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Binding Sites in Transition Metal–Pyrimidine Complexes and Evidence for a Measurable Trans Influence in Copper(II) Complexes.

Crystal and Molecular Structure of an N(1)-Bonded Copper(II)–Thymine Complex, (Aquo)(diethylenetriamine)(thyminato)copper(II) Bromide Dihydrate

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The synthesis and structural characterization of the complex (aquo)(diethylenetriamine)(thyminato)copper(II) bromide, $CuBrO_3N_5C_9H_{20}$, are reported. The complex crystallizes, as the dihydrate, in the monoclinic system, space group $P2_1/n$, with a = 6.341 (1) Å, b = 12.840 (8) Å, c = 20.805 (12) Å, β = 95.50 (3)°, V = 1686.1 Å^3, Z = 4, d_{measd} = 1.68(1) g cm^{-3}, and d_{calcd} = 1.68 g cm^{-3}. Intensities for 4938 independent reflections (560 zeros) were collected by counter methods. The structure was solved by standard heavy-atom Patterson and Fourier methods. Full-matrix, least-squares refinement has led to final R(excluding zeros), weighted R, and goodness-of-fit values of 0.077, 0.062, and 1.4, respectively. The primary coordination sphere about the copper is approximately square pyramidal. The tridentate diethylenetriamine ligand, with its terminal nitrogen atoms in trans positions, and N(1) of the coordinated thymine monoanion define the equatorial plane. This complex represents the first report of metal binding to the N(1) position of pyrimidines. The coordination sphere about the copper is completed by an axially bonded water molecule, Cu–O = 2.465 (3) Å. Comparison of the Cu–N(middle nitrogen atom of the diethylenetriamine ligand) distance in the thyminato complex, 2.009 (3) Å, and the closely related cyano complex, 2.036 (4) Å, indicates a significant trans influence in carbon-bonded cyano complexes of copper(II). The square-pyramidal complex cations form columns along the short a axis such that the coordinated water molecule lies approximately below the copper atom of a translationally related complex. The complexes form hydrogen-bond dimers about centers of symmetry via the coordinated thymine monoanion. The bromide anion and the waters of crystallization play an important role in both the stability of the cationic columns and the complete three-dimensional structural network.

Introduction

Thymine and uracil and their natural nucleoside and nucleotide derivatives have no unprotonated heterocyclic nitrogens at neutral pH's. Coordination of metals to these heterocyclic sites is less favorable than in the other common nucleic acid constituents which have at least one nitrogen atom with an available lone pair.[1] Consequently, metal complexes of these two bases and their derivatives have been less extensively investigated. In some respects, however, these heterocycles are the most interesting of the bases. For example, platinum complexes react with uracils and thymines to produce "platinum blues" which have proven to be powerful anticancer agents.[2] Additionally, mercury(II) and monoalkyl derivatives of mercury(II) appear to interact preferentially with the thymine moieties in DNA.[3,4] The binding site implicated by the available evidence is N(3).[3,4]

Early line-broadening studies of thymidine suggested that little interaction between this nucleoside and Cu(II) took place.[5] Later it was shown using the same technique that the similar nucleoside, uridine, did form complexes with Cu(II), but at relatively high metal concentration.[6] Relaxation studies using ^{13}C NMR have revealed similar spectral changes for C(5), C(2), and C(4) for the nucleosides of cytosine, uracil, and thymine.[7] The changes in the cytosine derivative are seen at much lower concentrations, however. The relaxation results are consistent with binding at N(3). ^{1}H NMR line broadening was less evident in studies using thymine because the broadening results largely from the scalar coupling contribution to T_2,[8,9] which is particularly large at C(5). Thymine has no proton on C(5) but has a methyl substituent at this position.

Irrespective of the importance of the metal interactions in drugs and in influencing nucleic acid conformations, thymine and uracil and their derivatives are interesting ligands, worthy of study because of their multifaceted coordination possibilities. In addition to possible coordination of a metal to N(3), it is likely that coordination could take place at N(1), O(2), and O(4) and, in uracil derivatives, at C(5).[7] The favored reaction site will depend on the metal, the pH, the reaction time, etc.

Table I. Crystal Data for (Aquo)(diethylenetriamine)(thyminato)copper(II) Bromide Dihydrate

$a = 6.341$ (1) Å	$CuBrO_5N_5C_9H_{24}$
$b = 12.840$ (8) Å	Space group $P2_1/n$
$c = 20.805$ (12) Å	$d_{measd} = 1.68$ (1) g cm^{-3}
$\beta = 95.50$ (3)°	$d_{calcd} = 1.68$ g cm^{-3}
$V = 1686.1$ Å^3	$Z = 4$
Mol wt 425.78	$\mu = 23.2$ cm^{-1}

Sundaralingam and Carrabine[10] have shown, for example, that at low pH both uracil and dihydrouracil bind $HgCl_2$ through the exocyclic oxygen at C(4) of the pyrimidine ring. However, as has been pointed out by Kosturko, Folzer, and Stewart,[11] the low pH at which these complexes were obtained makes binding at one of the pyrimidine nitrogen atoms highly unlikely.

