Metal Complexes of Purine-N-Oxides.
I. The Crystal Structure of a Copper(II) Complex of Doubly Deprotonated Adenine-N^1-Oxide

EINAR SLETTEN, TERJE MARTHINSEN and JORUNN SLETTEN

Department of Chemistry, University of Bergen, 5000 Bergen, Norway

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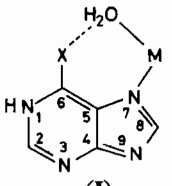
Abstract

$Cu(C_5H_3NO)_2Na_2(H_2O)_8$, triclinic, space group $P1$, a = 5.418(1) Å, b = 10.246(1) Å, c = 10.600(1) Å, α = 106.41(1)°, β = 96.71(1)°, γ = 99.71(1)°, Z = 1. 1907 intensities above background were collected on a CAD-4 diffractometer using MoKα radiation. The structure was refined by full-matrix least-squares to R = 0.045. The adenine-N^1-oxide ligand appears as a dianion with both the imidazole ring and the amino group deprotonated. The Cu ion, situated at a center of symmetry, has a square coplanar coordination, binding at the imino nitrogen (Cu–N6 = 1.898 Å) and at the oxygen on N1 (Cu–O1 = 1.948 Å). The sodium ions are octahedrally surrounded by water molecules, forming a polymeric chain through the crystal.

Introduction

Through the years our group has been involved in a systematic investigation of metal complexes of nucleic acid components [1, 2]. Recently we have extended our studies to include metal bonding properties of N-oxides of purine bases. The chemistry of purine N-oxides has been extensively studied by Brown and coworkers [3]. Metal bonding to this type of ligand has been studied by UV and potentiometric methods [4, 5], and more recently by IR-spectroscopy [6, 7]. Procedures for synthesizing copper(II) complexes of adenine-N^1-oxides have been published [8].

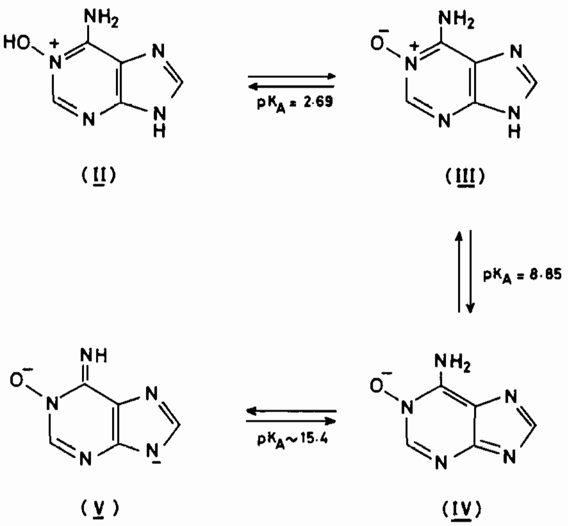
The predominant coordination pattern for transition metal complexes of naturally occurring purine nucleotides and nucleotide analogues is indicated (I).



(I)

In the pH-region pertinent to biological systems the ligand is monodentately bonded through N(7); and the substituent in the 6-position is hydrogen bonded to a water molecule in the coordination sphere [1, 2].

The oxygenation of the N^1-position in purines is expected to alter the coordination pattern. The following ligand species exist for adenine-N^1-oxide (AdNO), depending on the pH of the solution.



A multitude of binding sites exist and it is difficult *a priori* to decide which coordination pattern will emerge. In this paper we report the crystal structure of a copper(II)–AdNO complex obtained at basic pH. Spectroscopic studies on the compound in solution are in progress.

Experimental Section

Preparation

A modification of the procedure described by Weiss and Venner [8] was used for preparing the compound. 200 mg adenine-N^1-oxide was dissolved in 2 ml warm 1 *N* NaOH. The solution was diluted

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by 6 ml H_2O, and 0.4 ml 1 M $CuSO_4$ was added dropwise. After filtering, the solution was left in the refrigerator for a couple of days. Green crystals suitable for X-ray work were obtained.

