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Synthesis and Properties of the First [Au(dien)(N-heterocycle)]$^{3+}$ Compounds

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Supporting Information

ABSTRACT: Novel Au^{III}(dien)(N-heterocycle) compounds, including the first $Au^{III}N_3$(*N*-purine) examples, are reported. The acidity of the dien ligand is affected by the nature of the fourth ligand as a leaving group. The metal center of [Au(dien)(N-heterocycle)]$^{3+}$ compounds was shown to be more stable to reduction than when Cl^- is present, with consequences for reactivity with biomolecules: specifically, significant enhancement of $\pi-\pi$-stacking interactions with tryptophan relative to isostructural and isoelectronic platinum(II) and palladium(II) compounds.

We are currently exploring the use of small-molecule coordination compounds as electrophiles to alter the zinc finger peptide structure and function.[1,2] Electrophilic attack by [MCl(dien)]$^{n+}$ (M = Pt^{II}, Pd^{II}, Au^{III}; dien = diethylenetriamine) on the C-terminal finger of HIV Nucleocapsid NCp7(F2) results in conformational changes and ejection of Zn^{2+}.[3] Platinated nucleobases such as [Pt(dien)(9-EtG)]$^{2+}$ (9-EtG = 9-ethylguanine) with a more substitution-inert nitrogen donor as the "leaving group" stack effectively in a "noncovalent" manner with tryptophan of NCp7(F2).[4] We therefore wanted to study the more reactive gold(III) system for comparison as well as to examine models for the interaction of [AuCl(dien)]$^{2+}$ with DNA.[5] In this paper we report on the synthesis and characterization of [Au^{III}(dien)X] chelates with purines and nitrogen-donor heterocycles, the first isolated $Au^{III}N_3$(*N*-purine)/heterocycle compounds (Figure 1). The acidity of the primary and secondary amines is a long-recognized feature of [AuCl(dien)]$^{2+}$ chemistry.[6−11] The presence of the pyridine or purine affects this acidity and the redox properties of the gold(III) complex as a whole. These differences further translate to variations in the reactivity with biomolecules, where, for 9-EtG, tryptophan stacking is significantly enhanced over that of the platinum(II) and palladium(II) analogues.

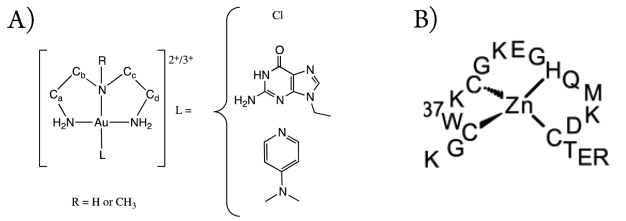

Figure 1. Structures of [Au^{III}(dien)X] chelates studied (A) and the C-terminal finger of HIV Nucleocapsid NCp7(F2) (B).

Tetranitrogen donor complexes of gold(III) are known for porphyrin-[12] and cyclam-based macrocycles,[13] but the [Au^{III}(dien)X] species discussed herein are the first to be synthesized where X is a purine or planar N-heterocyclic ligand. Nitrogen-donor planar amines are good σ-donor and π-acceptor groups, and the kinetics of L(N-heterocycle) substitution by Cl^- in $AuCl_3L + Cl^- \rightarrow [AuCl_4]^- + L$ showed a linear relationship between the basicity of the leaving group and the reactivity with respect to chloride substitution.[14] The complex [$AuCl_3$(9-EtG)] has been isolated, confirming Au−N7 binding,[15] and solution studies show that guanosine(inosine) monophosphate and histidine bind with high affinity to gold(III) centers.[16]

The reaction of [AuCl(dien)]Cl_2 with 9-EtG in the presence of 3 equiv. of $AgNO_3$ afforded orange [Au(dien)(9-EtG)]-$(NO_3)_3$. NMR and potentiometry showed three major distinct species for this complex over a wide pH range (Figures 2 and S1−S3 in the Supporting Information, SI). The initial pH* of a 10 mM aqueous solution is 2.63, where pH* is the measurement of the pH meter. The ^{1}H NMR spectrum shows that as the pH is increased the purine H8 signal first broadens and shifts upfield (Figure 2). This is followed by the appearance of sharp peaks in the intermediate pH 5−7 range and eventually purine dissociation at basic pH. Potentiometric titration also showed three midpoints with approximate pK_a values of 3.3, 5.3, and 7.5 (Figure S1 in the SI).

