Synthesis of a New Triazine Derived Macrocycle and a Thermodynamic Study of Its Complexes with Some Transition and Heavy Metal Ions in Acetonitrile Solution

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A synthetic procedure has been developed for the preparation of a new triazine derived macrocycle (13,29-diphenyl-4,7,20,23-tetraoxa-1,10,12,14,16,17,26,28,30,32-decaaza-[10,10](2,6)triazinophane). The formation of some transition and heavy metal complexes with the macrocycle was investigated in acetonitrile solution conductometrically at different temperatures. The formation constants of the resulting 1:1 complexes were determined from the molar conductance-mole ratio data and found to vary in the sequence 

\[ \text{Hg}^{2+} > \text{Pb}^{2+} > \text{Cd}^{2+} > \text{Ag}^{+} > \text{Cu}^{2+} > \text{Tl}^{+} > \text{Co}^{2+} > \text{Ni}^{2+} > \text{Zn}^{2+} \]

The enthalpy and entropy of complexation reactions were determined from the temperature dependence of the formation constants. In all cases, the complexes were found to be enthalpy stabilized but entropy destabilized.

Key words: complexes, synthesis, thermodynamics, conductometry

Despite the substantial number of papers on the synthesis and complexation of benz-annelated crown ethers [1,2] and pyridine-derived macroheterocycles [3–7], little attention has been paid to the diazine- [8] and triazine-derived macroheterocycles [9–10]. However, in view of the biological and medicinal interests in substituted pyrimidines [11,12], as well as the limited examples of pyrimidino inclusion in macrocyclic framework, there is still a continuing interest in the synthesis and metal ion complexion of pyrimidine-substituted macrocyclic crown ethers.

In this paper we report the first synthesis of 13,29-diphenyl-4,7,20,23-tetraoxa-1,10-12,14,16,17,26,28,30,32-decaaza[10,10](2,6)triazinophane (I) and a thermodynamic study of its complexes with 

\[ \text{Hg}^{2+}, \text{Pb}^{2+}, \text{Cd}^{2+}, \text{Cu}^{2+}, \text{Co}^{2+}, \text{Ni}^{2+}, \text{Zn}^{2+}, \text{Ag}^{+} \text{ and Tl}^{+} \]

complexes in acetonitrile solution conductometrically.

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EXPERIMENTAL

Reagents: Reagent grade nitrate salts of silver, thallium, cobalt, nickel, copper, zinc, cadmium, mercury and lead (all from Merck) were of the highest purity available and used without any further purification except for vacuum drying over P₂O₅. Reagent grade acetonitrile (Merck) was purified and dried by the previously described method [13]. The conductivity of the solvent was less than 1.0 × 10⁻⁷ S m⁻¹. 3,5-Dioxoocanadiamine, dioxane, phenol, cyanuric chloride, sodium hydroxide and silica gel were purchased from Merck chemical company and used as received.

Apparatus: The ¹³C NMR spectra with ¹H noise decoupling are the ¹H NMR spectra were recorded on a JOEL spectrometer at 22.6 MHz and 90 MHz, respectively. All chemical shifts are reported in ppm downfield from TMS using CDCl₃ as solvent. The IR spectra were obtained with a Perkin Elmer 783 instrument using KBr disks. A Varian GC/MS instrument used consisted of a Star 3400 CX GC and a Saturn 44 MS. A DBS column with 30 m length and 0.32 mm diameter was used at an operation temperature range of 60–325°C. A COMPAQ PROLINEA 5100 computer was used for data analysis. Conductivity measurements were carried out with a Metrohm 660 conductivity meter. A dip-type conductivity cell, made of platinum black, with a cell constant of 0.8210 cm⁻¹ was used. In all experiments, the cell was thermostated at the desired temperature using a Phywe immersion thermostat.

Procedure: In a typical experiment 50 cm³ of metal nitrate solution (5.0 × 10⁻⁵ M) was placed in the titration cell, thermostated at the desired temperature and the conductance of the solution was measured. Then, a known amount of the macrocycle I solution was added in a stepwise manner, using a calibrated micropipette. The conductance of the solution was measured after each addition. Addition of the ligand was continued until the desired ligand to cation mole ratio was achieved.

