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Preparation and Spectrochemical Investigation of Copper(II), Nickel(II), Cobalt(II), and Zinc(II) Complexes of 2-Hydrazino-4-hydroxy-6-methylpyrimidine

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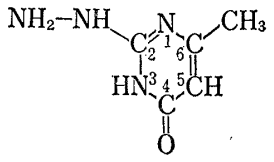
Copper(II), cobalt(II), nickel(II), and zinc(II) complexes of 2-hydrazino-4-hydroxy-6-methylpyrimidine were synthesized, and their infrared (IR) and nuclear magnetic resonance (NMR) spectra were examined. In the IR spectra of the complexes, the amide-I (carbonyl) bands were present and it was assumed that the ligand molecules were coordinated in the keto form of the isocytosine ring. The low frequency shift of the NH_2 stretching bands by about 40—45 cm^{-1} on combining with Cu and Co indicated the formation of a metal-nitrogen bond.

Preferential broadening of methine proton to methyl proton in the NMR spectra of the complexes of 2-hydrazino-4-hydroxy-6-methylpyrimidine can be explained by the binding of Co(II), Cu(II), and Ni(II) to N(3) site of the isocytosine ring.

An ESR spectrum of the copper(II) complex would suggest the presence of copper(II) ion in a square-pyramidal conformation.

Keywords——copper; nickel; cobalt; zinc; metal complex; 2-hydrazino-4-hydroxy-6-methylpyrimidine; spectral (IR, ESR, NMR) analysis

Earlier it was shown that 2-hydrazino-4-hydroxy-6-methylpyrimidine (LH) was an excellent chemotherapeutic for *Mycobacterium tuberculosis* (human type H_2-strain).[2] This compound has a structure with the hydrazino group attached to C(2) of the isocytosine ring. Irrespective of the importance of the chemotherapeutic agent of LH, this compound is an interesting ligand, worthy of study because of its multifaceted coordination possibilities with metal ions. In this paper, preparation and infrared spectrum (IR) investigation for copper(II), cobalt(II), nickel(II), and zinc(II) complexes of 2-hydrazino-4-hydroxy-6-methylpyrimidine as a derivative of isocytosine are reported. Metal complexes of cytosine and isocytosine have been investigated by means of IR techniques.[3] The study of the formation of complexes between transition metal ions and benzoylhydrazine revealed the presence of two types of compounds differing sharply in structure and properties.[4] The coordination site and the structure of LH-metal complexes, accordingly, will be considered from IR spectra which can probably be interpreted approximately on the basis of the analysis of normal vibrations of isocytosine and coordinated acetylhydrazine or benzoylhydrazine.[5,6] Previously, McConnell and his associates demonstrated the presence of two tautomers in the crystal structure of isocytosine.[7] Consequently, it is likely that two tautomeric forms



LH

1) Location: *a) Sagamihara-shi, Kanagawa, 228, Japan; b) Yayoi-cho, Chiba, 280, Japan.*
2) T. Matsukawa, S. Ban, K. Sirakawa, and M. Yoneda, *Yakugaku Zasshi*, **73**, 159 (1953).
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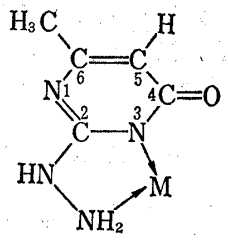
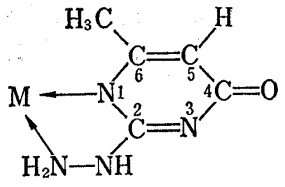
can exist in metal complexes of LH, forming metal-containing rings of types A or B, where M is the complex-forming metal atom. Nuclear magnetic resonance (NMR) studies involving



A



B

LH, will serve to demonstrate whether the primary metal-base binding site of Co^{2+}, Ni^{2+}, and Cu^{2+} is N(1) or N(3) in the pyrimidine ring. In addition, we studied electron spin resonance (ESR) spectrum of the copper(II) complex of this ligand (LH) for the purpose of elucidating the structure of the metal complex.