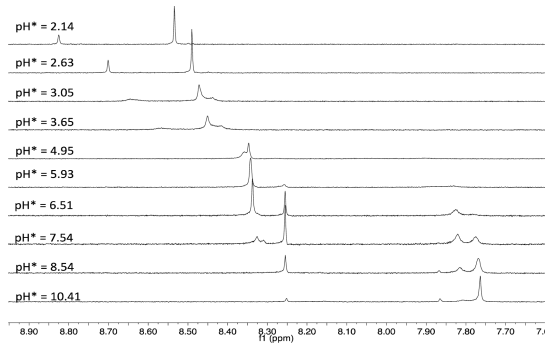

Figure 2. ^{1}H NMR spectra showing the H8 proton of 9-EtG in [Au(dien)(9-EtG)]$(NO_3)_3$ over the pH range.

The pK_a for deprotonation of the secondary central amine in [AuCl(dien)]$^{2+}$ is in the range of 4.0−4.7 depending on the

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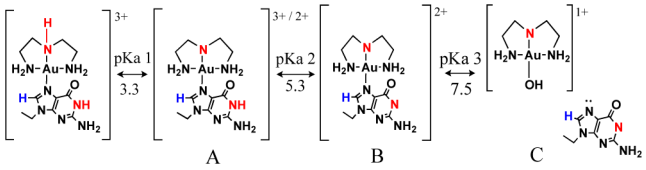
conditions.[7,11] The dien region of the ^{1}H and ^{13}C NMR spectra for $[Au(dien)(9\text{-EtG})](NO_3)_3$ was similar to that reported for $[AuCl(dien)]Cl_2$ (Scheme 1 and Figures S2 and S3 in the SI).[11]

Scheme 1. Proposed Structures for $[Au(dien)(9\text{-EtG})](NO_3)_3$ over a Broad pH Range



The ^{13}C chemical shifts are a sensitive diagnostic of chelate deprotonation[11] and were fitted in this case to a pK_a of 3.3 for the central nitrogen on the dien. At pH* >6.3, new signals appear, attributed, as for $[AuCl(dien)]Cl_2$, to hydrolysis of the gold(III) species,[11] also supported by dissociation of 9-EtG at basic pH. A reasonable explanation for the three species observed is therefore a "fully" protonated species, a species with dien-H but N1 protonated, and a fully "deprotonated" species. The pK_a of N1H of 9-EtG (9.57) is reduced to 8.17 in $[Pt(dien)(9\text{-EtG})]^{2+}$.[17] Binding to gold(III) further decreases this value to 5.3.

To confirm these interpretations, analogous $[Au^{III}(N\text{-Medien})X]$ (N-Medien = 2,2′-diamino-*N*-methyldiethylamine) compounds were prepared. In comparison to the free ligand, the ^{1}H NMR N−Me peak shifts significantly downfield by approximately 1.35 ppm for both Cl^- and 9-EtG. The pH dependency of the ^{1}H NMR spectrum shows only two major peaks, as expected (Figure S4 in the SI). At pH* 2.96, one peak is present, likely representing the fully protonated species. At pH* 4.05, an additional upfield peak appears, indicating N1H deprotonation. At pH* >5.6, the 9-EtG ligand is completely dissociated. A pK_a of 5.7−6.8 has been assigned for deprotonation of the primary amine in $[AuCl(N\text{-Medien})]^{2+}$.[18] Such deprotonation may destabilize of the Au−9EtG bond.