Synthesis of 4-phenoxy-2,6-dichloro-S-triazine (2): A suspension of cyanuric chloride (7.2 g, 0.04 mol) in 50 cm³ dichloromethane in a 100 cm³ round bottom flask, equipped with a magnetic stirrer, was cooled in an ice bath. A solution of phenol (3.76 g, 0.04 mol) and sodium hydroxide (1.6 g, 0.04 mol) in 20 cm³ H₂O was added dropwise to the suspension over a period of 15 min, keeping the temperature at about 5°C. The reaction mixture was then stirred for 3 h at room temperature. The nondissolved particles were removed by filtration, followed by evaporation of the solvent. The organic phase was then separated, washed with dilute sodium hydroxide solution and dried over calcium chloride. The solvent was removed by rotary evaporator. A white crude product was obtained which, upon recrystallization from n-hexane/chloroform (3:1), yielded 8.0 g (90%) of pure product 2, m.p. 112–113°C. ¹³C NMR (CDCl₃), δ (ppm): 173.02, 171.07, 151.03, 129.86, 126.89, 120.94. IR (KBr), ν (cm⁻¹): 3080–3020 (w), 1550–1510 (s), 1485 (s), 1415 (s), 1300 (s), 1200 (s), 1160 (s), 1070 (m), 1025 (s), 1010 (s), 970 (w), 915 (m), 900 (w), 870 (s), 800 (s), 770 (s) 695 (s), 665 (w), 615 (w) 605 (m). ¹H NMR (CDCl₃), SH (ppm): 7.0–7.6 (m). GC/MS: A peak at 2.43 min.; MS (m/z): 241 (M⁺, 29.5%), 206 (100%), 138 (12.7%), 77 (18.9), 65 (17.6%), 51 (17.9%), 39 (27.1 %).

Synthesis of 13,29-diphenoxy-4,7,20,23-tetraoxa-1,10,12,14,16,17,26,28,30,32-decaaza-(10.10)(2,6)triazinophane: 4-Phenoxy-2,6-dichloro-S-triazine (2.26 g, 0.01 mol) was dissolved with stirring in dioxane (400 cm³) in a 1000 cm³ round bottom flask, equipped with a condenser and a magnetic stirrer. A solution of 3,5-dioxo-1,8-octanediamine (1.5 g, 0.01 mol) in dioxane (20 cm³) was added dropwise to the flask over a period of 20 min while stirring. The clear solution turned to cloudy and some insoluble white particles appeared. A solution of sodium hydroxide (0.2 g, 0.02 mol) in 3 cm³ distilled water was then gradually added to the reaction mixture while vigorously stirring. The stirring was...
continued for 1 h at room temperature, followed by 1 h reflux. The reaction mixture was then cooled to room temperature, filtered and the solvent was removed by a rotary evaporation. An impure yellowish product (mp 165–168°C) was obtained. The crude product was purified by column chromatography on silica gel (grade 60, 230–400 mesh). Elution with a mixture of chloroform/ethyl acetate (3:1) yielded 0.8 g (26%) of white powdered product, m.p. 171–172°C. ¹H NMR (CDCl₃), δH (ppm): 8.2 (s, 4H, –NH–), 7.2–7.3 (m, 10 H, phenyl CH), 3.6–3.8. ¹³C NMR (CDCl₃), δc (ppm): 170.5, 166.6, 152.2, 128.5, 124.5, 121.3, 70.6, 66.7, 40.6. IR (KBr): 6 (cm⁻¹): 3270 (m), 2940–2860 (m), 1590 (s), 1550 (s), 1490 (s), 1410 (s), 1350 (s), 1210 (s), 1120 (s), 1120 (m), 1020 (w), 1000 (w), 870 (m), 810 (m), 780 (w), 690 (m). MS: (m/z) 635 (M⁺, 41%), 307 (21%), 154 (100%), 136 (72%), 107 (25%), 77 (21%).