In a recent study,[11] the structure of a 2:1 complex of 1-methylthymine and Hg(II) has been determined. This complex was prepared at moderately high pH in order to reproduce the conditions in Hg^{II}–DNA binding studies.[3] The complex shows binding of Hg(II) to two 1-methylthymine monoanions through the deprotonated ring nitrogen N(3). This result is relevant to some binding studies where, for example, the complexation of Hg(II) by the polynucleotide dAT is accompanied by the release of two protons.[12]

In an attempt to explore further the binding of transition metals and transition metal complexes to thymine and thymine derivatives under basic conditions, we have prepared and determined the structure of the (diethylenetriamine)copper(II) [(dien)Cu^{II}] complex of the monoanion of thymine. Besides giving detailed information as to the binding of the complex to the pyrimidine monoanion and the molecular conformation, the structure allows an assessment of the trans influence[13] in the closely related, carbon-bonded cyano complex[14] of (dien)Cu^{II}.

The present study is important as it presents further information as to the ability of interligand interactions to be discriminatory in the selection of metal binding sites in multisite ligands. Furthermore, it represents the first example of binding of a pyrimidine base through N(1).

Experimental Section

Preparation of (Aquo)(diethylenetriamine)(thyminato)copper(II) Bromide. A basic solution was prepared by dissolving $Cu(NO_3)_2$ (1.21 g, 5 mmol) in 3 ml of 0.1 *N* KOH with the addition of diethylenetriamine (0.52 g, 5 mmol, in 2 ml of 0.1 *N* KOH). Thymine (0.63 g, 5 mmol, in 5 ml of 1.0 *N* KOH) was added slowly, with stirring, to the above solution. Finally, NaBr (0.51 g, 5 mmol, in 2 ml of 0.1 *N* KOH) was added.

Slow evaporation of the solvent yielded deep purple crystals of the product after a few days at room temperature (21°) or in a refrigerator (12°). The ir spectrum of this material contained bands attributable to thymine, in particular bands at 1600, 1300–1400, and 1280 cm^{-1}.

Collection and Reduction of the X-Ray Intensity Data. The deep purple (aquo)(diethylenetriamine)(thyminato)copper(II) bromide crystallizes as rectangular prisms with [100] as the prism axis. Preliminary diffraction photographs showed the crystal system to be monoclinic with systematic absences ($h0l$, $h + l = 2n + 1$, and $0k0$, $k = 2n + 1$) consistent with the space group $P2_1/n$. Unit cell dimensions and their associated standard deviations were derived on the basis of a least-squares fit to the 2θ, ω, and χ settings for 11 carefully centered reflections. The crystal density was measured by neutral buoyancy methods and indicated one formula unit plus two water molecules per asymmetric volume. Complete crystal data are given in Table I.

A crystal, 0.15 × 0.20 × 0.50 mm, was mounted on a Syntex $P\bar{1}$ computer-controlled diffractometer. The long axis of the crystal, a, was approximately aligned along the ϕ axis of the spectrometer. Molybdenum graphite-monochromatized radiation was employed in the data collection. Intensity data were collected by the θ–2θ scan technique; individual scan speeds were determined by a rapid scan at the calculated Bragg peak, and the rate of scanning varied from 2° min^{-1} (less than 100 counts during the rapid scan) to 24° min^{-1} (more than 1000 counts during the rapid scan). The 2θ maximum was set at 60°.

The course of the data collection was unusual and will be described in some detail. Three standard reflections were monitored after every 100 reflections in order to assess both crystal and electronic stability. The data collection proceeded smoothly through three octants of data (hkl, $hk\bar{l}$, and $h\bar{k}l$) with a maximum deviation of any standard from its mean of about 3–4%. Approximately one-tenth of the way through a fourth octant, $h\bar{k}\bar{l}$, the intensities of the standards dropped precipitously to about 65% of their initial values. A normal-beam, flat-film rotation photograph was then taken with the crystal still mounted on the diffractometer, and it showed that significant changes had taken place in the diffraction properties of the crystal. An oscillation photograph showed that the a axis had approximately doubled. Zero-, "first"- and second-level Weissenberg photographs indicated that the space group had apparently been retained as $P2_1/n$ and that there were significant changes in both the b and c axis lengths [cell data: $a = 12.36$ (5) Å, $b = 11.93$ (5) Å, $c = 21.3$ (1) Å, $\beta = 93$ (1)°]. By this time the crystal had completely fractured, and further analysis or a density measurement was impossible. Assuming that there are now 8 formula units per cell, the calculated volume (3142 Å^3) is consistent with the formulation of the crystal as the monohydrate as opposed to the initial trihydrate.

The 8691 reflections in the octants hkl, $hk\bar{l}$, and $h\bar{k}l$, which included standards and systematic absences as well as symmetry-related data, were then reduced to a set of 4938 independent values. All reflections were assigned observational variances based on 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 individual background extremum counts, T_S and T_B are the scan and individual background counting times ($T_B = {}^1/_4 T_S$ for all reflections), and $p = 0.05$ and represents the expected error proportional to the diffracted intensity.[15] Intensities and their standard deviations were corrected for Lorentz and polarization effects; the amplitudes of reflections with negative intensities were set equal to zero (560/4938). No correction for absorption was deemed necessary ($\mu = 23.2$ cm^{-1}); the maximum error introduced by the neglect of absorption effects was estimated to be about 4% in I. the squared structure factors were placed on an approximate absolute scale by the method of Wilson.[16]

Solution and Refinement of the Structure. The positions of the Cu and Br atoms were determined from a three-dimensional Patterson synthesis. A subsequent structure factor–Fourier calculation ($R = \sum||F_o| - |F_c||/\sum|F_o| = 0.40$) allowed the positioning of the remaining 19 heavy atoms. Four cycles of isotropic least-squares refinement, minimizing the quantity $\sum w(|F_o| - |F_c|)^2$ where $w = 4F_o^2/\sigma^2(F_o^2)$, reduced the R value to 0.13. At this point a difference Fourier map was computed and positional assignments were obtained for the 24 independent hydrogen atoms. No attempt was made to include the hydrogen atom parameters in the least-squares refinements. Three cycles of refinement, in which anisotropic thermal parameters for all heavy atoms were included, led to a final R value of 0.094 [R(excluding zeros) = 0.077]. The final weighted R value [$(\sum w(F_o - F_c)^2/\sum wF_o^2)^{1/2}$] and goodness of fit [$(\sum w(F_o - F_c)^2/(\mathrm{NO} - \mathrm{NV}))^{1/2}$, where NO = 4938 independent observations and NV = 190 variables] were 0.062 and 1.4, respectively.

