Published in final edited form as:

Inorg Chem. 2006 March 20; 45(6): 2688–2694. doi:10.1021/ic051411p.

Synthesis, Structures, and Electrochemistry of Au(III)-ethylenediamine Complexes and Interactions with Guanosine 5'-Monophosphate

Shourong Zhu^a, Waldemar Gorski^a, Douglas R. Powell^b, and Judith A. Walmsley^a

^aDepartment of Chemistry, The University of Texas at San Antonio, 6900 N. Loop 1604 W., San Antonio, Texas 78249–0698

^bDepartment of Chemistry, University of Kansas, Lawrence, Kansas 66045–7582

Abstract

[Au(en)Cl₂]Cl·2H₂O has been synthesized and its structure has been solved for the first time by the single crystal X-ray diffraction method. The complex has square planar geometry about the Au(III) and the anionic Cl[−] is located in the apical position and at a distance of 3.3033(10) Å compared to 2.2811(9) and 2.2836(11) Å for the coordinated Cl[−]. [Au(en)Cl₂]Cl·2H₂O belongs to the space group Pbca with *a* = 11.5610(15) Å, *b* = 12.6399(17) Å, *c* = 13.2156(17) Å, α = β = γ = 90° and Z = 8. Bond lengths of Au–N are 2.03 Å. [Au(en)Cl₂]Cl·2H₂O is less thermally stable than [Au(en)₂]Cl₃ due to the replacement of 2 Cl ligands by a second ethylenediamine ligand in the latter. Cyclic voltammetry shows that the formal potential of Au(III)/Au(0) becomes more negative in the series [AuCl₄][−], [Au(en)Cl₂]⁺, [Au(en)₂]³⁺. ¹H, ¹³C, and ³¹P NMR reveal that in aqueous solution [Au(en)Cl₂]⁺ bonds to guanosine 5'-monophosphate, 5'-GMP, (1:1 mole ratio) via N7, although the stability is not very high. NMR data also indicate that N7–O6 or N7-phosphate 5'-GMP chelation, as found in some Au(III)-nucleotide complexes, is not present. The Au(III) complex undergoes hydrolysis at pH > 2.5–3.0 and, therefore N1 coordination to 5'-GMP is not observed. No direct coordination between 5'-GMP and [Au(en)₂]Cl₃ is observed.

Keywords

Gold(III); guanosine 5'-monophosphate; NMR; cyclic voltammetry; X-ray structure

Gold(III) complexes are isoelectronic and generally isostructural to platinum(II) complexes, and therefore it is anticipated that they will have similar activity to the Pt(II) antitumor drugs.^{1–5} However, compared to the corresponding Pt(II) complexes, Au(III) complexes have not been well explored chemically or electrochemically, possibly because few gold(III) complexes have been shown to be sufficiently stable in aqueous solution.^{6,7}

Ethylenediamine (en) is a common chelating ligand that is widely used in transition metal complexes. Its gold complexes have been known since 1931,^{8–10} and the crystal structure of [Au(en)₂Cl₂]Cl was determined.¹¹ This complex has a square bipyramidal geometry with 2 Cl at the apical positions. [Au(en)Cl₂]Cl was reported to be isolated in 1967 by Brodersen et al.¹² However, the crystal structure for this 1:1 complex is first reported herein, as well as

judith.walmsley@utsa.edu.

Supporting Information Available Crystallographic data file in CIF format, CV as a function of scan rate, diffusion coefficients, ¹H NMR of [Au(en)Cl₂]Cl as a function of pD, ¹³C NMR available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

the electrochemical properties and the reactivity with guanosine 5'-monophosphate (Figure 1) for both $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}$ and $[\text{Au}(\text{en})_2\text{Cl}_2]\text{Cl}$.

Interest in the reactions of nucleobases, nucleosides and nucleotides on gold surfaces has received considerable attention. Relatively few studies have been directed toward the isolation and characterization of these compounds with Au(III). Reaction of AuCl_4^- with a variety of nucleosides and nucleotides has shown that the bonding mode of the Au(III) is dependent upon the nucleoside or nucleotide. Based on solution studies, possible N7-O6 chelation is suggested for guanosine and possible N7-phosphate macrochelation for 5'-GMP.^{13,14} Mixed ligand complexes have been reported, such as $[\text{Au}(\text{L}-\text{N},\text{N}')(\text{5'-GMP})_2]$, where L is N-(4-methylphenyl-2-pyridinecarboxamide)¹⁵ and the dimethylgold complex, $[(\text{CH}_3)_2\text{AuCl}(\text{guanosine})]$.¹⁶

Cytotoxicity studies of Au(III) complexes of polydentate amines, including ethylenediamine, have shown that they are as effective, or even more effective against certain tumor cell lines than cis-platin. When tested against cis-platin resistant cell lines, the Au(III) complexes remained nearly as effective against non-resistant cell lines. It was also shown that the bis(ethylenediamine)Au(III) complex binds to calf thymus DNA non-covalently, most probably through electrostatic interactions.¹⁷

