

chromatography of the residue on silica gel using hexane as eluent afforded three separate fractions shown to be *t*-BuSSBu-*t*, *t*-BuSSePh, and PhSeSePh, respectively, by examination of their spectral properties.

References and Notes

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Preparation and Crystal and Molecular Structure of Sodium [Bis(inosine 5'-monophosphate)(diethylenetriamine)-copper(II)] Decahydrate. Possible Implications for Intrastrand Cross-Linking of Polynucleotides by Copper(II) and Platinum(II) Complexes

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Abstract: The synthesis and crystal and molecular structure of sodium [bis(inosine 5'-monophosphate)(diethylenetriamine)-copper(II)] decahydrate, Na₂[Cu(5'-IMP)₂(dien)]·10H₂O, are reported. The complex crystallizes in the orthorhombic system, space group *P*2₁2₁2, with *a* = 8.706 (4), *b* = 21.074 (12), and *c* = 12.171 (7) Å, *Z* = 2, *d*_{measd} = 1.60 (2) g/cm³, and *d*_{calcd} = 1.61 g/cm³. The structure was solved by direct methods. Full-matrix least-squares refinement, based on 2051 counter-collected *F*_o's, has led to a final *R* value of 0.08. The copper positions in the unit cell were found to be disordered such that the copper atom occupies each of two sites 50% of the time. The primary coordination sphere about the copper is (4 + 1 + 1) with the equatorial plane defined by the tridentate dien chelate and N(7) of a 5'-IMP ligand. The axial positions are occupied by a second N(7) atom of a symmetry-related 5'-IMP anion and a water molecule. Extensive intramolecular hydrogen bonding is observed. Comparison of the equatorial-axial binding mode of the two purine ligands in [Cu(5'-IMP)₂(dien)]²⁻ vs. the cis equatorial binding found in [Pt(5'-IMP)₂(NH₃)₂]²⁻ and [Pt(5'-IMP)₂(ethylenediamine)]²⁻ is explored in terms of the possible effect of intrastrand cross-linking of polynucleotides by Cu(II) and Pt(II) complexes.

Introduction

Rosenberg¹ observed that certain Pt(II) compounds are effective anticancer agents. Subsequent in vivo and in vitro studies implicate the binding of Pt(II) compounds to nucleic

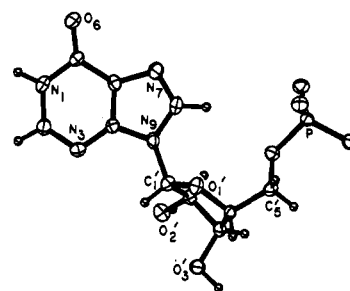
acids.² Numerous solution and solid-state studies aimed at elucidating the nature of the metal binding have been undertaken.² Beyond an accumulation of evidence that Pt(II) is readily bound to N(7) of guanosine and inosine and their nu-

Table I. Crystal Data for Sodium [Bis(inosine 5'-monophosphate)-(diethylenetriamine)copper(II)] Decahydrate

$a = 8.706$ (4) Å	Cu(C ₁₀ N ₄ O ₈ PH ₁₁) ₂ (C ₄ N ₃ H ₁₃)Na ₂ ·10H ₂ O
$b = 21.074$ (12) Å	mol wt = 1085.4
$c = 12.171$ (7) Å	space group $P2_12_12$
$V = 2233.0$ Å ³	$d_{\text{measd}} = 1.60$ (2) g cm ⁻³
$Z = 2$	$d_{\text{calcd}} = 1.61$ g cm ⁻³
	$\mu(\text{Mo K}\alpha) = 7.08$ cm ⁻¹

cleotides, the exact nature of the binding has yet to be established, although intrastrand cross-linking has been increasingly mentioned as a possible binding mode to explain the stoichiometry of the binding to polynucleotides.³ Such intrastrand cross-linking could explain the antineoplastic activity of the *cis*-[Pt(NH₃)₂Cl₂] isomer and the inactivity of the *trans*-[Pt(NH₃)₂Cl₂] isomer.^{1,2}

While numerous crystallographic investigations have been undertaken on metal species bound to nucleotides,⁴ many of these have been shown to involve polymeric species in the solid which are likely to depolymerize in solution and, therefore, only obliquely indicate the nature of the binding mode in solution. Two crystallographic studies seem to bear directly on the intrastrand cross-linking problem and both of these complexes have Pt(II) bound, in a *cis* linkage, to two inosine 5'-monophosphate anions (I). The *cis*-[Pt(5'-IMP)₂(NH₃)₂]²⁻ and *cis*-[Pt(5'-IMP)₂en]²⁻ (where en = ethylenediamine) anionic complexes^{5,6} are formed, respectively, by the reaction of *cis*-[Pt(NH₃)₂(H₂O)₂]²⁺ and *cis*-[Pt(en)(H₂O)₂]²⁺ cations with the disodium salt of 5'-IMP. In each case, the two water ligands of the diaquo complexes are replaced by the N(7) atoms of two

5'-IMP⁻

I

symmetry-related 5'-IMP ligands. Moreover, the complexes are both nonstoichiometric with about 56% occupancy in the diammine complex⁵ and about 38% occupancy in the en complex.⁶ Interestingly, the *cis*-[Pt(5'-IMP)₂(NH₃)₂]²⁻ complex has been shown by Raman and ¹H NMR data to be a prominent species in aqueous solution.⁷ The unique features of these two 5'-IMP structures, which will be discussed below, might then have some bearing on the environment about the Pt(II) when bound to polymer.

Two structural studies^{8,9} involving the nucleoside guanosine bound to Pt(II), [Pt(guanosine)₂en]²⁺ and [Pt(guanosine)₂(NH₃)₂]²⁺, have also been reported. Somewhat surprisingly, there are important differences between the guanosine and the 5'-IMP complexes, although in all of the compounds the two purine bases occupy *cis* positions and are bound to the Pt(II)