RESULTS AND DISCUSSION

Synthesis and characterization of the macrocycle (I): The synthesis scheme for 13,29-diphenyl-4,7,20,23-tetraoxa-1,10,12,14,16,17,26,28,30,32-decaaza[10.10](2,6)triazinophane (I) is depicted in Scheme 1:

In the first step, one of the three electrophilic centers of (I) was blocked by a phenoxy group, so that in the resulting compound (2) two other active positions remain available for the next step’s ring closure. Moreover, by such substitution of a –Cl group by an O–Ph group, possible polymerization process, which is normal in work compound (I), will also be minimized. It is noteworthy, that the well known unusual feature of the stepwise replacement of the three –Cl groups of compound (I) by different nucleophiles allowed us to control the substitution reaction at the first step. However, depending on the reaction conditions used, small amounts of the 2,4-diphenoxy-derivative was also obtained. The dichloro-derivative (2) (m.p. 112–113°C from n-hexane/chloroform) was obtained in a rather high yield (90%). The purity of compound (2) was checked by both NMR and GC/MS. The GC showed a single peak with a retention time of 2.43 min. The M⁺ peak at m/z 241, the relative intensity of 9:6:1 for the peaks at m/z 241, 243 and 245 and the observed base peak at 206 for M–35 were all in accordance with the 4-phenoxy-2,6-dichloro-s-triazine (2) structure.

The synthesis of macroheterocycle (I) was carried out by the reaction of equi-molar amounts of the dichloro-derivative (2) and 3,5-dioxo-octanediamine under high dilution condition in dioxane using NaOH as a base and 1 h reflux. The product of the cyclization step was a white powder (m.p. 171–172°C from chloroform/ethyl acetate), which was obtained at a low yield (26%). The resulting macrocycle (I) was characterized by NMR and MS. The main problem here is the possible formation of a [1+1] macrocycle (II):
which have the same number of $^1\text{H}$ and $^{13}\text{C}$ NMR signals as macrocycle (I) of very close positions. Since none of the macrocycles (I) and (II) have been reported previously, the exact NMR data were not available to be compared with those of the product obtained. The CIMS could not solve the problem. The EIMS resulted in a very weak peak for $M^+$ a m/z of 634 once the sample was heated at 400°C. However, FABMS was found as the best technique to determine precisely the exact structure of the product. The resulting FABMS spectrum for the product is shown in Fig. 1. The sharp $(M+1)^+$ peak at a m/z of 635 clearly confirms the structure of macrocycle (I) as the reaction product.

![Figure 1](image)

**Conductance studies:** In order to evaluate the influence of adding ligand (I) on the molar conductance of the cations in acetonitrile solution, the conductivity at a constant salt concentration ($5.0 \times 10^{-5}$ M) was monitored, while increasing the
macrocycle at four different temperatures. The resulting molar conductance vs. ligand/cation mole ratios at various temperatures are shown in Figs. 2–5. As it is seen, while the macroheterocycle I solution possesses a negligible conductance, its addition to all the metal ion solutions in acetonitrile caused a rather large and continuous increase in molar conductance. This could be due to the lower mobility of the solvated cation, existence of some ion pairing in the initial salt [14–16] and/or the release of some high mobility protons into solution brought about upon complexation of the metal ions with the ligand.

From Figs. 2–5 it is seen that, in the case of Hg$^{2+}$, Pb$^{2+}$, Cu$^{2+}$, Cd$^{2+}$ and Ag$^+$ ions, especially at lower temperatures, the slopes of the corresponding molar conductance-mole ratio plots change sharply at the point, where the ligand to cation mole ratio is one, emphasizing the formation of relatively stable 1:1 complex between the macrocycle and the cations used. However, in other cases, the relatively large increase in molar conductance of the cation solutions upon addition of the ligand does not show any tendency of leveling off, even at a mole ratio of 3, indicating the formation of weaker complexes. It is noteworthy that, in all cases studied, an increase in temperature will result in expected increase in molar conductance of solutions as well as the decreased curvature of the mole ratio plots at a mole ratio of about 1. These are indicative of the decreased viscosity of acetonitrile and the diminished stability of the resulting complexes at higher temperatures.

**Figure 2.** Molar conductance vs. [macrocycle]/[M$^{n+}$] curves for different metal ions in acetonitrile solution at 10°C.

