

## Platinum coordination chemistry with nucleobases

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**Abstract** - Synthetic, structural and reactivity aspects of metal complexes of Pt, Pd and Au, containing the pyrimidine nucleobases 1-methyluracil and 1-methylthymine, are reported. A particularly rich coordination chemistry is found within the *cis*-A<sub>2</sub>Pt system (A = NH<sub>3</sub> or A<sub>2</sub> = chelating diamine) and attributed to a combination of favorable geometry (relative positions of exocyclic oxygens of pyrimidine bases adjacent to the Pt binding site N3), high basicity of these sites, and ready oxidizability of Pt(II). Examples discussed include mixed-nucleobase complexes, dinuclear Pt(II) complexes, mixed-metal complexes, and mixed-valence state compounds.

### INTRODUCTION

Among Pt complexes of nucleobases, those containing the pyrimidine bases uracil and thymine display a particularly rich coordination and redox chemistry (ref. 1). Work in this area was initiated by Rosenberg and coworkers in the early seventies (ref. 2) when they described a class of so called "platinum pyrimidine blues", derived from aquated *cis*-(NH<sub>3</sub>)<sub>2</sub>PtCl<sub>2</sub> and 2,4-dioxypyrimidines (uracils) and related ligands. The "blues" displayed interesting antitumor activity and provided a challenging coordination chemistry. A major breakthrough in the understanding of the nature of these "blues" came from the description of a related  $\alpha$ -pyridone blue, shown to be a tetranuclear, mixed-valence Pt compound with a metal average oxidation state of +2.25 (ref. 3) and from findings that dinuclear  $\alpha$ -pyridone complexes undergo ready oxidation to diplatinum(III) compounds (ref. 4). This chemistry has subsequently been shown to also hold up for the related 1-methyluracil (1-MeU) system (ref. 5,6).

The present paper summarizes some of the coordination chemistry of Pt(II), Pd(II) and, in part, Au(III) with the model nucleobases 1-methyluracil and 1-methylthymine (Fig. 1) related to the "blues" as well as mixed nucleobase complexes as models of hypothetical Pt-DNA cross-links.

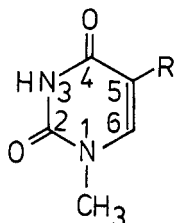


Fig. 1. Structure and atom numbering scheme of model nucleobases 1-methyluracil (R = H), 1-MeUH, and 1-methylthymine (R = CH<sub>3</sub>), 1-MeTH.

### MONONUCLEAR Pt(II) COMPLEXES

Mono(nucleobase) complexes of type *cis*-[(NH<sub>3</sub>)<sub>2</sub>Pt(L)H<sub>2</sub>O]<sup>+</sup> (L = 1-MeU or 1-MeT) are conveniently prepared by controlled protonation of *cis*-(NH<sub>3</sub>)<sub>2</sub>PtL<sub>2</sub> via the intermediate *cis*-[(NH<sub>3</sub>)<sub>2</sub>Pt(LH)L]<sup>+</sup> which contains the pyrimi-

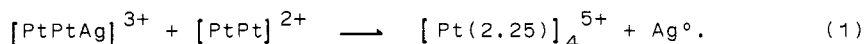
dine nucleobase LH in a rare tautomeric structure (2-oxo,4-hydroxo form), platinated at N3 (ref. 7). A second nucleobase L, when reacted with  $\text{cis}-(\text{NH}_3)_2\text{PtL}(\text{H}_2\text{O})^+$ , gives  $\text{cis}-(\text{NH}_3)_2\text{Pt}(\text{L})(\text{L}')$  (ref. 8). Applying a N7-platinated 9-methylguanine as the second base L', it is possible to obtain mixed pyrimidine-N3, purine-N1 complexes which represent novel models of hypothetical cross-links of this type in the DNA interior (ref. 9).

### DIPLATINUM(II) COMPLEXES

Condensation of  $\text{cis}-(\text{NH}_3)_2\text{Pt}(\text{L})(\text{H}_2\text{O})^+$  gives the dinuclear  $\text{cis}-(\text{NH}_3)_2\text{Pt}_2\text{Pt}(\text{NH}_3)_2^{2+}$  with head-tail arranged L-N3,04 ligands (ref. 10). The corresponding head-head isomer is prepared from  $\text{cis}-(\text{NH}_3)_2\text{PtL}_2$  after reaction with  $\text{cis}-(\text{NH}_3)_2\text{Pt}(\text{H}_2\text{O})_2^{2+}$ . In a similar way, dinuclear complexes with different amines at the two Pts can be obtained (ref. 11,12). Novel dinuclear complexes of composition  $\text{cis}-(\text{NH}_3)_2\text{PtL}_2\text{Pt}(\text{NH}_3)\text{Cl}^+$  and  $\text{cis}-(\text{NH}_3)_2\text{PtL}_2\text{PtCl}_2$  containing head-head oriented 3-MeT ligands have recently been isolated and structurally characterized (ref. 13).