Table II. Final Heavy-Atom Parameters (×10⁴)^a

atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> ₁₁	<i>B</i> ₂₂	<i>B</i> ₃₃	<i>B</i> ₁₂	<i>B</i> ₁₃	<i>B</i> ₂₃
Cu ^b	956 (3)	-4 (1)	11 750 (1)	257 (4)	15 (1)	63 (1)	-5 (1)	54 (2)	3 (1)
P	4040 (2)	2059 (1)	12 225 (1)	86 (3)	14 (1)	40 (1)	2 (1)	0 (2)	2 (1)
Na	3862 (4)	1985 (2)	5 772 (2)	164 (6)	74 (2)	59 (2)	-24 (3)	-10 (4)	2 (2)
O (1)	4082 (5)	2016 (2)	10 892 (3)	84 (7)	21 (1)	45 (3)	-2 (3)	-7 (5)	1 (2)
O(2)	4562 (5)	2730 (2)	12 543 (3)	99 (8)	18 (1)	50 (3)	-1 (2)	-1 (4)	0 (2)
O(3)	5114 (5)	1564 (2)	12 664 (3)	112 (8)	20 (1)	62 (3)	6 (3)	-5 (5)	5 (2)
O(4)	2385 (5)	1937 (2)	12 498 (3)	87 (7)	23 (1)	60 (4)	-4 (3)	14 (5)	2 (2)
O(1')	5287 (5)	1210 (2)	9 171 (3)	87 (8)	18 (1)	67 (4)	3 (3)	-19 (5)	-4 (2)
O(2')	2312 (5)	1725 (2)	7 371 (3)	99 (8)	26 (1)	57 (4)	9 (3)	-15 (5)	-1 (2)
O(3')	5131 (5)	2237 (2)	7 353 (3)	138 (8)	30 (1)	47 (3)	-26 (3)	-5 (5)	2 (2)
O(6)	544 (6)	-1274 (2)	9 750 (4)	227 (12)	16 (1)	79 (4)	-12 (3)	33 (6)	-3 (2)
N(1)	1427 (6)	-1071 (2)	8 042 (5)	115 (10)	13 (1)	71 (5)	-4 (3)	-14 (6)	-2 (2)
N(3)	2778 (7)	-155 (2)	7 471 (4)	147 (11)	16 (2)	54 (4)	-2 (3)	4 (6)	4 (2)
N(7)	1846 (7)	70 (3)	10 315 (4)	200 (12)	13 (1)	70 (4)	7 (4)	9 (7)	-1 (3)
N(9)	3097 (6)	591 (2)	8 987 (4)	136 (10)	13 (1)	49 (4)	5 (3)	-1 (6)	-5 (2)
C(1')	4045 (8)	1091 (3)	8 494 (5)	83 (10)	18 (2)	55 (5)	-1 (4)	-9 (8)	1 (3)
C(2')	3159 (7)	1716 (3)	8 357 (5)	65 (10)	18 (2)	42 (5)	8 (4)	0 (6)	-4 (2)
C(3')	4473 (8)	2192 (3)	8 425 (5)	109 (13)	15 (2)	50 (5)	2 (4)	2 (7)	-6 (2)
C(4')	5587 (7)	1883 (3)	9 215 (5)	74 (11)	14 (2)	47 (5)	-2 (3)	10 (6)	-6 (2)
C(5')	5557 (7)	2114 (3)	10 395 (5)	75 (12)	19 (2)	59 (5)	-7 (4)	-6 (6)	-2 (3)
C(2)	2180 (9)	-711 (3)	7 285 (5)	160 (14)	18 (2)	56 (5)	-6 (4)	-9 (8)	-2 (3)
C(4)	2573 (7)	36 (3)	8 535 (4)	86 (11)	13 (1)	50 (5)	5 (4)	1 (7)	0 (3)
C(5)	1788 (8)	-286 (3)	9 339 (5)	101 (12)	15 (2)	49 (5)	13 (4)	-2 (7)	-3 (2)
C(6)	1187 (8)	-904 (3)	9 118 (5)	106 (12)	12 (2)	62 (6)	0 (4)	-1 (8)	2 (3)
C(8)	2613 (10)	573 (3)	10 053 (6)	197 (15)	18 (2)	66 (6)	-13 (5)	-3 (9)	-9 (3)
N(10) ^b	1784 (15)	-878 (5)	11 981 (9)	173 (24)	20 (3)	48 (9)	13 (7)	19 (13)	5 (4)
N(11) ^b	0	0	13 099 (8)	527 (40)	94 (6)	45 (8)	145 (14)	0	0
N(12) ^b	-281 (13)	-899 (5)	11 892 (9)	123 (22)	17 (3)	73 (10)	-4 (6)	-2 (13)	11 (4)
C(10)	934 (13)	-1064 (5)	12 862 (9)	202 (19)	73 (5)	112 (9)	-16 (9)	-20 (14)	-21 (6)
C(11)	559 (13)	-541 (5)	13 698 (6)	335 (28)	58 (4)	57 (7)	-52 (9)	9 (11)	-1 (4)
W(1)	961 (7)	3454 (3)	5 191 (4)	215 (11)	70 (3)	70 (4)	-6 (5)	9 (7)	-3 (3)
W(2)	3987 (7)	2994 (3)	4 722 (4)	213 (11)	49 (2)	65 (4)	10 (5)	8 (7)	-13 (3)
W(3)	1959 (6)	1623 (3)	4 662 (4)	130 (10)	77 (3)	68 (4)	-22 (5)	11 (6)	14 (3)
W(4)	3650 (8)	409 (3)	12 914 (7)	293 (16)	28 (2)	281 (10)	-5 (4)	6 (12)	31 (4)
W(5)	3726 (12)	476 (4)	5 439 (6)	595 (3)	74 (3)	179 (8)	0 (9)	87 (15)	64 (4)

^a Estimated standard deviations are enclosed in parentheses. The form of the anisotropic ellipsoid is $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$. ^b Population parameter = 0.5.

Table III. Structural Parameters in a Variety of Bis(purine)copper(II) and Bis(purine)platinum(II) Complexes

complex ^a	M-N(7), Å	N(7)-M-N(7) angle, deg	N(7)...N(7) distance, Å	dihedral angle between purine planes, deg [ref]
[(NH ₃) ₂ Pt(Guo) ₂] ²⁺	1.992 (12)			
	2.018 (12)	85	2.7	74 [9]
[(en)Pt(Guo) ₂] ²⁺	1.967 (15)	87.0 (7)	2.71 (2)	71 [8]
[(dien)Cu(Theo) ₂]	2.007 (3) _{eq}	90.1 (2)	3.129 (4)	66.5 (2) [21]
	2.397 (3) _{ax}			
[(NH ₃) ₂ Pt(5'-IMP) ₂] ²⁻	2.02	89	2.83	43 [5]
[(en)Pt(5'-IMP) ₂] ²⁻	2.07 (2)	104	3.26	31 [6]
[(dien)Cu(5'-IMP) ₂] ²⁻	1.917 (5) _{eq}	78.6 (2)	3.228 (7)	30.4 (3) [this study]
	3.003 (5) _{ax}			
Na[5'-IMPH]·8H ₂ O	2.59 ^b	84 ^b	3.48	22 [19]

^a Abbreviations: Guo, guanosine; Theo, theophyllinato monoanion; 5'-IMP, inosine 5'-monophosphate dianion; 5'-IMPH, the monoanion of 5'-IMP. ^b Hydrogen-bond parameters involving a water of crystallization; see Figure 1.

