(18) W. Lotz, *J. Opt. Soc. Am.*, **60**, 206 (1970).
(19) For instance, see ref 11–16 of ref 9b.
(20) T. A. Albright, P. Hofmann, and R. Hoffmann, *J. Am. Chem. Soc.*, **99**, 7546 (1977).
(21) T. A. Albright, R. Hoffmann, Y. Tse, and T. D'Ottavio, *J. Am. Chem. Soc.*, **101**, 3812 (1979).
(22) M. Brookhart, T. H. Whitesides, and J. M. Crockett, *Inorg. Chem.*, **15**, 1550 (1976).

Coordination Chemistry of 7,9-Disubstituted 6-Oxopurine Metal Compounds. 1. Copper(II) Coordination at N(1). Molecular and Crystal Structure of (Glycylglycinato)(7,9-dimethylhypoxanthine)copper(II) Tetrahydrate

Luigi G. Marzilli,* Kenneth Wilkowski, Chian C. Chiang, and Thomas J. Kistenmacher*

Contribution from the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218. *Received April 18, 1979*

Abstract: The synthesis, ^{1}H NMR line broadening, and molecular and crystal structure of the complex (glycylglycinato)(7,9-dimethylhypoxanthine)copper(II), $Cu(ON_4C_7H_8)(O_3N_2C_4H_6)$, are reported. The complex crystallizes as the tetrahydrate in the orthorhombic system, space group $P2_12_12_1$, with $a = 14.314$ (6) Å, $b = 7.741$ (2) Å, $c = 16.032$ (6) Å, $V = 1776.4$ Å^3, $Z = 4$, $d_{measd} = 1.62$ (1) g cm^{-3}, $d_{calcd} = 1.61$ g cm^{-3}. Intensities for 2841 symmetry-averaged reflections were collected in the θ-2θ scan mode on an automated diffractometer employing graphite-monochromatized Mo Kα radiation. The structure was solved by standard heavy-atom Patterson and Fourier methods. Full-matrix least-squares refinement has led to a final R value of 0.036, a final weighted R value of 0.039, and a goodness-of-fit value of 1.75. The absolute configuration of the structure has been established. The primary coordination sphere about the copper is approximately square planar with the tridentate glycylglycine dianion and N(1) of the 7,9-dimethylhypoxanthine ligand, Cu-N(1) = 1.977 (3) Å, occupying the four coordination sites. In addition to the strongly coordinated equatorial plane, the copper also forms two weak, axial interactions with O(6) of the 7,9-dimethylhypoxanthine ligand: one intramolecular, Cu-O(6) = 2.970 (2) Å, and one intermolecular, Cu-O(6) = 2.769 (2) Å. The coordination geometry displayed is very similar to that observed in a variety of copper(II) complexes with N(3)-coordinated cytosine derivatives as ligands. The crystal structure is dominated by helical arrays of complexes, stabilized by the intermolecular Cu-O(6) interaction, and of hydrogen-bonded water molecules about twofold screw axes parallel to the crystallographic b axis. ^{1}H NMR line-broadening data in H_2O suggest that N(1) is the primary coordination site for Cu(II) in solution. It seems probable that the N(1),O(6) grouping may have a similar coordination chemistry to the N(3),O(2) grouping of cytosine in N(1)-substituted cytosine derivatives.

Introduction

Beginning in the early part of this decade, a number of investigators began to study the details of the binding of metal species to nucleic acid components.[1] This activity was motivated in large part by the known influence of metal species on the biochemistry and structure of nucleic acids[2] and by the likely involvement of such interactions in the mode of action of the important metalloantineoplastic drugs based on and including *cis*-($Pt^{II}(NH_3)_2Cl_2$).[3] Rosenberg[3] has summarized current speculation on the mechanism of action of the platinum antitumor agents. Binding to the 6-oxopurine base in guanosine is frequently cited as being involved in the important lesion. In turn, two diverse classes of possibilities have been put forward which involve binding to the purine base and which provide a possible explanation for the antitumor activity of cis but not trans isomers of the type $Pt^{II}(ammine)_2Cl_2$. The first type of explanation invokes intrastrand cross-linking between adjacent guanosine bases with the Pt binding exclusively to N(7) of the purine base.[4] Good structural models for such compounds have been studied.[5-7] The second type of explanation invokes participation of the 6-oxo group in binding to the metal.[8] Repair enzymes act relatively slowly on 6-oxo alkylated guanosine in DNA.[9] There is general agreement that monodentate coordination of the 6-oxo group to a metal will be quite unstable and that involvement of the 6-oxo group would require chelation. Most workers favoring chelate complex formation have championed the controversial suggestion that N(7),O(6) chelation is involved.[10-12] However, consideration of the geometry required for such chelation has led many to suggest that such a structure is unlikely.[1] A bonding arrangement which is more feasible and for which there is some precedence involves N(1),O(6) chelation.[13]

In past studies, we have evaluated the feasibility of the N(7),O(6) chelation mode by investigating Cu(II) Schiff base complexes.[14,15] The versatility of the Cu(II) center in forming long axial bonds permitted the isolation and structural characterization of the only established example of a complex exhibiting the controversial N(7),O(6) chelation mode,[14] albeit the Cu-O(6) interaction is weak. In this study, we extend this approach and report the preparation and structure of a Cu(II) complex containing an N(1)-bound 6-oxopurine, namely, [(glycylglycinato)(7,9-dimethylhypoxanthine)copper(II)]-tetrahydrate. To our knowledge, this is the first structural study of such a compound with any metal species, although the N(1) bonding mode is well established in solution.[1]

Experimental Section

The title complex was prepared by the addition of 7,9-dimethylhypoxanthine[16] (0.85 g, 5 mmol) dissolved in a minimum amount of H_2O and hydrated glycylglycinatocopper(II)[17] (1.1 g, 5 mmol) in

0002-7863/79/1501-7504$01.00/0

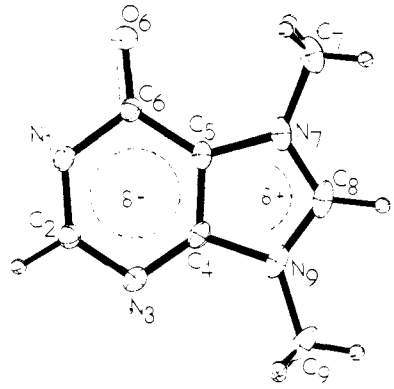


Figure 1. Molecular structure and electronic delocalization for 7,9-dimethylhypoxanthine.