Our interest has been the cyclic polynuclear complexes of the d8 metal ions, especially those in which the metal ions are bridged by nucleotides. Complexes of $[\text{Pd}(\text{en})]^{2+}$ with purine nucleotides, in which the nucleotide uses two N donor sites (N7 and N1) to bridge between the Pd(II) centers, have been shown to be cyclic tetramers in aqueous solution.^{18,19} However, we have not found any evidence for cyclic species in the $[\text{Au}(\text{en})\text{Cl}_2]^+$ system so far. Herein we report the synthesis of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$ and $[\text{Au}(\text{en})_2\text{Cl}_3]$, their thermogravimetric and electrochemical properties, reactions with 5'-GMP in solution, and the crystal structure of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$.

Methods and Materials

Materials

$\text{NaAuCl}_4\cdot 2\text{H}_2\text{O}$, ethylenediamine, D_2O , and $\text{dms}\text{-d}_6$ were purchased from Aldrich Chemical Co. and used as received. $\text{H}_2(5'\text{-GMP})$ and $\text{Na}_2(5'\text{-GMP})$ were purchased from Sigma and used as received. All solutions other than those for NMR measurements were prepared using deionized water that was purified with a Barnstead NANOpure cartridge system (18 M Ω).

Syntheses

$[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$ — $\text{NaAuCl}_4\cdot 2\text{H}_2\text{O}$ (0.218 g; 0.548 mmol) was dissolved in 20 mL of absolute ethanol at room temperature. To this solution was added 37 μL of ethylenediamine (0.55 mmol). An orange-brown precipitate formed immediately. After stirring the mixture for 20 min, the precipitate disappeared and the solution became slightly turbid. After filtration, the solution was concentrated to 5 mL and left to stand at room temperature. Pale yellow crystals of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$ formed gradually. Yield: 0.15 g. (68 %). Elemental analysis for $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$: Found %: C, 6.11; H, 2.97; N, 6.94, Cl, 26.71; calc %: C, 6.01; H, 3.03; N, 7.01; Cl, 26.63. ^1H NMR: 3.30 ppm in D_2O . The complex darkens in color at 105 $^\circ\text{C}$; decomposes at 195 $^\circ\text{C}$.

$[\text{Au}(\text{en})_2]\text{Cl}_3\cdot 0.5\text{HCl}$ — $\text{NaAuCl}_4\cdot 2\text{H}_2\text{O}$ (0.20 g; 0.50 mmol) was dissolved in 5 mL of deionized H_2O . To this solution was added 1.0 mL of 1.0 M aqueous solution of en. An orange precipitate formed at once and gradually redissolved (pH 4.3). A trace amount of

undissolved precipitate was removed by filtration and 30 mL of ethanol was added to the filtrate. The very pale yellow precipitate which formed immediately was filtered off and air dried. Yield: 0.16 g (72 %). Elemental analysis for $[\text{Au}(\text{en})_2]\text{Cl}_3 \cdot 0.5\text{HCl}$: Found %: C, 11.45; H, 3.72; N, 12.98, Cl, 27.87; calc %: C, 10.87; H, 3.76; N, 12.69; Cl, 28.09. ^1H NMR: 3.27 ppm in D_2O . The complex darkens in color at 170 °C; decomposes at 195 °C.

Nucleotide Stock Solutions— $\text{Na}_2(5' \text{'-GMP})$ or $\text{H}_2(5' \text{'-GMP})$ was dissolved in H_2O or D_2O and the concentration of the nucleotide was determined by UV spectroscopy (λ_{max} 252 nm; $\epsilon = 1.37 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$; pH 7). The required amount of Au(III) compound was added to the 5'-GMP solution.

Methods

Thermogravimetric Analysis—Measurements were made on a Shimadzu TGA-50 analyzer under N_2 atmosphere with a flow rate of 20 mL min^{-1} in a Pt cell. Samples weighed 3–7 mg. The temperature increased at 20 °C min^{-1} from room temperature to 900 °C.

NMR—Spectra were obtained in D_2O on a Varian Inova 500 MHz in D_2O . The temperature dependent ^1H studies were referenced to internal tetramethylammonium ion at 3.185 ppm and the spectra at 26 °C were referenced to the HOD line at 4.800 ppm (The TMA^+ resonance is very near that of ethylenediamine and can overlap at times). ^{31}P spectra were referenced to external 85 % H_3PO_4 and ^{13}C spectra to DSS. pD = pH (meter reading) + 0.40.