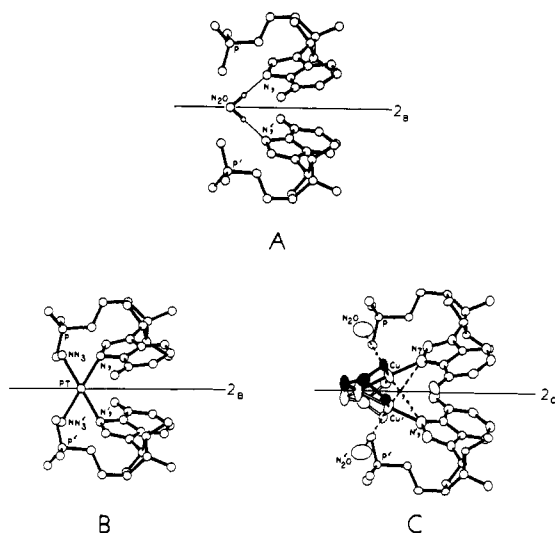


Figure 1. A comparison of the coupling of twofold related inosine 5'-monophosphate molecules via (A) a water molecule in monosodium inosine 5'-monophosphate octahydrate, (B) a diammineplatinum(II) moiety in the [bis(inosine 5'-monophosphate)(diammine)platinum(II)]²⁻ anion, and (C) an aquadiethylenetriaminecopper(II) moiety in the title complex.

through N(7). It is therefore important to understand the underlying reasons for the differences.

In this report, we describe the preparation and structure of the sodium salt of [Cu(5'-IMP)₂dien]²⁻, where dien = diethylenetriamine. We initially selected the compound for study since (1) the number of potential binding sites at the metal center is limited by the presence of the tridentate chelate dien, thus a polymeric species would be discouraged, and (2) interligand interactions between chelate ligands and nucleic acid derivatives in the primary coordination sphere have been shown to be important in influencing the stereoselectivity of the binding of metal complexes to the bases and nucleosides.¹⁰ In addition to extending the generality of such interactions to larger nucleic acid fragments (nucleotides), the structure of [Cu(5'-IMP)₂dien]²⁻ bears directly on the question of the structural differences among the Pt(II) complexes described above and possibly on intrastrand cross-linking in Pt(II) and Cu(II) systems.

Experimental Section

(a) **Preparation of Na₂[Cu(5'-IMP)₂(dien)]·10H₂O.** The dien complex of Cu(II) was obtained in solution by the combination of 0.5 mmol of Cu(NO₃)₂ (0.12 g) and 0.5 mmol of dien (0.05 g) in a 1:1 by volume

mixture of (CH₃)₂SO-H₂O. To this solution was added 0.5 mmol of Na₂[5'-IMP] dissolved in warm water. The dark purple solution was allowed to stand at room temperature (21 °C) for a few days, after which time purple elongated platelets were harvested. Successive crops of crystals were suitable for elemental analysis and diffraction studies. Anal. Calcd for Na₂[Cu(5'-IMP)₂(dien)]·10H₂O: Cu, 5.9; N, 14.2; C, 26.5; H, 5.1. Found: Cu, 5.9; N, 13.6; C, 26.2; H, 4.9. Analyses for elements other than Cu were done by Heterocyclic Chemical Corp.; Cu analysis was done in these laboratories by atomic absorption methods.

(b) **X-ray Diffraction Data.** Preliminary oscillation and Weissenberg photographs showed the crystal system to be orthorhombic with systematic absence (*h*00, *h* = 2*n* + 1; 0*k*0, *k* = 2*n* + 1) consistent with the space group *P*2₁2₁2; the long axis of the platelets is coincident with the *a* axis. Unit-cell dimensions and their associated standard deviations were derived on the basis of a least-squares fit to the setting angles of 14 reflections measured on a Syntex P-1 automated diffractometer. The crystal density, measured by neutral buoyancy methods in a mixture of bromoform and carbon tetrachloride, indicated two formula units per cell. Standard crystallographic data are collected in Table I.

The 5180 reflections in the *hkl*-*h* \bar{k} *l* quadrant to $2\theta = 50^\circ$ were surveyed on the diffractometer, employing graphite-monochromatized Mo K α radiation. The crystal used in data collection, mounted approximately along the *a* axis, had the following mean separations between principal faces: (001)-(00 $\bar{1}$), 0.11 mm; (010)-(0 $\bar{1}$ 0), 0.14 mm; (100)-(1 $\bar{0}$ 0), 0.21 mm. The intensity measurements were made in the θ - 2θ scan mode; individual scan speeds, 1-12° min⁻¹, were determined by a rapid scan at the calculated Bragg peak. Three standard reflections were monitored after every 100 reflections; their intensities showed no systematic variation over the course of the experiment (maximum deviation of any standard from its mean intensity of about 3%). The 5180 measured intensities were symmetry averaged and reduced to a set of 2051 unique reflections with $I > 0.5\sigma(I)$ (based on counting statistics). These 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 extremum background counts, *T*_S and *T*_B are the scan and individual background counting times (*T*_B = *T*_S/4), and *p* was taken to 0.03 and represents the expected error proportional to the diffracted intensity.¹¹ Intensities and their standard deviations were corrected for Lorentz and polarization effects, but no correction for absorption was applied [μ (Mo K α) = 7.1 cm⁻¹]; the maximum error introduced by the neglect of absorption effects was estimated to be about 2% in *F*. The squared structure factors were placed on an approximate absolute scale by the method of Wilson.¹²

(c) **Solution and Refinement of the Structure.** The presence of two formula units of the title complex in space group *P*2₁2₁2, in the absence of disorder, indicates that the Cu atom should be positioned on the 2_c axis. Three-dimensional Patterson syntheses (sharpened and unsharpened) were surveyed with this symmetry restriction in mind and also with a more global view. Several trial structures were tested, but vector overlap proved insurmountable.

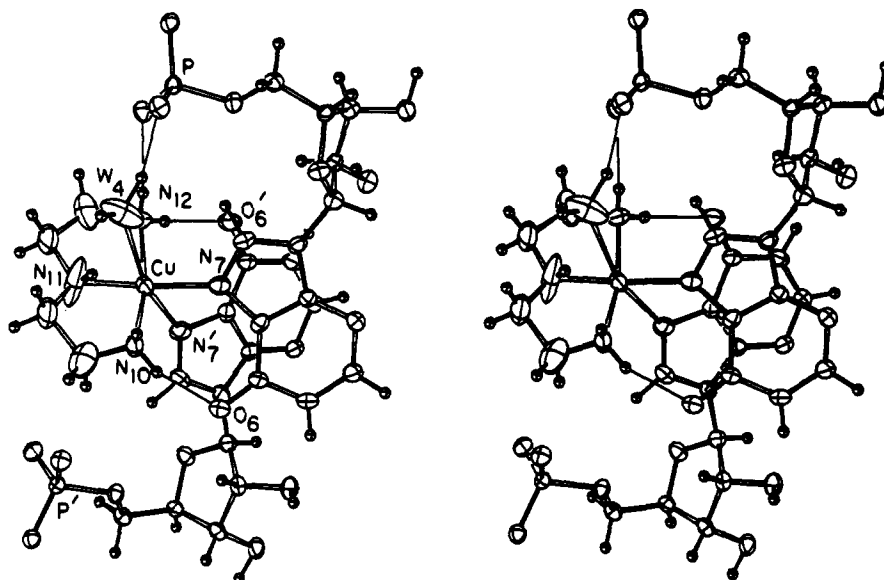


Figure 2. A stereoview of the $[\text{bis}(\text{inosine } 5'\text{-monophosphate})\text{aquo}(\text{diethylenetriamine})\text{copper}(\text{II})]^{2-}$ anion. Thin lines denote the intramolecular hydrogen bonds. The thermal ellipsoids are drawn at the 30% probability level. In this and all further figures, the thermal parameters of the hydrogen atoms have been artificially set to 1.0 \AA^2 .