The scattering factors for all of the heavy atoms were taken from the compilation of Hanson, Herman, Lea, and Skillman;[17] the form factor for H was that of Stewart, Davidson, and Simpson.[18] The real parts of the scattering curves for Cu and Br were corrected for anomalous dispersion effects.[19] Final heavy-atom parameters are collected in Table II, while those for the hydrogen atoms are given in Table III. The final observed and calculated structure factor amplitudes are available.[20]

The structure factor and Fourier calculations were done using the X-RAY 67 series of programs;[21] the least-squares refinements were performed with an extensively modified version of ORFLS;[22] best planes were computed with the program of Pippy and Ahmed;[23] the illustrations were prepared with the aid of the computer program ORTEP.[24] All other calculations were done with locally written programs.

Discussion

Experimental[25] and theoretical[26] studies have shown that the ionization of a proton from neutral thymine is equally facile from both the N(1) and N(3) positions of the pyrimidine ring.

Table II. Final Heavy-Atom Parameters (× 10^4)

Atom	x^a	y	z	$B_{11}{}^b$	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br	6706 (0.7)	537 (0.4)	2618 (0.2)	237 (1.3)	98 (0.4)	26 (0.1)	−9 (0.5)	22 (0.3)	10 (0.2)
Cu	1277 (0.6)	2159 (0.3)	1430 (0.2)	201 (1.2)	41 (0.2)	13 (0.1)	−0 (0.4)	11 (0.2)	−4 (0.1)
O(2)	4340 (4)	1054 (2)	531 (1)	261 (8)	53 (2)	22 (1)	−18 (3)	29 (2)	−8 (1)
O(4)	1523 (4)	−2191 (2)	334 (1)	280 (8)	49 (2)	32 (1)	−6 (3)	18 (2)	−15 (1)
O(5)	5689 (5)	3504 (2)	115 (2)	329 (10)	76 (2)	46 (1)	15 (4)	28 (3)	−12 (1)
O(6)	3194 (6)	4653 (3)	−796 (2)	495 (14)	111 (3)	32 (1)	20 (5)	−4 (3)	−4 (1)
O(7)	−2600 (4)	2274 (2)	1440 (1)	261 (8)	78 (2)	26 (1)	6 (3)	−8 (2)	−1 (1)
N(1)	1325 (4)	756 (2)	1026 (1)	219 (8)	43 (2)	15 (1)	−3 (3)	18 (2)	−4 (1)
N(3)	2806 (4)	−548 (2)	433 (1)	200 (8)	48 (2)	15 (1)	5 (3)	13 (2)	−6 (1)
N(4)	1671 (5)	2990 (2)	636 (1)	231 (9)	50 (2)	17 (1)	−12 (3)	8 (2)	−3 (1)
N(5)	1524 (5)	3546 (2)	1878 (1)	214 (8)	50 (2)	18 (1)	1 (3)	12 (2)	−6 (1)
N(6)	1615 (5)	1587 (2)	2349 (1)	221 (9)	58 (2)	17 (1)	6 (3)	8 (2)	1 (1)
C(2)	2878 (5)	464 (2)	664 (1)	194 (9)	46 (2)	12 (1)	0 (4)	4 (2)	−2 (1)
C(4)	1348 (5)	−1298 (2)	551 (2)	175 (9)	46 (2)	15 (1)	1 (3)	−5 (2)	−3 (1)
C(5)	−277 (5)	−963 (3)	926 (2)	217 (10)	47 (2)	15 (1)	−8 (4)	−1 (2)	1 (1)
C(6)	−191 (5)	36 (3)	1137 (2)	191 (10)	58 (2)	16 (1)	1 (4)	18 (2)	−1 (1)
C(7)	−1989 (6)	−1711 (3)	1083 (2)	243 (11)	61 (3)	24 (1)	−21 (5)	21 (3)	0 (1)
C(8)	1535 (7)	4108 (3)	781 (2)	319 (13)	52 (2)	21 (1)	−3 (5)	15 (3)	2 (1)
C(9)	2549 (7)	4281 (3)	1461 (2)	336 (14)	49 (2)	24 (1)	−20 (5)	20 (3)	−7 (1)
C(10)	2578 (8)	3390 (3)	2533 (2)	373 (14)	75 (3)	17 (1)	−20 (5)	−10 (3)	−15 (1)
C(11)	1621 (7)	2455 (3)	2809 (2)	319 (13)	82 (3)	14 (1)	1 (5)	8 (3)	−4 (1)

[a] Estimated standard deviations are enclosed in parentheses. [b] The form of the anisotropic thermal ellipsoid is $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$.

