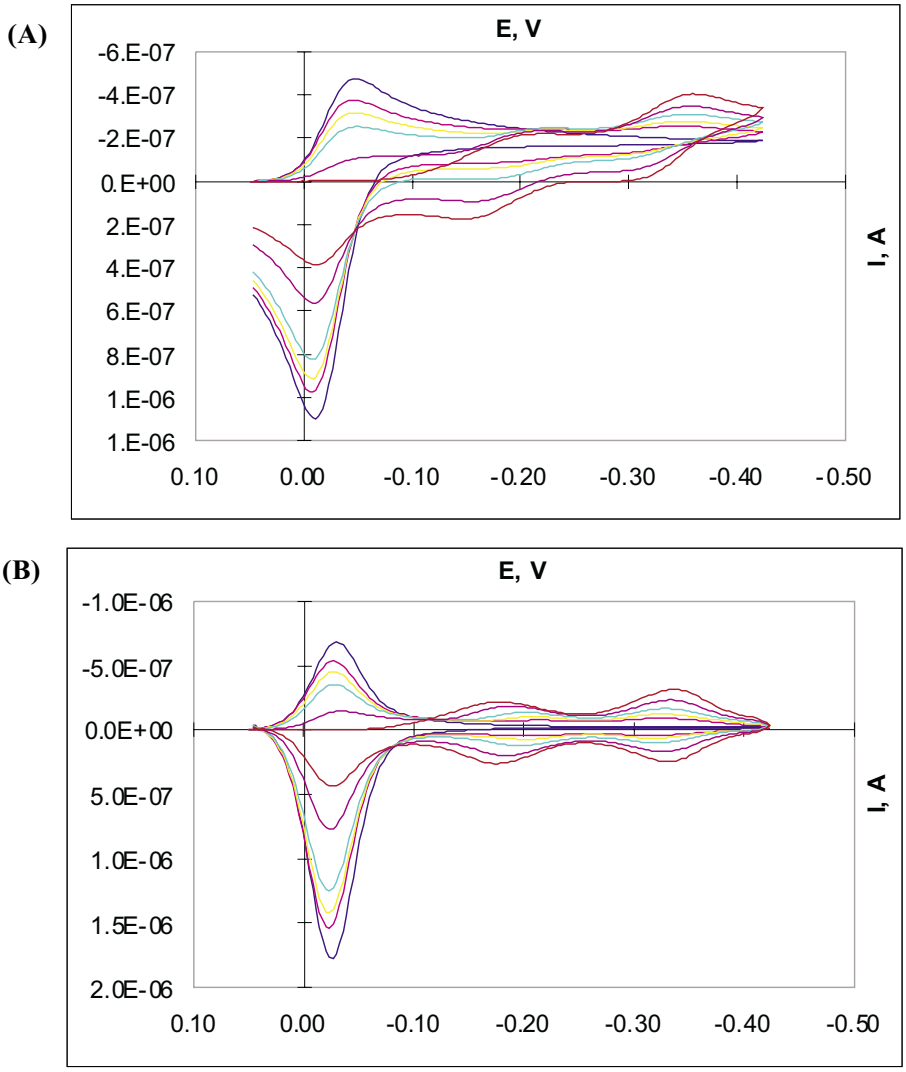
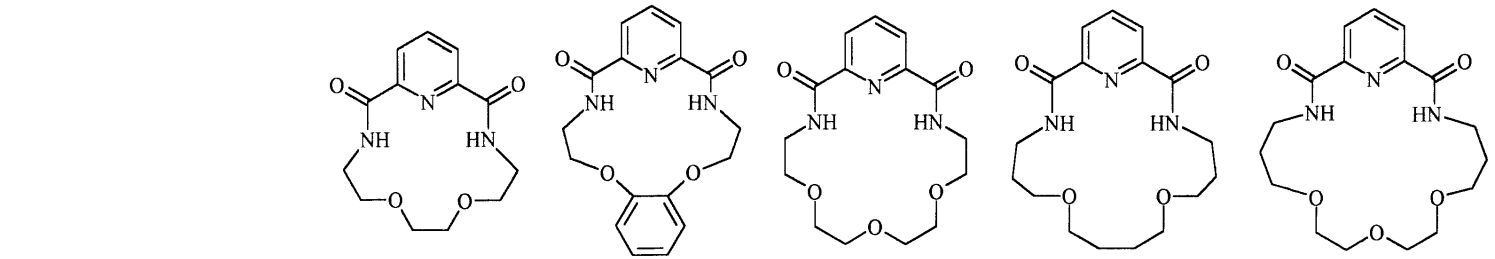


Figure 1. Voltammograms (A) and semiderivative voltammograms (B) of Pb^{2+} ions upon addition of ligand **8**. Solvent: 0.1 M tetrabutylammonium perchlorate in acetonitrile, $c_{Pb} = 1.6 \cdot 10^{-4}$ M, scan rate 0.1 V/s. Lines on plots correspond to the addition of 0, 0.25, 0.375, 0.5, 0.75 and 1 molar equivalent of the ligand.

