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Studies on Metal Complexes of Isocytosine Derivative: The Crystal Structure of Zinc(II) Complex of 2-Hydrazino-4-hydroxy-6-methylpyrimidine

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The crystal structure of Zn(II) complex of 2-hydrazino-4-hydroxy-6-methylpyrimidine (LH), has been determined from three-dimensional X-ray diffractometer data by heavy atom Fourier methods. Crystals of $[Zn(C_5H_8N_4O)_2(H_2O)_2]Cl_2 \cdot 2H_2O$ are triclinic with unit cell dimensions $a=8.912(3)$, $b=9.298(2)$, $c=6.821(5)$ Å, $\alpha=93.11(5)°$, $\beta=102.14(4)°$, $\gamma=114.33(2)°$, space group $P\bar{1}$, and $Z=1$. Block-diagonal least-squares refinement using 1537 independent reflexions yielded the R value of 0.050. The zinc(II) ion completes an octahedral coordination with two ring nitrogen and two amino nitrogen atoms of the two neighbouring ligand molecules and two water molecules. The chloride ions are not bonded to zinc(II) ion but to N(1)-H of the pyrimidine base.

Keywords——zinc(II) complex; 2-hydrazino-4-hydroxy-6-methylpyrimidine; crystal structure of Zn(II) complex of isocytosine derivative; Zn(II) complex of pyrimidine derivative; Zn(II) complex of isocytosine derivative; Zn(II) complex of 2-hydrazino-4-hydroxy-6-methylpyrimidine; X-ray structure of Zn(II) complex of pyrimidine derivative

Introduction

There is a growing interest in the interaction of transition metal ions with nucleic acids and bases.[2] Many studies of metal nucleotide complexes have aimed primarily at elucidating the structure and base sequences of these biopolymers. The effect of bivalent metal ions especially of Zn^{2+} and Cu^{2+} ions in stabilizing or destabilizing the structures of DNA or t-RNA have been well established.[3]

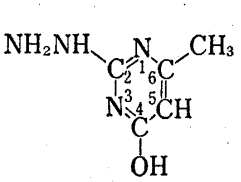
It has recently been shown that zinc (II) stimulates the diffusion of adenine nucleotides across bimolecular lipid membrane (nucleotide-transport process)[4] and inhibits replication of some viruses.[5] However, understanding of the role of zinc in nucleotide containing systems has been hindered by lack of definite information concerning its binding sites.

As part of a programme of crystallographic studies on transition metal complexes with nucleotide bases we have determined the structure of the complex between zinc (II) and a new ligand of isocytosine derivative, 2-hydradino-4-hydroxy-6-methylpyrimidine which has been reported to be effective to *Mycobacterium tuberculosis* (human type H_2-strain) as chemotherapeutic agent.[6]

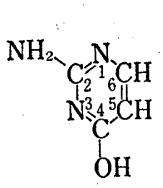
1) Location: *a) Sagamihara-shi, Kanagawa, 228, Japan; b) Shirokane, Minato-ku, Tokyo, 108, Japan; c) Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
2) G.L. Eichhorn, N.A. Berger, J.J. Butzow, P. Clark, J.M. Rifkind, Y.A. Shin, and E. Tarien, *Adv. Chem. Ser.*, No. 100, 135 (1971).
3) G.L. Eichhorn and Y.A. Shin, *J. Am. Chem. Soc.*, **90**, 7323 (1968).
4) W. Stillwell and H.C. Winter, *Biochem. Biophys. Res. Commun.*, **56**, 617 (1974).
5) B.D. Korant, J.C. Kaner, and B.E. Butterworth, *Nature*, **248**, 588 (1974).
6) T. Matsukawa, S. Ban, K. Sirakawa, and M. Yoneda, *Yakugaku Zasshi* (*J. Pharm. Soc. Japan*), **73**, 159 (1953).

Several papers[7–9] have been reported on the metal complexes of cytosine and isocytosine but the metal ions in these complexes are bonded only to N(1) or N(3) of the pyrimidine rings and not to NH_2 or OH groups of the bases. Furthermore, no papers has been presented on the complex containing hydrazino group as substituent of pyrimidine bases.

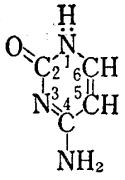
We prepared Zn (II) complex of 2-hydrazino-4-hydroxy-6-methylpyrimidine (LH) having hydrazino group ($-NHNH_2$) as C(2) substituent of isocytosine. The hydroxyl group at C(4) substituent of LH residue in this complex was suggested by us[10] to be the keto form by infrared (IR) spectra. But it is difficult to determine, to which N of the pyrimidine ring the proton is transferred or where the coordination site to the metal ion is.