Table III. Hydrogen Atom Positional (× 10^3) and Thermal Parameters

Atom	x	y	z	B, Å^2
H(1)	381	−75	19	3.3
H(2)	−132	26	138	3.3
H(3)	−142	−239	129	4.4
H(4)	−275	−192	59	4.4
H(5)	−294	−139	136	4.4
H(6)	71	281	33	3.5
H(7)	292	285	51	3.5
H(8)	8	433	73	4.1
H(9)	226	451	47	4.1
H(10)	402	416	150	4.4
H(11)	231	499	161	4.4
H(12)	27	381	194	3.2
H(13)	253	398	279	4.7
H(14)	410	324	249	4.7
H(15)	233	226	321	4.0
H(16)	17	262	288	4.0
H(17)	60	115	241	3.4
H(18)	283	125	242	3.4
H(19)	725	302	0	6.5
H(20)	642	414	28	6.5
H(21)	321	485	−132	7.1
H(22)	458	448	−64	7.1
H(23)	−271	154	176	4.6
H(24)	−375	212	104	4.6

Substitution for the proton at N(1) by a nonacidic group, such as CH_3 in 1-methylthymine and the ribose moiety in thymidine, limits the first proton ionization to N(3).[25] Consistent with this, the binding of metal ions to 1-methylthymine[11] and thymidine residues in DNA[3] and poly(dAT)[12] occurs at the N(3) position at moderate and high pH.

The binding of metal ions and metal complexes to thymine at pH >7, however, would seem to be possible at both N(1) and N(3), with the most likely binding site determined by considerations other than the negligible difference in the nucleophilicity at the deprotonated N(1) or N(3) ring positions.[26]

Our recent studies on the binding of chelate metal complexes to nucleic acid constituents[27-35] suggest that secondary forces, both favorable (interligand hydrogen bonds and semichelation by exocyclic groups on the purine or pyrimidine bases) and unfavorable (interligand steric repulsions), may play an important role in determining the most favorable binding site in multisite ligands. The binding of chelate metal complexes to thymine at high pH presents then an interesting study of a multisite ligand system. The base binding sites N(1) and N(3) are clearly differentiated by the exocyclic groups on adjacent atoms, N(3) being contiguous to two carbonyl groups while N(1) has a carbonyl oxygen atom and a proton at adjacent sites.

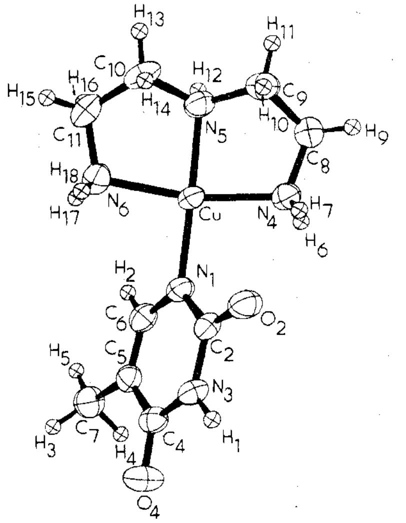

Figure 1. Perspective view of the (diethylenetriamine)(thyminato)copper(II) ion. The view direction is approximately along the normal to the equatorial plane of the complex cation. The second hydrogen atom off C(8) is obscured in this view. The thermal ellipsoids are drawn at the 50% probability level.

The conformation of the (diethylenetriamine)(thyminato)copper(II) ion is illustrated in Figure 1. The primary coordination sphere about the copper(II) atom is approximately square pyramidal with the tridentate diethylenetriamine ligand and N(1) of the thymine monoanion occupying the four equatorial coordination sites. The pyrimidine ring is tilted at an angle of 55.8 (4)° to the plane defined by the four ligated atoms, Figure 2, and as such allows the occupation of one of the axial positions by a water molecule, Cu–O(7) = 2.465 (3) Å. The extension of the coordination sphere to the so-called (4 + 1) coordination geometry is common to square-planar copper(II) complexes.[36,37] Typical values for Cu–O(water) distances for equatorial and axial coordination are 1.946 (1) and 2.383 (1) Å, respectively.[38]

A point of some interest is that we find no evidence for a significant axial Cu–O(2) interaction in this complex, Cu···O(2)

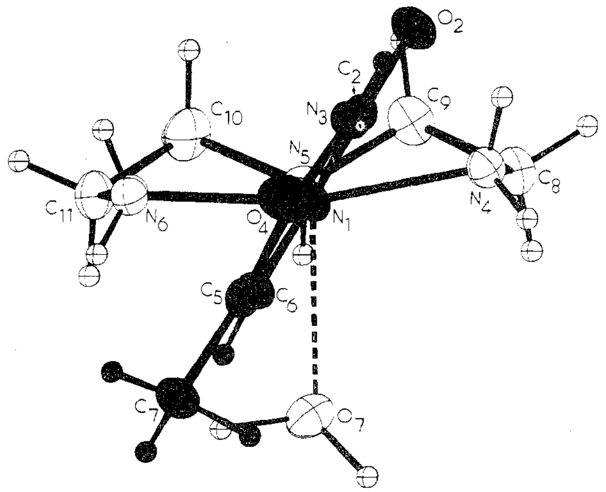

Figure 2. Projection of the complex cation down the N(1)-Cu bond. The axially bonded water molecule, Cu-O = 2.465 Å, is also shown. The dihedral angle between the equatorial plane and the six-atom plane of the thymine anion is 55.8 (4)°. The thermal ellipsoids are drawn at the 25% probability level.