Table I. Crystal Data for (Glycylglycinato)(7,9-dimethylhypoxanthine)copper(II) Tetrahydrate

a = 14.314 (6) Å	$(C_4H_6N_2O_3)(C_7H_8N_4O)Cu\cdot 4H_2O$
b = 7.741 (2) Å	mol wt 429.9
c = 16.032 (6) Å	d_m = 1.62 (1) g cm^{-3}
V = 1776.4 Å^3	d_c = 1.61 g cm^{-3}
Z = 4	μ = 13.4 cm^{-1}
space group $P2_12_12_1$	λ(Mo Kα) = 0.710 69 Å

a 1:1 mixture of H_2O and MeOH. The solution was filtered and allowed to slowly evaporate under a hood. Dark-blue, plate-like crystals were obtained after a few days.

Preliminary oscillation and Weissenberg photographs showed the crystal system to be orthorhombic with systematic absences $h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$, consistent with the space group $P2_12_12_1$. Unit-cell dimensions and their associated standard deviations were derived from a least-squares fit to the setting angles of 15 carefully centered reflections measured on a Syntex P$\bar{1}$ automated diffractometer. The crystal density, measured by neutral buoyancy methods in a mixture of carbon tetrachloride and bromoform, indicated one complex and four water molecules per asymmetric volume. Complete crystal data are collected in Table I.

The intensities of the 5886 reflections in the octants hkl and hkl to $2\theta = 60°$ were measured on the diffractometer, employing graphite-monochromatized Mo Kα radiation. The crystal used in data collection was mounted approximately parallel to the crystallographic b axis and had the following mean separations between principal faces: (100)-($\bar{1}$00) 0.25 mm, (001)-(00$\bar{1}$) 0.25 mm, and (010)-(0$\bar{1}$0) 0.40 mm. Intensity data were collected in the θ-2θ scan mode with individual scan speeds (2-24° min^{-1}) determined from a rapid scan at the calculated Bragg peak. The intensities of three standards were monitored after every 100 reflections and showed no systematic variation over the course of the experiment. The measured intensities were symmetry averaged and reduced to a set of 2841 independent intensities with $I \geq \sigma(I)$. Observational variances were assigned on the basis of the equation $\sigma^2(I) = S + (B_1 + B_2)(T_S/2T_B)^2 + (pI)^2$ where S, B_1, and B_2 are the scan and extremum background counts, T_S and T_B are the scan and individual background counting times ($T_B = T_S/4$ for all reflections), and p was taken to be 0.03 and represents an estimate of the error proportional to the diffracted intensity.[18] The intensities and their standard deviations were corrected for Lorentz and polarization effects. An absorption correction was also applied based on the dimensions and face assignments given above and led to maximum and minimum transmission factors of 0.74 and 0.68, respectively. An approximate absolute scale was determined by the method of Wilson.[19]

A structural solution was readily accomplished utilizing standard Patterson-Fourier techniques. Several cycles of isotropic refinement, minimizing the quantity $\sum w(|F_o| - |F_c|)^2$ where $w = 4F_o^2/\sigma^2(F_o^2)$, led to an R value ($\sum||F_o| - |F_c||/\sum|F_o|$) of 0.102. Two further cycles, employing anisotropic thermal parameters for the nonhydrogen atoms, reduced the R value to 0.065. A difference-Fourier synthesis allowed the positioning of the 22 independent hydrogen atoms. Two subsequent cycles of anisotropic refinement, holding the hydrogen-atom parameters fixed, led to an R value of 0.053. The weighted R value $[[\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}]$ and goodness of fit $[[\sum w(|F_o|^2 - |F_c|^2)/(NO - NV)]^{1/2}$ where NO = 2841 observations and NV = 235 variables] were 0.058 and 2.62, respectively. At this point, the structure was mirrored through the bc plane and the enantiomer of opposite hand was tested. Three cycles of refinement led to convergence, all shift/error less than 1.0, and to R, weighted R, and goodness-of-fit values of 0.036, 0.039, and 1.75, respectively. This second enantiomer is statistically favored[20] at the $\alpha = 0.001$ level. A final difference Fourier was essentially featureless, with a maximum peak in the difference density of about 0.5 e/Å^3 near the copper atom.

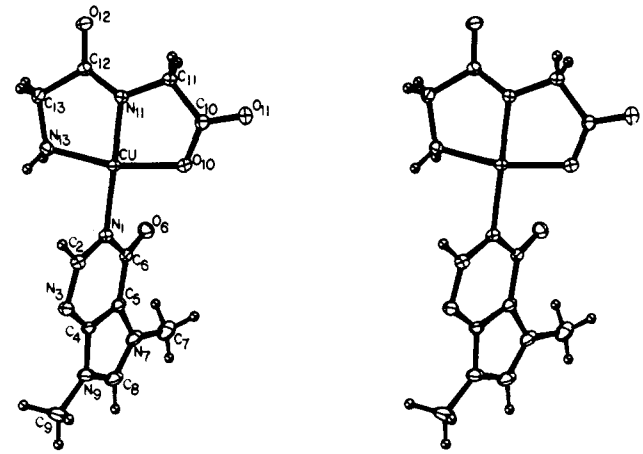


Figure 2. A stereoview of the molecular structure of (glycylglycinato)-(7,9-dimethylhypoxanthine)copper(II).

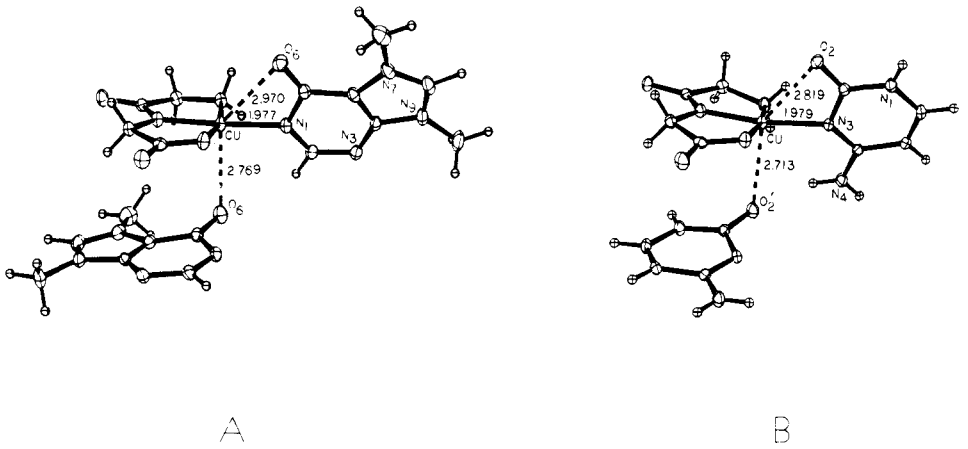
Neutral scattering factor curves for the nonhydrogen[21] and hydrogen[22] atoms were taken from common sources. Anomalous dispersion corrections were applied to the scattering curves for all the nonhydrogen atoms.[23] Final atomic positional parameters for the nonhydrogen atoms are collected in Table II. Tables of anisotropic thermal parameters, parameters for the hydrogen atoms, and final calculated and observed structure factor amplitudes have been deposited.[24] The crystallographic calculations were performed with a standard set of computer programs.[25]