2-hydrazino-4-hydroxy-6-methylpyrimidine (LH)



isocytosine



cytosine

Experimental

The complex, $[Zn(C_5H_8N_4O)_2(H_2O)_2]Cl_2 \cdot 2H_2O$ was prepared according to ref. 10). This complex was recrystallized from 1 N HCl. The crystals of the complex are colorless prisms, and stable in air. The specimen employed for the data collection has dimensions of $0.4 \times 0.4 \times 0.3$ mm which was mounted on a glass fiber. The crystal data are given in Table I.

Table I. Crystal Data of $[Zn(C_5H_8N_4O)_2(H_2O)_2]Cl_2 \cdot 2H_2O$

Crystal system	triclinic	
Cell constants	$a = 8.912(3)$ Å	$\alpha = 93.11(5)°$
	$b = 9.298(2)$ Å	$\beta = 102.14(4)°$
	$c = 6.821(5)$ Å	$\gamma = 114.33(2)°$
	$V = 497.1 \ (4)$ Å^3	
Space group	$P\bar{1}$	
Z	1	
Density (Obsd)	$D_m = 1.630$ g·cm^{-3}	
(Calcd)	$D_x = 1.632$ g·cm^{-3}	

$C_{10}H_{24}Cl_2N_8O_6Zn$: F. W. = 488.6

The intensities were measured on a Rigaku four-circle automatic diffractometer using monochromated Cu-K_α radiation by graphite plate. Intensities of reflexions with 2θ values up to 152° were collected by the θ-2θ scan method with a 2θ scan rate of 2° min^{-1}. The background was measured at each end of the scan range for 10 s. The intensities were corrected for Lorentz and polarization factors but not for absorption factors. The total number of independent observed reflexions above the $2\sigma(F)$ level was 1537 out of 2075 theoretically possible reflexions.

Determination and Refinement of the Structure

The crystal structure was solved by the heavy-atom technique. Since the space group is $P\bar{1}$ and $Z = 1$, Zn (II) ion was placed at (0, 0, 0). The resulting Fourier map showed all atoms with the exception of hydrogen atom.

7) M. Sundaralingam and J.A. Carrabine, *J. Mol. Biol.*, **61**, 287 (1971).
8) T. Sakaguchi and M. Tanno, *Nippon Kagaku Kaishi*, **1974**, 1637.
9) K. Saito, R. Terashima, T. Sakaki, and K. Tomita, *Biochem. Biophys. Res. Commun.*, **61** (1), 83 (1974).
10) H. Sakaguchi, H. Anzai, T. Fujita, and T. Sakaguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 1555 (1977).

Refinement of the structure was carried out by the block-diagonal least-squares method (program by Okaya & Ashida, 1967).[11]

Finally, four cycles of least-squares refinement gave the R index of 0.050. In this calculation, anisotropic thermal motions were assumed for all 14 atoms and the following weighting system was applied: $\sqrt{w}=30/F_o$, when $F_o \geq 30$ and $\sqrt{w}=1$ otherwise. The atomic scattering factors for the Zn^{2+} and Cl^- ions, and C, N and O atoms were those cited in International Tables for X-ray Crystallography[12] as SX–45, SXC–55, SX–6,7 ans 8, respectively. The real part of the anomalous dispersion, $\Delta f'=-1.7$ was taken into cosideration for the Zn (II) ion.[13] The final atomic coordinates are listed in Table II. The difference electron density map was calculated at this stage to reveal the hydrogen atoms. The five hydrogen atoms bonded to N(1), N(3), N(7), N(8) were clerly seen on the map and it was confirmed that the LH residue exists in a keto form. No further refinement including hydrogen atoms was attempted.

