

# Au<sub>2</sub>trien: a dinuclear gold(III) complex with unprecedented structural features

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The X-ray structure of a dinuclear gold(III) complex, Au<sub>2</sub>trien, shows the presence of two square planar gold(III) centers bridged by a nitrogen donor, in a very unusual fashion.

Today there is renewed interest in gold(III) complexes as possible cytotoxic and antitumor drugs. Indeed, a number of gold(III) complexes were recently described that possess sufficient stability under physiological conditions and exhibit relevant cytotoxic effects on cultured human tumor cell lines.<sup>1–3</sup> In all cases only mononuclear gold(III) complexes were considered.

Specifically, we have reported on a series of gold(III) polyamine complexes characterized by high stability at neutral pH and by significant cytotoxic properties.<sup>4</sup> Within this frame the reaction of tetrachloroauric acid with the ligand triethylenetetramine (trien) has been carried out to obtain the homologue of the well known diethylenetriamine gold(III) complex (Audien).<sup>5</sup> The reaction,<sup>6</sup> performed at low pH, led to the formation of a gold(III) product with a yield of *ca.* 20%. This compound was isolated and recrystallised from water as small pale yellow crystals. To our surprise, elemental analysis data did not confirm formation of the expected mononuclear Autrien complex but rather indicated a 2:1 gold to ligand stoichiometry.<sup>†</sup> The compound [Au<sub>2</sub>(trien)Cl<sub>3</sub>]Cl<sub>2</sub>·2H<sub>2</sub>O (Au<sub>2</sub>trien) was further characterized by crystallographic methods that clearly revealed its dimetallic nature.<sup>‡</sup> The structure of the dication [Au<sub>2</sub>(trien)Cl<sub>3</sub>]<sup>2+</sup> is shown in Fig. 1.

Notably this dinuclear gold(III) complex presents two square planar gold(III) centers with different sets of donors. Au1 is coordinated to three nitrogens and one chloride while Au2 is coordinated to two nitrogens and two chlorides. The distance between the two gold(III) ions is 3.46 Å. Most interestingly there

is a deprotonated amino nitrogen bridging the two gold(III) centers. The two gold(III) coordination planes (Au1, N1, N4, N7, Cl1) and (Au2, N7, Cl2, Cl3) form an angle of 76.6(2)°.

After completing the crystallographic determination, some features of the solution behavior of Au<sub>2</sub>trien were analyzed by electronic absorption and <sup>1</sup>H NMR spectroscopies. Water solutions of Au<sub>2</sub>trien are pale yellow and markedly acidic as commonly found for gold(III) complexes with gold-coordinated chlorides (indeed, the pH of freshly prepared mM solutions of Au<sub>2</sub>trien falls in the range 2.5–3.0). The absorption spectra are dominated by a main band, centered at 360 nm, that is tentatively assigned as a N<sup>–</sup> to gold(III) LMCT transition.<sup>6</sup> Notably, the complex is stable in water, at low pH, for several hours as suggested by the substantial stability of the visible and <sup>1</sup>H NMR spectra. No significant spectroscopic changes were observed over 3 h even after raising the temperature to 50 °C.

In contrast, the <sup>1</sup>H NMR spectrum changes greatly by increasing the pH and a complicated spectral pattern is observed diagnostic of the presence of multiple species.§ Complex pH dependent spectral patterns were previously reported by Sadler for the simpler Audien compound.<sup>7</sup> Studies are in progress to elucidate the pH dependent equilibria of Au<sub>2</sub>trien. Eventually, near physiological pH, gold partially precipitates as colloidal gold. The yellow compound remaining in solution, at pH 7.4, most likely corresponds to mononuclear Autrien as suggested by ESI-MS measurements.¶

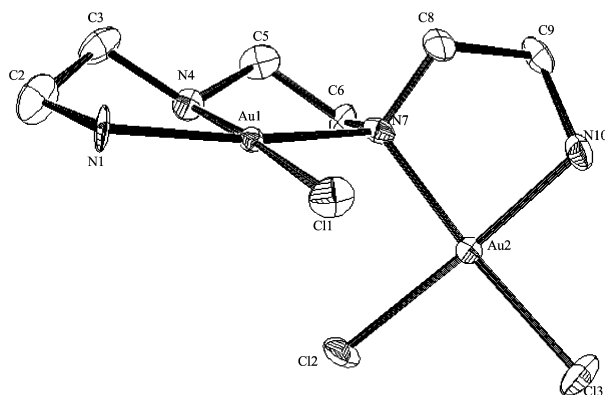
To our knowledge Au<sub>2</sub>trien is the first example of a water soluble dinuclear gold(III) complex with N- and Cl-donors and with asymmetric gold(III) centers. The crystal structure showing a deprotonated amino group bridging two gold(III) centers is unprecedented. Remarkably, the two gold(III) ions lower the pK<sub>a</sub> of the bridging R<sub>2</sub>NH group to well below 3. Also, it is of interest to observe that dinuclear Au<sub>2</sub>trien forms preferentially with respect to mononuclear Autrien even in the presence of excess ligand, suggesting that binding of gold(III) to trien is cooperative and that formation of the compact dinuclear complex is thermodynamically favored.