Electrochemical Measurements—A CHI 832 workstation (CH Instruments, Inc.) was used to collect electrochemical data. Experiments were performed at room temperature ($20 \pm 1 \text{ °C}$) in a conventional three-electrode system with 3.0 mm-diameter glassy carbon (GC) disk working electrode (Bioanalytical Systems, Inc.), a Pt wire as the auxiliary electrode, and a Ag/AgCl/3M NaCl (BAS) reference electrode. Prior to use, the glassy carbon electrodes were wet polished on an Alpha A polishing cloth (Mark V Lab) with successively smaller particles (0.3 and 0.05 μm diameter) of alumina. The slurry that accumulated on the electrode surface was removed by ultrasonication for 30 s in methanol and deionized water.

The concentration of the Au complexes was 1.0 mM and the background electrolyte was 0.40 M NaCl. The experiments were repeated at least three times and the means of measurements are presented with the standard deviations or relative standard deviations.

Bulk electrolysis of stirred solutions of Au complexes was performed using a GC rod ($\sim 0.6 \text{ cm}^2$) as a working electrode. The reductive electrolysis was continued for $\sim 4 \text{ h}$ until the current dropped to $\sim 1 \%$ of its initial value. The progress of electrolysis was also followed by using UV-visible spectrometry.

X-Ray Structure Determination—. A colorless prism-shaped crystal of dimensions $0.54 \times 0.36 \times 0.20 \text{ mm}$ was selected for structural analysis. Intensity data were collected using a Bruker D8 instrument with an APEX detector and graphite-monochromated Mo $K\alpha$ radiation. A total of 11,038 reflections were measured in the range $2.84 \leq \theta \leq 26.00^\circ$ using ω scan frames. The intensity data were corrected by a face-indexed, analytical absorption correction²¹ and an empirical absorption correction²² giving transmittances in the range of 0.0421 – 0.1419. These data were merged to form a set of 1897 independent data with $R_{\text{int}} = 0.0337$ and a completion of 99.8%. The space group $Pbca$ was determined by systematic absences and confirmed by refinement. The structure was solved by direct

methods and refined by full-matrix least squares on F^2 .²¹ The final difference map had maxima and minima of 1.766 and $-1.140 \text{ e}/\text{\AA}^3$, respectively.

Results and Discussion

Structure of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$

The crystal data and structure refinement are given in Table 1 and the ORTEP view and crystal packing of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$ are shown in Figures 2 and 3. Selected bond distances [$\text{\AA}$] and angles [$^\circ$] are listed in Tables 2 and 3 and hydrogen bond distances are given in Table 4. The Au(III) ion is four coordinated in a square planar geometry as expected. The Au-N bond lengths are 2.029(4) and 2.030(3) $\text{\AA}$, which is roughly the same as those found in $[\text{Au}(\text{phen})\text{Cl}]\text{Cl}_2$ (2.03~2.06 $\text{\AA}$)⁶ and macrocyclic polyamine complexes,²³ but slight longer than in Au(III)-peptide complexes (1.98~2.02 $\text{\AA}$)^{24,25} and a pyridine-2-carboxamido complex.²⁶ They are slightly shorter than in an EDTA complex (2.06~2.11 $\text{\AA}$).²⁷ The Au(III)-Cl bond lengths for the coordinated Cl^- are 2.2811(9) and 2.2836(11) $\text{\AA}$, which is roughly the same as found in the literature.^{6,11,27} The root mean square deviation from planarity for the 5 atoms comprising the square plane (N(1), N(4), Au, Cl(1), Cl(2)) is 0.0177.

The Au(III)-Cl(3) (ionic) distance is 3.3033(10) $\text{\AA}$ with the Cl^- -Au vector $\sim 90^\circ$ relative to the $\text{Au}(\text{N}_2\text{Cl}_2)$ square plane. Although much longer than the Au-Cl covalent bond distance and a little longer than the 3.103(4) $\text{\AA}$ found by Minacheva¹¹ for the square bipyramidal $[\text{Au}(\text{en})_2\text{Cl}_2]\text{Cl}$ compound, it is short enough to suggest a possible weak interaction between the Cl^- and the Au(III). The bonding of a fifth ligand, and sometimes a sixth, to a primarily square planar complex is well known.²⁸ An unusual compound, $\text{Au}(2,2'\text{-bpy})\text{Cl}_3\cdot 2.25\text{H}_2\text{O}$, has been reported by Lippert et al, in which two square planar $[\text{Au}(\text{bpy})\text{Cl}_2]^+$ ions are connected by a long Au-Cl-Au bridge (av. Au-Cl of 3.218(3) $\text{\AA}$).²⁹ Since the bpy ligands in the two units are said to be parallel to each other, it is likely that stacking holds the units sufficiently close to allow bridging.