Four of the resulting triazacoronands **7–10** are crystalline, and compound **8** formed the monocrystals suitable for X-ray analysis. Figure 2 shows conformation of ligand **8** in the solid state and packing of molecules in the crystal lattice. In concentrated solution, complexation of Pb^{2+} with ligand **8** in acetonitrile caused precipitation of crystalline complex, also appropriate for X-ray analysis (Fig. 3). In all other cases studied we were unable to obtain crystalline complexes with investigated heavy metals.

Table 1. Reactions of diester **6** with diamines **1**–**5**.

	1	**2**	**3**	**4**	**5**
6	**7**, 75%	**8**, 36%	**9**, 41%	**10**, 26%	**11**, 37%



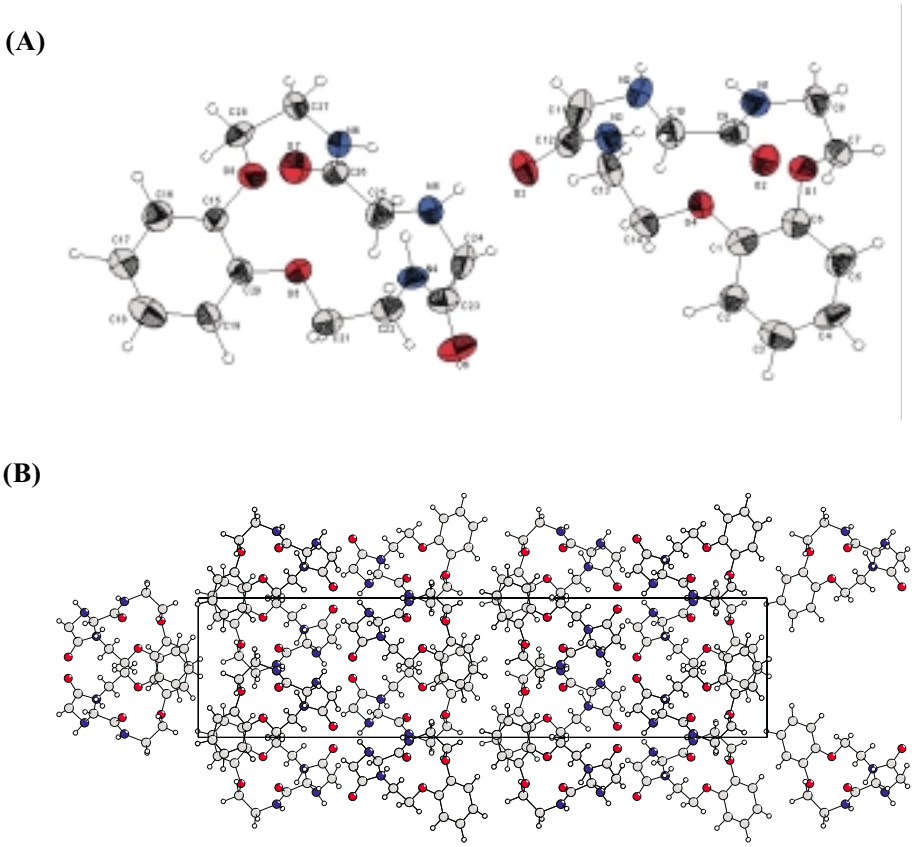


Figure 2. The structure of ligand **8** in a crystalline form: (A) projection in ORTEP, (B) part of packing of molecules in the crystal lattice.

All synthesized macrocycles form complexes with the studied heavy metal cations (Table 2). The only exception are small pyridinophanes **12** and **13** for which no interactions with Cd^{2+} and Tl^{+} ions could be detected.

There is a clear difference of complexation properties between the group of triazacoronands studied (**7–11**) and pyridinophanes (**12–16**). In pyridinophanes, all observed complexes have 1:1 stoichiometry and are labile in the voltammetric time scale, thus the metal ion exchange in the complex is rapid. The determined complexation constants for lead cations are generally in the order of 10^2 for macrocycles with smaller cavities (**12**, **13**) and 10^3 for larger cavity ligands (**14**–**16**). Complexes with thallium and cadmium ions are less stable than those with lead; for larger cavities this difference is of one order of magnitude, while for the small cavity ligands no formation of complexes is detected. In triazacoronands group the type of formed complex depends much more on the involved cation. Complexes with Tl^{+} are labile, complexes with lead and cadmium are inert. Also, in the case of Pb^{2+}, it is possible

that not only 1:1 complex is formed, but also that M_2L species can be formed (the appearance of two additional signals suggests that two complex species are present). In all cases the formation constants are high, for inert complexes their values exceed 10^4 and therefore they cannot be exactly measured using voltammetric method.