Crystal Data

$Cu(C_5H_3NO)_2Na_2(H_2O)_8$, F.W. 551.86, triclinic, $P\bar{1}$ (No. 2). Cell dimensions: $a = 5.418(1)$ Å, $b = 10.246(1)$ Å, $c = 10.600(1)$ Å, $\alpha = 106.41(1)^\circ$, $\beta = 96.71(1)^\circ$, $\gamma = 99.71(1)^\circ$, $V = 547.9(3)$ Å^3. $Z = 1$, $D_x = 1.670$ g cm^{-3}, $\mu(\mathrm{MoK}\alpha) = 11.51$ cm^{-1}.

Crystallography

A crystal of dimension 0.290 × 0.085 × 0.160 mm was mounted along the needle axis. The cell parameters were determined at 20 °C from 25 centered general reflections on an Enraf Nonius CAD-4 diffractometer. The data were collected by the $\theta/2\theta$ scan technique. The scan rate was determined by a fast prescan (10° min^{-1}). Reflexions having $\sigma(I)/I \geqslant 0.5$ were considered unobserved and were not remeasured. The relative standard deviation, $\sigma(I)/I$, required for the final data was set equal to 0.03, provided that the maximum time spent on any one reflexion would not exceed 90 sec. Backgrounds were measured by extending the scan by 25% on either side of the peak. A total of 2381 unique reflexions was recorded in the range $1^\circ \leqslant \theta \leqslant 27^\circ$. Of these, 1907 had $I > 2\sigma_c$ where σ_c is the estimated error due to counting statistics. During data collection three standard reflexions were remeasured every two hours to check the stability of the crystal and electronics. The intensities of the standards were plotted and showed fluctuations of less than ±1%. The expression used for calculating the random error in any one reflexion is: $\sigma_I = [\sigma_c{}^2 + (0.02\sigma_c{}^2)^2]^{1/2}$. Here both counting statistics errors and errors due to instrumental instability are taken into account. The data were corrected for absorption using Gaussian integration with grid 16 × 6 × 10, giving transmission factors in the range 0.925–0.862. The usual corrections for Lorentz and polarization effects were carried out.

The structure was solved by the Patterson method and refined by full-matrix least-squares calculations. The copper atom is situated at a center of symmetry. A Fourier synthesis based on the phases determined by the heavy atom revealed the positions of the adenine atoms and the water molecules. At this stage the presence of a sodium ion was not expected; thus the succeeding structure factor calculations were based on the copper ion, the adenine ring and five water molecules per asymmetric unit. Later it was concluded from the geometry and from the unreasonably low thermal parameter of one of the tentative water molecules that the structure in addition to the copper complex contained a hydrated sodium ion. This is not in accordance with the elemental analysis reported for the compound synthesized by a similar procedure by Weiss and Venner [8].

TABLE I. Final Atomic Parameters with their Estimated Standard Deviations from the Least-squares Refinement. For the Anisotropically Refined Non-hydrogen Atoms the Isotropic Equivalent Thermal Parameter is Given: $B_{eq} = 4/3\ \Sigma_i\Sigma_j B_{ij}\, \mathbf{a}_i \cdot \mathbf{a}_j$.
Hydrogen Atoms were Isotropically Refined; Isotropic Temperature Factor: $\exp[-B \sin^2\theta/\lambda^2]$.

