The First Trigonal-bipyramidal Structure of Zinc(II) Complex of a Bleomycin Model

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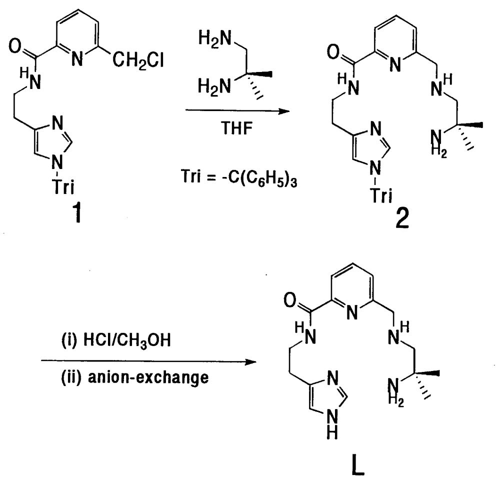
A new bleomycin analogue 2-[((2-(imidazolyl)ethyl)amino)-carbonyl]-6-[((2-amino-2-methylpropyl)amino)methyl]pyridine, L, was prepared and the coordination mode of L to Zn(II) was characterized in both solution and solid state as a Zn(II)-bleomycin model complex. With L, Zn^{II} forms 4-coordinate, tetrahedral $[ZnL]^{2+}$ at pH < 6 and 5-coordinate $[ZnH_{-1}L]^+$ at pH > 8. The $[ZnH_{-1}L]ClO_4 \cdot H_2O$ complex has a trigonal-bipyramidal complex structure by the X-ray crystal study.

Bleomycins (BLM) are a family of antitumor metalloglycopeptides used clinically for the treatment of certain malignancies.[1] It was first isolated in 1966 as a copper(II) complex.[2] The coordination structures of various metallo-BLMs have been predicted on the basis of the crystal structure of Cu(II)-P3A, a biosynthetic intermediate of BLM. For Zn(II)-BLM complex, the solution structure is mainly studied by NMR techniques in order to clarify the structure of paramagnetic Fe(II) and Fe(III)-BLMs. Previously, Lenkinski et al.[3] postulated to have a tetrahedral geometry. In contrast, Akkarman et al. and Hecht et al. suggested five nitrogen atoms in the metal chelating moiety and the mannose carbamoyl group are coordinated to zinc ion.[4] Thus, the structure of Zn(II)-BLM complex remains unidentified.

The pH-dependent complexing behavior with Zn(II) of a new synthetic BLM model, which contains dimethyl group on the carbon atom adjacent to the primary amine to protect the model from oxidation, established the presence of two structures depending on the deprotonation of amide moiety. X-ray crystallography of the high-pH form revealed an unprecedented trigonal-bipyramidal structure as the BLM-metal ion complexes.

The treatment of **1**[5] with 6 equiv. of 2-methylpropane-1,2-diamine afforded the corresponding condensation product **2** (yield 37 %). Deprotection of the trityl group of **2** by HCl-MeOH yielded the potentially pentadentate ligand L·3HCl, from which free form of L was obtained as brown solids (yield 96 %, Scheme 1)[6] by an anion exchange Amberlite IRA-400 chromatography.



Scheme 1.

Colorless microcrystallines of $\mathbf{3}\cdot(ClO_4)_2$[7] separated from a mixture of L (100 mg, 0.32 mmol) and $Zn(ClO_4)_2 \cdot 6H_2O$ (118 mg, 0.32 mmol) in 10 mL of water on adjusting the pH to 6 with 0.1 M HCl within a few minutes and collected on a filter (yield 57 %). The other colorless crystals, $\mathbf{4}\cdot ClO_4$, (18 %) were obtainted by dissolving $\mathbf{3}\cdot(ClO_4)_2$ (100 mg) in 10 mL of water followed by adjusting the pH to 9.8 with 0.1 M NaOH and were collected by filtration after 4 d.[8]

The protonation constants (K_n) of L were determinted by potentiometric titration at I = 0.10 M KNO_3 and 25 °C. Three protonation constants ($\log K_1$-$\log K_3$) are 9.9, 6.9, and 5.2 and are almost the same for the analogous BLM models.[5]

The 1:1 L·3HCl-Zn^{II} titration curve is shown in Figure 1, where two flections occurred at a = 3 and 4. The first buffer region (pH < 6) until a = 3 is ascribed to the loss of the three protons from the imidazolyl nitrogen, secondary amine, and primary amine. The complex **3** showed the amide $\nu_{C=O}$ at 1642 cm^{-1} supporting the 4-coordinate with the uncoordinated protonated amide, whose elementary analysis agreed with formula $[Zn^{II}L](ClO_4)_2 \cdot H_2O$. Complete removal of proton, which took place with a pK_a value of 7.3, converted **3** to a 5-coordinate, trigonal-bipyramidal $[Zn^{II}H_{-1}L]^+$, **4** (Scheme 2). The formation constants $K_{ZnH_{-1}L}$ (=$[ZnH_{-1}L][H^+]/[Zn^{2+}][L]$) is 10^2 for L at 25 °C and is smaller than that of BLM ($10^{4.2}$).[9]