The N(1)-Au-N(4) bond angle is $84.47(15)^\circ$, while the Cl(1)-Au-Cl(2) bond angle is $94.32(4)^\circ$. The difference between these is expected because of the greater non-bonding to non-bonding electron pair repulsions between the two coordinated Cl. The same type of variation between the $\text{N}_a\text{-Au-N}_b$ and $\text{Cl}_a\text{-Au-Cl}_b$ bond angles was reported for $[\text{Au}(\text{phen})\text{Cl}_2]\text{Cl}$,⁶ although both bond angles were smaller than those we report for $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$. The Au-N, Au-Cl bond lengths and Cl-Au-Cl and N-Au-N angles are comparable with $\text{Au}_2(\text{trien})\text{Cl}_5$ complex, where trien is triethylenetetraamine.³⁰

The cations and water molecules crystallize in layers in the b direction. A layer of chlorides separates every two layers of the cations and waters. There is extensive H-bonding between the NH_2 , Cl(3), and the water of hydration which serves to stabilize the structure (Table 4). As shown in Figure 3, two H_2O molecules are associated with each other through a H-bond. One of the pair ($\text{H}_2\text{O}(1\text{S})$) also forms hydrogen bonds to two Cl(3) and to the N of one en. The other $\text{H}_2\text{O}(2\text{S})$ hydrogen bonds to one Cl(3) and to en in 2 different cations. There is additional H-bonding between NH_2 and Cl(3).

Thermal analysis

As shown in Figure 4, $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$ loses its water of hydration beginning at 77°C and all water is lost by 127°C . The 9% weight loss agrees with the loss of 2 moles of H_2O . Scheme 1 gives the temperature ranges of the decompositions, the experimental mass losses, and the products.

[Au(en)₂]Cl₃·0.5HCl behaves in a similar manner. After loss of 0.5 mole HCl (4%), it loses 2 Cl and 2 ethylenediamine (42%) between 220–390 °C and the remaining AuCl decomposes between 390–600 °C. The ethylenediamine and Cl are lost at a higher temperature in Au(en)₂Cl₃·0.5HCl than in [Au(en)Cl₂]Cl·2H₂O, probably due to the stronger coordination of the ethylenediamine ligand compared to the Cl[−] ligand.

Electrochemistry of Gold Complexes

The survey cyclic voltammograms recorded at glassy carbon electrodes in aqueous solutions of gold complexes (1.0 mM in 0.40 M NaCl) displayed a series of distinct current peaks A, B, B1, and C (Figure 5). The original reduction peak A shifted toward more negative potentials in the order $E_p(\text{AuCl}_4^-, 0.410 \text{ V}) > E_p(\text{Au(en)Cl}_2^+, 0.140 \text{ V}) > E_p(\text{Au(en)}_2^{3+}, -0.290 \text{ V})$. This indicated that a bidentate ethylenediamine ligand stabilized the Au(III) oxidation state against reduction, as previously reported for chelating N donor ligands.³¹ The position of the peaks B, B1, and C, which developed on consecutive voltammetric scans, was essentially not influenced by the composition of the gold complex. The gold complexes displayed good electrochemical stability as indicated by their peak currents and peak potentials, which were stable ($\pm 10\%$) at least for 4 h.

The origin of the current peaks can be conveniently discussed by using the cyclic voltammogram for the Au(en)Cl₂⁺ complex (Figure 5a) as an example. On the first cathodic (negative-going) potential scan, the current peak A at 0.14 V was formed due to the reduction of the gold complex. The reduction process involved three electrons per molecule ($n = 3$) as indicated by the coulometric analysis of the exhaustive electrolysis at 0.0 V. The Au(III) → Au(0) reduction was also confirmed by the presence of gold deposit on the electrode surface after the electrolysis. The voltammetric and chronoamperometric analyses showed no intermediate Au(I) complexes, which is compatible with the fact that the ethylenediamine is not a π -acceptor ligand that could stabilize the intermediate oxidation state of gold. Such stabilization has been demonstrated in the case of the gold complexed with the π -acceptor phosphine ligands.³²

On the anodic (positive-going) backward scan, a symmetrical current peak B was formed at $\sim 1.00 \text{ V}$. This peak was present only when the potential on the forward scan was scanned beyond the peak A. Thus, the peak B was ascribed to anodic dissolution Au(0) → Au(III) of the gold presence of high chloride concentration in the solution, the anodic stripping of Au(0) deposit was deposit. In the driven by the complexation of Au(III) ions with Cl[−] ions. A small peak B1 that appeared at $\sim 0.80 \text{ V}$ was probably due to the competing process of gold oxide formation. The current after the peak B did not decay to zero, which suggested that the formation of gold oxide precluded a total dissolution of the Au(0) deposit from the electrode surface.

The scanning of the potential again toward more negative values yielded a broad reduction peak C at $\sim 0.40 \text{ V}$, which was not present during the first cathodic scan. The peak C can be ascribed to two parallel processes, which involved the reduction of gold oxide and AuCl₄[−] complex that were formed at the electrode/solution interface during the preceding anodic scan. The supportive argument for the latter process was that the reduction of the AuCl₄[−] reference complex yielded a current peak (Figure 5c, peak A) at the same potential as that of the peak C. The foregoing discussion can be summarized by the following overall peak assignments

Such an interpretation of peaks B, B1, and C is in agreement with the independence of the peak potentials upon the composition of the starting gold complex.