Atom	x	y	z	B(Å^2)
Cu	0.000	0.000	1.000	2.40(1)
Na	0.7068(2)	0.4048(1)	0.4122(1)	2.10(3)
N1	0.2205(5)	0.0442(3)	0.7924(3)	1.87(6)
N3	0.4417(6)	0.1166(3)	0.6374(3)	2.55(7)
N6	0.3180(6)	0.1210(3)	1.0190(3)	2.38(7)
N7	0.8091(6)	0.2965(3)	0.9613(3)	2.60(7)
N9	0.8393(6)	0.2817(3)	0.7444(3)	2.53(7)
C2	0.2522(7)	0.0442(4)	0.6683(3)	2.56(8)
C4	0.6191(7)	0.1972(3)	0.7462(3)	1.95(7)
C5	0.5989(6)	0.2057(3)	0.8767(3)	1.84(7)
C6	0.3866(6)	0.1282(3)	0.9068(3)	1.72(7)
C8	0.9411(8)	0.3358(4)	0.8748(4)	2.91(9)
O1	0.0089(5)	−0.0398(2)	0.8098(2)	2.29(5)
O2	0.8821(5)	0.3082(3)	0.2239(2)	2.68(6)
O3	0.4011(5)	0.2003(3)	0.4030(2)	2.77(6)
O4	0.6439(5)	0.5119(3)	0.6532(3)	2.83(6)
O5	1.0541(4)	0.3573(2)	0.5394(2)	2.34(5)
H2	0.139(7)	−0.006(4)	0.611(3)	3.1(9)*
H6	0.399(5)	0.161(3)	1.063(3)	1.0(6)*
H8	1.091(6)	0.396(3)	0.898(3)	2.4(8)*
H21	0.912(5)	0.244(3)	0.216(3)	1.0(6)*
H22	0.872(8)	0.307(4)	0.150(4)	4(1)*
H31	0.414(6)	0.167(3)	0.448(3)	2.5(8)*
H32	0.326(6)	0.153(3)	0.350(3)	1.8(7)*
H41	0.659(7)	0.460(4)	0.680(4)	3.3(9)*
H42	0.750(6)	0.562(3)	0.686(3)	2.5(8)*
H51	0.991(6)	0.334(3)	0.594(3)	2.0(8)*
H52	1.134(5)	0.313(3)	0.515(3)	0.9(6)*

Isotropic refinement led to $R = \Sigma\|F_o| - |F_c\|/\Sigma|F_o| = 0.092$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.097$. The hydrogen atoms were all visible in a ΔF map at this stage. They were included and isotropically refined, whereas the non-hydrogen atoms were refined anisotropically. The agreement factors at convergence were $R = 0.045$ and $R_w = 0.047$. The goodness of fit ratio was 1.93. The final ΔF map had a few peaks in the range 0.3–0.2 eÅ^{-3} near Cu.

The refined coordinates and isotropic equivalent thermal parameters are listed in Table I. Tables of anisotropic temperature factors and structure factors are available from the authors on request.

The scattering curves were those of Cromer and Waber [9]. All calculations were carried out on a PDP 11/55 computer using the Enraf-Nonius Structure Determination Programs (SDP) [10].

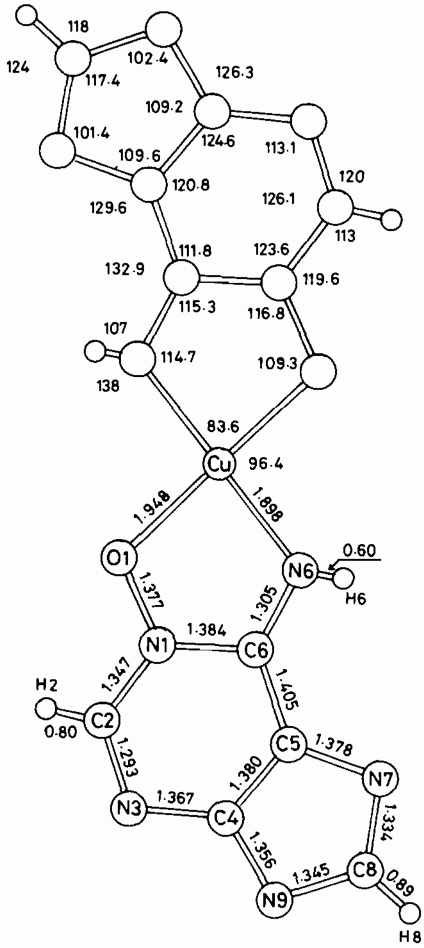

Fig. 1. Interatomic distances (Å) and angles (°) in the complex unit. The σ's in bond lengths are: Cu–N(O) 0.002 Å, C–C(N) and N–O 0.003 Å. The σ's in angles at Cu are 0.1°; and at C(N)(O), not involving H atoms, 0.2°.