TABLE II. Atomic Parameters

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Zn	0(0)	0(0)	0(0)	105(1)	80(1)	90(2)	41(1)	50(1)	21(1)
Cl	1711(2)	7057(2)	4290(2)	144(2)	120(2)	122(3)	79(2)	68(2)	27(2)
O(0)	2256(4)	−131(4)	1747(5)	113(6)	110(6)	146(8)	56(5)	27(6)	28(6)
N(1)	2107(5)	5020(5)	926(6)	109(7)	72(6)	125(9)	29(5)	65(7)	28(6)
C(2)	1382(6)	3463(6)	959(6)	84(7)	88(8)	84(9)	42(6)	44(7)	25(7)
N(3)	1407(5)	2361(5)	−339(5)	90(6)	88(6)	74(7)	43(5)	46(6)	16(6)
C(4)	2224(6)	2893(6)	−1875(6)	84(7)	91(8)	84(9)	35(6)	43(7)	34(7)
C(5)	3062(6)	4560(6)	−1898(7)	102(8)	92(8)	116(10)	48(7)	47(8)	38(7)
C(6)	3023(6)	5625(6)	−513(7)	82(7)	91(8)	99(9)	33(6)	41(7)	30(7)
N(7)	542(6)	2981(5)	2435(6)	159(8)	83(7)	127(9)	43(6)	106(7)	31(6)
N(8)	−147(5)	1346(5)	2610(6)	136(7)	74(6)	108(8)	46(5)	78(7)	24(6)
O(9)	2190(4)	1839(4)	−3155(5)	139(6)	100(6)	104(7)	54(5)	81(6)	17(5)
C(10)	3842(7)	7391(6)	−339(8)	128(9)	81(8)	173(12)	22(7)	58(9)	26(8)
O(1)	4413(5)	2577(5)	4402(5)	135(7)	173(8)	152(9)	32(6)	79(7)	5(7)

Non-hydrogen atoms. Values are x10^4. Anisotropic temperature factors are of the form: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

Description of the Structure and Discussion

There is one complex molecule having two five-membered chelate rings in the unit cell. The Zn (II) ion is situated at the crystallographic centre of symmetry and assumes an octahedral coordination. By necessity, the Zn (II) ion lies precisely on each of the three planes formed by [N(3), N(8), N(3),[14] N(8)[14]], [N(3), O(0), N(3),[14] O(0)[14]] and [N(8), O(0), N(8),[14] O(0)[14]]. The ligand molecule, LH is coordinated to the Zn (II) ion through nitrogen atom N(3) of pyrimidine ring and also through its amino nitrogen atom N(8) of hydrazino group. The two LH residues are coordinated *trans* to each other forming a square planar coordination. The fifth and sixth coordination sites are occupied by the two water oxygen atoms.

In Table III, all the bond lengths and angles found in the LH residue are listed. The C(4)–O(9) bond length is 1.264(7) Å, suggesting the keto form in conformity with the assignment by IR spectra of LH and its complex.[10] As described before, the difference electron

11) Y. Okaya and T. Ashida, "HBLS 4. The Universal Crystallographic Computing System (I)," p. 65. Tokyo: The Crystallographic Society of Japan.
12) "International Tables for X-ray Crystallography," Vol. III, Birmingham, Kynoch Press, 1962.
13) A list of structure factors may be obtained from the author (H.S.) on request.
14) Inverted by a centre of symmetry at (0, 0, 0).