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## Notes and references

<sup>†</sup> <sup>‡</sup> <sup>§</sup> <sup>¶</sup> **Synthesis:** A solution of trien·4HCl (1.36 g, 4.7 mmol) in water (2 ml) was added slowly, with stirring, to a solution of HAuCl<sub>4</sub>·3H<sub>2</sub>O (0.70 g, 1.8 mmol) in the same solvent (2 ml). A yellow precipitate immediately formed. The pH was adjusted to 1.7 by addition of sodium hydroxide. The mixture was left stirring at 0 °C for 2 h. The light yellow precipitate was then filtered off, washed twice with cold ethanol and dried over P<sub>4</sub>O<sub>10</sub>. The yield was *ca.* 20%. Found C 10.9%.

**Crystallographic data:** Slight yellow crystals of Au<sub>2</sub>trien were obtained from slow evaporation of a water solution at room temperature. C<sub>6</sub>H<sub>21</sub>Cl<sub>5</sub>N<sub>4</sub>O<sub>2</sub>Au<sub>2</sub>, *M* = 753.46, monoclinic, *a* = 11.504(4), *b* = 11.909(2), *c* = 13.031(4) Å, β = 100.18(2)°, *V* = 1757.2(13) Å<sup>3</sup>, *T* = rt, space group *P*2<sub>1</sub>/*c*, *Z* = 4, μ = 37.98 mm<sup>–1</sup>, 3628 reflections measured, 2806 unique (*R*<sub>int</sub> = 0.05) which were used in all calculations. The final agreement factor was *R* = 0.0393 for 2537 *F*<sub>o</sub> > 4σ(*F*<sub>o</sub>) and 0.0431 for all 2806 data. Data were collected at 20 °C on a P4 Siemens installed on a



**Fig. 1** Molecular structure of the dication [Au<sub>2</sub>(trien)Cl<sub>3</sub>]<sup>2+</sup>. All H omitted for clarity. Selected bond distances (Å) and angles (°): Au1–N1 2.045(9), Au1–N4 2.017(9), Au1–N7 2.060(9), Au1–Cl1 2.287(3), Au2–N7 2.074(8), Au2–N10 2.024(9), Au2–Cl2 2.275(3), Au2–Cl3 2.282(3), N1–Au1–N4 84.2(4), N4–Au1–N7 85.9(4), N1–Au1–Cl1 95.2(3), N7–Au1–Cl1 95.0(2), N4–Au1–Cl1 176.4(3), N1–Au1–N7 168.7(4), N7–Au2–N10 85.2(4), N10–Au2–Cl3 90.5(3), N7–Au2–Cl2 91.7(2), Cl2–Au2–Cl3 92.6(1), N10–Au2–Cl2 176.6(3), N7–Au2–Cl3 175.6(2).

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rotating anode using Cu-K $\alpha$  radiation. Indexing and data correction were done with the Xscans-Siemens program. The structure was solved using SIR97<sup>8</sup> and refined with the SHELXL97 program.<sup>9</sup> CCDC reference number 176425. See <http://www.rsc.org/suppdata/cc/b1/b111395j/> for crystallographic data in CIF or other electronic format.

§ <sup>1</sup>H NMR measurements: <sup>1</sup>H NMR spectra were recorded on a Varian Gemini 2000 spectrometer operating at 300 MHz. 1.0 mM aqueous solutions of [Au<sub>2</sub>(trien)Cl<sub>3</sub>]Cl<sub>2</sub>·2H<sub>2</sub>O were prepared at different pH values (2.8, 4.0, 7.4, 9.0). Spectra were recorded over a period of 3 h after dissolution.

¶ *Electrospray measurements*: Electrospray mass spectra were registered in positive ion mode. The positive ion MS spectra were recorded on an LCQ electrospray (ThermoQuest, San Jose, CA, USA) directly coupled to the HPLC-DAD (DAD = Diode Array Detection) (Hewlett & Packard, Palo Alto, CA, USA). Capillary temperature was 220 °C, capillary voltage 3.0 V, source voltage 4.2 kV, tube lens voltage 30 V and collision energy 35%. A 1 mg ml<sup>-1</sup> solution of the analyte in the reference buffer (100 mM NaCl, 50 mM phosphate, pH 7.4 at 25 °C) was introduced into the interface by a syringe pump at a flow of 5  $\mu$ l min<sup>-1</sup>; the ES mass spectrum reveals an intense peak corresponding to the [Au(trien)]<sup>3+</sup> species (*m/z* 341.4).

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