Results and Discussion

IR spectra of metal complexes of 2-hydrazino-4-hydroxy-6-methylpyrimidine revealed that the coordination occurred at hydrazino-amino nitrogen and N(1) or N(3) of the isocytosine ring in the keto form. The spectra of complexes of this isocytosine derivative showed absorption of C=O band at about 1682 cm^{-1} in $Cu(LH)_2Cl_2 \cdot 3H_2O$, at 1672 cm^{-1} in $Co(LH)_2Cl_2 \cdot 3H_2O$, at 1662 cm^{-1} in $Ni(LH)_2Cl_2 \cdot 4H_2O$, and at 1660 cm^{-1} in $Zn(LH)_2Cl_2 \cdot 4H_2O$ (Table I). In the range of 3050—3300 cm^{-1}, the spectra contain complex bands due to the strech-

Table I. IR Data of LH, LHCl and Its Metal Complexes (cm^{-1})

Tentative assignment	LH	LHCl	$Cu(LH)_2Cl_2 \cdot 3H_2O$	$Co(LH)_2Cl_2 \cdot 3H_2O$	$Ni(LH)_2Cl_2 \cdot 4H_2O$	$Zn(LH)_2Cl_2 \cdot 4H_2O$
OH str.				3450m	3460m	3450 s
NH, NH_2 str.	3330m	3298m	3270 s	3285 s	3285 s	3325 s
		3130 s	3150w			
	3050w	3045w	3060m	3075w		
CH str.	2925 s	2975w	2930w			
		2885w	2850m	2850m	2840 s	2830 s
CO, CC str., NH_2,	1658 s	1696 s	1682 s	1672 s	1662w	1660 s
HNC, HCO def.		1654w	1631 s	1656 s	1635 s	
CN, CC str.	1570 s	1588m	1596 s	1568 s	1570 s	1570 s
		1560m	1550 s			
CO str., CCO,	1535 s			1538 s	1535 s	1535 s
NCO def.	1486w	1465m	1475m	1482m	1486 s	1480w
CH_3 def.		1425m	1436m			
	1408m		1405m	1407m	1400m	1405m
	1378m	1382m	1371m	1376m		1375m
CO str.,	1205w		1210m	1200w	1214m	1200w
HNC, NH_2, def.	1190 s	1140m	1179 s	1188 s	1176m	1185 s
NH_2 torsional	1090 s	1056m	1100 s	1098m	1078m	1081 s
Pyrimidine ring vib.	978w	972m	976w	970w	974m	972w
	915m	935w		920w	912m	

s: strong m: medium w: weak.

ing vibrations of the N-H bonds in amino and imino groups. The corresponding wave numbers are displaced towards a long wavelength region compared with the spectrum of LH ligand to the extent of about 40—45 cm^{-1} in Cu and Co, and 5 cm^{-1} in Zn, owing to the formation of the metal-amino nitrogen bond. The band at about 1570 cm^{-1} may be assigned to a complex stretching deformation vibration of ν C=N, ν C=C and δ (NCO).[4] In the spectra of LH, LHCl, $Cu(LH)_2Cl_2 \cdot 3H_2O$, $Co(LH)_2Cl_2 \cdot 3H_2O$, $Ni(LH)_2Cl_2 \cdot 4H_2O$, and $Zn(LH)_2Cl_2 \cdot 4H_2O$, this band is at about 1570, 1588 and 1560, 1590 and 1550, 1568, 1570, and 1570 cm^{-1}, respectively. Therefore it is shown that there are C=N and C=C bonds in the ligand molecule of these metal complexes.