We further prepared $[Au(dien)(DMAP)]^{3+}$ [DMAP = 4-(dimethylamino)pyridine] because the more basic DMAP (4-Me_2Npyr) has a pK_a of 9.1, compared to that of 2.7 for 9-EtG.[17] The UV/vis spectra in the 3−5 pH range shows one isosbestic point (Figure S5 in the SI). In the ^{13}C NMR spectrum at pH* up to 6.4, two ^{13}C signals were observed, assigned to C_b and C_c (peak 1) and C_a and C_d (peak 2) (Figure 3). The pH dependence of the peak shifts was fitted to a pK_a of 4.7 for the secondary central amine of the dien, higher than that for 9-EtG but similar to $[AuCl(dien)]^{2+}$.[7,11] Additional peaks appear at pH* >6, peaks

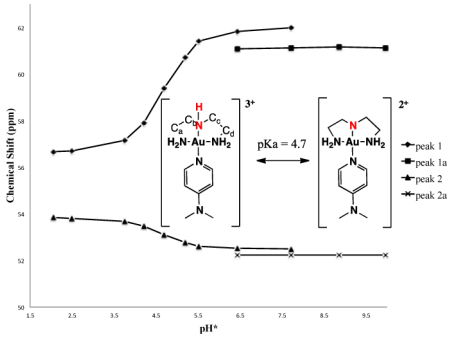


Figure 3. ^{13}C NMR chemical shift values of dien carbon atoms versus pH* for 50 mM $[Au(dien)(DMAP)]Cl_3$ in D_2O and proposed structures over the pH range shown.

1a and 2a in Figure 3, but the DMAP ligand remains bound, thus protecting the compound from hydrolysis (Figure S6 in the SI). The extra peaks may be due to deprotonation of the primary amines.

The contrast between X = Cl^- and the N-heterocycle as the fourth ligand is clearly seen in the $[Au(N\text{-Medien})X]^{n+}$ case. The ^{1}H NMR N−Me peak in the DMAP complex is shifted downfield similar to Cl^- and 9-EtG. In excess Cl^-, chelate displacement occurs for $[AuCl(N\text{-Medien})]^{2+}$ by a ring-opening mechanism with a large absorption band at 317 nm indicative of the production of $[AuCl_4]^-$.[18] A similar trend is seen at low pH even in the absence of Cl^-, with a large absorption band at 310 nm (Figure S7A in the SI). The development of this band is not seen for the DMAP case, suggesting that no ring opening occurs and that the N-Medien ligand is stabilized by the DMAP ligand (Figure S7B in the SI). At low pH*, one dien N−Me peak is present in the ^{1}H NMR spectrum of both compounds, with a new peak appearing 0.15 ppm upfield at higher pH* (Figure S8 in the SI). At pH* 6.1, these peaks are present at 50:50 integration, suggesting that the pK_a of both compounds is ∼6.1 under these conditions and indicating deprotonation of the primary amines on the N-Medien ligand, as reported.[18] At high pH*, the DMAP ligand remains bound to the gold(III) center (Figure S8C in the SI).

The basic and more substitution-inert nitrogen donor stabilizes the gold(III) metal center. Cyclic voltammetry (CV) of $[Au^{III}(dien)X]$ (X = Cl^-, 9-EtG, and DMAP) in a phosphate buffer (to maintain a constant pH for all compounds) showed only one peak indicating a one-step reduction of Au^{III}/Au^0 but with more negative reduction potentials for the nitrogen donors compared to the AuN_3Cl species, indicating a more stable metal center (Table 1). CV in water gave two reduction peaks for separated Au^{III}/Au^{I} and Au^{I}/Au0 steps.