Results and Discussion

The 7,9-disubstituted 6-oxopurine ligand 7,9-dimethylhypoxanthine, Figure 1, is eminently suited as a ligand for the preparation of N(1)-coordinated 6-oxopurine metal complexes. Alkylation of 9-methylhypoxanthine at N(7), and subsequent deprotonation at N(1), leaves only the ring nitrogen atom N(1) as a convenient metal binding site on the purine framework itself. The ring nitrogen atom N(3) also has lone-pair density available for participation in a coordination bond; however, the steric restrictions imposed by the methyl substituent at N(9), Figure 1, make metal coordination at N(3) very unlikely.[26,27]

As indicated in Figure 1, the alkylation at N(7) in conjunction with deprotonation at N(1) is expected to induce a shift in π-electron density from the imidazole to the pyrimidine ring and to the exocyclic carbonyl oxygen atom at C(6). The coordination pocket formed by N(1) and O(6) is then an attractive site for direct metal coordination at N(1), with the possible extension to an intramolecular chelation mode through the involvement of O(6). Similar considerations hold for the coordination pocket formed by N(3) and O(2) for cytosine and its derivatives. In fact, as we will show below, the coordination properties of 7,9-dimethylhypoxanthine with a chelated copper(II) center are essentially identical with those displayed by cytosine and its N(1)-substituted derivatives.

X-ray Structural Characterization of the Metal Coordination Geometry. (Glycylglycinato)(7,9-dimethylhypoxanthine)-copper(II) exists as a slightly distorted, square-planar complex



A B

Figure 3. Secondary intramolecular and intermolecular Cu-O(base) interactions in (glycylglycinato)(7,9-dimethylhypoxanthine)copper(II) (A), Cu-O(6), and in (glycylglycinato)(cytosine)copper(II) (B), Cu-O(2).

Table II. Final Nonhydrogen Atom Parameters[a]

atom	x	y	z	atom	x	y	z
Cu	−6028(2)	2083(5)	22309(2)	C(5)	1738(2)	−371(4)	3747(2)
O(6)	1244(2)	−1491(3)	2429(1)	C(6)	1127(2)	−571(4)	3049(2)
O(10)	174(1)	1336(3)	1356(1)	C(7)	3254(2)	−1889(6)	3319(3)
O(11)	129(2)	2270(3)	50(1)	C(8)	2865(2)	−501(5)	4666(4)
O(12)	−2819(2)	−1379(3)	909(1)	C(9)	2180(3)	1149(6)	5860(2)
N(1)	308(2)	417(4)	3152(1)	C(10)	−222(2)	1476(4)	645(2)
N(3)	638(2)	1313(3)	4552(2)	C(11)	−1154(2)	559(4)	532(2)
N(7)	2645(2)	−976(4)	3897(2)	C(12)	−2215(2)	−988(4)	1445(2)
N(9)	2170(2)	367(4)	5023(2)	C(13)	−1279(2)	−1531(4)	2348(2)
N(11)	−1451(1)	−96(4)	1332(1)	W(1)	−4554(2)	−2967(4)	874(2)
N(13)	−1540(2)	−1227(3)	2861(1)	W(2)	484(2)	4649(4)	−2838(2)
C(2)	123(2)	1252(4)	3864(2)	W(3)	−641(2)	3074(4)	−1537(2)
C(4)	1449(2)	479(4)	4449(2)	W(4)	1712(2)	4322(4)	400(2)

[a] Parameters for Cu × 10^5; parameters for other atoms ×10^4; estimated standard deviations in the least significant figure are enclosed in parentheses here and in succeeding tables.

with the four equatorial coordination sites occupied by the tridentate glycylglycine dianion and N(1) of the 7,9-dimethylhypoxanthine ligand, Figure 2. The primary coordination geometry and dimensions shown here in the 7,9-dimethylhypoxanthine complex are virtually identical with those displayed in the complex (glycylglycinato)(cytosine)copper(II),[28] Figure 3. The strengths of the metal-coordination bonds to the purine and pyrimidine ligands are expected to be similar as their dimensions, Cu-N(1) = 1.977 (3) Å in the 7,9-dimethylhypoxanthine complex and Cu-N(3) = 1.979 (3) Å in the cytosine complex, are equivalent within 1 esd.

A point of particular interest in such systems is the elucidation of the involvement of the carbonyl oxygen atom near to the metal coordination site, leading to N(3),O(2) participation in N(3)-coordinated cytosine complexes and to N(1), O(6) participation in N(1)-coordinated 6-oxopurine complexes. For complexes containing cytosine or an N(1)-substituted cytosine ligand, it now is well established[26,27,29] that both M-N(3) and M-O(2) bonding interactions are important. Specific examples include (a) Cu(II)-N(3),O(2) chelation,[28,30,32] (b) Hg(II)-N(3),O(2) chelation;[33] (c) N(3) bonding with a suggestion of O(2) participation for Pt(II)[34,35] and Pd(II);[36] (d) Mn(II)-O(2) bonding alone;[37] (e) Ag(I)-N(3),O(2) multiple bridging where O(2) plays a unique and fundamentally important role.[38]

In this regard, we find in the present 7,9-dimethylhypoxanthine complex, in addition to the strong Cu-N(1) bond, two weak, axial interactions of the type Cu-O(6): one interaction is intramolecular with a Cu-O(6) distance of 2.970 (2) Å and one is an intermolecular interaction (between complexes related by a twofold screw operation parallel to *b* with a symmetry transform, $-x, \frac{1}{2}+y, \frac{1}{2}-z$) with a Cu-O(6) distance of 2.769 (2) Å. In the cytosine complex of glycylglycinatocopper(II),[28] a very similar situation obtains. In each case, the intermolecular Cu-O interaction is the stronger of the two types of interactions. In both cases, however, there is definite indication that the Cu is significantly attracted to the oxygen atom in the intramolecular interaction, as the exocyclic bond angles at the nitrogen atom bonded to the copper are such that the copper lies toward the participating oxygen atom.