We were successful, however, in obtaining a sufficient fragment of the structure by direct methods employing the MULTAN series of programs.¹³ An *E* map with a relatively large figure of merit and a low residual value¹³ clearly revealed the positions of the 5'-IMP anion and the Cu^{2+} cation. The copper is randomly disordered (50% occupancy) over two sites near to and related by the 2_c axis. Subsequent structure factor-Fourier calculations allowed the positioning of the atoms in the dien chelate and the five independent water oxygen atoms. Several cycles of isotopic refinement, minimizing the quantity $\Sigma w(|F_o| - |F_c|)^2$ where $w = 4F_o^2/\sigma^2(F_o^2)$, reduced the *R* value ($\Sigma ||F_o| - |F_c||/\Sigma |F_o|$) to 0.120 for the 1321 reflections with $(\sin \theta/\lambda) \leq 0.5$. Two further cycles of refinement employing anisotropic thermal parameters and the complete set of data reduced the *R* value to 0.097. A difference-Fourier synthesis at this stage yielded positions for the 32 independent hydrogen atoms. The contribution from the hydrogen atoms [$B_{\text{iso}}(\text{H}) = B_{\text{iso}}(\text{C,N,O}) + 1.5$] was included in subsequent cycles but no attempt was made to refine any of their parameters. Three further cycles of refinement produced convergence (maximum shift/error of 0.6) and a final *R* value of 0.080. The final weight *R* value [$[\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$] and goodness of fit [$[\Sigma w(|F_o| - |F_c|)^2/(\text{NO} - \text{NV})]^{1/2}$ where $\text{NO} = 2051$ observations and $\text{NV} = 312$ parameters] were 0.050 and 1.54, respectively.

Neutral scattering factors for the hydrogen¹⁴ and nonhydrogen¹⁵ atoms were taken from recent sources. Anomalous dispersion corrections ($\Delta f'$ and $\Delta f''$) were applied to the scattering factors for all of the nonhydrogen atoms.¹⁶ In all calculations we have assumed that the absolute configuration of the crystal was such that the sugar moiety had the absolute configuration *D*.

Final nonhydrogen atom parameters are given in Table II. The parameters for the hydrogen atoms and a listing of calculated and observed structure factors are available.¹⁷ The crystallographic calculations were performed with a standard set of programs.¹⁸

Discussion

The structure of $\text{Na}_2[(\text{dien})\text{Cu}(5'\text{-IMP})_2]\cdot 10\text{H}_2\text{O}$, like the nonstoichiometric Pt(II) complexes with 5'-IMP,^{5,6} bears a strong resemblance to the structures of the monosodium¹⁹ and disodium²⁰ salts of 5'-IMP [the Pt(II) complexes are, in fact, isomorphous]. In the structure of the sodium salts of 5'-IMP, a water molecule lies on a crystallographic twofold axis and links, via hydrogen bonds of the type $\text{OH}_2\cdots\text{N}(7)$, two symmetry-related 5'-IMP anions. In the isomorphous $(\text{NH}_3)_2\text{Pt}^{\text{II}}$ ⁵ and $(\text{en})\text{Pt}^{\text{II}}$ ⁶ complexes, this water molecule is partially substituted [about 38% in the $(\text{en})\text{Pt}^{\text{II}}$ complex and about 56% in the $(\text{NH}_3)_2\text{Pt}^{\text{II}}$ complex] by the Pt(II) moiety with the Pt atom situated on the crystallographic twofold axis. The hy-

drogen bond network in the sodium salts is replaced then by cis coordination bonds between the Pt and the N(7) atoms of the two symmetry-related 5'-IMP ligands. While the structure of the $(\text{dien})\text{Cu}^{\text{II}}$ complex presented here is very similar to the sodium salts of 5'-IMP, and consequently the Pt(II) complexes, it is not isomorphous with them. In fact, the $(\text{dien})\text{Cu}^{\text{II}}$ complex is stoichiometric but disordered. The disorder in the $(\text{dien})\text{Cu}^{\text{II}}$ complex arises from the inability of the Cu(II) center, in the presence of the tridentate chelate dien, to form equatorial bonds to both symmetry-related 5'-IMP ligands. Thus, it alternately forms a strong equatorial bond to N(7) of one of the 5'-IMP ligands and a substantially weaker axial interaction with N(7) of the related ligand and vice versa.

In Figure 1, we attempt to show the relationship, near the metal binding sites, between the structures of the sodium salts, the Pt(II) complexes, and the $(\text{dien})\text{Cu}^{\text{II}}$ complex.

In terms of the possible effect on a polynucleotide structure owing to intrastrand cross-linking by a metal complex, the structural similarities displayed by the sodium salts, the Pt(II) complexes and the $(\text{dien})\text{Cu}^{\text{II}}$ complex of 5'-IMP are particularly important. In Table III, we present some of the relevant structural parameters for these systems plus parameters for two $\text{Pt}^{\text{II}}(\text{guanosine})_2$ ^{8,9} complexes and $[(\text{dien})\text{Cu}(\text{Theo})_2]$ ²¹ where Theo = the monoanion of theophylline. First, it is clear that the two $\text{Pt}^{\text{II}}(\text{guanosine})_2$ complexes form a self-consistent set with very similar structural parameters. Secondly, the parameters for the $(\text{dien})\text{Cu}(\text{Theo})_2$ complex differ from those shown by the $\text{Pt}(\text{guanosine})_2$ complexes since the two purines are bound to the Cu via an equatorial and an axial site whereas the Pt(II) complexes bind the purines in cis-equatorial positions. The dihedral angle between the two purine ligands in the Cu(II) complex is close, however, to that shown by the Pt(II) systems, with all values being about 70° .

The parameters for the 5'-IMP complexes given in Table III are quite obviously different from those for the $\text{Pt}^{\text{II}}(\text{guanosine})_2$ and the $\text{Cu}^{\text{II}}(\text{theo})_2$ complexes. In particular, the dihedral angle between the purine planes in the 5'-IMP complexes is in the range $30\text{--}40^\circ$, with the assumed values close to that displayed by the monosodium salt, 22° (Table III).