Table II. Properties and Elemental Analyses of Metal Complexes of 2-Hydrazino-4-hydroxy-6-methylpyrimidine

Complex	mp (°C)	Appearance	Yield (%)	Analysis (%) Found (Calcd.) C	H	N	Metal
$Cu(LH)_2Cl_2 \cdot 3H_2O$ $C_{10}H_{22}Cl_2CuN_8O_5$	226 (dec.)	Deep blue prisms	29.9	25.51 (25.62)	4.73 (4.72)	23.55 (23.90)	13.92 (13.55)
$Co(LH)_2Cl_2 \cdot 3H_2O$ $C_{10}H_{22}Cl_2CoN_8O_5$	289 (dec.)	Amber prisms	65.5	25.77 (25.87)	5.13 (4.77)	24.38 (24.14)	12.41 (12.65)
$Ni(LH)_2Cl_2 \cdot 4H_2O$ $C_{10}H_{24}Cl_2NiN_8O_6$	300<	Violet prisms	77.8	24.82 (24.91)	4.99 (5.01)	22.85 (23.25)	12.45 (12.18)
$Zn(LH)_2Cl_2 \cdot 4H_2O$ $C_{10}H_{24}Cl_2ZnN_8O_6$	256 (dec.)	Colorless prisms	64.4	24.65 (24.57)	4.92 (4.95)	23.31 (22.93)	13.27 (13.37)

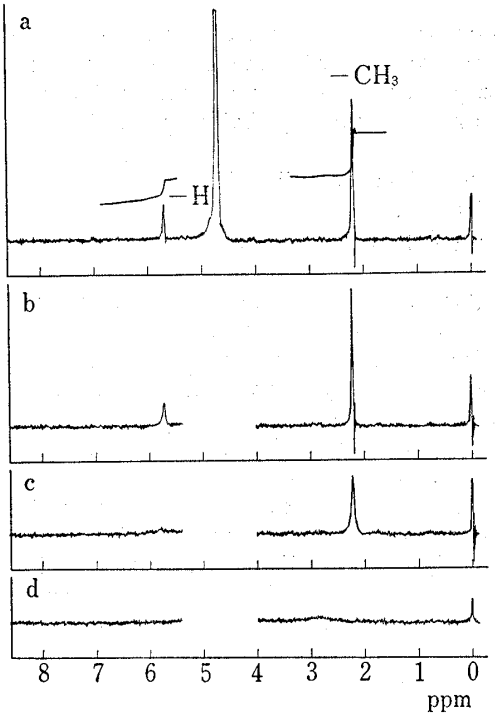


Fig. 1. NMR Spectra of 0.1M 2-Hydrazino-4-hydroxy-6-methylpyrimidine in D_2O, in the Presence of Co(II) Ion

(a) no addition; (b) Co^{2+} 1×10^{-4}M; (c) Co^{2+} 1×10^{-3}M; (d) Co^{2+} 1×10^{-2}M.

In order to obtain a deeper understanding of the relative binding tendencies of these sites on the pyrimidine ring, an experiment was made to elucidate the NMR line broadening upon interaction of LH with Co^{2+}, Cu^{2+}, and Ni^{2+}.

Studies on the interaction of Cu(II) ions with purine components of nucleotides such as 5′-AMP confirmed the ability of metal ions to bind to a variety of sites on the same purine.[8-10] In the purine components of nucleotides and nucleosides,

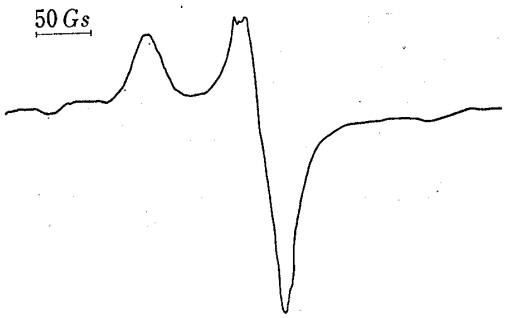


Fig. 2. ESR Spectrum of $Cu(LH)_2Cl_2 \cdot 3H_2O$

8) M. Cohn and T.R. Hughes, Jr., *J. Biol. Chem.*, **237**, 176 (1962).
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resonance peaks of the proton of purine in proximity to the paramagnetic metal binding site become broadened, while the peaks of proton that are further away from metal ion are unaffected.