= 3.159 (3) Å. We[31,32,34] and others[39] have noted such interactions in N(3)-bonded cytosine and cytidine complexes, Cu···O(2) ≈ 2.8 Å. The formation of such Cu···O(2) interactions in the cytosine or cytidine complexes, but the lack of such an interaction in the present complex, is consistent with molecular electrostatic calculations.[32,40]

Our studies on copper(II)–pyrimidine complexes[31,32,34] suggest that exocyclic oxygens on the six-membered ring will not hydrogen bond strongly to hydrogens on the donor nitrogens of chelate ligands. If the exocyclic oxygen of thymine, O(2), does not favorably interact with the copper, as in this case, then the only method whereby the complex can gain further stability through intramolecular bond formation is to add a fifth ligand. As noted above, the pyrimidine nitrogens have similar nucleophilicities. However, coordination via N(1) permits expansion of the coordination sphere of the copper to the (4 + 1) geometry whereas N(3) coordination leads to the blocking, by the exocyclic oxygens, of both axial positions on the copper. We believe this feature of N(1) bonding may, in this case, determine the preferred bonding mode. The well-known lability of copper(II) complexes[36] makes this explanation somewhat tentative. There is an obvious need for more investigations into the complex chemistry of uracil and thymine.

As is typical of (dien)Cu^{II} complexes,[14,41–43] the conformation of the dien ligand is such that the primary amine nitrogen atoms occupy trans positions in the coordination sphere. The conformations of each half of the tridentate system are λ for the ring N(4)–C(8)–C(9)–N(5) and δ for the ring N(6)–C(11)–C(10)–N(5); the δλ conformation also exists in the crystal owing to the centrosymmetric space group. The methylene carbons at N(5) [C(9) and C(10)] show substantial deviations from the three-atom dien plane N(4)–N(5)–N(6), 0.65 and 0.69 Å, respectively, while the methylene carbon atoms near the termini of the chelate [C(8) and C(11)] lie approximately in the plane with out-of-plane deviations of 0.03 and 0.07 Å, respectively. The bond lengths and angles in the dien ligand, Table IV, are similar to those observed in the oxalato complex[42] and the formato complex[43] and are in nearly quantitative agreement (differences about 1σ) with those reported for the cyano complex.[14]

There are relatively few examples of X-ray structure determinations which allow assessment of the trans influence for complexes where only one ligand is varied.[13,30] Information of this type is important since a detailed knowledge of the factors which determine the trans influence is yet to be obtained.[13] Table V contains a comparison of the structural parameters in four recent Cu^{II}–dien complexes including the present study. The near equivalence of the conformational properties of these four complexes is of particular note. Evidence for the trans influence in square-planar copper(II) systems is clearly seen in the elongation of the copper–central nitrogen bond length of the dien ligand in going from the thyminato to the cyano complex. The difference in the Cu–N$_{\text{mid}}$ bond lengths in the thyminato and the cyano complexes of 0.027 Å is highly significant (about 9σ) and parallels the expected trend since the cyano group is expected to have a moderate trans influence from studies on other

Table IV. Interatomic Distances (Å) and Angles (deg)[a]

(a) Primary Coordination Sphere about the Copper Atom

Distances

Cu-O(7)	2.465 (3)	Cu-N(5)	2.009 (3)
Cu-N(1)	1.989 (3)	Cu-N(6)	2.040 (3)
Cu-N(4)	2.002 (3)		

Angles

O(7)-Cu-N(1)	96.5 (1)	N(1)-Cu-N(5)	174.3 (1)
O(7)-Cu-N(4)	100.3 (1)	N(1)-Cu-N(6)	93.8 (1)
O(7)-Cu-N(5)	88.7 (1)	N(4)-Cu-N(5)	84.3 (1)
O(7)-Cu-N(6)	91.7 (1)	N(4)-Cu-N(6)	162.7 (1)
N(1)-Cu-N(4)	97.2 (1)	N(5)-Cu-N(6)	83.6 (1)

(b) Diethylenetriamine Chelate Ring

Distances

N(4)-C(8)	1.471 (5)	N(6)-C(11)	1.469 (5)
C(8)-C(9)	1.513 (5)	C(11)-C(10)	1.485 (6)
C(9)-N(5)	1.474 (5)	C(10)-N(5)	1.473 (5)

Angles

Cu-N(4)-C(8)	109.7 (2)	Cu-N(6)-C(11)	109.3 (2)
N(4)-C(8)-C(9)	107.9 (3)	N(6)-C(11)-C(10)	109.7 (3)
C(8)-C(9)-N(5)	106.5 (3)	C(11)-C(10)-N(5)	107.6 (3)
Cu-N(5)-C(9)	108.3 (2)	Cu-N(5)-C(10)	108.5 (2)
C(9)-N(5)-C(10)	116.4 (3)		

(c) Comparison of the Bond Lengths and Angles in the Coordinated Thymine Anion (KSM), Thymidine (Young, Tollin, and Wilson;[49] YTW), and Thymine Monohydrate (Gerdil;[46] G)

Distances

	KSM	G	YTW
N(1)-C(2)	1.349 (5)	1.355 (4)	1.385 (6)
C(2)-N(3)	1.385 (5)	1.361 (4)	1.381 (7)
C(2)-O(2)	1.249 (4)	1.234 (3)	1.206 (7)
N(3)-C(4)	1.373 (5)	1.391 (3)	1.378 (7)
C(4)-C(5)	1.418 (5)	1.447 (4)	1.453 (6)
C(4)-O(4)	1.241 (4)	1.231 (4)	1.230 (6)
C(5)-C(6)	1.355 (5)	1.349 (4)	1.343 (7)
C(5)-C(7)	1.509 (5)	1.503 (4)	1.504 (8)
C(6)-N(1)	1.369 (5)	1.382 (3)	1.374 (6)