The comparative parameters shown in Table III suggest strong competition between the crystal packing forces operative in the solid (nominally those of the mono- and disodium salts) and the distortion of the basic structure owing to the simulta-

Table IV. Final Heavy-Atom Interatomic Distances (Å) and Angles (Degrees)

(a) primary coordination sphere about the copper atom			
bond lengths			
Cu-N(7) ^a	1.917 (5)	Cu-N(12) ^b	1.999 (11)
Cu-N(10)	1.998 (11)	Cu-W(4)	2.875 (8)
Cu-N(11)	1.841 (9)	Cu-N(7) ^b	3.003 (5)
bond angles			
N(7) ^a -Cu-N(10)	93.3 (4)	N(10)-Cu-W(4)	85.2 (4)
N(7) ^a -Cu-N(11)	174.3 (3)	N(10)-Cu-N(7) ^b	109.4 (4)
N(7) ^a -Cu-N(12) ^b	96.9 (4)	N(11)-Cu-N(12) ^b	77.6 (4)
N(7) ^a -Cu-W(4)	95.4 (2)	N(11)-Cu-W(4)	85.9 (2)
N(7) ^a -Cu-N(7) ^b	78.6 (2)	N(11)-Cu-N(7) ^b	98.7 (3)
N(10)-Cu-N(11)	92.4 (4)	N(12) ^b -Cu-W(4)	84.8 (3)
N(10)-Cu-N(12) ^b	166.3 (4)	N(12) ^b -Cu-N(7) ^b	81.7 (4)
		W(4)-Cu-N(7) ^b	164.4 (2)
(b) diethylenetriamine chelate ring			
bond lengths			
N(10)-C(10)	1.361 (16)	C(11)-N(11)	1.438 (11)
C(10)-C(11)	1.535 (14)	C(10) ^b -N(12) ^b	1.623 (16)
bond angles			
Cu-N(10)-C(10)	100.4 (8)	Cu-N(12) ^b -C(10) ^b	117.3 (6)
Cu-N(11)-C(11)	107.2 (5)	N(10)-C(10)-C(11)	115.5 (10)
Cu-N(11)-C(11) ^b	127.5 (5)	C(11) ^b -C(10) ^b -N(12) ^b	100.9 (8)
		C(10)-C(11)-N(11)	107.8 (8)
(c) inosine 5'-phosphate ligand			
bond lengths			
P-O(1)	1.625 (4)	N(3)-C(2)	1.302 (8)
P-O(2)	1.535 (5)	N(3)-C(4)	1.368 (7)
P-O(3)	1.499 (5)	N(7)-C(5)	1.406 (8)
P-O(4)	1.501 (5)	N(7)-C(8)	1.293 (9)
O(1)-C(5')	1.434 (7)	N(9)-C(1')	1.467 (8)
O(1')-C(1')	1.382 (8)	N(9)-C(4)	1.371 (8)
O(1')-C(4')	1.443 (8)	N(9)-C(8)	1.365 (9)
O(2')-C(2')	1.409 (7)	C(1')-C(2')	1.535 (9)
O(3')-C(3')	1.428 (7)	C(2')-C(3')	1.524 (9)
O(6)-C(6)	1.230 (8)	C(3')-C(4')	1.513 (9)
N(1)-C(2)	1.362 (9)	C(4')-C(5')	1.517 (9)
N(1)-C(6)	1.372 (9)	C(4)-C(5)	1.373 (9)
		C(5)-C(6)	1.429 (9)
bond angles			
O(1)-P-O(2)	107.2 (2)	O(2')-C(2')-C(1')	111.5 (5)
O(1)-P-O(3)	107.6 (2)	O(2')-C(2')-C(3')	115.5 (5)
O(1)-P-O(4)	103.5 (2)	C(1')-C(2')-C(3')	100.5 (5)
O(2)-P-O(3)	111.5 (2)	O(3')-C(3')-C(2')	107.1 (5)
O(2)-P-O(4)	112.7 (2)	O(3')-C(3')-C(4')	110.6 (5)
O(3)-P-O(4)	113.6 (3)	C(2')-C(3')-C(4')	103.4 (5)
P-O(1)-C(5')	115.7 (4)	O(1')-C(4')-C(3')	106.5 (5)
C(1')-O(1')-C(4')	110.0 (5)	O(1')-C(4')-C(5')	110.3 (5)
C(2)-N(1)-C(6)	125.2 (6)	C(3')-C(4')-C(5')	116.9 (5)
C(2)-N(3)-C(4)	112.2 (5)	O(1)-C(5')-C(4')	111.6 (5)
C(5)-N(7) ^a -C(8)	104.3 (6)	N(1)-C(2)-N(3)	125.2 (6)
Cu-N(7) ^a -C(5)	135.4 (5)	N(3)-C(4)-N(9)	126.0 (5)
Cu-N(7) ^b -C(5) ^b	115.9 (5)	N(3)-C(4)-C(5)	126.5 (6)
Cu-N(7) ^a -C(8)	120.0 (5)	N(9)-C(4)-C(5)	107.5 (5)
Cu-N(7) ^b -C(8) ^b	126.9 (5)	N(7) ^a -C(5)-C(4)	108.7 (6)
C(1')-N(9)-C(4)	129.5 (5)	N(7) ^a -C(5)-C(6)	131.2 (6)
C(1')-N(9)-C(8)	125.6 (5)	C(4)-C(5)-C(6)	119.9 (6)
C(4)-N(9)-C(8)	104.8 (5)	O(6)-C(6)-N(1)	120.2 (6)
O(1')-C(1')-N(9)	109.1 (5)	O(6)-C(6)-C(5)	128.8 (6)
O(1')-C(1')-C(2')	107.6 (5)	N(1)-C(6)-C(5)	111.0 (6)
N(9)-C(1')-C(2')	112.2 (5)	N(7) ^a -C(8)-N(9)	114.6 (6)
(d) coordination about the sodium atom			
bond lengths			
Na-O(2')	2.430 (5)	Na-W(2)	2.484 (7)
Na-O(3')	2.280 (5)	Na-W(3)	2.271 (6)
Na-W(1) ^c	2.360 (7)	Na-W(5)	3.208 (9)
bond angles			
O(2')-Na-O(3')	69.3 (2)	O(3')-Na-W(3)	159.0 (2)
O(2')-Na-W(1) ^c	137.7 (2)	O(3')-Na-W(5)	110.8 (2)
O(2')-Na-W(2)	129.0 (2)	W(1) ^c -Na-W(2)	92.6 (2)

Table I (Cont.)

O(2')-Na-W(3)	89.8 (2)	W(1) ^c -Na-W(3)	97.9 (2)
O(2')-Na-W(5)	81.8 (2)	W(1) ^c -Na-W(5)	65.0 (2)
O(3')-Na-W(1) ^c	97.8 (3)	W(2)-Na-W(3)	90.7 (2)
O(3')-Na-W(2)	102.4 (2)	W(2)-Na-W(5)	141.7 (3)
		W(3)-Na-W(5)	64.2 (2)

^a Symmetry transforms: x, y, z ; ^b $-x, -y, z$; ^c $1/2 + x, 1/2 - y, 1 - z$.