X-ray quality single crystals of $\mathbf{4}\cdot ClO_4 \cdot H_2O$ grown by slow evaporation of pH 9 aqueous solution were subjected to X- ray crystallography and the structure of the complex cation was proved. An ORTEP drawing of the molecular cation as well as selected bond lengths and angles for **4** is shown in Figure 2[10]. The Zn atom is coordinated by five nitrogens from the pyridine, imidazole, secondary amine, primary amine, and the deprotonated amide group. The structure of **4** is different to that of the related Cu(II) complexes,[5,11] in which the geometry is a

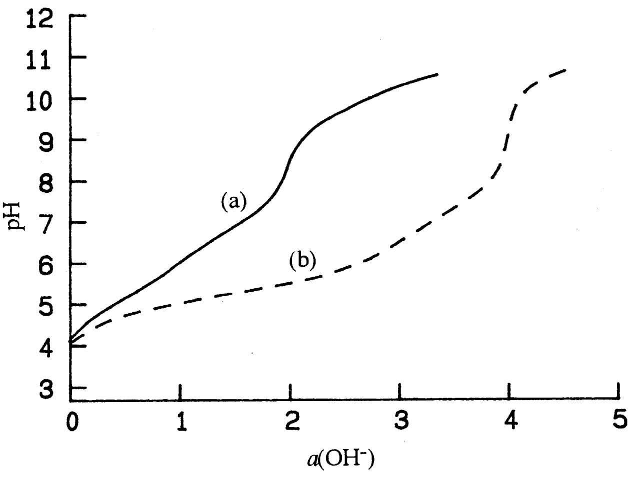
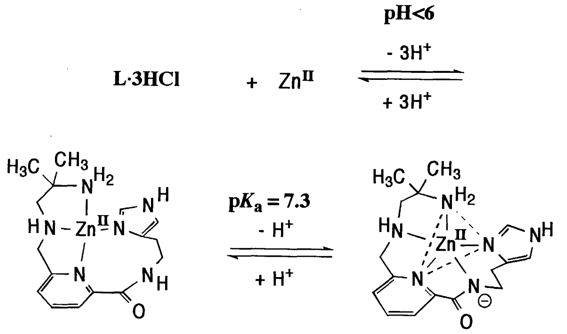


Figure1. pH titration curves of triprotonated ligand L in the absence and the presence of equimolar of Zn^{II} at 25 °C and I = 0.1 (KNO_3). Key: (a) 1.0 mM L·3HCl; (b) (a) + 1.0 mM $Zn(NO_3)_2 \cdot 6H_2O$.



3 $[Zn^{II}\text{-}L]^{2+}$ $\nu_{C=O}$ 1642 cm^{-1}

4 $[Zn^{II}(H_{-1}L)]^+$ $\nu_{C=O}$ 1569 cm^{-1}

Scheme 2.

distorted square pyramid. The geometry around zinc(II) is a distorted trigonal bipyramid, $\tau = 0.50$ ($\tau = (\beta-\alpha)/60$, where β = N3-Zn-N5, 154.5° and α = N1-Zn-N4, 124.5°). The Zn atom is located in the trigonal plane defined by the N1 (imidazole), N4 (pyridine), and N6 (primary amine) atoms with the displacement of 0.011 Å from this plane. The apical coordination sites are occupied by the secondary amine (N5) and deprotonated amide (N3). The bond angle of N3-Zn-N5 is 154.5(1)° and the sum of the equatorial angles of 124.5(1)° (N1-Zn-N4), 123.1(1)° (N1-Zn-N6), and 112.4(1)° (N4-Zn-N6) is 360°. The apical Zn-N3 (2.114(3) Å) and Zn-N5 (2.248(3)Å) bonds are significantly longer than the average distance (2.038 Å) of the three equatorial bond distances. The dihedral angles of the least-square planes difined by either N1-C1-N2-C2-C3 and N4-C7-C8-C9-C10-C11 and the equatorial plane are 108.06° and 95.74°, respectively.

