

## Molecular Interactions of a Zinc(II) Macrocycle towards Carboxylate Ligands

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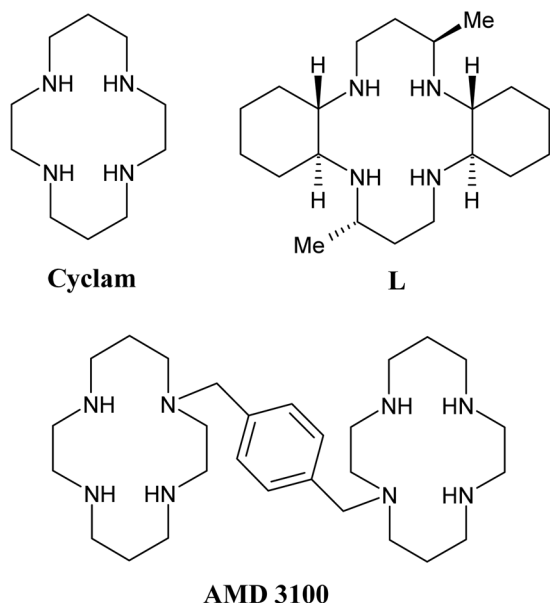
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Received May 25, 2006

**Key Words :** Zinc(II) complex, Crystal structure, Tetraazamacrocycle

Cyclam and its derivatives attract great interests due to their highly potent and selective anti-HIV activity by specifically blocking the co-receptor CXCR4.<sup>1-5</sup> Particularly, the xylyl-bicyclam known as AMD3100 has recently been on clinical trials for the treatment of AIDS. The aspartate residues (Asp 171 and Asp 262) having carboxylate groups of the CXCR4 co-receptor have been understood to participate in the recognition of cyclams.<sup>3,6</sup> The antiviral activity is greatly enhanced by metal complexation, especially zinc(II) ion, to macrocycles.<sup>7,8</sup> It is believed that the metal ions of the zinc(II) complexes preferentially recognize the aspartates of the CXCR4 co-receptor by coordination. Therefore, the better knowledge of interactions between zinc(II) macrocycles and carboxylates is crucial for the improved design and development of more effective anti-HIV agents. In this context, we have made an effort to expand upon the examples of carboxylato zinc(II) macrocycles to elucidate the nature of interactions between zinc(II) macrocycles and carboxylates. Herein, we report the synthesis, structure and properties of a new carboxylato zinc(II) complex  $Zn(L)(apc)_2$  (**1**) (**L** = 5,16-dimethyl-2,6,13,17-tetraazatricyclo[16.4.0<sup>1,18</sup>.0<sup>7,12</sup>]docosane, apc = 3-amino-2-pyrazinecarboxylate) in which the macrocycle **L** has a close resemblance to a cyclam.



### Experimental Section

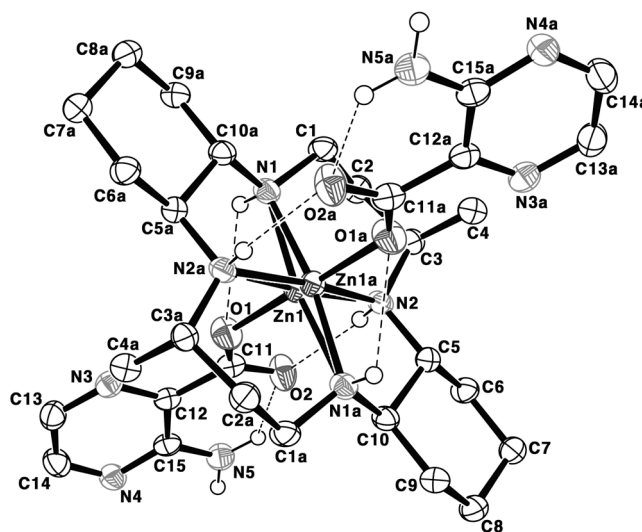
**Materials, Methods and Apparatus.** All chemicals used in the synthesis were of reagent grade and used without further purification. Distilled water was used for all procedures. Infrared spectra of solid samples were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer between 4000  $\text{cm}^{-1}$  and 400  $\text{cm}^{-1}$  as Nujol mulls on KBr discs. Thermal analysis (TGA-DTG) was performed on a Perkin-Elmer Model TGA-7 Thermogravimetric Analyzer under air from 50 to 800  $^{\circ}\text{C}$  at a heating rate of 10  $^{\circ}\text{C}/\text{min}$ . Elemental analysis was performed by the Korea Research Institute of Chemical Technology, Daejeon, Korea. The free ligand **L** was prepared according to a literature procedure.<sup>9</sup> The precursor complex  $Zn(L)(NO_3)_2$  was prepared by refluxing ligand **L** (3.36 g, 1.0 mmole) and  $Zn(NO_3)_2 \cdot 6H_2O$  (3 g, 1.01 mmole) in stirring methanol for a day, filtering the white powder, washing with methanol, and finally drying in air.