In order to avoid complications from excessive deposition/dissolution processes, the AuCl_4^- , $[\text{Au}(\text{en})\text{Cl}_2]^+$, and $[\text{Au}(\text{en})_2]^{3+}$ complexes were studied in narrower potential windows that included only their original reduction peak A (Figure S1, Supporting Information). The analysis of scan rate (ν) dependence of the peak currents (I_p) and peak potentials (E_p) revealed that the I_p increased linearly with $\nu^{1/2}$ ($R^2=0.997-0.994$) and E_p was directly proportional to $\log(\nu)$ ($R^2=0.998-0.991$) while shifting toward higher overpotentials. This indicated that molecules of gold complexes were transported by diffusion to the electrode surface, where they underwent electrochemically irreversible reduction. The voltammetry and chronoamperometry revealed that the substitution of Cl^- ions with bulkier ethylenediamine ligands resulted in lowering of the diffusion coefficient (Table 1S, Supporting Information).

Interaction with 5'-GMP

The AuCl_4^- ion and other Au(III) chloro complexes are known to undergo hydrolysis in water at relatively low pH.^{7,13} $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}$ hydrolyzed in aqueous solution above pD ~ 2.5 as shown by changes in the ^1H NMR of the ethylenediamine ligand (Figure S2, Supporting Information). At pD 1.4, the ethylenediamine chemical shift was 3.28 ppm, which is assigned to the $[\text{Au}(\text{en})\text{Cl}_2]^+$ complex. At pD 3.4, a new line appeared at 3.30 ppm and the intensity of the 3.28 ppm resonance was greatly reduced. The NMR line at 3.0 ppm is likely to be an hydroxo complex, such as $\text{Au}(\text{en})(\text{OH})\text{Cl}^+$ or $\text{Au}(\text{en})(\text{OH})_2^+$.⁶ At the even higher pD of 5.8, three distinct species were present (3.22, 3.27, 3.30 ppm) and a brown precipitate was observed, which precluded continuing above pD 5. This precipitate contained no ethylenediamine or 5'-GMP and was assumed to be an oxide or hydroxide of Au(III). A line at 3.22 ppm was broad and was probably a soluble polymeric Au(III) hydroxo or oxo species.

The ^1H NMR spectra of 10 mM aqueous solutions of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}$ containing different amounts of 5'-GMP in acidic solution are shown in Figure 6. There are clearly two 5'-GMP H8 signals and two H1' signals, one each from unreacted $\text{H}_2(5'\text{-GMP})$ and from a $\text{Au}(\text{en})\text{-}5'\text{-GMP}$ complex. The upfield of the two H8 (8.84 ppm) and the downfield of the two H1' (6.13 ppm) resonances are assigned to $\text{Au}(\text{en})\text{-}5'\text{-GMP}$, while the other H8 (8.92 ppm) and H1' (6.09 ppm) signals are those of unreacted 5'-GMP. The unreacted 5'-GMP resonance assignments were made on the basis of a pD-dependent experiment (Figure 7) which clearly showed the expected upfield shift of the H8 line of unreacted 5'-GMP with increasing pD.¹⁸ Even in the 2 mM 5'-GMP solution where there was a five-fold excess of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}$, a considerable amount of unreacted $\text{H}_2(5'\text{-GMP})$ was still present. This indicates that either the stability constant of the $\text{Au}(\text{en})\text{-}5'\text{-GMP}$ complex is rather small or the acidity of the solution is such that the N7 of 5'-GMP is partially protonated, or possibly both. Integration of the NMR spectra in Figure 6 shows that the mole ratio of reacted 5'-GMP to reacted $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}$ remained at 1:1, irrespective of the amounts of the two components in the solution. Although it appears (Figure 6) that the concentration of

Au(en)-5'-GMP complex is decreasing with increasing 5'-GMP concentration, it is simply the large excess of 5'-GMP that gives that appearance in the spectra.

The pD study of a solution of 20 mM Au(en)Cl₃ containing 20 mM 5'-GMP was carried out over the pD range 2.3–4.6 (Figure 7). Some precipitate of hydrolyzed Au(III) species was observed at pD 4.3 and above. The chemical shift of the H8 of the Au(en)-GMP complex remained constant at 8.83 ppm over the pD range studied, but that of unreacted 5'-GMP gradually shifted upfield with increasing pD until it reached 8.2 ppm, the chemical shift at which N7 is completely deprotonated. It is well known that metal-N7 purine bonding causes a large downfield shift of the H8 resonance. Therefore, the fact that the H8 resonance in the Au(en)-GMP complex remained constant at 8.83 ppm proves that the Au(III) is bonding to the N7 of the 5'-GMP. The ³¹P NMR of solutions under the same conditions and pD 3.6 also showed two resonances, 0.88 ppm (unreacted 5'-GMP) and 0.53 ppm (reacted 5'-GMP). Although this indicated a slightly different environment for the bonded 5'-GMP, it showed that a possible N7-phosphate macrochelate structure was not being formed because the ³¹P resonance for Au(III)-OPO₃R bonding would be located considerably downfield, as observed in a Co(III)-5'-GMP complex at 12 ppm.³³

