Notes

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Preparation of Mixed-Ligand Copper(II) Complexes with Uracil or 6-Methyluracil and Glycylglycine

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Mixed ligand complexes containing uracil and 6-methyluracil were prepared. The complexation and coordination sites of the mixed ligand complexes, Cu(II)(GG)(UraH)-HBr·3/2H_2O and Cu(II)(GG)(6-MeuraH)HBr·H_2O, were discussed. It is suggested that the nitrogen atom N1 of uracil bases is the coordination site and that glycylglycine behaves as a tridentate chelate.

Keywords——mixed ligand copper (II) complex; uracil; 6-methyluracil; glycylglycine; IR spectra; nucleic acid; coordination site; pyrimidine ring;

The authors have studied the mixed ligand complexes containing adenine and cytosine.[2–6] Though uracil is the ligand of biochemical importance, no copper (II) complex with uracil has been reported. Platinum complexes react with uracil to produce a powerful anticancer agent.[7] Nevertheless, the coordination site of these complexes with uracil has not been determined by X-ray diffraction methods.

Sundaralingam and Carrabine[8] have shown that uracil and dihydrouracil bind $HgCl_2$ through C(4)=O. In a recent study, Kistenmacher, Sorrel, and Marzilli[9] have prepared (aqua) (diethylenetriamine) (thyminato) copper (II) bromide and shown the coordination site on N1 of thymine by X-ray diffraction methods. In this paper, the complexation and coordination sites of these mixed ligand complexes are discussed from infrared (IR) spectroscopic analysis.

Results and Discussion

The IR spectra of uracil was reported by Susi and Ard.[10] In the following, the IR spectra of the mixed ligand complexes will be discussed compared with that of the uracil.

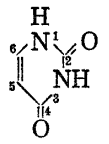

Fig. 1. Structure of Uracil

IR Spectra of Cu(II) (GG) (UraH) HBr·3/2H_2O[11]

The absorption at 3280 cm^{-1} may be assigned to NH_2 stretching vibration of glycylglycine.[12] No bands assigned to NH stretching of glycylglycine are observed. The band at

1) Location: *1–33, Yayoi-cho, Chiba, 280, Japan*
2) T. Sakaguchi and M. Tanno, *Nippon Kagaku Kaishi*, **1974**, 1637.
3) T. Fujita and T. Sakaguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 1055 (1977).
4) T. Fujita and T. Sakaguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 1694 (1977).
5) T. Fujita and T. Sakaguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 2419 (1977).
6) T. Fujita and T. Sakaguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 2953 (1977).
7) J.P. Davidson, P.J. Faber, R.G. Fisher, Jr., S. Mansy, H.J. Peresie, B. Rosenberg, and L. VanCamp, *Cancer Chemother., Rep.*, **59**, 287 (1975).
8) J.A. Carrabine and M. Sundaralingam, *J. Am. Chem. Soc.*, **92**, 369 (1970).
9) T.J. Kistenmacher, T. Sorrel, and L.G. Marzilli, *Inorg. Chem.*, **14**, 2479 (1975).
10) H. Susi and J.S. Ard, *Spectrochim. Acta*, **27A**, 1539 (1971).
11) GG denotes the zwitter anion of glycylglycine and UraH denotes uracil.
12) M.L. Bair and E.M. Larsen, *J. Am. Chem. Soc.*, **93**, 1140 (1971).

Fig. 2. IR Spectra of Uracil (upper) and Cu(UraH)(GG)HBr·3/2H_2O (down) in KBr Disk (cm^{-1})

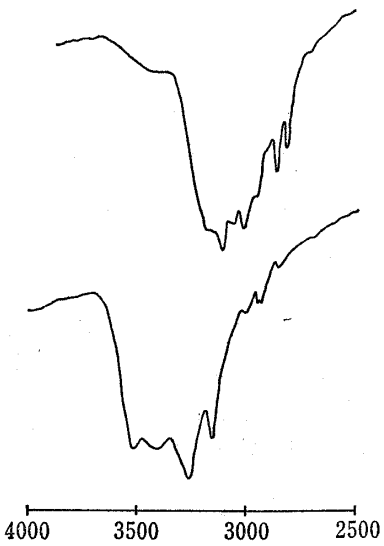

Fig. 3. IR Spectra of 6-Methyluracil (upper) and Cu(6-MeuraH)·(GG)-HBr·H_2O (down) in KBr Disk (cm^{-1})

