Precious Metals Consortium

Precious Metals & Rhenium Consortium

Pt genetox review

9 September 2016 | MCC, Brussels

Agenda

Welcome, tour-de-table and anti-trust	*9 – 9.05*
PGM chemistry – some introductory remarks	*9.05 – 9.20*
Discussion on Pt genetox review	*9.20 – 13.20*
(Lunch)	
Conclusions	*13.20 – 13.30*

PGM Chemistry – some introductory remarks

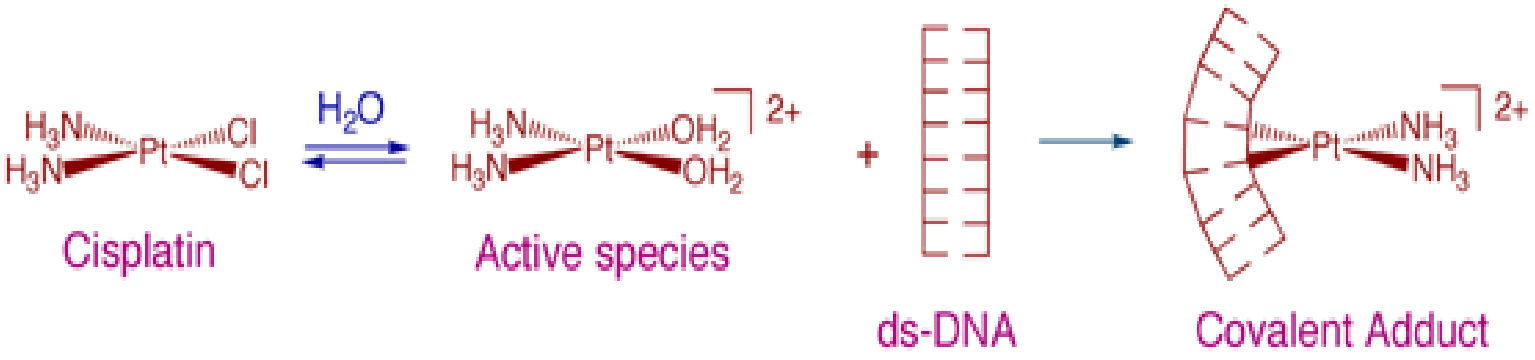
Complex PGM chemistry

- **Pt nitrate**
  - No stoichiometric compound
  - Undefined polymeric nature: oxo or hydroxyl bridged Pt (IV) complexes
  - Nitric acid (an oxidising agent): present for stabilisation purposes, pH < 1
- **Karstedt Concentrate**
  - Complex Pt(0) with siloxane ligand
  - NMR spectra: peaks in region associated with Pt-Cl species (from the original chloroplatinic acid starting material? Polymerisation?)

    -> complex and unclear chemistry

Requires ligand exchange for DNA reactive species

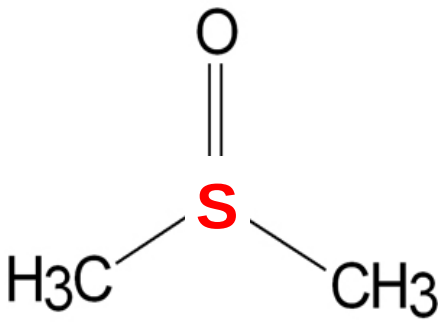
Platins - Aquation generates the DNA reactive species



- Aquated forms of platin (charged species) after chloride exchange
- Then binds to DNA
- But for PMC Pt substances of interest, chloroplatinate salts also undergo aquation reactions….forming complex chloro/aquo- species
- The genetic toxicity of such species is unstudied