We have previously postulated[26,28,31,32] that the intramolecular Cu-O(2) interaction in the cytosine systems[28,30-32] is primarily electrostatic in character, and we believe that a similar situation obtains here in the 7,9-dimethylhypoxanthine complex.

Thus, we find that the binding of 7,9-dimethylhypoxanthine and cytosine to glycylglycinatocopper(II) is markedly similar in all aspects of the type and strength to the binding of the copper to the purine or pyrimidine base. This analogy extends even to the nature of the intermolecular interactions involving the copper center and the participating exocyclic oxygen atom.

Molecular Dimensions. A. The Glycylglycine Dianion. The dimensions found for the coordinated glycylglycine dianion here in the 7,9-dimethylhypoxanthine complex, Table III, are in excellent agreement with those observed in the cytosine complex.[28] For the 11 intraligand bond lengths, including the coordination bonds to the copper, the maximum bond-length difference, 0.016 Å, occurs in the C(11)-N(11) bond. The root mean square difference in the 11 intraligand bond lengths is only 0.008 (5) Å. The root mean square difference in the 16 intraligand bond angles, including those involving the coor-

Table III. Final Nonhydrogen Atom Interatomic Distances (Å) and Angles (deg)

A. Primary Coordination Sphere about the Copper Atom			
Bond Lengths			
Cu-O(10)	1.992(2)	Cu-N(13)	2.013(3)
Cu-N(1)	1.977(3)	Cu-O(6)	2.970(2)
Cu-N(11)	1.900(2)	Cu-O(6)[a]	2.769(2)
Bond Angles			
O(10)-Cu-N(1)	97.0(1)	N(1)-Cu-O(6)[a]	89.8(1)
O(10)-Cu-N(11)	82.9(1)	N(11)-Cu-N(13)	83.5(1)
O(10)-Cu-N(13)	165.3(1)	N(11)-Cu-O(6)	126.5(1)
O(10)-Cu-O(6)	76.8(1)	N(11)-Cu-O(6)[a]	93.0(1)
O(10)-Cu-O(6)[a]	85.4(1)	N(13)-Cu-O(6)	107.2(1)
N(1)-Cu-N(11)	177.3(1)	N(13)-Cu-O(6)[a]	100.9(1)
N(1)-Cu-N(13)	96.3(1)	O(6)-Cu-O(6)[a]	133.0(1)
N(1)-Cu-O(6)	50.9(1)		
B. Glycylglycinato Chelate Ligand			
Bond Lengths			
O(10)-C(10)	1.278(4)	N(11)-C(12)	1.305(4)
O(11)-C(10)	1.241(4)	N(13)-C(13)	1.474(4)
O(12)-C(12)	1.257(4)	C(10)-C(11)	1.522(4)
N(11)-C(11)	1.442(4)	C(12)-C(13)	1.526(4)
Bond Angles			
Cu-O(10)-C(10)	114.7(2)	O(11)-C(10)-C(11)	119.6(3)
Cu-N(11)-C(11)	116.2(2)	N(11)-C(11)-C(10)	108.5(2)
Cu-N(11)-C(12)	119.7(2)	O(12)-C(12)-N(11)	127.5(3)
C(11)-N(11)-C(12)	123.8(2)	O(12)-C(12)-C(13)	118.5(3)
Cu-N(13)-C(13)	110.5(2)	N(11)-C(12)-C(13)	114.0(3)
O(10)-C(10)-O(11)	123.3(3)	N(13)-C(13)-C(12)	111.1(2)
O(10)-C(10)-C(11)	117.1(3)		
C. 7,9-Dimethylhypoxanthine Ligand			
Bond Lengths			
O(6)-C(6)	1.235(4)	N(7)-C(8)	1.324(5)
N(1)-C(2)	1.337(4)	N(9)-C(4)	1.385(4)
N(1)-C(6)	1.409(4)	N(9)-C(8)	1.331(5)
N(3)-C(2)	1.327(4)	N(9)-C(9)	1.471(5)
N(3)-C(4)	1.339(4)	C(4)-C(5)	1.368(4)
N(7)-C(5)	1.400(4)	C(5)-C(6)	1.430(4)
N(7)-C(7)	1.455(4)		
Bond Angles			
Cu-N(1)-C(2)	123.1(2)	N(3)-C(4)-N(9)	126.5(3)
Cu-N(1)-C(6)	114.6(2)	N(3)-C(4)-C(5)	126.6(3)
C(2)-N(1)-C(6)	121.8(3)	N(9)-C(4)-C(5)	106.9(3)
C(2)-N(3)-C(4)	111.3(3)	N(7)-C(5)-C(4)	107.5(3)
C(5)-N(7)-C(7)	127.5(3)	N(7)-C(5)-C(6)	131.7(3)
C(5)-N(7)-C(8)	106.7(3)	C(4)-C(5)-C(6)	120.7(3)
C(7)-N(7)-C(8)	125.8(3)	O(6)-C(6)-N(1)	121.4(3)
C(4)-N(9)-C(9)	107.6(3)	O(6)-C(6)-C(5)	127.5(3)
C(4)-N(9)-C(9)	126.0(3)	N(1)-C(6)-C(5)	111.0(3)
C(8)-N(9)-C(9)	126.4(3)	N(7)-C(8)-N(9)	111.3(3)
N(1)-C(2)-N(3)	128.0(3)		

[a] $-x, \frac{1}{2}+y, \frac{1}{2}-z$.

dination bonds, is 0.7 (6)°, which falls slightly to 0.6 (4)° on the exclusion of the seven bond angles involving the coordination bonds. The glycylglycinato dianion geometry for these two complexes is also in good agreement with the molecular dimensions found, for example, in the dihydrate[39] and trihydrate[40] complexes of glycylglycinatocopper(II).

It is well known that the substitution of the coordination bond for the proton at the peptide nitrogen atom N(11) causes the overall system to be approximately planar.[40] The 7,9-dimethylhypoxanthine complex is consistent with this analysis, with a maximum deviation, Table IV, of any atom out of the ten-atom dipeptide plane, including the copper atom, of only 0.1 Å for C(13). As in related complexes,[28,39,40] there is a measurable folding about the Cu-peptide nitrogen, N(11) bond. The dihedral angles between the peptide and the carboxylate halves are 4.4 (3)° in the cytosine complex, 5.3 (3)° in the dihydrate complex, and significantly muted, 1.4 (3)°, in the 7,9-dimethylhypoxanthine complex.