Angles

	KSM	G	YTW
Cu[b]-N(1)-C(2)	122.0 (2)		116.6 (4)
Cu[b]-N(1)-C(6)	120.0 (2)		121.6 (3)
C(2)-N(1)-C(6)	117.9 (3)	122.8 (4)	121.8 (4)
N(1)-C(2)-N(3)	116.9 (3)	115.2 (4)	113.7 (4)
N(1)-C(2)-O(2)	123.5 (3)	122.7 (4)	124.3 (5)
N(3)-C(2)-O(2)	119.5 (3)	122.1 (4)	122.0 (4)
C(2)-N(3)-C(4)	126.6 (3)	126.3 (4)	127.5 (4)
N(3)-C(4)-C(5)	115.0 (3)	115.6 (4)	115.8 (4)
N(3)-C(4)-O(4)	119.8 (3)	118.3 (4)	119.7 (4)
C(5)-C(4)-O(4)	125.1 (3)	126.1 (4)	124.5 (5)
C(4)-C(5)-C(6)	117.2 (3)	118.2 (4)	117.2 (4)
C(4)-C(5)-C(7)	120.1 (3)	119.0 (4)	119.3 (4)
C(6)-C(5)-C(7)	122.7 (3)	122.8 (4)	123.5 (4)
N(1)-C(6)-C(5)	126.3 (3)	121.8 (4)	124.1 (4)

[a] Average estimated standard deviations in the least significant digit are enclosed in parentheses. [b] C(1') of the ribose ring in thymidine and the hydrogen at N(1) in thymine monohydrate.

Table V. Comparison of the Cu-N_{term} and Cu-N_{mid} distances (Å) for Several Copper(II)–Diethylenetriamine Complexes

Distances[e]	Thyminato[a]	Oxalato[b]	Formato[c]	Cyano[d]
Cu-N_{term}	2.002 (3)	1.996 (8)	2.009 (5)	2.028 (4)
	2.040 (3)	2.009 (8)	2.009 (5)	2.040 (4)
Cu-N_{mid}	2.009 (3)	2.021 (7)	2.023 (7)	2.036 (4)
Cu-X_{trans}	1.989 (3)	1.965 (6)	2.035 (5)	1.995 (4)
Cu-Y_{axial}	2.465 (3)	2.230 (6)	2.169 (5)	2.348 (4)
		2.994 (6)	2.610 (5)	
D_{Cu}	0.16	0.22	0.31	

[a] This study. [b] Stephens.[42] [c] Davey and Stephens;[43] the two Cu-N_{term} are identical by a mirror plane. [d] Yang and Corfield;[14] D_{Cu} not given by these authors. [e] Key: N_{term}, terminal nitrogen atoms of the diethylenetriamine ligand; N_{mid}, middle nitrogen atom of the diethylenetriamine ligand; X_{trans}, atom of the group trans to the N_{mid} of the diethylenetriamine [(a) N(1) of the thymine anion, (b) oxygen atom of the oxalato group, (c) oxygen atom of the formato group, (d) carbon atom of the cyano group]; Y_{axial}, atom of the group(s) occupying axial positions of the square-planar complex [(a) water oxygen, (b) oxygen atoms of the oxalato group, (c) oxygen atoms of the formato group, (d) nitrogen atom of the cyano group]; D_{Cu}, deviation of the copper atom from the three-atom plane of the nitrogen atoms of the diethylenetriamine ligand.

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

(a) Primary Coordination Sphere about Copper Atom
($-0.9955X + 0.0349Y - 0.0884Z = -0.8457$ Å)

N(1)	0.059	N(6)	−0.066
N(4)	−0.065	O(7)	2.611*
N(5)	0.072	Cu	0.159*

(b) Six-Atom Framework of Coordinated Thymine Monoanion
($-0.4810X + 0.2907Y - 0.8271Z = -1.7743$ Å)

N(1)	−0.007	C(6)	0.007
C(2)	−0.004	Cu	−0.122*
N(3)	0.014	O(2)	−0.015*
C(4)	−0.012	O(4)	−0.048*
C(5)	0.002	C(7)	−0.009*

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

transition metal systems.[13] This result could be somewhat complicated by axial substituents in these copper(II) systems, Table V. However, the thyminato and cyano complexes are each approximately square pyramidal with axial-ligand bond lengths which are not dramatically diffferent. It is suggested, then, that the elongation trend shown in Table V for the Cu–N_{mid} bond length may be attributed to the trans influence with the approximate ordering of trans influence ability being cyano > formato ~ oxalato > thyminato.

The four atoms in the equatorial plane about the Cu atom are approximately coplanar, but a small tetrahedral component to the coordination geometry is evident, Table VI; the deviations from planarity in this structure (~0.06 Å) are, however, substantially less than those observed in the oxalato and formato complexes (~0.17–0.18 Å). The copper lies 0.159 Å out of the equatorial plane toward the apical position occupied by the water molecule, O(7)H_2. This feature parallels the results obtained for the oxalato and formato complexes, but the deviation of the copper is substantially less in the thyminato complex than in either of the other two complexes.