Table V. Least-Squares Planes and the Deviations of Individual Atoms from These Planes^a

(a) equatorial plane about the copper atom: $-0.8555X + (-0.3131)Y + (-0.4125)Z = -6.6640 \text{ \AA}$			
Cu	0.056	N(12) ^b	-0.109
N(7)	0.065	C(10)	0.214*
N(10)	-0.100	C(11)	-0.272*
N(11)	0.088	C(10) ^b	0.201*
		C(11) ^b	-0.153*
(b) purine ligand planes			
(1) nine-atom framework: $-0.8586X + 0.4406Y + (-0.2619)Z = -4.6138 \text{ \AA}$			
N(1)	-0.011	N(7)	0.011
C(2)	0.002	C(8)	-0.012
N(3)	0.012	N(9)	-0.018
C(4)	0.003	O(6)	-0.084*
C(5)	0.034	C(1')	-0.105*
C(6)	-0.020	Cu	0.150*
		O(2) ^c	-0.199*
(2) imidazole ring: $-0.8480X + 0.4603Y + (-0.2627)Z = -4.5885 \text{ \AA}$			
C(4)	-0.005	N(7)	-0.004
C(5)	0.005	C(8)	0.001
		N(9)	0.002
(3) pyrimidine ring: $-0.8630X + 0.4299Y + (-0.2655)Z = -4.6425 \text{ \AA}$			
N(1)	0.001	C(4)	-0.016
C(2)	0.006	C(5)	0.022
N(3)	0.001	C(6)	-0.015
(c) best mean plane of the ribose moiety: $0.6394X + (-0.1190)Y + (-0.7596)Z = -5.8609 \text{ \AA}$			
O(1')	0.022	C(4')	-0.021
C(1')	-0.014	C(2')	-0.537*
C(3')	0.012	C(5')	-1.186*

^a In each of the equations of the planes, $X, Y,$ and Z are coordinates (\AA) 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. ^b Transformed by $-x, -y, z$. ^c Transformed by $1/2 - x, -1/2 + y, 2 - z$.

neous binding of the two purine bases by the metal complexes. The distortion of the structural parameters toward the values found in the Pt^{II}(guanosine)₂ complexes is most pronounced in the nonstoichiometric [(NH₃)₂Pt(5'-IMP)₂]²⁻ system where 56% of the water molecules are replaced by the Pt(II) moiety. The structural distortions are less pronounced in the [(en)Pt(5'-IMP)₂]²⁻ system where the Pt moiety replaces the water molecules only 38% of the time and in the [(dien)-Cu(5'-IMP)₂]²⁻ complex, which is stoichiometric, but the demands imposed by the equatorial-axial binding mode are less severe.

If one assumes that the crystal packing forces operative in the 5'-IMP complexes described above approximate those found in a base-stacked polynucleotide, the above results suggest that intrastrand cross-linking by a reagent such as cis-[Pt(NH₃)₂Cl₂] will place a significant strain on the conformational parameters in the polynucleotide. For Cu(II) complexes, where intrastrand cross-linking can be accommodated by an equatorial-axial binding mode, the demands are less and the strain imposed on the polynucleotide structure may be minimal.

Molecular Conformation and Dimensions A stereoview of the immediate environment about the (dien)Cu^{II} moiety is presented in Figure 2. The coordination geometry about the Cu(II) is best described as (4 + 1 + 1)^{22,23} with the equatorial

plane defined by the tridentate dien chelate, with its terminal amino groups in the commonly observed trans positioning,²⁴⁻²⁶ and N(7) of the strongly bound 5'-IMP ligand. The axial sites are weakly occupied by a water molecule and N(7) of the symmetry-related (about the 2_c axis) 5'-IMP anion.

The absence of any direct Cu-O(phosphate) interaction (Figures 1 and 2) suggests that the preferred metal binding site for the (dien)Cu^{II} moiety is N(7) of the 5'-IMP anion. Consistent with this suggestion, Aoki²⁷ has found that the complex cation [Cu(5'-IMP)(bipy)(H₂O)₂]¹⁺, where bipy is the bidentate chelate 2,2'-bipyridyl, contains a direct Cu(II) to base interaction via N(7) but the interactions with the phosphate group are through Cu-OH₂...O(phosphate) hydrogen bonds. In contrast, the complexes [Cu(5'-IMP)]_n²⁸ and [Cu₃(5'-GMP)₃(H₂O)₈]_n²⁹ are polymeric and contain direct metal to base [N(7)] and metal to phosphate coordination bonds. Thus, in each of the observed cases, the presence of a chelate ligand in the primary coordination sphere appears to favor copper binding to the base portion of the nucleoside monophosphate over direct copper to phosphate bonding. Further tests of this apparent selectivity are in progress. Moreover, the presence of two purine ligands, one axial and one equatorial, in the coordination sphere about (dien)Cu^{II} is particularly interesting. We have observed a similar such arrangement in the metal purine complex bis(theophyllinato)(dien)copper(II)

Table VI. Distances (Å) and Angles (Degrees) in the Interactions of the Type D-H...A

D	H	D-H	A	D...A	H...A	\angle D-H...A
O(2')	H(O2')	0.95	O(2) ^a	2.657 (6)	1.74	161
O(3')	H(O3')	1.08	O(4) ^b	2.631 (6)	1.56	173
N(1)	H(1)	0.89	O(2) ^c	2.763 (7)	1.89	173
W(1)	H(W1)	0.96	O(3) ^d	2.713 (6)	1.91	140
W(1)	H(W1')	1.14	W(5) ^d	3.075 (11)	2.04	149
W(2)	H(W2)	0.91	O(2) ^e	2.756 (8)	2.02	137
W(2)	H(W2')	1.07	W(1) ^f	2.865 (9)	1.84	159
W(3)	H(W3)	0.99	O(4) ^e	2.741 (8)	1.84	149
W(3)	H(W3')	1.06	W(2) ^d	2.812 (9)	1.77	166
W(4)	H(W4)	1.03	O(3) ^f	2.764 (8)	1.79	156* ^h
W(5)	H(W5)	0.97	N(3) ^f	2.927 (9)	2.03	153
W(5)	H(W5')	1.04	W(3) ^f	3.017 (11)	2.11	145
N(10)	H(10B)	0.87	O(6) ^f	3.039 (12)	2.27	147*
N(12)	H(N12A)	0.85	O(6) ^f	2.817 (12)	1.98	166*
N(12) ^g	H(N12B) ^g	0.89	O(4) ^f	2.947 (11)	2.10	158*

^a Symmetry transforms: $1/2 + x, 1/2 - y, 2 - z$; ^b $1/2 + x, 1/2 - y, 2 - z$; ^c $1/2 - x, 1/2 + y, 2 - z$; ^d $-1/2 + x, 1/2 - y, 1 - z$; ^e $x, y, -1 + z$; ^f x, y, z ; ^g $-x, -y, z$. ^h An asterisk indicates intracomplex hydrogen bonds.