B. The 7,9-Dimethylhypoxanthine Ligand. The bond lengths and angles in the N(1),O(6) coordinated 7,9-dimethylhypoxanthine ligand are presented in Table III. As noted above, there are no other structurally characterized N(1),O(6)-bonded 6-oxopurine complexes with which we can compare our geometrical parameters in the coordinated purine ring. An interesting comparison can be made, however, between the molecular dimensions found in hypoxanthine hydrochloride monohydrate,[41] with protons located off N(1), N(7), and N(9), and the dimensions we find for the coordinated 7,9-dimethylhypoxanthine ligand, where the substitution pattern at N(1), N(7), and N(9) is Cu-, H_3C-, and H_3C-. As expected, most of the differences in parameters in the two systems lie in the pyrimidine ring. Compared to the parameters found in the protonated hypoxanthine base,[41] the bond lengths N(1)-C(6), C(5)-C(6), and N(3)-C(2) are elongated by 0.02-0.03 Å, while the bonds N(1)-C(2) and N(3)-C(4) are contracted by about the same amount. For the bond angles, we find con-

Table IV. Least-Squares Planes and the Deviations (Å) of Individual Atoms from These Planes[a]

A. Primary Coordination Plane Including Copper Atom
$(0.4404X - 0.8596Y - 0.2593Z = -1.3860$ Å)

Cu	−0.060	N(13)	0.043
O(10)	0.043	N(1)	−0.008
N(11)	−0.018		

B. 7,9-Dimethylhypoxanthine Ligand
1. Nine-Atom Framework
$(0.4039X + 0.8378Y - 0.3675Z = -1.4420$ Å)

N(1)	0.034	C(8)	0.025
C(2)	0.049	N(9)	−0.025
N(3)	−0.019	Cu	−0.086*
C(4)	−0.031	O(6)	−0.237*
C(5)	−0.001	C(7)	0.143*
C(6)	−0.073	C(9)	−0.005*
N(7)	0.042		

2. Pyrimidine Ring
$(0.4283X + 0.8257Y - 0.3670Z = -1.4187$ Å)

N(1)	0.020	C(5)	0.043
C(2)	0.021	C(6)	−0.049
N(3)	−0.029	Cu	−0.131*
C(4)	−0.004	O(6)	−0.201*

3. Imidazole Ring
$(0.3789X + 0.8555Y - 0.3530Z = -1.4197$ Å)

C(4)	0.005	N(9)	−0.003
C(5)	−0.004	C(7)	0.055*
N(7)	0.002	C(9)	0.046*
C(8)	0.001		

C. Glycylglycine Chelate
1. The Ten-Atom Equatorial Plane Including Copper Atom
$(0.4644X - 0.8535Y - 0.2406Z = -1.3696$ Å)

Cu	−0.027	C(12)	−0.001
O(10)	0.079	O(12)	0.065
C(10)	−0.001	C(13)	−0.099
O(11)	−0.065	N(13)	0.058
C(11)	0.032	N(1)	0.082*
N(11)	−0.041		

2. The Carboxylate Half
$(0.4523X - 0.8562Y - 0.2496Z = -1.3829$ Å)

Cu	−0.038	O(11)	−0.058
O(10)	0.067	C(11)	0.052
C(10)	0.003	N(11)	−0.026

3. The Peptide Half
$(0.4693X - 0.8512Y - 0.2350Z = -1.3850$ Å)

Cu	−0.002	O(12)	0.053
N(11)	−0.033	C(13)	−0.094
C(12)	−0.001	N(13)	0.077

[a] In each of the equations of the planes, X, Y, and Z are coordinates (Å) referred to the orthogonal axes a, b, and c. Atoms designated by an asterisk were given zero weight in calculating the planes; other atoms were weighted equally.

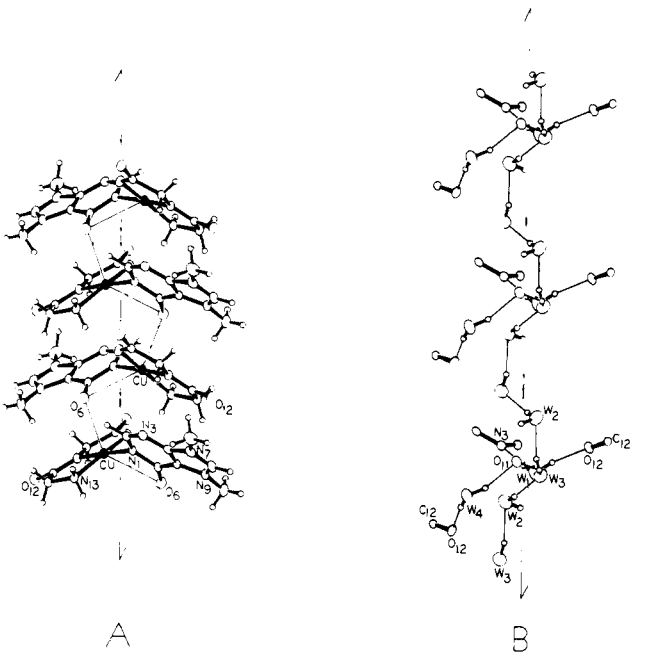


Figure 4. Helical arrays of (glycylglycinato)(7,9-dimethylhypoxanthine)copper(II) complexes (A) and hydrogen-bonded water molecules (B) generated about twofold screw axes parallel to the crystallographic b axis. Thin lines denote hydrogen bonds.

traction at C(6)-C(6)-N(1) by about 1° and an expansion of about 3° in the N(1)-C(2)-N(3) bond angle. The endocyclic bond angle at N(1), C(2)-N(1)-C(6), is noteworthy. In the protonated hypoxanthine base,[41] this bond angle is 124.9 (1)° and similar values of 126.1 (1),[42] 125.1 (3), and 124.4 (3)°[43] are found in N(7)-coordinated 9-methylhypoxanthine complexes. For a methyl substituent at N(1) [as found, for example, in theophylline (1,3-dimethyl-2,6-dioxopurine)[44,45] or in the N(7)-coordinated theophylline monoanion[46,47]], the bond angle at N(1) is about 126°. In the N(1)-coordinated 7,9-dimethylhypoxanthine ligand, we find the endocyclic bond angle at N(1) to be 121.8 (3)°, which is contracted by about 3-5° from the values given above for a proton or a methyl group at N(1). All of the above trends are in accord with the general notion that metal coordination at a ring nitrogen atom in a purine or a pyrimidine ring is less effective than a proton or an alkyl group in inducing molecular structural alterations.[26,38,42,43,47-50]