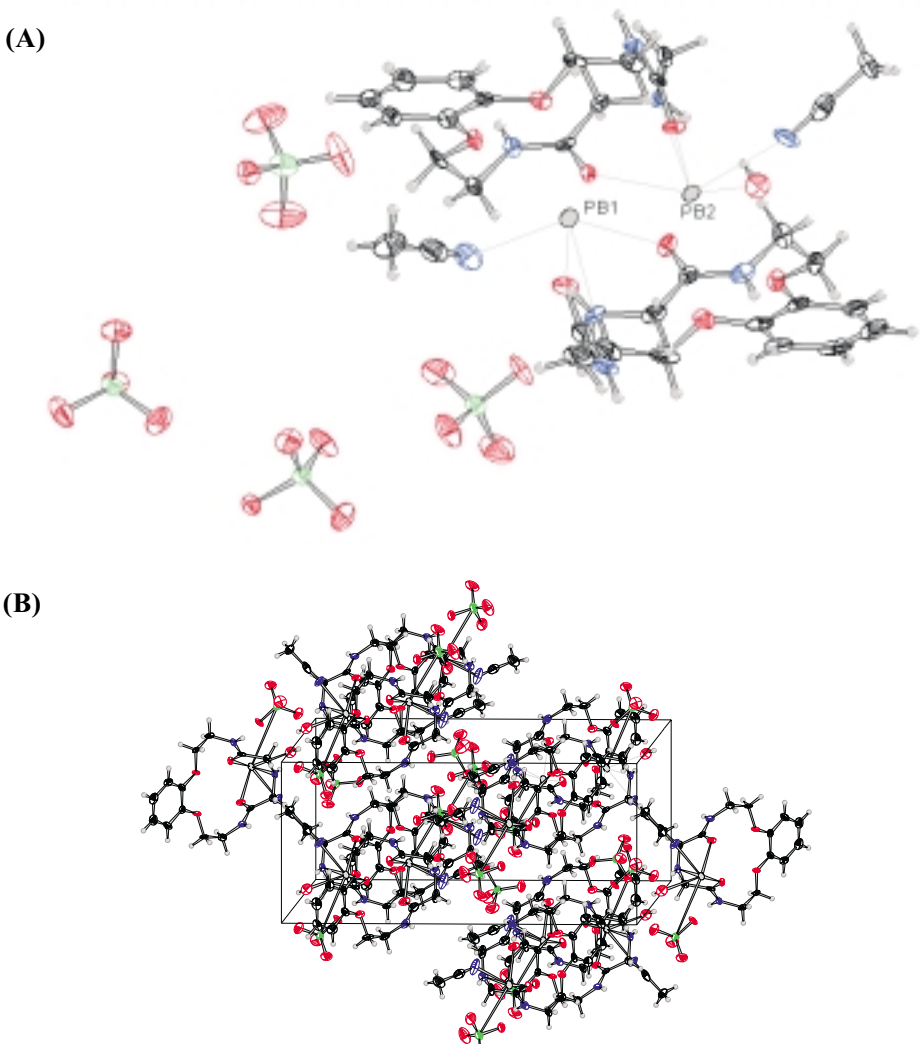


Figure 3. The structure of ligand **8** with cation Pb^{2+} in a crystalline form: (A) projection in ORTEP, (B) part of packing of molecules in the crystal lattice.

When complexation properties of each pyridinophane are compared with the properties of the triaza analog, in all cases triazacoronands appear to form more stable complexes with every studied metal cation. The general rule is that for thallium complexes the only difference lies in the value of the formation constant, being approximately one order of magnitude higher in triazacoronands. In the complex compounds

with cadmium and lead cations, the main difference is in the kinetics – the complexes formed with these two cations are labile if the pyridinium moiety is present in the macrocycle structure, otherwise the complexes are inert. It also should be noted, that the inability of small cavity pyridinophanes to form complexes with Tl^+ and Cd^{2+} is not observed in small cavity triazacoronands.

Table 2. Comparison of stability constants for triazacoronands studied (**7–11**) with pyridinophanes **12–16**.

Triaza-coronands	Pyridino-phanes	Cd^{2+}		Pb^{2+}		Tl^+	
		$\log \beta_t$	$\log \beta_P$	$\log \beta_t$	$\log \beta_P$	$\log \beta_t$	$\log \beta_P$
7	**12**	inert	–	inert	1.6*	3.1	–
8	**13**	inert	–	inert	2.75	2.8	–
9	**14**	inert	2.7	inert	3.4	2.66	1.6
10	**15**	inert	1.8	inert	3.6*	3.0	2.1
11	**16**	inert	2.6	inert	5.15 (3.8*)	3.3	1.9

* – measurements carried out in propylene carbonate.

Acknowledgments

This work was supported by the Polish State Committee for Scientific Research (Project T09A 087 21).

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