The same fact was revealed in isocytosine ring of LH. Thus, the demonstration that the methyl and methine proton peaks in LH are not equally broadened by interaction with Co^{2+}, Ni^{2+}, or Cu^{2+} indicates that the binding occurs to a particular nitrogen in the isocytosine ring. When N(1) position is bound by Co(II), Cu(II), or Ni(II) ion, methyl proton should be broadened in preferece to methine proton C(5)-H. On the other hand, when N(3) position is bound by Co(II), Cu(II), or Ni(II) ion, methine proton should be broadened in preference to methyl proton. Our experiment showed the preferential broadening of methine proton to methyl proton (Fig. 1). This preferential broadening of the methine proton peak in LH can be explained by the binding of Co(II), Cu(II), or Ni(II) to N(3) of the pyrimidine ring. Only the A isomer is capable of forming this kind of a complex. Additional supporting evidence for this conclusion will be presented from X-ray crystallographic study in the near future.

Indications of conformational structures in copper(II) complex of LH ligand are also to be found in the ESR spectrum of $Cu(LH)_2Cl_2 \cdot 3H_2O$. An ESR spectrum of this copper-(II) complex would suggest the presence of Cu(II) ion in a square-pyramidal structure with $g_{\parallel}=2.216$ and $g_{\perp}=2.052$ (Fig. 2).[11] The g-valeus were determined by the methods of Sands[12] and of Kneubuhl.[13]

Experimental

Apparatus——Infrared spectra were taken as KBr pellets on a Hitachi Infrared Spectrometer, Model EPI-G3. The ESR spectrum was recorded on a JES-ME-IX Spectrometer with modulation frequency of 100 KHz. The spectrum was measured on poly-crystalline samples at room temperature. NMR spectra were recorded on a Varian T-60 NMR Spectrometer, using sodium 3-(trimethylsilyl)propanesulfonate as the internal reference.

Reagents——Metal salts and other reagents were obtained from Wako Pure Chemical Industries, Tokyo. They were of reagent grade and were used without further purification.

Preparation——2-Hydrazino-4-hydroxy-6-methylpyrimidine (LH) was prepared by the method of Vanderhaeghe and Claesen.[14]

2-Hydrazino-4-hydroxy-6-methylpyrimidine Hydrochloride (LHCl)——The suspension of 2-hydrazino-4-hydroxy-6-methylpyrimidine in H_2O was added to excess of conc. HCl and a clear solution was obtained. The product was dissolved in a minimum volume of H_2O and the pure product was precipitated from the aqueous solution by addition of iso-PrOH. The melting point of colorless crystals was 240° (dec.).

$Ni(LH)_2Cl_2 \cdot 4H_2O$, $Co(LH)_2Cl_2 \cdot 3H_2O$, and $Zn(LH)_2Cl_2 \cdot 4H_2O$——Two mol of each reactant was used. Each metal chloride was dissolved in H_2O. 2-Hydrazino-4-hydroxy-6-methylpyrimidine in H_2O was added to solution containing each metal chloride. A few drops of 6N HCl was added to each solution and then the solution was warmed at 40° for 15 min, allowed to stand at room temperature, and evaporated under a reduced pressure. The crystals obtained after several hours were washed with a little ice-cold water and air dried.

$Cu(LH)_2Cl_2 \cdot 3H_2O$——In an ice bath, $CuCl_2$ was dissolved in H_2O and the ligand was dissolved in 1N HCl. The two solutions were combined and the blue mixed solution was evaporated under a reduced pressure at room temperature. Blue crystals, obtained after several hours, were washed with a little ice-cold water and dried under a reduced pressure. The melting point of the product was 226° (dec.).

Acknowledgement The authors are very grateful to Mr. S. Yoshii, Lecturer of Kitasato University, for his kind assistance in preparing this ligand.

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