Most uncoordinated and coordinated purine bases show some nonplanarity in the pseudoaromatic ring system.[26,41,51] The nine-atom framework of the 7,9-dimethylhypoxanthine ligand is quite nonplanar, Table IV, with a dihedral angle between a highly planar imidazole ring and a moderately planar pyrimidine ring of 3.4 (3)°. In hypoxanthine hydrochloride monohydrate,[41] this dihedral angle is only 0.8 (1)°, but theophylline[44,45] and the coordinated theophylline monoanion show similar degrees of folding, 2-3°, about the C(4)-C(5) bond.[46,47] The Cu atom and the exocyclic carbonyl oxygen atom O(6) both show substantial deviations from the pyrimidine ring plane of 0.13 and 0.20 Å, respectively. It is interesting, and surely significant, that in both instances the deviations are on the same side of the plane. The deviation of O(6) from the plane is clearly stimulated by both the intra- and the intermolecular Cu-O(6) interaction, with the latter probably having the more pronounced effect. In the cytosine complex,[28] there is a concerted deviation from the pyrimidine plane[28] of both the Cu and the carbonyl oxygen atom O(2), 0.10 and 0.19 Å, in accord with the results presented above and the strong similarity between the cytosine and 7,9-dimethylhypoxanthine complexes.

Crystal Packing. The most pronounced feature of the crystal packing is the formation of helical arrays of complexes, Figure 4A, and hydrogen-bonded water molecules, Figure 4B, about twofold screw axes parallel to the crystallographic b axis. In the helical arrays of complexes, it is the intermolecular Cu-O(6) interaction which provides the major source of stability. The coupling between the helical arrays of complexes and hydrogen-bonded water molecules, Figure 5, is provided by interhelix hydrogen bonding, with the peptide oxygen atom O(12), the uncoordinated carboxylate oxygen atom O(11), and the purine ring nitrogen atom N(3) acting as acceptors, Table V and Figure 5. The terminal amino group of the glycylglycinato ligand acts as a hydrogen-bond donor to W(4) in the helical array of hydrogen-bonded water molecules and as a hydrogen-bond donor to the coordinated carboxylate oxygen

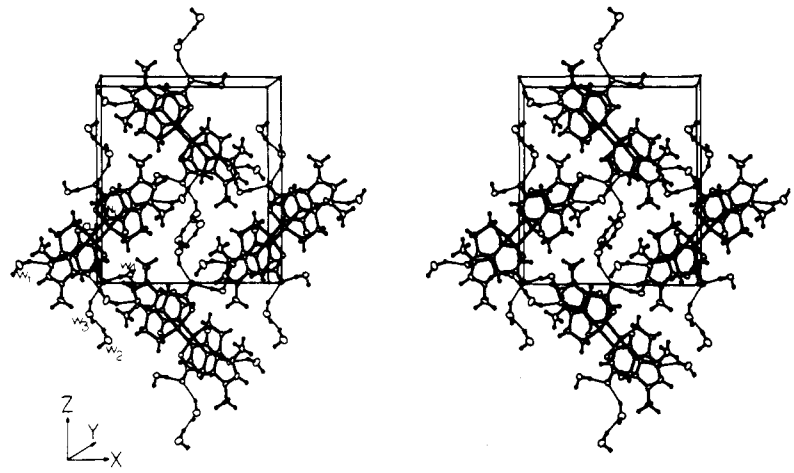


Figure 5. A stereoview of the crystal structure of (glycylglycinato)(7,9-dimethylhypoxanthine)copper(II) tetrahydrate. The view direction is along the crystallographic *b* axis.

Table V. Distances and Angles in the Intermolecular Interactions of the Type D-H---A

D	H	D-H	A	H---A	D---A	∠D-H---A
N(13)	H(N13a)	0.91	W(4)[a]	1.96	2.831(4)	158
N(13)	H(N13b)	0.94	O(10)[a]	2.17	2.993(4)	145
W(1)	H(W1a)	0.98	N(3)[b]	1.95	2.922(4)	172
W(1)	H(W1b)	0.99	O(12)	1.85	2.772(4)	154
W(2)	H(W2a)	0.91	W(3)	2.03	2.903(4)	160
W(3)	H(W3a)	0.98	O(11)	1.95	2.842(4)	151
W(3)	H(W3b)	0.97	W(2)[c]	1.94	2.843(4)	153
W(4)	H(W4a)	1.00	O(12)[d]	1.73	2.719(4)	174
W(4)	H(W4b)	0.92	O(11)	1.93	2.824(4)	163
W(2)	H(W2b)	0.92	W(1)[b]	2.28	2.781(4)	114
W(2)	H(W2b)	0.92	W(3)[e]	2.59	2.843(4)	96

[a] Symmetry transforms: $-x, -1/2 + y, 1/2 - z$. [b] $-1/2 - x, -y, -1/2 + z$. [c] $-x, -1/2 + y, -1/2 - z$. [d] $1/2 + x, 1/2 - y, -z$. [e] $-x, 1/2 + y, -1/2 - z$.

atom O(10) in the glycylglycinato ligand in an intercomplex hydrogen bond. This latter interaction also provides some degree of stabilization to the helical array of complexes.

It is noteworthy that in the cytosine complex[28] a very similar arrangement of helical arrays of complexes, again primarily stabilized by the intermolecular Cu-O interaction, and of hydrogen bonded water molecules is observed. Thus, even in their crystal packing, the two complexes are strikingly similar.

Solution Studies. Addition of $Cu(NO_3)_2$ or [CuglyglyH$_2$O] (Figure 6) to solutions of 7,9-dimethylhypoxanthine leads to severe line broadening of the H-2 resonance, consistent with the addition of the metal to N(1) in solution. Such data cannot be used to implicate the involvement of O(6) in the binding.

Summary

We find that the complex (glycylglycinato)(7,9-dimethylhypoxanthine)copper(II) provides the first example of an N(1)-bonded 6-oxopurine complex. Intra- and intermolecular Cu-O(6) interactions are important in the solid-state structure, and the intramolecular Cu-O(6) interaction probably obtains in solution. The striking similarity in both the molecular and crystal structure of the 7,9-dimethylhypoxanthine complex and that of the cytosine complex[28] with glycylglycinatocopper(II) is noteworthy. This close similarity suggests that the N(1),O(6) grouping can be expected to exhibit the same versatile bonding modes in solution and in the solid that have been found for cytosine derivatives.