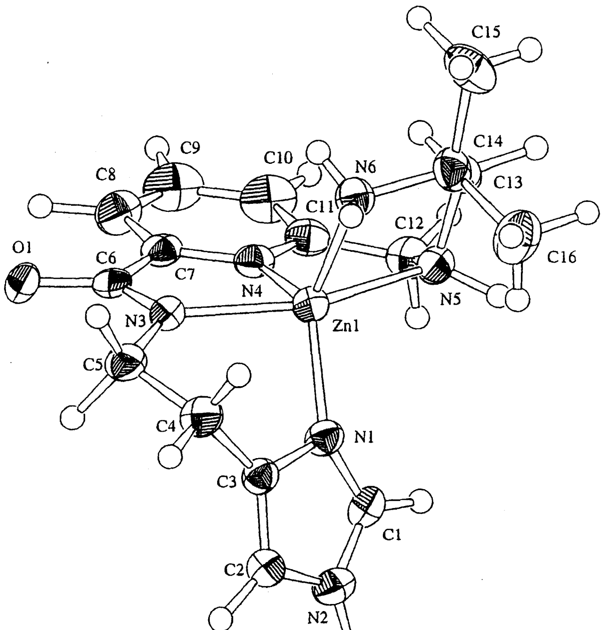


Figure 2. ORTEP drawing of $[ZnH_{-1}L_4]^+$. Selected bond distances (in Å): Zn-N1, 2.009(3); Zn-N3, 2.114(3); Zn-N4, 2.048(3); Zn-N5, 2.248(3); Zn-N6, 2.056(3). Selected bond angles (in deg): N1-Zn-N3, 89.4(1); N1-Zn-N4, 124.5(1); N1-Zn-N5, 108.2(1); N1-Zn-N6, 123.1(1); N3-Zn-N4, 77.9(1); N3-Zn-N5, 154.5(1); N3-Zn-N6, 104.0(1); N4-Zn-N5, 76.9(1); N4-Zn-N6, 112.4(1); N5-Zn-N6, 82.2(1).

In conclusion, the 5-coordinate $[Zn(H_{-1}L)]^+$ complex, **4**, is a good model of Zn(II)-BLM and the coordination mode indicates that a possible structure for Zn(II)-BLM is a trigonal-bipyramidal one.

References and Notes

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6 NMR data (D_2O, 298 K, 270 MHz, ppm from TSP) ^1H NMR: δ 1.10 (3H, s), 1.11 (3H, s), 2.48 (2H, s), 2.93 (2H, t, J = 5.2 Hz), 3.69 (2H, t, J = 5.0 Hz), 3.91 (2H, s), 6.93 (1H, s), 7.53 (1H, d, J = 7.6 Hz), 7.69 (1H, s), 7.89 (1H, d, J = 8.6 Hz), 7.93 (1H, t, J = 7.6 Hz); ν_{CO} (KBr pellet) 1660 cm^{-1}.

7 ^1H NMR (D_2O, pD 6.02, 278 K) δ 1.53 (6H, s), 3.12 (2H, t, J = 6.0 Hz), 3.34 (2H, s), 3.79 (2H, t, J = 6.59 Hz), 4.55 (2H, s), 7.27 (1H, s), 7.66 (1H, d, J = 7.3 Hz), 8.00 (1H, d, J = 7.3 Hz), 8.06 (1H, t, J = 8.1 Hz), 8.58 (1H, s); Anal. calcd for $C_{16}H_{24}N_6OZn(ClO_4)_2 \cdot H_2O$: C, 32.10; H, 4.38; N, 14.04. Found: C, 31.76, H, 4.20; N, 13.66. ν_{CO} (KBr pellet) 1642 cm^{-1}.

8 ^1H NMR (D_2O, pD 9.04, 278 K) δ 1.15 (3H, s), 1.18 (3H, s), 2.12 (1H, d, J = 13 Hz), 2.96 (1H, d-d-d, J = 13.4, 2.6, and <1 Hz), 3.08 (2H, d, J = 13.2 Hz), 3.35 (1H, t, J = 14 Hz), 3.67 (1H, d-d-d, J = 13.6, 2.6, and <1 Hz), 4.10 (1H, AB, J = 16.9 Hz), 4.36 (1H, AB, J = 16.9 Hz), 7.15 (1H, s), 7.62 (1H, d J = 8.1 Hz), 7.96 (1H, d, J = 7.3 Hz), 8.02 (1H, s), 8.13 (1H, t, J = 7.7 Hz); Anal. calcd for $C_{16}H_{23}N_6OZnClO_4 \cdot H_2O$: C, 38.57; H, 5.06; N, 16.87. Found. C, 38.31; H, 5.03; N, 16.46. ν_{CO} (KBr pellet) at 1569 cm^{-1}.

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10 Crystal data for **4**; F.W. = 498.24, colorless crystal (0.30 x 0.21 x 0.15 mm), monoclinic, space group *C2/c*, a = 22.177(2) Å, b = 14.010(3) Å, c = 17.562(2) Å, β = 130.44(5) °, Z = 8, V = 4153(10) Å^3, $F(000)$ = 2064, D_{calc} = 1.594 gcm^{-3}, μ(Mo-Kα) = 13.58 cm^{-1}, R = 0.040 (R_w = 0.031) for 4962 unique reflections with $I > 3\sigma(I)$ and 272 variables.

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