**Abstract**

*N,N*-Bis-(quinolin-8-ylmethyl)diaza-18-crown-6 (L) was prepared in a high yield by treating diaza-18-crown-6 with 8-bromomethylquinoline in the presence of triethylamine. Ligand L interacted strongly with Na⁺, K⁺, Mg²⁺, Co²⁺, Cu²⁺, Ni²⁺, and Zn²⁺ as shown by calimetric titration and UV-Visible spectrophotometric techniques. The ligand exhibited a good selectivity for Cu²⁺ over Ni²⁺. The calimetric titration indicated that ligand L forms both mononuclear and binuclear complexes with Cu²⁺.
Bis-(quinolin-8-ylmethyl)-substituted Diaza-18-crown-6: Synthesis and Metal Ion Complexation Properties

by

Jerald S. Bradshaw, Guoping Xue, Xian Xin Zhang, Paul B. Savage, Krzysztof E. Krakowiak, and Reed M. Izatt

Department of Chemistry and Biochemistry,
Brigham Young University, Provo, UT 84602

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Bis-(quinolin-8-ylmethyl)-substituted Diaza-18-crown-6: Synthesis and Metal Ion Complexation Properties

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Results and Discussion

Synthesis. The synthetic route to ligand 7,16-bis(quinolin-8-ylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane L is depicted in Scheme 1. Intermediate 8-bromomethylquinoline (2) was easily isolated as crystals from EtOH in an 88% yield after the reaction of 8-methylquinoline (1) with NBS in the presence of benzoyl peroxide in refluxing CCl₄. The reaction of diaza-18-crown-6 with 8-bromomethylquinoline (2) in the presence of Et₃N as base in anhydrous benzene gave L in an 87% yield after purification by column chromatograph on silica gel and recrystallization from CH₂Cl₂/EtOH.

Complexation Thermodynamics. Interactions of L with Na⁺, K⁺, Mg²⁺, Ba²⁺, Cu²⁺, Ni²⁺, and Zn²⁺ were evaluated by calorimetric and UV-visible spectrophotometric titrations in absolute MeOH solution. The values of equilibrium constants (log K) and enthalpy (ΔH) and entropy changes (TΔS) for these interactions are listed in Table 1. With the exception of Ni²⁺, ligand L forms stable complexes with the metal ions studied (log K > 3). We first intended to determine the stability constant for the interaction of Ni²⁺ with L by the calorimetric method. The very small reaction heat suggested a weak complexation for which the log K value cannot be accurately calculated due to insufficient heat. Therefore, we used a spectroscopic method to evaluate the interaction and obtained a log K < 1.5 which is consistent
Scheme 1. Syntheses of Bis(quinolin-8-ylmethyl)-substituted ligand L
with the calorimetry study. The ligand shows a good selectivity for Cu\(^{2+}\) over Ni\(^{2+}\) by about three orders of magnitude. Among the metal ions studied, Ba\(^{2+}\) forms the most stable complex with the ligand. Selectivity factors for Ba\(^{2+}\) over the other cations are more than two orders of magnitude.

The calorimetric titration indicated that ligand L forms a binuclear complex with Cu\(^{2+}\). Both 1:1 and 2:1 (Cu\(^{2+}\):L) complexes are observed while all other cations studied form only 1:1 complexes. The data in Table 1 indicate that differences in thermodynamic quantities between 1:1 and 2:1 Cu\(^{2+}\)-L complexation are small. The binuclear Cu\(^{2+}\) complex with a tetraazacrown ether containing two 8-hydroxyquinoline arms has been previously observed in our laboratory.\(^4\) Most of the binuclear Cu(II) complexes reported were formed with all-nitrogen-containing macrocyclic ligands.\(^5\) To the best of our knowledge, the Cu(II) complex described in this paper is the first binuclear Cu(II) complex formed with a diaza-18-crown-6 ligand.

It can be seen in Table 1 that entropy effects play a major role in the complexation of Mg\(^{2+}\), Ba\(^{2+}\), and Co\(^{2+}\). The high stability constant of Ba\(^{2+}\)-L results from both enthalpy and entropy effects. On the other hand, the formation of Mg\(^{2+}\) and Co\(^{2+}\) complexes is essentially entropy driven.

**Experimental Section**

**Preparation of 8-Bromomethylquinoline (2) (Scheme 1).** 8-Bromomethylquinoline was prepared by a similar manner as that described by Kimura et.al.\(^10\) A solution of 8-methylquinoline (1) (12.6 g, 88 mmol) in 400 mL of CCl\(_4\) was refluxed with NBS (16.0 g, 90 mmol) in the presence of benzoyl peroxide (0.7 g) for 12 h. The hot solution was filtered and the
**Table 1.** Thermodynamic Quantities for the Interactions of Macrocyclic Ligand L with Metal Ions in Methanol Solution