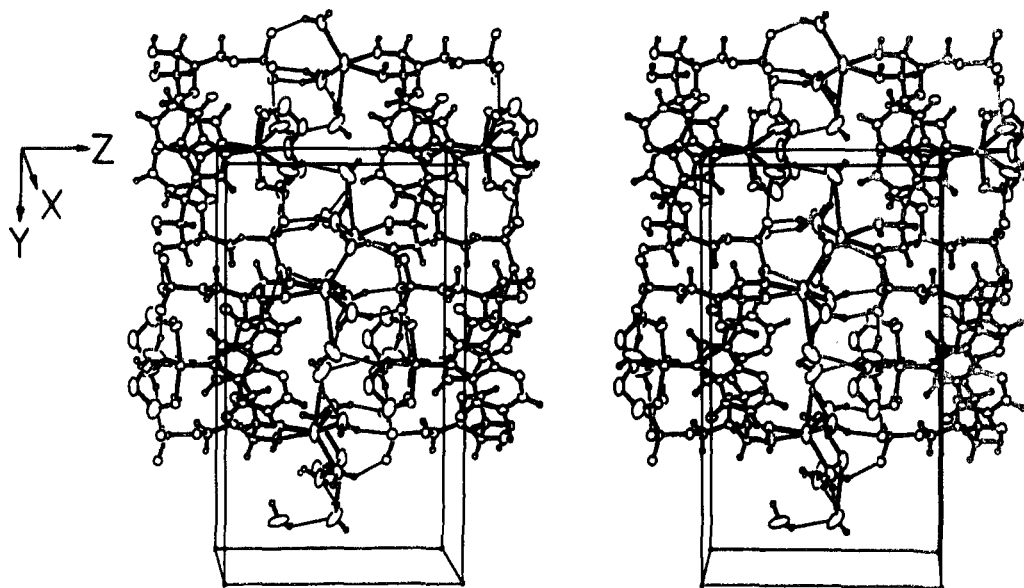


Figure 3. A stereoview of the crystal packing.

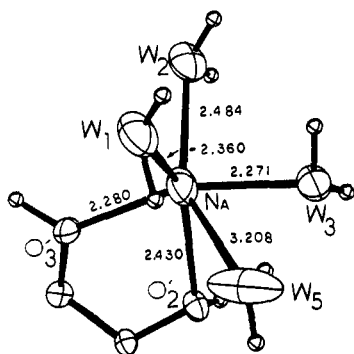


Figure 4. A perspective view of the immediate environment about the sodium ion.

dihydrate,²¹ where the equatorial and axial Cu-N(7) bond lengths are 2.007 (3) and 2.397 (3) Å, respectively. The considerably longer Cu-N(7) axial interaction in the present complex (Table III) underscores the weakness of this type of interaction and its susceptibility to other forces operative in the crystal.

Another point of particular interest is the interligand interactions between the water and dien ligands and the coordinated 5'-IMP anions. As is seen in Figure 2, there are four interligand hydrogen bonds. The dien chelate donates to the carbonyl oxygen atom O(6) of both the axially and the equatorially bound 5'-IMP ligands as well as being involved in a hydrogen bond to one of the phosphate oxygen atoms of the equatorial 5'-IMP ligand. The axial water molecule also acts as a donor in a hydrogen bond to one of the phosphate oxygen atoms of the equatorial 5'-IMP ligand. Both the M-NH₂(dien)···O (base and phosphate) and M-OH₂···O (phosphate) types of hydrogen bonds have been found in other systems.² The presence in this system of multiple interligand hydrogen bonding is, however, noteworthy.

The Cu-N(dien) terminal bond lengths (Table IV) are typical of other studies.²⁴⁻²⁶ The Cu-N(dien) distance to the central nitrogen atom, 1.841 (9) Å, is, however, shorter than usually observed by about 0.1 Å. We have in our model for the disorder in this system placed this atom on the 2_c axis, which may not, in fact, be rigorously correct. Considering the disorder problems, then, we place no particular significance in this shortened bond length. The Cu-N(7) bond length at 1.917 (5) Å is measurably shorter than that found, for example, in the

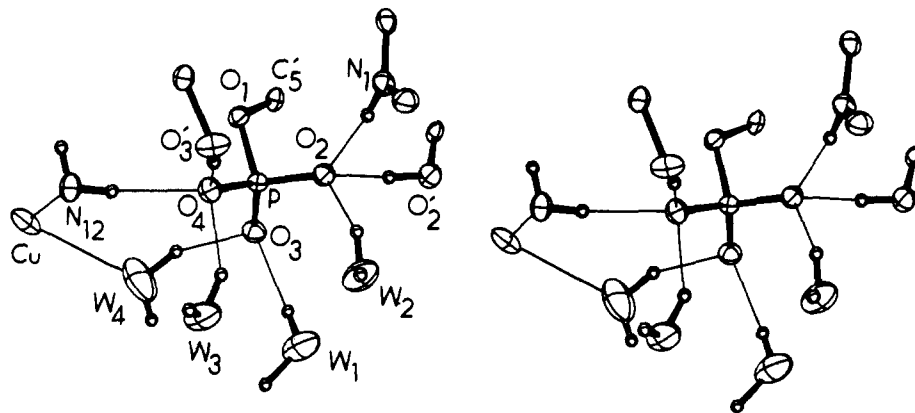


Figure 5. A stereoview of the hydrogen-bonding environment about the phosphate group.

bis(theophyllinato)(dien) Cu^{II} complex,²¹ 2.007 (3) Å, and is probably related to the rather dramatic difference in the strength of the axial interactions in the two systems. Of some interest is the deviation of the Cu from the planes of the axial and equatorial 5'-IMP ligands (Table V). In the present structure, the angle between the Cu-N(7) vector and the plane of the equatorial ligand is 4.2 (2)°, while the analogous vector displacement leads to an angle of 31.6 (2)° for the axial ligand. We have noted before³⁰ that when interligand interactions are formed to an equatorial site, the geometry about N(7) of a purine ligand tends to be trigonal with a nominal deviation of the Cu-N(7) vector from the plane; contrastingly, interligand hydrogen bonding to an axial ligand tends to induce a significant pyramidal component to the geometry about N(7) and to significant displacement of the Cu-N(7) vector from the plane. Clearly, the present complex is in accord with this general observation.

We have also noted that interligand hydrogen bonding tends to cause a significant dissymmetry in the exocyclic bond angles about N(7) of metal-purine complexes.¹⁰ Again, the present complex is in accord with this general observation, with the Cu-N(7)-C(5) bond angle being about 15° larger than the Cu-N(7)-C(8) bond angle for the equatorial 5'-IMP ligand and about 11° larger for the axial 5'-IMP ligand.