The NMR results strongly support the formation of a 1:1 complex of a monomeric Au(III) (en) complex with monodentate N7-GMP bonding and a fourth ligand of Cl⁻, OH⁻, or H₂O. Alternatively, an N7-O6 chelate structure, proposed, but not confirmed by several authors, 13,14 could be formed. In order to determine the presence of this type of bonding, the ¹³C NMR spectrum of 11 mM Au(en)Cl₃-GMP (1:1 mole ratio) in D₂O at pD 2.8 was run and compared with that of 5'-GMP under the same conditions ((Table 5) and Figure S3, Supporting Information). As was observed for the ¹H spectrum of Au(en)Cl₃-GMP (1:1 mole ratio), lines were present for both complexed and unreacted H₂(5'-GMP). In all cases the resonances of the complexed species were located downfield of the corresponding resonances of the unreacted 5'-GMP. The only ¹³C resonances that exhibited significant differences in the chemical shifts between the complexed and unreacted species were C8 (Δδ = 2.9 ppm), C5 (Δδ = 1.6 ppm), and C1' (Δδ = 1.3 ppm). The relatively large Δδ values for the C8 and C5 carbons flanking the N7 position is just what is expected for Au(III)-N7 GMP bonding, while the small Δδ of 0.1 ppm for C6 suggests that the C6-O6 is not involved in the bonding. Therefore, these data eliminate the N7-O6 chelate structure as a possible Au(III) bonding mode at pD 2.8. The Δδ for C1' was ascribed to a conformational change of the ribose in the complexed species. These data also confirm that bonding of the Au(en) moiety is to the N7 of the 5'-GMP.

The thermal stability of a solution which was 10 mM in [Au(en)Cl₂]Cl and 15 mM in H₂(5'-GMP) (pD 2.4), was investigated over the temperature range 2–50 °C. The complex decomposed slightly as the temperature was raised, decreasing from 33 % [Au(en)Cl₂]Cl reacted at 2 °C to 27 % reacted at 50 °C. This implies that the coordination of 5'-GMP to [Au(en)Cl₂]⁺ is an exothermic process.

As one might expect, there is no significant reaction between Au(en)₂Cl₃ and Na₂(5'-GMP). The only ¹H NMR signals of 5'-GMP observed were those typical of unreacted nucleotide. This is due to the fact that the two coordinated bidentate en ligands bind to the Au(III) more strongly than 5'-GMP. Although no direct coordination of 5'-GMP was observed in Au(en)₂Cl₃-GMP system, H-bonding between 5'-GMP and the ethylenediamine in the Au(en)₂Cl₃ complex, as reported for other coordinatively saturated complexes,^{33,34} cannot be ruled out.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the National Institutes of Health (NIGMS/SCORE program, grant SO6-08194) and The University of Texas at San Antonio for research support.