<table>
<thead>
<tr>
<th>Cation</th>
<th>log $K$</th>
<th>$\Delta H$</th>
<th>$T\Delta S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$</td>
<td>3.73 ± 0.02</td>
<td>-22.5 ± 0.3</td>
<td>-1.2</td>
</tr>
<tr>
<td>K$^+$</td>
<td>4.58 ± 0.03</td>
<td>-39.1 ± 0.3</td>
<td>-13.0</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>4.02 ± 0.07</td>
<td>9.9 ± 0.6</td>
<td>32.8</td>
</tr>
<tr>
<td>Ba$^{2+}$</td>
<td>6.73 ± 0.08$^c$</td>
<td>-19.4 ± 0.4$^c$</td>
<td>19.0</td>
</tr>
<tr>
<td>Co$^{2+}$</td>
<td>3.21 ± 0.06</td>
<td>14.4 ± 0.8</td>
<td>32.7</td>
</tr>
<tr>
<td>Cu$^{2+}$(1)$^b$</td>
<td>4.43 ± 0.04</td>
<td>-35.7 ± 0.5</td>
<td>-10.4</td>
</tr>
<tr>
<td>Cu$^{2+}$(2)$^b$</td>
<td>4.15 ± 0.04</td>
<td>-32.8 ± 0.6</td>
<td>-9.11</td>
</tr>
<tr>
<td>Ni$^{2+}$</td>
<td>&lt; 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn$^{2+}$</td>
<td>3.66 ± 0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Both $\Delta H$ and $T\Delta S$ values are in kJ/mol. Except Cu$^{2+}$, all thermodynamic parameters are for 1:1 interactions. The log $K$ values for Ni$^{2+}$ and Zn$^{2+}$ interactions were evaluated at 23°C by UV-visible spectrophotometric titrations and other log $K$ values were determined at 25°C by calorimetric titrations.

$^b$ Thermodynamic parameters for Cu$^{2+}$(1) and Cu$^{2+}$(2) refer to the formation of 1:1 complex Cu$^{2+}$L and 2:1 complex (Cu$^{2+}$)$_2$L (from Cu$^{2+}$ and Cu$^{2+}$L), respectively.

$^c$ Determined by a competitive calorimetric titration.
brown filtrate was evaporated under reduced pressure. The residue was dissolved in 50 mL of CHCl₃, and the solution was washed twice with saturated aqueous Na₂CO₃ and once with water. The organic phase was dried (Na₂SO₄) and evaporated. The residue was recrystallized from EtOH to give 17.2 g (88%) of 2 as white crystals. The mp and NMR spectral data were identical to those reported.¹⁰

7,16-Bis(quinolin-8-ylmethyl)-1,4,10,13-tetroxa-7,16-diazacyclooctadecane monohydrobromide (L) (Scheme 1). A solution of 2 (2.0 g, 9.0 mmol) in 50 mL of benzene was added dropwise to a solution of diaza-18-crown-6 (1.0 g, 3.8 mmol) and Et₃N (1.6 g, 15.8 mmol) in 50 mL of benzene under N₂. The mixture was stirred at room temperature for 20 h and then refluxed for 2 h. The solvent was evaporated under reduced pressure. The residue was treated with a mixture of water and CHCl₃ (1:2). The organic layer was separated, washed with water, and dried (Na₂SO₄). After evaporation, the residue was purified by column chromatography on silica gel with acetone as eluent. The product was recrystallized from CH₂Cl₂/EtOH to give 1.81 g (87%) of L·HBr as yellow crystals, mp 95-96 °C; ¹H NMR: δ 2.93 (t, 8H), 3.66 (m, 16H), 4.43 (S, 4H), 7.36 (dd, 2H), 7.52 (d, 2H), 7.65 (dd, 2H), 8.02 (d, 2H), 8.11 (dd, 2H), 8.90 (dd, 2H); ¹³C NMR (CDCl₃): δ 54.78, 54.86, 70.33, 71.00, 120.95, 126.53, 126.74, 128.36, 129.20, 136.54, 138.23, 147.02, 149.42; HRMS: m/z calcd. for C₃₂H₄₀N₄O₄·CH₂Cl₂·H₂O: C, 61.20; H, 6.85. Found: C, 61.24; H, 6.62.

Calorimetric Measurements. Values of log K, ΔH, and ΔS for the interactions of metal ions (except Ni²⁺ and Zn²⁺) with L were determined as described earlier¹ in absolute MeOH
solutions at 2.50 ± 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 2-fold excess of metal ions. In general, concentrations of the ligands were (2.2 - 3.2) x 10^{-3} \text{M} and those of the metal ions 7.5 x 10^{-2} \text{M} (K^+) - 0.1 \text{M}. In the case of Cu^{2+}, concentration of the ligand was 1.5 x 10^{-3} \text{M} and that of Cu^{2+}, 5.1 x 10^{-2} \text{M}. After a 2:1 (Cu^{2+}:L) complex was observed, the Cu^{2+} concentration was increased to 0.11 \text{M}. The method used to process the calorimetric data and to calculate the log K and ΔH values has been described.\textsuperscript{2} Calorimetric titrations showed no detectable heat for the Ni^{2+}-L interaction and a white precipitate was observed when the ligand ((1.5 - 2.1) x 10^{-3} \text{M}) was titrated with Zn^{2+}. Therefore, log K values for Ni^{2+} and Zn^{2+} interactions were evaluated by a UV-visible spectrophotometric method.

**UV-Visible Spectral Measurements.** UV-visible spectra were recorded at 23 ± 1 °C in a 1-cm quartz cell by using a Hewlett-Packard 8453 spectrophotometer. Absolute MeOH was used as the solvent. For the determination of stability constants, a 5.0 x 10^{-5} \text{M} L solution (2.50 mL) was titrated by Ni^{2+} or Zn^{2+} solution and the UV-visible spectra were recorded after each titration. The method described by Bourson and Valeur\textsuperscript{3} was employed to calculate log K values. Absorbence data at 280 and 284 nm were used to make the calculations for L-Zn^{2+} and L-Ni^{2+} interactions respectively. Since nickel nitrate showed a weak absorption at 284 nm in MeOH solution (ε = 10.9 M^{-1} \text{cm}^{-1}), the values of ligand absorbance were corrected by subtracting the Ni^{2+} absorption.
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