Results and Discussion

The AdNO-ligand is formally a dianion and forms a bis-chelate with copper (Fig. 1), binding through the N^1-oxygen and the imino group. The copper ion has a square coplanar coordination with relatively short Cu–O (1.948 Å) and Cu–N (1.898 Å) bonds. The closest approximately axial contact distance is more than 3 Å, (Cu–––N7 = 3.483 Å). The doubly negative charge on AdNO and the possibility of Cu–––O(N) π-bonding both favour a square coplanar coordination [11, 12].

The geometry of the AdNO ligand is shown in Fig. 1. The imidazole ring is almost symmetrical around an axis through C8 and the midpoint of the C4–C5 bond. The imino bond N6–C6 of 1.305(3) Å is significantly shorter than the average amino bond length of 1.33 found in adenines, but equal within the error limit to the amino bond in the AdNO cation [13]. AdNO is essentially planar, and makes a dihedral angle of 12.9° with the equatorial coordination plane.

TABLE II. Bond Lengths (Å) and Angles (°) in the Coordination Sphere of the Sodium Ion. Numbers in Parentheses are Standard Deviations as Obtained from the Inverse Least-squares Matrix.

Na–O2	2.348(2)	Na–$O4^a$	2.322(3)
Na–O3	2.413(3)	Na–O5	2.384(2)
Na–O4	2.567(3)	Na–$O5^b$	2.440(2)
O2–Na–O3	98.4(1)	O3–Na–O5	96.3(1)
O2–Na–O4	164.3(1)	O3–Na–$O5^b$	164.8(1)
O2–Na–$O4^a$	109.3(1)	O4–Na–$O4^a$	86.6(1)
O2–Na–O5	86.3(1)	O4–Na–O5	77.6(1)
O2–Na–$O5^b$	96.2(1)	O4–Na–$O5^b$	79.4(1)
O3–Na–O4	87.8(1)	$O4^a$–Na–O5	164.0(1)
O3–Na–$O4^a$	85.4(1)	$O4^a$–Na–$O5^b$	85.7(1)
		O5–Na–$O5^b$	89.0(1)

Symmetry operations: $^a1 - x, 1 - y, 1 - z$. $^b2 - x, 1 - y, 1 - z$. $^cx - 1, y, z$.

The purine-stacking pattern found in the present structure features partially overlapping bases in which the overlap involves interaction of the N^1-oxygen with the imidazole ring of an adjacent base. The distance between the ring plane and O1 of 3.508 Å is in the range expected for this type of overlap. A number of similar stacking patterns which appear to be stabilized by interactions of polar regions of one base with the polarizable ring system of an adjacent base have been surviewed by Bugg [14]. The apparent lack of influence on stacking by metal complexation has already been pointed out [15].

The sodium ion is surrounded by six water molecules forming a polymeric chain through the crystal (Fig. 2, Table I). The sodium ions are doubly bridged by centrosymmetrically related water molecules.

The hydrogen bonding network in the crystal involves all acceptor atoms and all donor groups except N6–H6, (Table III). O1 participates in two hydrogen bonds, completing a tetrahedral arrangement in accordance with sp^3-hybridization. More unexpectedly the imidazole nitrogen N9 with a formal sp^2 lone pair is also involved in two hydrogen bonds.

Quite unexpectedly the AdNO ligand appears as a dianion with both the proton on N9 and one of the amino protons lost. Deprotonation of the amino group in AdNO is estimated to take place at a pK ~ 15.4 [4]. However, the compound was synthesized at pH ~ 12, at which pH only N9 is expected to be deprotonated. To account for this apparent discrepancy one may envisage the complexation as a two step reaction. First the copper ion binds to the N-oxygen monodentately. The metal binding in turn increases the acidity of the ring, facilitating a

TABLE III. Hydrogen Bond Distances and Angles [σ(D···A) = 0.002–0.003 Å, σ(H···A) = 0.03–0.04 Å, σ(angle) = 3–4°].