Abbrev

en	ethylenediamine (1,2-diaminoethane)
5'-GMP	guanosine 5'-monophosphate

References

- Messori L, Marcon G. *Met. Ions Biol. Syst.* 2004; 42:385–424. [PubMed: 15206109]
- Messori L, Marcon G, Orioli P. *Bioinorg. Chem. Appl.* 2003; 1:177–187. [PubMed: 18365052]
- Tiekink ERT. *Gold Bull. (London)*. 2003; 36:117–124.
- Zhang CX, Lippard SJ. *Curr. Opin. Chem. Biol.* 2003; 7:481–489. [PubMed: 12941423]
- Marcon G, Carotti S, Coronello M, Messori L, Mini E, Orioli P, Mazzei T, Cinellu MA, Minghetti G. *J. Med. Chem.* 2002; 45:1672–1677. [PubMed: 11931621]
- Abbate F, Orioli P, Bruni B, Marcon G, Messori L. *Inorg. Chim. Acta.* 2000; 311:1–5.
- Fry FH, Hamilton GA, Turkevich J. *Inorg. Chem.* 1966; 5:1943–1946.
- Gibson CS, Colles WM. *J. Chem. Soc.* 1931:2407–2416.
- Block BP, Bailar JC Jr. *J. Am. Chem. Soc.* 1951; 73:4722–4725.
- Makotchenko EV. *Russ. J. Coord. Chem. (Trans. of Koord. Khim.)*. 2003; 29:720–723.
- Minacheva LK, Gladkaya AS, Sakharova VG, Don GM, Shchelokov RN, Porai-Koshits MA. *Zh. Neorg. Khim.* 1988; 33:683–687.
- Brodersen K, Kahlert T. *Z. Anorg. Allg. Chem.* 1967; 355:323–327.
- Gibson DW, Beer M, Barnett RJ. *Biochemistry.* 1971; 10:3669–3679. [PubMed: 4328868]
- Chatterji D, Nandi US, Podder SK. *Biopolymers.* 1977; 16:1863–1878. [PubMed: 901918]
- Yang T, Zhang J-Y, Tu C, Lin J, Liu Q, Guo Z-J. *Wuji Huaxue Xuebao.* 2003; 19:45–48.
- Mizuno Y, Komiya S. *Inorg. Chim. Acta.* 1986; 125:L13–L15.
- Marcon G, O'Connell T, Orioli P, Messori L. *Metal-Based Drugs.* 2000; 7:253–256. [PubMed: 18475953]
- Zhu S, Matilla A, Tercero JM, Vijayaragavan V, Walmsley JA. *Inorg. Chim. Acta.* 2004; 357:411–420.
- Wirth W, Blotvogel-Baltronat J, Kleinkes U, Sheldrick WS. *Inorg. Chim. Acta.* 2002; 339:14–26.
- SMART Software Reference Manual (1998) and SAINT Software Reference Manual (1998). Bruker-AXS, 5465 E. Cheryl Pkwy, Madison, WI 53719–1173 USA.
- Sheldrick GM. 2000 International Tables for Crystallography, Vol C. 1965KluwerBoston
- Sheldrick, GM. SADABS. University of Göttingen; Germany: 2002.
- Suh MP, Kim IS, Shim BY, Hong D, Yoon T-S. *Inorg. Chem.* 1996; 35:3595–3598.
- Wienken M, Lippert B, Zangrando E, Randaccio L. *Inorg. Chem.* 1992; 31:1983–1985.
- Best SL, Chattopadhyay TK, Djuran MI, Palmer RA, Sadler PJ, Sovago I, Varnagy K. *J. Chem. Soc., Dalton Trans.* 1997:2587–2596.
- Hill DT, Burns K, Titus DD, Girard GR, Reiff WM, Mascavage LM. *Inorg. Chim. Acta.* 2003; 346:1–6.
- Cornejo AA, Castineiras A, Yanovsky AI, Nolan KB. *Inorg. Chim. Acta.* 2003; 349:91–96.

28. Marangoni G, Pitteri B, Bertolasi V, Ferretti V, Gilli G. *J. Chem. Soc., Dalton Trans.* 1987:2235–2240.
29. Micklitz W, Lippert B, Müller g, Mikulcik P, Riede J. *Inorg. Chim. Acta.* 1989; 165:57–64.
30. Messori L, Abbate F, Orioli P, Tempi C, Marcon G. *Chem. Commun.* 2002:612–613.
31. Messori L, Abbate F, Marcon G, Orioli P, Fontani M, Mini E, Mazzei T, Carotti S, O'Connell T, Zanello P. *J. Med. Chem.* 2000; 43:3541–3548. [PubMed: 11000008]
32. Koelle U, Laguna A. *Inorg. Chim. Acta.* 1999; 290:44–50.
33. Fletcher TM, Walmsley JA. *J. Inorg. Biochem.* 1997; 68:239–249.
34. Farmer PJ, Cave JR, Fletcher TM, Rhubottom JA Jr. Walmsley JA. *Inorg. Chem.* 1991; 30:3414–3420.

Scheme 1.

Figure 1.
Guanylic acid, $H_2(5'-GMP)$

Figure 2.
ORTEP drawing of $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$ with the atomic numbering scheme.

Figure 3.
Packing diagram of [Au(en)Cl₂]Cl·2H₂O. ● Cl; ◐ N; ◑ Au; ○ O

Figure 4. TGA curves of (a) [Au(en)Cl₂]Cl·2H₂O; (b) [Au(en)₂Cl₂]Cl·0.5HCl, run in an N₂ atm with flow rate of 20 mL/min and temperature increase 20 °C/min.

Figure 5. Survey cyclic voltammograms recorded at a glassy carbon electrode in 1.0 mM solutions of Au(III) complexes: (a) Au(en)Cl_2^+ , (b) Au(en)_2^{3+} , (c) AuCl_4^- . The vertical arrows indicate a direction of change in peak currents upon repetitive scanning of the electrode potential. Background electrolyte, 0.40 M NaCl. Scan rate, 100 mV s^{-1} .

Figure 6.

^1H NMR of 10 mM $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}$ with various concentrations of $\text{H}_2(5'\text{-GMP})$ in D_2O , pH 2.5. U = unreacted 5'-GMP; R = $\text{Au}(\text{en})\text{-GMP}$ complex.

Figure 7.
 ^1H NMR of 10 mM Au(en)-5'-GMP in D_2O at various pD. U = unreacted 5'-GMP; R = Au(en)-GMP complex.