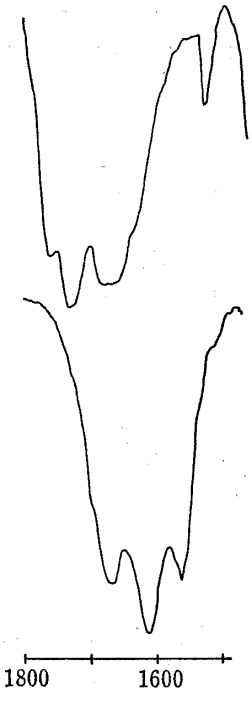

Fig. 4. IR Spectra of 6-Methyl-uracil(upper) and Cu(6-MeuraH)·(GG)HBr·H_2O(down) in KBr Disk (cm^{-1})

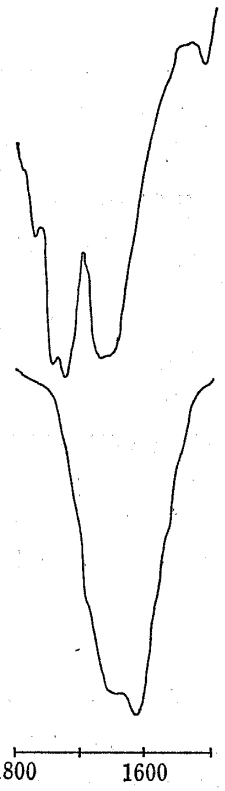

Fig. 5. IR Spectra of Uracil (upper) and Cu(UraH)(GG)-HBr·3/2H_2O (down)

1610 cm^{-1} is assigned to COO^- asymmetric stretching. Therefore, the glycylglycine molecule is assumed to behave as a zwitter anion.

The band assignable to C(2)=O stretching of uracil disappeared on complexation. This fact shows that the C(2)=O bond of uracil has nature of a single bond to considerable extent. In contrast, the shoulder bands assignable to C(4)=O are observed in the region 1665—1650

Table I. Elementary Analysis for the Complexes

Compound		C%	H%	N%
$Cu(GG)\cdot 3H_2O$	Found	19.45	4.85	11.34
	Calcd.	19.39	4.89	11.30
$Cu(II)(GG)(6\text{-}MeuraH)HBr\cdot H_2O$	Found	25.89	3.56	13.25
	Calcd.	25.80	3.62	13.41
$Cu(II)(GG)(UraH)HBr\cdot 3/2H_2O$	Found	23.12	3.28	13.19
	Calcd.	23.22	3.42	13.55

Table II. IR Data for $Cu(II)(GG)(6\text{-}MeuraH)HBr\cdot H_2O$ and $Cu(II)(GG)(UraH)HBr\cdot H_2O$[a)]

Tentative assignment	$Cu(GG)(UraH)HBr\cdot 3/2H_2O$	$Cu(GG)(6\text{-}MeuraH)HBr\cdot H_2O$
OH str.		3515 s
	3400 s	3400 s
NH_2 str. due to GG	3280 s	3250 s
C(4)=O and C=C str.	1655 s	1665 s
	1650 sh	
COO^- asym. str.	1610 s	1610 s
N(3)-H bending	1415m	1420m

a) s, strong; m, medium; sh, shoulder.

cm^{-1}. No bands assigned to N(1)–H bending near 1500 cm^{-1} are observed and this fact shows the deprotonation N(1)–H. In contrast, the band assignable to N(3)–H bending is observed at 1415 cm^{-1}.

IR Spectra of Cu(II) (GG) (6-MeuraH) HBr·H_2O[13)]

The band at 1515 cm^{-1} is assigned to OH stretching. The absorption assignable to NH_2 stretching of glycylglycine is observed at 3250 cm^{-1}.[12)] Also in this complex, the C(2)=O bond of 6-methyluracil may have much nature of a single bond. For the band assigned to C(2)=O disappeared by complexation. The band at 1610 cm^{-1} may be assigned to COO^- asymmetric stretching.