**Figure 3.** Molar conductance vs. [macrocycle]/[M$^{n+}$] curves for different metal ions in acetonitrile solution at 18°C.
The 1:1 binding of the metal ions, $M^{n+}$, used with the macrocycle used $L$, can be expressed by the following equilibrium

$$K_f = M^{n+} + L \rightleftharpoons ML^{n+}$$ (1)

The corresponding equilibrium constant, $K_f$, is given by

$$K_f = \frac{[ML^{n+}]}{[M^{n+}][L]} \times \frac{f(ML^{n+})}{f(M^{n+})f(L)}$$ (2)

where $[ML^{n+}]$, $[M^{n+}]$, $[L]$ and $f$ represent the equilibrium molar concentrations of the complex, free cation, free ligand and the activity coefficients of the species indicated, respectively. Under the highly dilute conditions we used the activity coefficient of uncharged ligand, $f(L)$, can be reasonably assumed as unity [16–18]. The use of Debye–Hückel limiting law [19] leads to the conclusion that $f(M^{n+}) \approx f(ML^{n+})$, so the activity coefficients in (2) cancel. Thus, the complex formation constant in terms of the molar conductance can be expressed as [14–16,20]:

**Figure 4.** Molar conductance vs. [macrocycle]/[M$^{n+}$] curves for different metal ions in acetonitrile solution at 25°C.

**Figure 5.** Molar conductance vs. [macrocycle]/[M$^{n+}$] curves for different metal ions in acetonitrile solution at 35°C.
\[ K_f = \frac{[ML^{n+}]}{[M^{n+}][L]} = \frac{(\Lambda_M - \Lambda_{\text{obs}})}{(\Lambda_{\text{obs}} - \Lambda_{ML})[L]} \]

where \[ [L] = C_L - \frac{C_M(\Lambda_M - \Lambda_{\text{obs}})}{(\Lambda_M - \Lambda_{ML})} \]

Here, \( \Lambda_M \) is the molar conductance of the metal nitrate before addition of the ligand, \( \Lambda_{\text{obs}} \) – the molar conductance of solution during titration, \( \Lambda_{ML} \) – the molar conductance of the complex, \( C_L \) – the analytical concentration of the ligand added and \( C_M \) – the analytical concentration of the metal nitrate. The complex formation constant, \( K_f \), and the molar conductance of the complex, \( \Lambda_{ML} \), were evaluated by computer fitting of (3) and (4) to the molar conductance-mole ratio data using a non-linear least-squares program KINFIT [21]. A simple computer fit of the resulting mole ratio data is shown in Fig. 6. The assumed 1:1 stoichiometry for the \( M^{n+} \) macrocycle I complexes seems reasonable in the light of the fair agreement between the observed and calculated molar conductances. A better understanding of the thermodynamics of the complexation reactions can be achieved by considering the enthalpic and entropic contributions to these reactions. The \( \Delta H^\circ \) and \( \Delta S^\circ \) values in acetonitrile solution were determined by measuring the formation constants as a function of temperature. The formation constants of all \( M^{n+} \) – macrocycle I complexes in acetonitrile at various temperatures, obtained by computer fitting of the mole ratio data, are listed in Table 1. Plots of log \( K_f \) vs. \( 1/T \) for different complexes were linear for all cases studied (Fig. 7). The enthalpies and entropies of complexation were determined in the usual manner from the slopes and intercepts of the plots, respectively, and the results are also included in Table 1. Comparison of the formation constants given in Table 1 revealed that the stability of the macrocycle I varies in the sequence \( \text{Hg}^{2+} > \text{Pb}^{2+} > \text{Cd}^{2+} > \text{Ag}^{+} > \text{Sn}^{2+} \).
Cu²⁺ > Tl⁺ > Co²⁺ > Ni²⁺ > Zn²⁺. It is well known that the large crown ethers, such as macrocycle I, due to their high degree of flexibility and increased number of donating atoms in the macrocyclic ring, can wrap themselves around the metal ions of proper size to form tridimensional “wrap around” complexes, in which all donating atoms of the ring are coordinated to the central cation [14,16,22–25]. In this case, the size of cation is expected to influence strongly the extent of complex formation.

Table 1. Formation constants and enthalpy and entropy values for different Mn³⁺-macrocycle I complexes in acetonitrile solution.