Acknowledgment. This investigation was supported by the National Institutes of Health, Public Health Service Grant GM 20544.

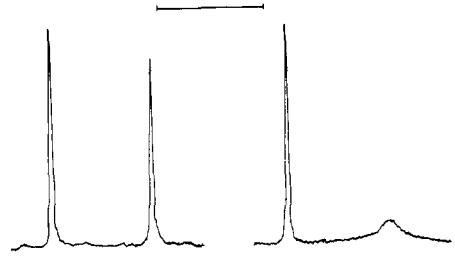


Figure 6. Left: ^{1}H NMR spectra in the aromatic region of 7,9-dimethylhypoxanthine (0.8 M) in H$_2$O (JEOL MH 100 100-MHz spectrum), bar = 100 Hz. The downfield peak at δ is assigned to H-8 since addition of D$_2$O causes this signal to diminish with respect to the signal at γ which is assigned to H-2. It is known that, in 7,9-dialkylated hypoxanthines, the hydrogen at position 8 undergoes exchange.[52] Right: spectrum after the addition of [CuglyglyH$_2$O], 1.61×10^{-4} M. $Cu(NO_3)_2$ causes similar broadening of the H-2 signal.

Supplementary Material Available: Tables of nonhydrogen atom anisotropic thermal parameters (Table D1), parameters for the hydrogen atoms (Table D2), and a list of calculated and observed structure factor amplitudes (Table D3) (20 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Marzilli, L. G. *Prog. Inorg. Chem.* **1977**, *23*, 255. Hodgson, D. J. *Ibid.* **1977**, *23*, 211. Swaminathan, V.; Sundaralingam, M. *Crit. Rev. Biochem.*, in press. Martin, R. B. In "Metal Ions in Biological Systems," Sigel, H., Ed.; Marcel Dekker: New York, in press. Gellert, R. W.; Bau, R. *Ibid.*, in press. Marzilli, L. G. *Adv. Inorg. Biochem.*, in press. Marzilli, L. G.; Kistenmacher, T. J.; Eichhorn, G. L. In "Perspectives of Metals in Biology", Spiro, T. G., Ed.; Wiley: New York, in press.