**Preparation of 1.** To a DMF solution of  $Zn(L)(NO_3)_2$  (526 mg, 1.0 mmole) were added an aqueous solution of Hapc (278 mg, 2.0 mmole) and several drops of triethylamine. The mixture was allowed in an open beaker at room temperature. Colorless blocks of **1** were obtained in a week. Suitable crystals of **1** for X-ray diffraction studies and other measurements were manually collected under a microscope. Anal. Calcd. for  $C_{30}H_{48}ZnN_{10}O_4$ : C, 53.08; H, 7.08; N, 20.64. Found C, 52.95; H, 7.28; N, 20.51%. IR (Nujol,  $\text{cm}^{-1}$ ): 3227 ( $\nu_{\text{NH}}$ ), 3145 ( $\nu_{\text{NH}}$ ), 1587 ( $\nu_{\text{CO}}$ ).

**X-ray Crystallography.** A summary of selected crystallographic data and selected interatomic distances and angles for **1** are given in Tables 1 and 2. X-ray data were collected on a Nonius Kappa CCD diffractometer, using graphite monochromated Mo  $K_{\alpha}$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). A combination of  $1^{\circ} \phi$  and  $\omega$  (with  $\kappa$  offsets) scans were used to collect sufficient data. The data frames were integrated and scaled using the Denzo-SMN package.<sup>10</sup> The structure was solved and refined using the SHELXTL/PC V5.1 package.<sup>11</sup> Refinement was performed by full-matrix least squares on  $F^2$  using all data (negative intensities included). Hydrogen atoms were included in calculated positions, except for those involving in hydrogen bonding specifically for the hydrogen atoms bonded to the nitrogen atoms, which were refined with isotropic thermal parameters.

**Table 1.** Crystal data and structure refinement for **1**

Empirical formula	C <sub>30</sub> H <sub>48</sub> ZnN <sub>10</sub> O <sub>4</sub>
Formula weight	678.15
Temperature (K)	150(2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub> /n
Unit cell dimensions	a = 8.4493(6) Å b = 17.2927(15) Å c = 10.9936(7) Å β = 104.809(4)°
Volume	1552.9(7) Å <sup>3</sup>
Z	2
Density (calcd)	1.450 Mg/m <sup>3</sup>
Absorption coefficient	0.845 mm <sup>-1</sup>
Independent reflections	3518 [R(int) = 0.0801]
Goodness-of-fit on F <sup>2</sup>	1.028
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0534, wR <sub>2</sub> = 0.1225
R indices (all data)	R <sub>1</sub> = 0.1123, wR <sub>2</sub> = 0.1494

**Figure 1.** Molecular structure for **1** with atom-labeling scheme. Hydrogen atoms other than those participating in hydrogen bonding are omitted for clarity.**Table 2.** Selected bond distances (Å) and angles (°) for **1**

Zn1-N1	2.033(3)	Zn1-N2	2.113(3)
Zn1-N1#1	2.153(3)	Zn1-N2#1	2.143(3)
Zn1-O1	2.099(2)	O1-C11	1.260(4)
N1-Zn1-O1	90.46(11)	N1-Zn1-N2	98.12(10)
O1-Zn1-N2	92.04(11)	N1-Zn1-N2#1	83.96(10)
O1-Zn1-N2#1	99.87(10)	N2-Zn1-N2#1	167.91(4)
N1-Zn1-N1#1	168.12(4)	O1-Zn1-N1#1	101.42(11)
N2-Zn1-N1#1	81.86(10)	N2#1-Zn1-N1#1	93.65(10)