Pt complex affinity for soft ligands

Example DMSO

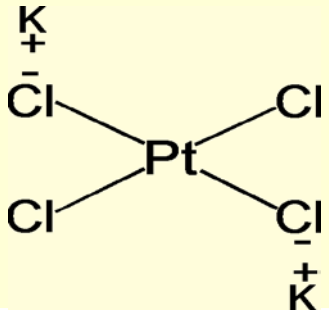


- Cisplatin (and CHPS/chloroplatinates) love soft ligands such as sulphur !
- Will readily ligand exchange
- Reason why DMSO & similar agents quench mutagenic activity
- Caution needed in interpreting studies using such vehicles

Coordination complexes: Leaving groups vs Reactivity

- ChloroPt complexes (tetra- & hexachloroplatinates) ▶ labile leaving groups (chlorides)
- Reactive to macromolecules, particularly proteins ▶ Haptens ▶ Sensitizers
- For simple chloroPt salts mechanistics of interaction with DNA not well studied (only inferences made from platins)
- So, how significant are DNA lesions & mutagenic potential vs those of platins?

Potassium tetrachloroplatinate(II)

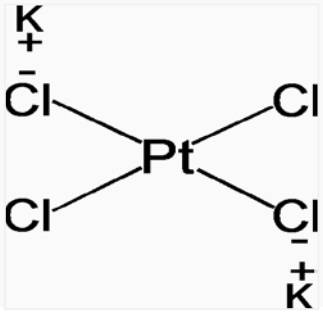


Chloroplatinate complex

Coordination complexes: Leaving groups vs Reactivity

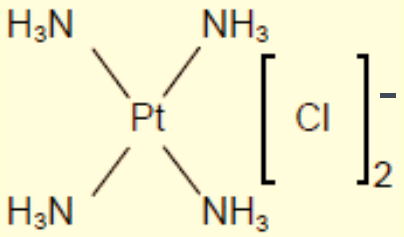
- **Tetraammine Pt(II) compounds**
- **Pt oxidation state same as KTCP**
- **But Ammine ligands very firmly bound**
- **Chloride is ionic/<u>not</u> coordinated to Pt & <u>not</u> a leaving group**
- **Non-protein reactive* & unequivocally Non-sensitizing**
- **However, Tetraammine Pt <u>is apparently mutagenic</u> Mechanism ??**

Potassium tetrachloroplatinate(II), KTCP



Chloroplatinate complex

Tetraammine platinum(II) chloride, TPC



Tetraammine Pt

* IPA STF have some confirmatory peptide reactivity studies underway

Discussion on Pt Genetox Review

- **Grouping of Pt substances**

  Suggestions: separate $Pt(0)_{massive}$ – $Pt(0)_{nano}$ – Karstedt Concentrate

  separate HHPA – HHPA/2AE

  justification of basis for initial grouping

  verification of initial grouping based on genetox data

- **Interpretation of available test data**

  Use of DMSO as vehicle

  Test substance purity

  What with existing negative in vivo results?

  Comparison with existing reviews

Discussion on Pt Genetox Review

- **Selection further assays (*in vitro* and/or *in vivo*)**

  Are other in vitro or supporting test (not requiring a TP) that would significantly aid precision on hazard characterization or fill data gaps?

  ECHA's preference for in vivo transgenic mutation assay rather than comet assay

- **Selection test substance for further testing**

  Suggestions: reconsider Pt(0) group

  Pt(II) anionic – K rather than NH4 salt

  Pt(IV) group – reconsider Pt nitrate

  Pt(IV) anionic – select K or Na hexahydroxyplatinate

Discussion on Pt Genetox Review

- **Platins vs non-platins**
  - Sufficient evidence available for both groups?
  - Different profiles (or not), and why?

- **Regulatory interpretation**
  - Anticipation on regulatory interpretation of the available Pt data
  - Anticipation on expected classification(s)

- **Graphical representations of results and state of data availability**
  - Possible to summarise the data, the current situation, identify groupings etc?
  - For example: summary graph of all Ames text data, one graph of all the in vitro chrom ab data, etc – something like below
  - cfr example next slide

Discussion on Pt Genetox Review