Table 1. Peak Potential Values (vs Ag/AgCl) for the Reduction of Gold(III) Complexes at a Platinum Electrode

complex[a]	E_p[b] (V)	E_p^1[c] (V)	E_p^2[c] (V)
$[AuCl(dien)]^{2+}$	−0.280	0.1	−0.418
$[Au(dien)(9\text{-EtG})]^{3+}$	−0.349	0.064	−0.446
$[Au(dien)(DMAP)]^{3+}$	−0.328	N/A	−0.563
$[AuCl(N\text{-Medien})]^{2+}$	−0.232	0.043	−0.407
$[Au(N\text{-Medien})(9\text{-EtG})]^{3+}$	−0.263	0.047	−0.358
$[Au(N\text{-Medien})(DMAP)]^{3+}$	−0.238	0.0482	−0.5504

[a]Anions omitted for clarity. [b]50 mM phosphate buffer, 4 mM NaCl, and pH 7.4. [c]H_2O and 0.1 M NaCl.

Stabilization was not observed for $[Au(N\text{-Medien})(9\text{-EtG})]^{3+}$ attributed to the observed dissociation of the purine ligand, while the low peak potential for $[Au(N\text{-Medien})(DMAP)]^{3+}$ at pH 7.4 may suggest that deprotonation of the primary amines affects the stability of the metal center.

A primary reason for the synthesis of these compounds has been to compare their potential biological properties with those of their isoelectronic and isostructural platinum analogues. Fluorescence studies with tryptophan, a planar amino acid present in the C-terminal finger of the NCp7-HIV Zn finger (Table 2), shows that the π-stacking affinity of Au^{III}(9EtG) compounds is increased over those of their platinum(II) and palladium(II) analogues.[19,20] All DMAP compounds give K_a values significantly higher than those for their direct 9-EtG analogues, reflecting the greater basicity of the DMAP ligand.[21] The low K_a for $[Au(N\text{-Medien})(9EtG)]^{3+}$ in a Tris buffer, pH 7.4

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Table 2. Association Constants Obtained from Eadie–Hoftsee Plots of *N*-Acetyltryptophan with Different Gold(III) Quenchers[a]

compound	K_a ($\times 10^3$ M^{-1})	SD
free 9-EtG	3.3[19]	0.1[19]
[Pt(dien)(9-EtG)]$^{2+}$	7[19,20]	0.1[19]
[Pd(dien)(9-EtG)]$^{2+}$	5.1[19]	0.3[19]
[Au(dien)(9-EtG)]$^{3+}$	16.7 (16.6)[b]	1.5 (1.9)
[Au(N-Medien)(9-EtG)]$^{3+}$	10.0 (16.7)	0.4 (0.5)
free DMAP	29.0	1.1
[Pt(dien)(DMAP)]$^{2+}$	25.0[20]	0.9[20]
[Au(dien)(DMAP)]$^{3+}$	25.5 (26.5)	0.3 (0.9)
[Au(N-Medien)(DMAP)]$^{3+}$	31.2 (26.1)	0.8 (0.3)

[a]In a Tris HCl buffer, pH 7.4. Anions omitted for clarity. [b]Values in parentheses were obtained in water.

(but not in water), may be explained again by dissociation of 9EtG at biological pH.

In summary, the use of N-heterocycle ligands allows for manipulation of the metal–ligand electronic communication, leading to new insight into well-known chemistry including (i) the first isolated $Au^{III}N_3$(*N*-purine)/heterocycle compounds, (ii) recognition of the effect of the N-heterocycle on the acidity of the Au(dien) ligands; (iii) stabilization of the gold(III) center, and (iv) enhancement of $\pi-\pi$-stacking interactions relative to isostructural and isoelectronic platinum(II) and palladium(II) compounds. While many diverse gold(III) complexes have been reported with interesting cytotoxicity, information on speciation and stability at physiological pH is lacking. The use of more substitution-inert ligands within the MN_4 chemotype allows for greater control and more specific interactions with biomolecules, especially those with strongly nucleophilic thiolates.[22]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, compound characterization, and supplementary pH dependency studies by NMR, UV/vis, and potentiometry. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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