### MIXED METAL COMPLEXES

Of the many heteronuclear complexes containing Pt, 1-MeU or 1-MeT and another metal, which we have prepared and studied over the years (ref. 1), two trinuclear examples are of particular interest with regard to the "blues":  $\text{cis}-(\text{NH}_3)_2\text{Pt}_2(1\text{-MeU})_2\text{Ag}^{3+}$  (PtPtAg), and  $\text{cis}-(\text{NH}_3)_2\text{PtL}_2\text{PdL}_2\text{Pt}(\text{NH}_3)_2^{n+}$  (PtPdPt). We consider PtPtAg a precursor of the Pt(2.25)-1-MeU-blue (ref. 14) based on structural criteria (shortening of Pt-Pt separation on Ag binding) and the redox process



PtPdPt represents the prototype of a yet unknown Pt<sub>3</sub> complex,  $\text{cis}-(\text{NH}_3)_2\text{PtL}_2\text{PtL}_2\text{Pt}(\text{NH}_3)_2^{n+}$ , which is considered a potential component of the "blues" (ref. 15).  $[\text{PtPdPt}]^{n+}$  has been structurally characterized both for n = 2 and n = 3, and cyclic voltammetry has revealed the existence of two additional interconvertible redox states:

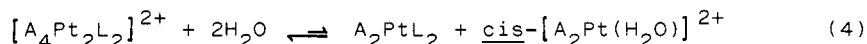


### TETRANUCLEAR Pt(2.25) BLUES

We have recently prepared several analogues of the tetranuclear Pt(2.25)-1-MeU blue (ref. 5), including examples containing heterocyclic amine ligands (2,2'-bpy) and mixed amines ((NH<sub>3</sub>)<sub>2</sub>, 2,2'-bpy) (ref. 12). In the course of these studies we were confronted with the fact that virtually all "blues" isolated from strongly acidic medium contained acid, either as an impurity or in stoichiometric amounts. Additional complications arose from the instability of Pt(2.25) blues in weakly acidic solution due to water oxidation, a process



that also generates protons, and a partial dissociation of the formed diplatinum(II) complex,



which generates weakly acidic protons. Potentiometric titrations and UV-vis spectroscopy have been applied to identify the various processes.

### PARTIALLY REDUCED DIPLATINUM(III) COMPLEXES

While tetranuclear Pt(2.25), logically, are considered partially oxidized Pt(II) species, mixed-valence compounds derived from chloro-capped diplatinum(III) complexes (ref. 16) should be considered partially reduced Pt(III) species. Formation of intensely colored ( $\lambda_{\text{max}}$  500 - 550 nm) species takes place spontaneously in the solid state (loss of Cl<sub>2</sub>) and in solution (water oxidation?) and through reduction by either mono- or dinuclear Pt(II) com-

pounds (ref. 17). More recently, we found that these species are also formed upon oxidation of diplatinum(II) complexes with  $H_2PtCl_6$ . The general composition of the partially reduced diplatinum(III) compounds appears to be that of two chloro bridged diplatinum units with Pt-Pt separations differing markedly from the Pt oxidation state (ref. 18).

### COMPARISON WITH Pd(III), Au(III) AND *trans*-PT(III)

The richness of the coordination chemistry on the *cis*- $A_2Pt(II)/1-MeU$  (1-MeT) system with regard to formation of homo- or heteronuclear oligomeric structures (ref. 1), Pt-heterometal interactions (ref. 19), metal-metal bond formation (ref. 1), and its redox chemistry is unique. Attempts to establish a similar broad chemistry with the  $d^8$  analogues Pd(II) and Au(III) as well as *trans*- $(NH_3)_2Pt(II)$  were unsuccessful. The problem with Pd(II) appears to be related to its fast kinetics, which makes the coordination chemistry, compared to Pt(II), considerably less predictable (ref. 20), and the fact that oxidation of dipalladium(II) requires much higher potentials (ref. 21). Au(III), on the other hand, exerts too high a polarizing effect when coordinated to N3 of 1-MeU or 1-MeT to leave any appreciable electron density at the exocyclic oxygens adjacent to the metal coordination site to permit additional metal binding at these sites (ref. 22). As a consequence, the tendency of di- or heteronuclear complex formation is very much reduced or even lost. Finally, *trans*- $(NH_3)_2PtL_2$ , while similar to the *cis*-isomer with respect to principles of heteronuclear complex formation (ref. 23), appears to be inferior to the latter for steric reasons (larger O...O separations), as concluded from considerably smaller association constants with heterometals.

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