<table>
<thead>
<tr>
<th>Cationa</th>
<th>log Kf</th>
<th>ΔH°</th>
<th>ΔS°</th>
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<tr>
<td></td>
<td>10°C</td>
<td>18°C</td>
<td>25°C</td>
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<tr>
<td>Hg²⁺</td>
<td>6.5 ± 0.2</td>
<td>6.5 ± 0.2</td>
<td>5.8 ± 0.1</td>
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<td>(1.19 Å)</td>
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<tr>
<td>Pb²⁺</td>
<td>5.48 ± 0.05</td>
<td>5.27 ± 0.06</td>
<td>4.92 ± 0.05</td>
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<tr>
<td>(1.19 Å)</td>
<td></td>
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<tr>
<td>Cd²⁺</td>
<td>5.21 ± 0.04</td>
<td>4.89 ± 0.04</td>
<td>4.63 ± 0.04</td>
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<tr>
<td>(0.95 Å)</td>
<td></td>
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<tr>
<td>Cu²⁺</td>
<td>5.15 ± 0.06</td>
<td>4.80 ± 0.05</td>
<td>4.55 ± 0.05</td>
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<tr>
<td>(0.77 Å)</td>
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<tr>
<td>Co²⁺</td>
<td>4.33 ± 0.05</td>
<td>4.05 ± 0.05</td>
<td>3.80 ± 0.04</td>
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<tr>
<td>(0.75 Å)</td>
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<tr>
<td>Ni²⁺</td>
<td>3.68 ± 0.06</td>
<td>2.8 ± 0.1</td>
<td>&lt; 3</td>
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<tr>
<td>(0.69 Å)</td>
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<tr>
<td>Zn²⁺</td>
<td>3.02 ± 0.06</td>
<td>&lt; 3</td>
<td>&lt; 3</td>
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<tr>
<td>(0.74 Å)</td>
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<tr>
<td>Ag⁺</td>
<td>5.25 ± 0.05</td>
<td>4.93 ± 0.04</td>
<td>4.60 ± 0.04</td>
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<tr>
<td>(1.15 Å)</td>
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<tr>
<td>Tl⁺</td>
<td>4.60 ± 0.05</td>
<td>4.33 ± 0.03</td>
<td>4.04 ± 0.06</td>
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<tr>
<td>(1.50 Å)</td>
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Values given in parentheses are the ionic radii of the metal ions, [26].

The observed stability sequence revealed that cations with ionic radii 1.0–1.2 Å (i.e. Cd²⁺, Pb²⁺, Hg²⁺ and Ag⁺ ions [26]) have a proper size to fit conveniently inside the cavity formed by twisting of the large molecule with all donating nitrogen and oxygen atoms of the ring participating in the bond formation with the central cation [22,23]. In the case of Tl⁺ (r =1.5 Å), the complete tridimensional structure cannot be formed and only some donating atoms have the opportunity of bond formation with the cation; consequently, a weaker complex results. On the other hand, if the ligand’s cavity is much larger than the cation, as is in the case of Co²⁺, Ni²⁺, Cu²⁺ and Zn²⁺ ions (with ionic radii of 0.7 to 0.8 Å [26]), the ligand can still form a “wrap around” structure, but in this case the donating atoms of the ring will have to be in close proximity and, therefore, the resulting repulsion forces will weaken the complex. It is worthy to
note that among the cations possessing the most convenient size for the complex formation, Ag$^+$ ion forms the weakest complex. This is apparently due to the single charge of the cation, which results in a decreased cation-macrocycle electrostatic interaction. Moreover, the increased stability of the Hg$^{2+}$ complex with ligand 1 over that of Pb$^{2+}$ ion, with the same ionic size, is most probably related to the enhanced polarizability and softer acid character of Hg$^{2+}$ ion, which tend to have a stronger binding to the donating nitrogens of the macrocyclic ring as soft bases [27]. Finally, the sequence of the first transition metal complexes with the macrocycle used follows the Irving-Williams order [28], which generally holds for the equilibrium constants of transition metals [29].

The thermodynamic data given in Table 1 show that, in all cases studied, the complexes are enthalpy stabilized but entropy destabilized. It should be noted that a similar behavior has previously been observed for most of the macrocyclic complexes studied in nonaqueous solvents [2,25,29]. It has been reasonably assumed, that the decrease in entropy upon complexation is related to a change in the conformational entropy of the macrocyclic ligands, from a rather flexible structure in the free state to a rigid conformation in the complex [25,29]. Thus, it is not surprising to observe that the soft Hg$^{2+}$ ion with the best fitting condition for the twisted structure of the ligand will result in the most negative $\Delta S^\circ$ and $\Delta H^\circ$ values in the series.

![Figure 7. Log $K_f$ vs. 1/T for different M$^{2+}$-macrocycle 1 complexes in acetonitrile solution.](image)
REFERENCES