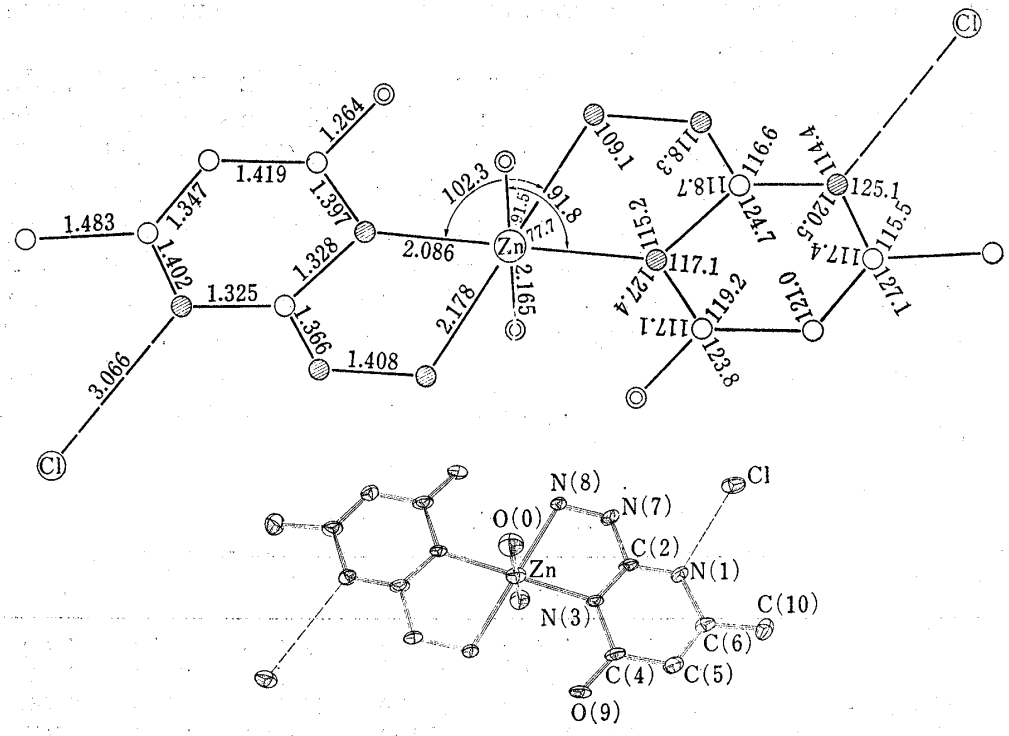


Fig. 1. The Bond Lengths and Angles, and the Perspective View of the Complex Molecule

The zinc ion is on the crystallographic centre of symmetry.

TABLE III. Bond Lengths (Å) and Angles (°)

Zn–O (0)	2.165(4)	N (3)–C (4)	1.397(6)
Zn–N (3)	2.086(4)	C (4)–C (5)	1.419(7)
Zn–N (8)	2.178(5)	C (4)–O (9)	1.264(7)
N (1)–C (2)	1.325(6)	C (5)–C (6)	1.347(8)
N (1)–C (6)	1.402(6)	C (6)–C (10)	1.483(7)
C (2)–N (3)	1.328(7)	N (7)–N (8)	1.408(6)
C (2)–N (7)	1.366(7)		
O (0)–Zn–N (3)	91.8(1)	C (4)–N (3)–C (2)	117.1(4)
O (0)–Zn–N (3)$^{a)}$	88.2(1)	Zn–N (3)–C (2)	115.2(3)
O (0)–Zn–N (8)	91.5(2)	C (5)–C (4)–N (3)	119.2(4)
O (0)–Zn–N (8)$^{a)}$	88.5(2)	C (5)–C (4)–O (9)	123.8(5)
N (3)–Zn–N (8)	77.7(2)	N (3)–C (4)–O (9)	117.1(4)
N (3)–Zn–N (8)$^{a)}$	102.3(2)	C (6)–C (5)–C (4)	121.0(5)
C (2)–N (1)–C (6)	120.5(4)	C (10)–C (6)–N (1)	115.5(4)
N (3)–C (2)–N (1)	124.7(4)	C (10)–C (6)–C (5)	127.1(5)
N (3)–C (2)–N (7)	118.7(4)	N (1)–C (6)–C (5)	117.4(5)
N (1)–C (2)–N (7)	116.6(4)	N (8)–N (7)–C (2)	118.3(4)
C (4)–N (3)–Zn	127.4(3)	Zn–N (8)–N (7)	109.1(3)

a) Inverted by a centre of symmetry at (0, 0, 0).
Standard deviations are referred to the last digits.

density map also showed that the hydrogen of the hydroxyl group is transferred to N(1) and forms the hydrogen bond to the chloride ion (the N(1)···Cl distance is 3.066(5) Å). The coordination bond lengths, Zn–N(3), Zn–(8) and Zn–O(0) are 2.086(4), 2.178(5) and 2.165(4) Å, respectively.

The planarities of the chelate ring and the pyrimidine ring, are shown in Table IV by denoting the deviations of atoms from the least-squares planes through the planar groups.