There seem to be no unusual features in the 5'-IMP anion observed here in comparison to its monosodium¹⁹ salt and 5'-IMP in its acid form.³¹ The nine-atom framework of the purine is quite planar with a maximum deviation from the mean plane of 0.034 Å for C(5) (Table V). The substituent atoms O(6) and C(1') are displaced from the mean plane by 0.084 and 0.105 Å, respectively. Similar values are observed in the sodium¹⁹ and acid forms³¹ of 5'-IMP. As found in a variety of coordinated and uncoordinated purine derivatives,^{32,33} there is a measurable fold about the C(4)-C(5) vector leading to a dihedral angle between the imidazole and pyrimidine planes of 1.9 (2)°.

The ribosyl moiety is observed in the common C(2') endo pucker³⁴ and its orientation to the purine framework is anti [torsion angle C(8)-N(9)-C(1')-O(1') = 48.0 (2)°]. The conformation about the C(4')-C(5') bond is gauche-gauche.

Crystal Packing and Hydrogen Bonding. The crystal packing is illustrated in the stereoview of Figure 3. While the observed packing diagram is quite complex, it can qualitatively be broken down into two layers parallel to the *ab* plane. One of these layers consists of complexed 5'-IMP anions, while the second layer is dominated by the aquated Na^+ cation and its interactions. Within the layer of complexed 5'-IMP anions, the mode of intermolecular communication is through three hydrogen bonds: (1) one involving a hypoxanthine base to phosphate oxygen atom hydrogen bond, N(1)-H(1)···O(2),

and (2) two involving ribose hydroxyl to phosphate hydrogen bonds, O(2')-H(O2')···O(2) and O(3')-H(O3')···O(4) (Table VI). In the second layer, the coordination sphere about the Na^+ ions (Figure 4) is a highly distorted octahedron. Two of the cis coordination sites are occupied by the ribose hydroxyl oxygen atoms O(2') and O(3'), while the remaining four sites are occupied by water molecules. Thus, all water molecules interact with a metal center: W(4) with the Cu(II) and W(1), W(2), W(3), and W(5) with the Na^+ cation. All of the ligands about the Na^+ are tightly bound, except for one water molecule, W(5), which has a bond length nearly 0.8 Å longer than the other oxygen atoms in the coordination sphere (Figure 4). This relatively loosely bound water molecule donates a hydrogen bond to N(3) of the hypoxanthine base, W(5)-H(5)···N(3), while the remaining three-coordinated water molecules donate hydrogen bonds to oxygen atoms of the phosphate group (Table VI and Figure 3). Thus, the primary modes of communication between the layers of coordinated 5'-IMP anions and the aquated Na^+ cations are through the coordination of the Na^+ by the ribose hydroxyl oxygens O(2') and O(3') and the $\text{Na}^+\text{-OH}_2\cdots\text{O}(\text{phosphate})$ and $\text{Na}^+\text{-OH}_2\cdots\text{N}(\text{base})$ hydrogen bond systems.

The hydrogen bonding environment about the phosphate group is illustrated in Figure 5. Two of the nonester phosphate oxygen atoms act as acceptors in three hydrogen bond interactions, while the third acts as an acceptor in two hydrogen bonds (Table VI and Figure 5).

As noted earlier, the mono- and disodium salts, as well as the Pt(II) complexes, of 5'-IMP display similar packing arrangements.

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Supplementary Material Available: Listings of hydrogen atom parameters and structure factor amplitudes (14 pages). Ordering information is given on any current masthead page.

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Crystal and Molecular Structure of the *N,N*-Dimethylurea Derivatives of *exo*-5-Ethoxy-5-isocyanatobicyclo[2.1.0]pentane and *exo*-6-Ethoxy-6-isocyanatobicyclo[3.1.0]hexane. Confirmation of the γ -Steric Shift in Nitrogen-15 Nuclear Magnetic Resonance as a Tool for Stereochemical Assignment¹

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Abstract: The single-crystal X-ray analyses of the *N,N*-dimethylurea derivatives of *exo*-5-ethoxy-5-isocyanatobicyclo[2.1.0]pentane (**8**) and *exo*-6-ethoxy-6-isocyanatobicyclo[3.1.0]hexane (**5**) are described. The analyses were performed to establish the stereochemistry of **5** and **8** and to prove that the γ -steric shift in ¹⁵N NMR spectroscopy can be used to assign the stereochemistry of a nitrogen substituent relative to a carbon substituent in a rigid system. The bicyclohexane **5** crystallizes in the space group $P2_1/n$ with four molecules per unit cell of dimensions $a = 8.053$ (2), $b = 17.251$ (7), and $c = 9.123$ (2) Å, and $\beta = 107.11$ (2)°. From 1690 unique, observed reflections collected on an automated four-circle diffractometer, the structure was solved and refined to final values for the discrepancy indices of $R = 0.049$ and $R_2 = 0.061$. The bicyclopentane **8** crystallizes in the space group $Pbca$ with eight molecules per unit cell of dimensions $a = 10.187$ (5), $b = 13.822$ (7), and $c = 16.207$ (7) Å. From 900 unique, observed reflections similarly collected, the structure was solved and refined to final values for the discrepancy indices of $R = 0.044$ and $R_w = 0.057$. The molecular structure data are compared with data in the literature for other bicyclo[2.1.0]pentanes and bicyclo[3.1.0]hexanes. This comparison indicates that there is some error in a recent structure determination of bicyclo[3.1.0]hexane by a combination of microwave spectroscopy and electron diffraction. ¹⁵N NMR chemical shifts for the secondary urea nitrogens of **5** and **8** are discussed in terms of intramolecular contacts. The chemical shifts are consistent with a downfield, sterically induced δ shift and a dominant, upfield, sterically induced γ shift.

The γ -steric shift in ¹³C NMR has been used extensively for organic structural analysis² including conformational analysis,³ configurational assignments,⁴ and analysis of the spectra of complex molecules.⁵ We have recently proposed without absolute proof that an analogous γ -steric shift in ¹⁵N NMR can be used to assign the stereochemical relationship of a nitrogen substituent to a γ -carbon substituent in a rigid system.⁶ Here we report X-ray crystallographic data which unambiguously substantiate our previous stereochemical assignments and which confirm the γ -steric shift in ¹⁵N NMR as a tool for stereochemical assignment.

Prior evidence that the γ shift in ¹⁵N NMR is a sterically

induced upfield shift comes from the work of Roberts and co-workers.⁷ They have shown that linear regression analysis of the ¹⁵N chemical shifts of acyclic amines in terms of α , β , γ , δ , and ϵ substituent effects gives a γ effect of +2.7 ppm. Comparison of the ¹⁵N resonances of isobutylamine and (cyclopropylmethyl)amine suggests the steric nature of the γ effect. The ¹⁵N absorption of (cyclopropylmethyl)amine appears 4.6 ppm downfield from the ¹⁵N absorption of isobutylamine, presumably because the γ carbons sterically interact less with the nitrogen in (cyclopropylmethyl)amine. A dominant γ -steric effect is also given as the simplest interpretation for the observation that the nitrogens of *cis*-1,2-diaminocyclobutane