Symmetry transformations used to generate equivalent atoms: #1 -x+1, -y+1, -z+1

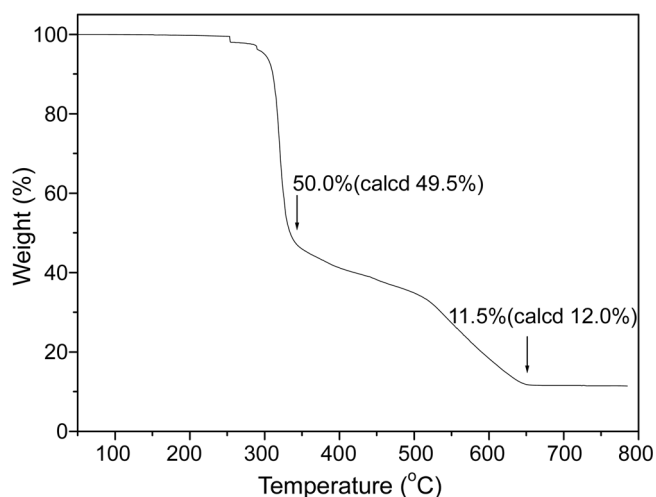
## Results and Discussion

**Structure.** The structure of the discrete neutral complex **1** shows that the central zinc(II) ion is coordinated axially by two apc ligands as shown in Figure 1. The macrocyclic ligand skeleton in **1** takes the most stable “trans III” conformation as usual. The coordination environment around the central zinc(II) ion exhibits an octahedron with four Zn-N and two Zn-O bonds. The Zn atom does not lie exactly on the inversion center (sits *ca.* 0.22 Å above the N1-N2-N1A-N2A mean plane) and is disordered. The Zn-N distances vary from 2.033(3) Å to 2.113(3) Å with an average distance of *ca.* 2.073 Å, which are comparable to those found in related complexes.<sup>2,12</sup> The Zn-O distance of 2.099(2) Å lies in the lower limit of the previously reported values ([Zn<sub>2</sub>(xylyl-bicyclam)(OAc)<sub>2</sub>](OAc)<sub>2</sub>·2CH<sub>3</sub>OH;<sup>1</sup> Zn-O = 2.089(2), 2.407(2) Å, {Zn(L)(phthalate)}<sub>n</sub>(CH<sub>3</sub>OH)<sub>2n</sub>;<sup>2</sup> Zn-O = 2.220(2), 2.190(2) Å, {Zn(L)(tp)·H<sub>2</sub>O}<sub>n</sub>;<sup>12</sup> Zn-O = 2.1559(12) Å, {Zn(L)(H<sub>2</sub>bta)·2H<sub>2</sub>O}<sub>n</sub>;<sup>12</sup> Zn-O = 2.2839(14) Å, Zn(L)(H<sub>2</sub>btc)<sub>2</sub>·2DMF;<sup>12</sup> Zn-O = 2.2222(12), {[Zn(L)(maleate)<sub>2</sub>·H<sub>2</sub>O]}<sub>n</sub>;<sup>13</sup> Zn-O = 2.1968(16), 2.2840(16); where tp = terephthalate, bta = 1,2,4,5-benzenetetracarboxylate and btc = 1,3,5-benzenetricarboxylate). The observed strong

interaction between the zinc(II) ion and carboxylates in **1** is supported by the concomitant presence of hydrogen bonding interactions between the N-H groups of the macrocycle and oxygen atoms of the carboxylates. The pre-organization of N-H groups of the zinc(II) macrocycle with its role in profacial selection of apc anion binding is achieved, ultimately resulting in the formation of one strong Zn-coordination bond as well as two weaker hydrogen bonds (N1-H1NA...O1 = 2.934(3) Å, N2-H2NA...O2 = 2.982(4) Å). In an earlier report by Gerlach *et al.*,<sup>3</sup> it has been raised that the acetate can make a strong coordination bond to the zinc(II) ion (Zn-O = 1.96 Å) and one weaker hydrogen bond to a nitrogen in the cyclam system by optimized density functional methods (DFT).

**Properties.** Compound **1** was stable indefinitely in air, and the microanalytical and thermal analyses clearly supported the structure determined by X-ray diffraction studies. The IR spectra of **1** gave evidences for the presence of the macrocycle and apc ligands as described in Experimental Section. The TGA curve for **1** showed a first weight loss of 50.0% (calculated 49.5%) over 290-335 °C with an endothermic processes centered at 320 °C, corresponding to the loss of the macrocycle. On further heating, gradual weight loss was observed in 335-645 °C range with the loss of apc ligands. Finally, the ZnO residue (observed 11.5%, calculated 12.0%) was remained above 645 °C (Figure 2).

In conclusion, we have prepared and fully characterized the new carboxylato zinc(II) complex **1**. The carboxylate groups of the apc ligands in the complex **1** show strong coordination behavior towards the zinc(II) ion with hydrogen bonding interactions between the N-H groups of the macrocycle and oxygen atoms of the apc ligands. From this account, we conclude that the coordination of carboxylate groups of apc ligands to the zinc(II) ion is reinforced by the presence of additional hydrogen bonding interactions between the macrocycle and carboxylates. Therefore, the



**Figure 2.** TGA curve for **1**.

zinc(II) complex **1** could be a good model system for the understanding of the nature of molecular interactions between the zinc(II) macrocycle and carboxylates as well as the importance of the role of hydrogen bonding interactions in forming a strong coordination bond.

**Supplementary Material.** Crystallographic data for the structure reported here have been deposited with Cambridge Crystallographic Data Center (Deposition No. CCDC 607957). These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: 44 1223 336033, email: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk).

**Acknowledgments.** This work was supported by Pukyong National University Research Foundation Grant in 2004.

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