Coordination Sites of Two Mixed Ligand Complexes

In the IR spectra, the bands assigned to C(2)=O stretching and N(1)–H bending are not observed. Accordingly, binding of copper(II) to N(1) may be suggested. The IR spectra also showed that glycylglycine acted as a tridentate chelate.

Conclusion

The mixed ligand complexes, $Cu(II)(GG)(UraH)HBr\cdot 3/2H_2O$ and $Cu(II)(GG)(6\text{-}MeuraH)\text{-}HBr\cdot H_2O$, were prepared and it was suggested that N(1) coordinated to Cu(II).[14)] The structures of the complexes are assumed to be similar.

Experimental

Apparatus——Infrared spectra were taken as KBr pellets on a Hitachi infrared Spectrometer, Model EPI-G3. Deuterated samples were prepared by dissolving nondeutetrated samples in hot heavy water and successive lyophylization of the solution.

13) The ligand of 6-methyluracil is denoted by 6-MeuraH.
14) B.E. Fisher and R. Bau, *Chem. Commun.*, 272 (1977).

Reagents——Uracil and 6-methyluracil were obtained from Wako Pure Chemical Industries, Tokyo. Glycylglycine was obtained from Tokyo Kasei Co. Other reagents were purchased from Wako Pure Chemical Industries, Tokyo

Preparation——Cu(II)(GG)(6-MeuraH)HBr·H_2O and Cu(II)(GG)(UraH)HBr·3/2H_2O: In 30 ml of 0.1 M KOH dissolving 5 mM of (Glycylglycinato)Cu(II)·3H_2O, 5 mM of 6-methyluracil in 5 ml of 1 M KOH added with stirring. Into this solution, 5 mM of NaBr in 2 ml of 0.1 M KOH was added with stirring and the color changed from dark-blue to violet. Evaporating this solution, a violet compound was obtained and recrystallized from water. This complex was washed with ethanol and dried under reduced pressure.

(Glycylglycinato)Cu(II)·3H_2O was prepared according to ref. 15.

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15) A.R. Manyak, C.B. Murphy, and A.E. Martell, *Arch. Biochem.*, **59**, 373 (1955).

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Synthesis of the Metabolites and Related Compounds of Diltiazem

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Major metabolites of the antianginal drug, Diltiazem, 3(*S*)-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, have been synthesized. In connection with these metabolites, several S- and N-oxides were prepared.

Keywords——metabolites of Diltiazem; synthesis of benzothiazepines; preferential N-oxidation; preferential S-oxidation; stepwise oxidation; catalytic hydrogenation of N-oxides

Diltiazem (**1**),[2] 3(*S*)-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one,[3] is an antianginal drug developed by Tanabe Seiyaku company in 1974. The metabolic fate of this drug has been investigated extensively by Sato and co-workers.[4] Thus, they obtained seven metabolites (M-1—M-7) and an unseparable mixture of N-oxide metabolites from the urine of the rats administered the drug and assigned their structures on the basis of the spectral data to 3-hydroxy-5-[2-(dimethylamino)-ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (M-1) and its congeners. This paper describes the synthesis of the major metabolites and related compounds achieved for confirmation of Sato's assignment.

M-1: Kugita and co-workers have prepared Diltiazem (**1**) starting with the methoxyphenylglycidate (**2a**) *via* **4a**, **5a**, **6a**, and **7a** (Chart 1).[5] One of the intermediates, (**7a**), was identical with M-1 by mixed melting point and spectral comparisons.

1) Location: *Kawagishi, Toda-shi, Saitama.*
2) International non-proprietary name. Code designation of the hydrochloride of Diltiazem is CRD-401, of which the brand name is "Herbesser".
3) The absolute configuration of this compound has been determined by X-ray crystallography; K. Kotera and T. Date, unpublished data.
4) T. Meshi, J. Sugihara and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **19**, 1546 (1971).
5) *a*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **19**, 593 (1971); *b*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2284 (1970); *c*) H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2028 (1970).