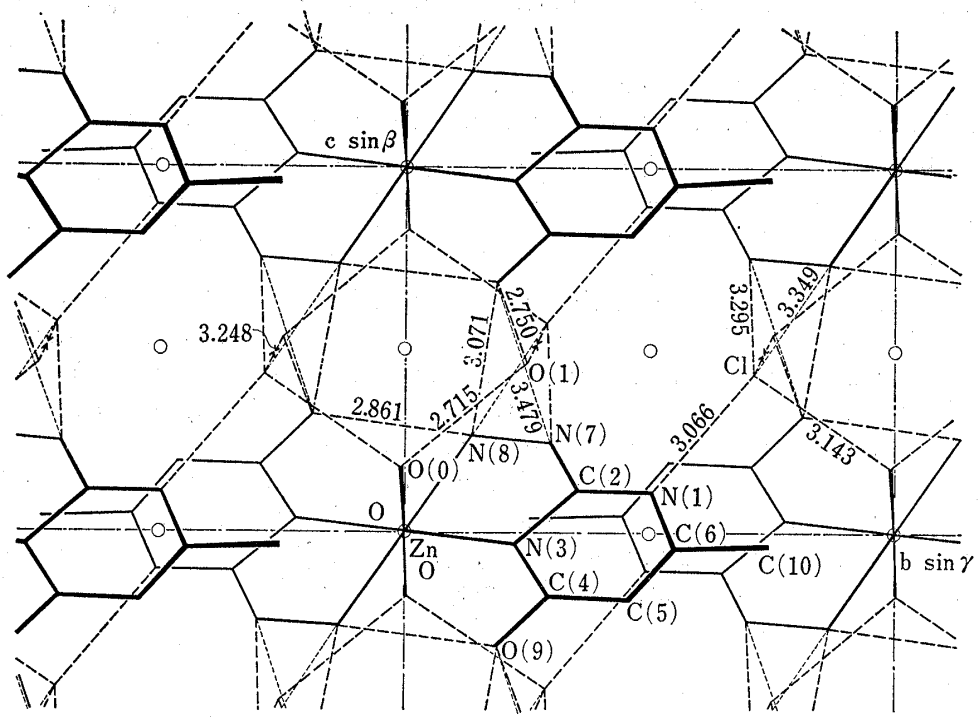


Fig. 2. The Projection of the Crystal Structure Along the *a* Axis

Centres of symmetry are denoted by ○. Hydrogen bonds are shown by broken lines, other intermolecular interactions less than 3.5 Å are shown by dotted lines.

TABLE IV. Deviations of Atoms from the Least-squares Planes

Chelate ring		Pyrimidine ring			
Zn	−0.049 Å	N (1)	−0.019 Å	N (7) [a]	−0.009 Å
C (2)	−0.011	C (2)	0.002	N (8) [a]	0.104
N (3)	0.049	N (3)	0.019	Zn [a]	−0.086
N (7)	−0.056	C (4)	−0.021	O (9) [a]	−0.057
N (8)	0.067	C (5)	0.005	C (10) [a]	0.050
N (1) [a]	−0.043	C (6)	0.015		
C (4) [a]	0.044				

a) These atoms are not included inthe least-squares calculation.

TABLE V. Important Intermolecular Interactions less than 3.5 Å

No.	From [a]	To	Distance
1	Cl	N (1^{i})	3.066(5) [b]
2	O (0)	O (1^{i})	2.715(5) [b]
3	Cl	O (0^{ii})	3.143(4) [b]
4	N (7)	O (9^{iii})	3.479(6)
5	N (8)	O (9^{iii})	3.071(5) [b]
6	O (1)	O (9^{iii})	2.750(6) [b]
7	Cl	N (7^{iv})	3.295(5) [b]
8	Cl	N (8^{iv})	3.349(5)
9	Cl	N (1^{v})	3.248(5) [b]

a) Atom at (i).
b) Hydrogen-bond suggested.
Key to the symmetry operation.
(i) x, y, z; (ii) $x, 1+y, z$; (iii) $x, y, 1+z$; (iv) $-x, 1-y, 1-z$; (v) $1-x, 1-y, 1-z$.

The *a* axis projection of the crystal structure is shown in Fig. 2. The complex ions are situated at the corners of the unit cells and are linked to the neighbouring complex ions in *c* direction mainly through the hydrogen bonds.

Table V lists the intermolecular interatomic distances less than 3.5 Å. In this table, hydrogen bonds are marked by an asterisk. The formation of the hydrogen bonds are suggested on the basis of the facts that the distances and the directions of the bonds are reasonable for the hydrogen bonds and that the hydrogen atoms can be placed at the reasonable positions around the donor atoms.

The only hydrogen bond connecting the complex ions directly is N(8)–H···O(9^{iii}) and its distanse is 3.071(5) Å. The other hydrogen bonds are formed through the water molecules or the chloride ions. Besides the intermolecular hydrogen bonds listed in Table V, there is an intramolecular hydrogen bond N(8)–H···O(9)[14] of length 2.861(5) Å which links the two ligand LH molecules coordinated to the same zinc (II) ion.

The plane of the complex ion is inclined from the a axis and the normal of the pyrimidine ring makes an angle of 25.1° to the *a* axis. The pyrimidine rings are arranged parallel to each other across the centre of symmetry at (0, 1/2, 0) and (1/2, 1/2, 0) and are stacked along the *a* axis. The rings are separated with perpendicular distances of 3.546 and 3.553 Å.