(2) Eichhorn, G. L. *Adv. Inorg. Biochem.*, in press.
(3) Rosenberg, B.; VanCamp, L.; Kuga, T. *Nature (London)* **1962,** *205*, 698. Rosenberg, B. *Cancer Chemother. Rep.* **1975,** *59*, 539. Thompson, A. J. *Platinum Met. Rev.* **1977,** *21*, 2. Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature (London)* **1969,** *222*, 385.
(4) Munchausen, L. L.; Rahn, R. O. *Biochim. Biophys. Acta* **1975,** *414*, 242.
(5) Kistenmacher, T. J.; Chiang, C. C.; Chalilpoyil, P.; Marzilli, L. G. *J. Am. Chem. Soc.* **1979,** *101*, 1143. Kistenmacher, T. J.; Chiang, C. C.; Chalilpoyil, P.; Marzilli, L. G. *Biochem. Biophys. Res. Commun.* **1978,** *84*, 70.
(6) Gellert, R. W.; Bau, R. *J. Am. Chem. Soc.* **1975,** *97*, 7379, Cramer, R. E.; Dahlstrom, P. L. *J. Clin. Hematol. Oncol.* **1977,** *7*, 330.
(7) Bau, R.; Gellert, R. W.; Lehovec, S. M.; Louie, S. *J. Clin. Hematol. Oncol.* **1977,** *7*, 51.
(8) See issues no. 1 and 2 of *J. Clin. Hematol. Oncol.* **1977,** *7*.
(9) O'Connor, P. J.; Capps, M. J.; Craig, A. W. *Br. J. Cancer* **1973,** *27*, 153. Loveless, A. *Nature (London)* **1969,** *223*, 206. Engelese, L. D. *Chem.-Biol. Interact.* **1974,** *8*, 329. Kleihues, P.; Buchezer, J. *Nature (London)* **1977,** *269*, 625. Golh, R.; Rasensky, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1974,** *71*, 639. Gerchman, L. L.; Ludcum, D. B. *Biochim. Biophys. Acta* **1973,** *308*, 310.
(10) Macquel, J.-P.; Theophanides, T. *Inorg. Chim. Acta* **1976,** *18*, 189. Macquel, J.-P.; Theophanides, T. *Bioinorg. Chem.* **1975,** *5*, 59.
(11) Goodgame, D. M. L.; Jeeves, I.; Phillips, F. L.; Skapski, A. C. *Biochim. Biophys. Acta* **1975,** 402, 166.
(12) DeHand, J.; Jordanov, J. *J. Chem. Soc., Chem. Commun.* **1976,** 598.
(13) Lippard, S. J. In ref 8, p 453.
(14) Szalda, D. J.; Kistenmacher, T. J.; Marzilli, L. G. *J. Am. Chem. Soc.* **1976,** *98*, 8371.
(15) Kistenmacher, T. J.; Szalda, D. J.; Chiang, C. C.; Rossi, M.; Marzilli, L. G. *Inorg. Chem.* **1978,** *17*, 2582.
(16) Jones, J.; Robins, R. *J. Am. Chem. Soc.* **1962,** *94*, 914.
(17) Manyak, A. R.; Murphy, C. B.; Martell, A. E. *Arch. Biochem. Biophys.* **1955,** *59*, 373.
(18) Busing, W. R.; Levy, H. A. *J. Chem. Phys.* **1957,** *26*, 563.
(19) Wilson, A. J. C. *Nature (London)* **1942,** *150*, 152.
(20) Hamilton, W. C. *Acta Crystallogr.* **1965,** *18*, 502.
(21) Hanson, H. P.; Herman, F.; Lea, J. D.; Skillman, S. *Acta Crystallogr.* **1964,** *17*, 1040.
(22) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965,** *42*, 3175.
(23) Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **1970,** *53*, 1891.
(24) See paragraph at end of paper regarding supplementary material.
(25) Crystallographic programs employed include Wehe, Busing, and Levy's ORABS; Busing, Martin, and Levy's ORFLS; Zalkin's FORDAP; Pippy and Ahmed's MEAN PLANE; Johnson's ORTEP. Calculations other than those specifically noted were performed with locally written programs.
(26) Kistenmacher, T. J.; Marzilli, L. G. In "Metal-Ligand Interactions in Organic and Biochemistry", Pullman, B., Goldblum, N., Eds.; Dordrecht: Holland, 1977; Part I, p 7.
(27) Marzilli, L. G.; Kistenmacher, T. J. *Acc. Chem. Res.* **1977,** *10*, 146.
(28) Kistenmacher, T. J.; Szalda, D. J.; Marzilli, L. G. *Acta Crystallogr., Sect. B* **1975,** *31*, 2416.
(29) Marzilli, L. G.; Stewart, R. C.; Van Vuuren, C. P.; de Castro, B.; Caradonna, J. P. *J. Am. Chem. Soc.* **1978,** *100*, 3967.
(30) Sundaralingam, M.; Carrabine, J. A. *J. Mol. Biol.* **1971,** *61*, 287.
(31) (a) Szalda, D. J.; Marzilli, L. G.; Kistenmacher, T. J. *Biochem. Biophys. Res. Commun.* **1975,** *63*, 601. (b) Szalda, D. J.; Kistenmacher, T. J. *Acta Crystallogr., Sect. B* **1977,** *33*, 865.
(32) Szalda, D. J.; Marzilli, L. G.; Kistenmacher, T. J. *Inorg. Chem.* **1975,** *14*, 2076.
(33) Authier-Martin, M.; Beauchamp, A. L. *Can. J. Chem.* **1977,** *55*, 1213.
(34) Melanson, R.; Rochon, F. D. *Inorg. Chem.* **1978,** *17*, 679.
(35) Lock, C. J. L.; Spernanzini, R. A.; Powell, J. *Can. J. Chem.* **1976,** *54*, 53.
(36) Sinn, E.; Flynn, C. M.; Martin, R. B. *Inorg. Chem.* **1977,** *16*, 2403.
(37) Aoki, K. *J. Chem. Soc., Chem. Commun.* **1976,** 748.
(38) (a) Marzilli, L. G.; Kistenmacher, T. J.; Rossi, M. *J. Am. Chem. Soc.* **1977,** *99*, 2797. (b) Kistenmacher, T. J.; Rossi, M.; Marzilli, L. G. *Inorg. Chem.* **1979,** *18*, 240.
(39) Kistenmacher, T. J.; Szalda, D. J. *Acta Crystallogr., Sect. B* **1975, 31,** 1659.
(40) (a) Hermodsson, Y.; Strandberg, B. *Acta Crystallogr.* **1957,** *10*, 434. (b) Strandberg, B.; Lindqvist, I.; Rosenstein, R. *Z. Kristallogr., Kristallgeom., Kristallphys., Kristallchem.* **1961,** *116*, 266. (c) Freeman, H. C. *Adv. Protein Chem.* **1967,** *22*, 257; private communication.
(41) Stellen, J.; Jensen, L. H. *Acta Crystallogr., Sect. B* **1969,** *25*, 1608.
(42) Stellen, E.; *Acta Crystallogr., Sect. B* **1974,** *30*, 1961.
(43) Stellen, E.; Kaale, R. *Acta Crystallogr., Sect. B* **1977,** *33*, 158.
(44) Sutor, D. J. *Acta Crystallogr.* **1958,** *11*, 83.
(45) Shefter, E. *J. Pharm. Sci.* **1971,** *58*, 710.
(46) Kistenmacher, T. J. *Acta Crystallogr., Sect. B* **1975,** *31*, 86.
(47) Kistenmacher, T. J.; Szalda, D. J.; Marzilli, L. G. *Inorg. Chem.* **1975,** *14*, 1686.
(48) Kistenmacher, T. J.; Shigematsu, T. *Acta Crystallogr., Sect. B* **1975,** *31*, 211.
(49) Kistenmacher, T. J.; Urmey, W. F.; Rossi, M. *J. Cryst. Mol. Struct.* **1977,** *7*, 219.
(50) Sorrell, T.; Epps, L. A.; Kistenmacher, T. J.; Marzilli, L. G. *J. Am. Chem. Soc.* **1978,** *100*, 5756.
(51) Voel, D.; Rich, A. *Prog. Nucleic Acids Res. Mol. Biol.* **1970,** *10*, 103.
(52) Ts'o, P. O. P.; Kondo, N. S.; Robins, R. R.; Broom, A. D. *J. Am. Chem. Soc.* **1969,** *91*, 5625.

Heterocyclic Photochemistry. 1. Phototranspositions in Hydroxypyrylium Cations. Permutation Pattern Analysis and Mechanistic Studies[1]

John A. Barltrop,* John C. Barrett, Roger W. Carder, A. Colin Day,* John R. Harding, William E. Long, and Christopher J. Samuel

Contribution from the Dyson Perrins Laboratory, Oxford University, Oxford, England. *Received August 13, 1978*

Abstract: A number of dialkyl-4-pyrones have been irradiated (as the corresponding 4-hydroxypyrylium cations) in sulfuric acid and the transposed 2-pyrones have been identified. A permutation pattern analysis of these and literature data shows that the photorearrangement follows a P_4 permutation pattern, thus defining the fate of all the ring atoms. This conclusion is supported by a total-labeling investigation: a study of the rearrangement of a ^{14}C-labeled 4-pyrone confirmed that the alkyl migrations are intramolecular, the alkyl groups remaining bonded to the ring atoms during the rearrangement. The irradiation of 3,5-dimethyl-4-pyrone in sulfuric acid led to the isolation of a new intermediate, the cyclic sulfate **22**, which in sulfuric acid is converted thermally or photochemically to the 2-pyrone **8**. In aqueous sulfuric acid, 2-acylfurans are also found as irradiation products. It is concluded that the excited 4-hydroxypyrylium cations relax to hydroxyoxabicyclohexenyl cations (**30**) as primary ground-state intermediates. A minor pathway of isomerization via a P_8 permutation pattern is also discussed. The photointerconversion of 2-hydroxypyrylium cations (e.g., eq 8) is shown to occur by a P_8 permutation pattern.

Introduction

Pyrones have displayed a wide variety of photochemical behavior[2] and a new facet was revealed when Pavlik reported the photoisomerization of 2,6-dimethyl-4-pyrone in sulfuric acid[3] (eq 1) in which solvent both 4- and 2-pyrones are protonated and are best described as hydroxypyrylium cations. Our interest in the photochemistry of pyrylium salts led us to consider these reactions, and, while not disputing Pavlik's postulated mechanisms, we recognized that they were based

0002-7863/79/1501-7510$01.00/0