The structural parameters in the coordinated thymine monoanion are of particular interest to us since we have been engaged in an attempt to deduce the effect on the molecular geometry of coordinated purine and pyrimidine ligands owing to the formation of a coordination bond.[27,28,44,45] Accurate structure determinations for thymine monohydrate,[46] 1-methylthymine,[47] 1-methylthymine–9-methyladenine,[48] and thymidine[49] have been reported. Thus, a detailed comparison for various substituents at the N(1) position of thymine is possible. Hoogsteen[47] has suggested that the major bond length differences between thymine and 1-methylthymine, an increase of 0.024 Å in the N(1)–C(2) bond length and a decrease of 0.020 Å in the C(2)–O(2) bond length in going from thymine to 1-methylthymine, are primarily due to the fact that carbon is more electronegative than hydrogen. In essence, Hoogsteen[47] suggested that the substitution of the methyl group for the hydrogen at N(1) tends to reduce the double-bond character in the N(1)–C(2) bond and, consequently, the double-bond character in the C(2)–O(2) bond is increased. This trend is supported by the excellent agreement in these bond lengths for 1-methylthymine,[47] 1-methylthymine–9-methyladenine,[48] and thymidine.[49]

The values we have determined for the N(1)-coordinated thymine monoanion are compared to those for thymine monohydrate and thymidine in part (c) of Table IV. The N(1)-coordinated thymine monoanion is observed to have a short N(1)–C(2) bond length, 1.349 (5) Å, compared to thymidine, 1.385 (6) Å, and, in fact, it is slightly contracted from the value in thymine, 1.355 (4) Å. The trend in the C(2)–O(2) bond length is consistent with this in that the observed value in the coordinated thymine monoanion, 1.249 (5) Å, is considerably longer than in thymidine, 1.206 (6) Å, and perhaps significantly longer than in thymine, 1.234 (4) Å.

The two major bond length trends noted above, plus other

Table VII. Distances and Angles in the Interactions of the Type D–H· · ·A

D	H	A	D–H, Å	H· · ·A, Å	D· · ·A, Å	D–H· · ·A, deg
			Hydrogen Bonds			
N(3)	H(1)	O(2)[a]	0.89	2.02	2.901	167
N(4)	H(6)	O(4)[b]	0.88	2.04	2.906	172
N(4)	H(7)	O(5)[c]	0.88	2.18	2.938	144
N(5)	H(12)	Br[d]	0.89	2.75	3.499	143
N(6)	H(17)	Br[e]	0.87	2.66	3.486	158
N(6)	H(18)	Br[c]	0.88	2.62	3.494	171
O(5)	H(19)	O(4)[a]	1.21	1.52	2.675	156
O(5)	H(20)	O(6)[f]	0.98	1.90	2.814	155
O(6)	H(21)	Br[g]	1.12	2.37	3.353	145
O(6)	H(22)	O(5)[c]	0.94	2.08	2.774	130
O(7)	H(23)	Br[e]	1.16	2.27	3.374	159
O(7)	H(24)	O(2)[e]	1.07	2.05	3.015	149
			Others			
N(4)	H(7)	O(2)[c]	0.88	2.47	3.027	122
C(6)	H(2)	Br[e]	0.96	2.98	3.865	153
C(8)	H(8)	O(6)[h]	0.96	2.46	3.397	163

[a] $1 - x, -y, -z$. [b] $-x, -y, -z$. [c] x, y, z. [d] $^1/_2 - x, ^1/_2 + y, ^1/_2 - z$. [e] $-1 + x, y, z$. [f] $1 - x, 1 - y, -z$. [g] $-^1/_2 + x, ^1/_2 - y, -^1/_2 + z$. [h] $-x, 1 - y, -z$.

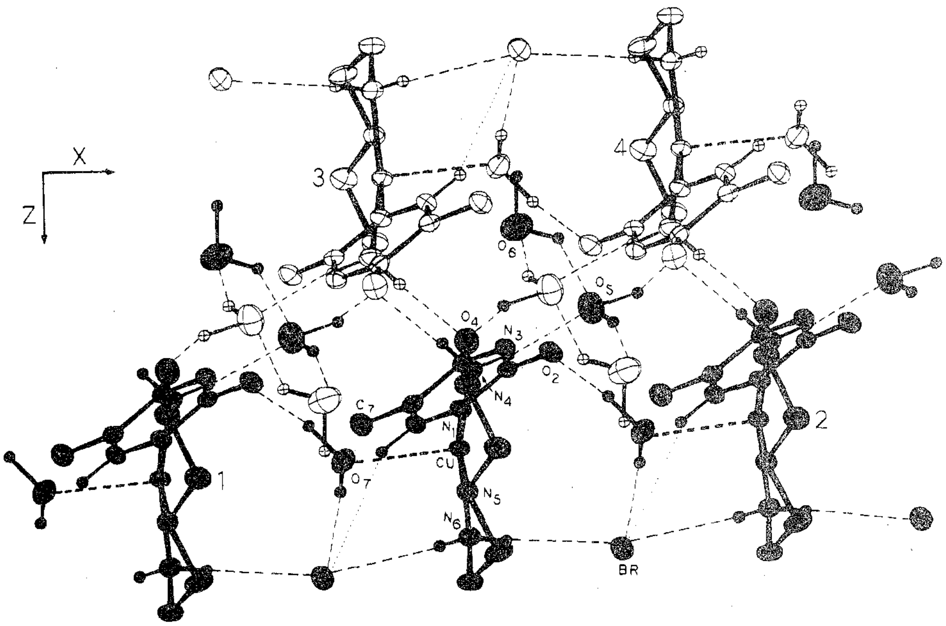

Figure 3. View of the columns of complexes along the x axis. The view direction is along the b^* axis. Heavy dashed lines indicate the axial Cu–O(7) bond; light dashed lines show the intra- and intercolumn hydrogen bonds, while the dotted lines show the C(6)–H· · ·Br^- interactions (see the text). The labeled atoms have their coordinates as given in Table II, while the numbered complex cations have the following symmetry transforms: (1) $-1 + x, y, z$; (2) $1 + x, y, z$; (3) $-x, -y, -z$; (4) $1 - x, -y, -z$.