Table 1Crystallographic data for $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl} \cdot 2\text{H}_2\text{O}$.

chemical formula	$\text{C}_2 \text{H}_{12} \text{Au} \text{Cl}_3 \text{N}_2 \text{O}_2$
formula weight	399.45
space group (No. 61)	<i>Pbca</i>
<i>a</i>	11.5610(15) Å
<i>b</i>	12.6399(17) Å
<i>c</i>	13.2156(17) Å
<i>V</i>	1931.2(4) Å ³
<i>Z</i>	8
<i>T</i>	−173(2) °C
λ	0.71073 Å
D_{calcd}	2.748 g cm ^{−3}
μ	160.19 cm ^{−1}
$R(F, \text{obsd})^*$	0.0221
$wR(I^2, \text{all})^*$	0.0620

$$^* R = \sum \|F_o| - |F_c|\| / \sum |F_o|, wR = \{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}^{1/2}$$

Table 2Selected Bond lengths [$\text{\AA}$] and angles [$^\circ$] for $[\text{Au}(\text{en})\text{Cl}_2]\text{Cl}\cdot 2\text{H}_2\text{O}$

Au(1)-N(1) 2.029(4)	Au(1)-N(4) 2.030(3)
Au(1)-Cl(1) 2.2811(9)	Au(1)-Cl(2) 2.2836(11)
Au(1)-Cl(3) 3.3033(10)	
N(1)-Au(1)-Cl(1) 89.90(11)	N(4)-Au(1)-Cl(1) 173.89(10)
N(1)-Au(1)-Cl(2) 175.65(11)	N(4)-Au(1)-Cl(2) 91.27(10)
Cl(1)-Au(1)-Cl(2) 94.32(4)	N(1)-Au(1)-N(4) 84.47(15)
Cl(1)-Au(1)-Cl(3) 87.63(3)	Cl(2)-Au(1)-Cl(3) 85.30(3)

Table 3Torsion angles [$^{\circ}$] for [Au(en)Cl₂]Cl·2H₂O

N(4)-Au(1)-N(1)-C(2)	-12.3(3)
Cl(1)-Au(1)-N(1)-C(2)	170.1(2)
Cl(2)-Au(1)-N(1)-C(2)	-24.0(16)
Au(1)-N(1)-C(2)-C(3)	38.8(4)
N(1)-C(2)-C(3)-N(4)	-53.7(4)
C(2)-C(3)-N(4)-Au(1)	42.5(4)
N(1)-Au(1)-N(4)-C(3)	-16.7(3)
Cl(1)-Au(1)-N(4)-C(3)	6.4(13)
Cl(2)-Au(1)-N(4)-C(3)	162.4(3)

Table 4Hydrogen bonds for [Au(en)Cl₂]Cl·2H₂O [$\text{\AA}$ and $^\circ$]

D-H...A*	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...O(2S)	0.93(6)	1.88(6)	2.791(5)	164(4)
N(1)-H(1B)...Cl(3) ^{#1}	0.80(5)	2.39(5)	3.180(4)	170(5)
N(4)-H(4A)...O(2S) ^{#2}	0.81(5)	2.04(5)	2.807(5)	157(5)
N(4)-H(4B)...O(1S)	0.82(5)	2.11(5)	2.925(5)	173(5)
O(1S)-H(1S1)...Cl(3)	0.81(5)	2.35(5)	3.135(3)	164(5)
O(1S)-H(1S2)...Cl(3) ^{#3}	0.81(6)	2.45(6)	3.243(3)	166(5)
O(2S)-H(2S1)...Cl(3)	0.66(5)	2.60(5)	3.218(3)	157(6)
O(2S)-H(2S2)...O(1S) ^{#4}	0.79(5)	2.04(5)	2.813(4)	168(5)

Symmetry transformations used to generate equivalent atoms:

^{#1}
-x+1/2, y+1/2, z^{#2}
x, -y+1/2, z+1/2^{#3}
-x, -y, -z+1^{#4}
x+1/2, y, -z+1/2*
D is H-bond donor; A is H-bond acceptor

Table 5¹³C NMR Chemical Shifts of 5'-GMP and Au(en)-5'-GMP in D₂O at pD 2.8

	5'-GMP/ppm ^a	Au(en)-5'-GMP complex/ppm ^{b,c}
C6	156.49	156.60, 156.38
C2	155.20	155.27, 155.25
C4	150.36	150.34
C8	136.31	139.21, 136.26
C5	110.95	112.65, 110.69
C1'	89.01 ^d	90.31, 89.14
C4'	84.19 ^e	84.40 ^e , 84.19 ^e
C2'	74.60	74.92, 74.63
C3'	69.82	69.78, 74.63
C5'	63.84 ^f	64.00, 63.66
en (react)		51.87, 50.90
en (unreact)		51.13

^a 15 mM^b 11 mM^c the more downfield line is 5'-GMP in Au(en)-5'-GMP and the upfield line is unreacted 5'-GMP^d doublet, J = 1.0 Hz^e split by ³¹P, J = 8.7 Hz^f split by ³¹P, J = 5.0 Hz