D–H···A	Position of acceptor atom	D···A	H···A	<D–H···A
O2–H21···O1	$1-x, -y, 1-z$	2.842 Å	2.15 Å	178°
O2–H22···N7	$x, y, z-1$	2.731	1.96	174
O3–H31···N3	x, y, z	2.846	2.20	163
O3–H32···O1	$-x, -y, 1-z$	2.868	2.23	162
O4–H41···N9	x, y, z	3.084	2.43	161
O4–H42···O2	$2-x, 1-y, 1-z$	2.820	2.15	170
O5–H51···N9	x, y, z	2.813	2.03	177
O5–H52···O3	$1+x, y, z$	2.925	2.24	166

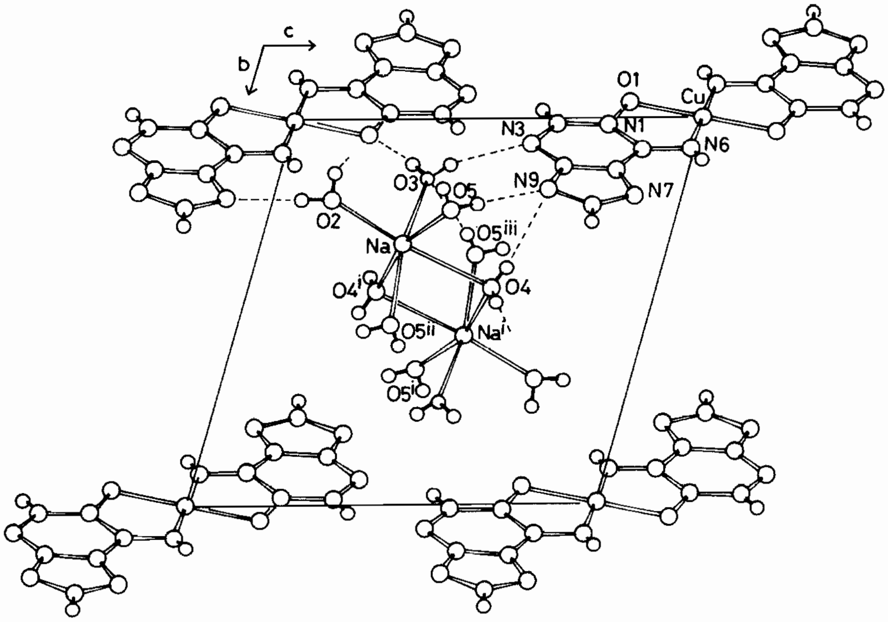

Fig. 2. The crystal packing in the unit cell, viewed approximately along the *a*-axis.

deprotonation of the amino group. In a consecutive reaction the chelate is formed.

The elemental analysis for the compound reported by Weiss and Venner [8] gives a composition corresponding to a monoionic AdNO species, excluding sodium, but with the same number of water of hydration as found in the present compound. Since the synthetic procedures are essentially the same, it is likely that the products are in fact identical.

In the singly deprotonated form of AdNO (pK_a = 8.48) several coordination schemes may be possible. The reported results from potentiometric measurements on AdNO–metal complexes were interpreted to be consistent with a N7–M–NH_2 chelate in which the ligand appears as a monoanion [4]. Corresponding data for the adenosine-N-oxide ligand, on the other hand, indicated the type of chelate observed in the present structure [4]. By comparison with the metal complexes of purines with N9 blocked, the proposed N7–M–NH_2 chelate for the AdNO-monoanion is not very likely. In those cases where N7 is a binding site an 'indirect' chelation with a hydrogen bond between the substituent on C6 and the coordination sphere has been observed (I) [1, 2]. Dinuclear structures involving N3 and N9 coordination have been found for unsubstituted adenine and hypoxanthine [16, 17]. Both the monodentate N7 and the dinuclear N3, N9 coordination modes are possible for the monoanion and the neutral AdNO. On the basis of spectral and magnetic data Mikulski and coworkers [6] have proposed an O1, N7 bridging of neutral and protonated AdNO ligands in a binuclear copper perchlorate complex.

In solution at neutral pH different species may coexist, both mononuclear and binuclear. The one crystallizing may not always be the predominant. Presently NMR studies are being undertaken in order to verify if some of the solid state features are present in solution.

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