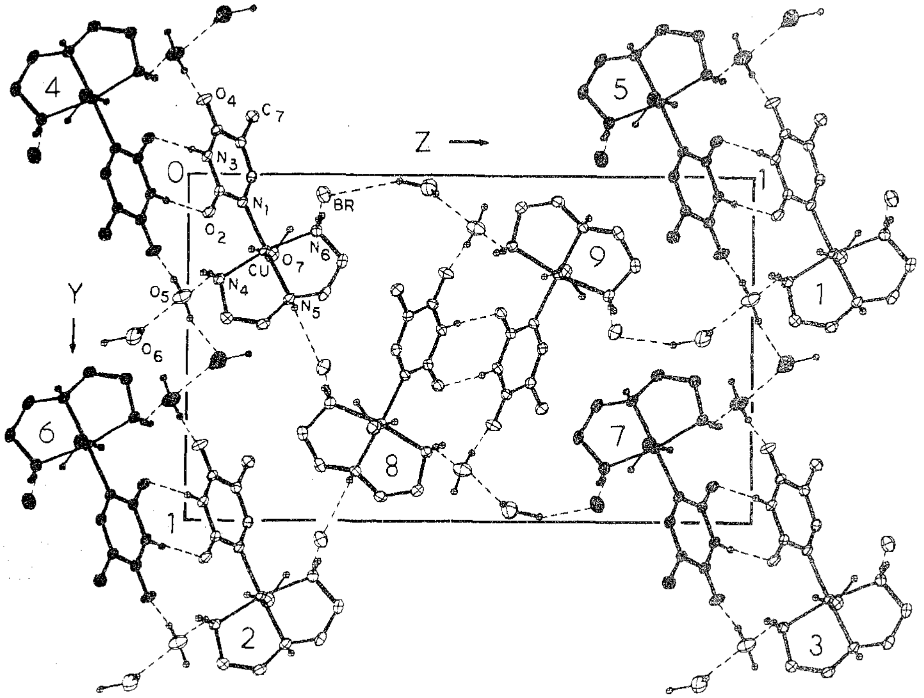

Figure 4. Projection of the unit cell contents down the a^* axis. The labeled atoms have their coordinates as given in Table II. Dashed lines indicate hydrogen bonds. The nine numbered complex cations have the following symmetry transforms: (1) $x, y, 1 + z$; (2) $x, 1 + y, z$; (3) $x, 1 + y, 1 + z$; (4) $1 - x, -y, -z$; (5) $1 - x, -y, 1 - z$; (6) $1 - x, 1 - y, -z$; (7) $1 - x, 1 - y, 1 - z$; (8) $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$; (9) $-\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$.

comparisons that appear in Table IV, consistently suggest that the electronegativity of the $[(dien)Cu^{II}]^{2+}$ ion is substantially less than for a methyl group or the ribose moiety and perhaps even less than a proton. Our recent experiments on the reactivity of coordinated purine monoanions[30] are in accord with this conclusion.

The six-atom framework of the coordinated thymine monoanion, Table VI, is quite planar with all exocyclic substituents [Cu, O(2), O(4), and C(7)] lying out of the plane in the same direction.

Crystal Packing. The square-pyramidal complex cations form columns along the a axis, Figure 3, such that the axially bound water molecule of one cation lies approximately below the copper atom of a translationally equivalent complex. The bromide ion plays an integral role in the stability of these columnar stacks, showing hydrogen bonds with the protons on the terminal primary amine nitrogen atom N(6) and the coordinated water molecule, Table VII and Figure 3. The bromide ion also has a close contact with the hydrogen atom off C(6) of the pyrimidine ring; the C(6)–H···Br^- distance, 2.98 Å, is on the order of the sum of the van der Waals radii (3.15 Å using van der Waals radii of 1.2 and 1.95 Å for H and Br, respectively; 2.95 Å using the probably more correct value of 1.0 Å for H; see Baur[50] for example). Similar interactions involving C(6)–H and good hydrogen-bond acceptor groups have been noted in 1-methylthymine,[47] uracil,[51,52] cytidylic acid,[53,54] and 1-(β-D-arabinofuranosyl)cytosine hydrochloride.[55] The intracolumn interactions are completed by the hydrogen bond formed between the coordinated water molecule and O(2) of a translationally related complex [−1 + *x*, *y*, *z*].

The interaction among the columns of complexes is achieved in a variety of ways. (1) The complex cations form hydrogen-bond dimers about centers of symmetry through the coordinated thyminato anions [C(2)–O(2)···H–N(3), Figure 4 and Table VII]; similar hydrogen-bond dimers are observed in thymine monohydrate[46] and 1-methylthymine.[47] (2) There are four types of intracolumn hydrogen-bond chains observed in the structure: complex$^+$···Br^-···complex$^+$, complex$^+$···water···complex$^+$, complex$^+$···Br^-···water···water···complex$^+$, and complex$^+$···water···water···water···complex$^+$, Figures 3 and 4, Table VII.

The importance of the waters of crystallization, O(5)H_2 and O(6)H_2, to the stability of the crystal is manifest in the intracolumn hydrogen-bond chains noted above. Furthermore, the crystal transformation from the initial trihydrate to the final monohydrate (see the Experimental Section) is probably due to the loss of these waters of crystallization. The high thermal parameters, Table II, for these water molecules are probably, at least in part, due to only partial occupancy of these sites.

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Supplementary Material Available. A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number AIC50194L-10-75.

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