# The Importance of the Trans Effect in the Synthesis of Novel Anti-Cancer Complexes

# This activity is based on the paper “Improvements in the synthesis and understanding of the iodo-bridged intermediate en route to the Pt(IV) prodrug satraplatin,” by Timothy C. Johnstone and Stephen C. Lippard (*Inorganica Chimica Acta,* Volume 424, 1 January 2015, Pages 254–259).

# Three square-planar Pt(II) complexes are currently approved by the F.D.A. for use in cancer treatment, the most famous of which is cisplatin, or *cis*-diamminedichloroplatinum(II). While cisplatin can be used to treat several different types of prostate cancers, one issue is that many patients can relapse with a cisplatin-resistant disease. Therefore, it is important to develop new chemotherapeutic drugs that demonstrate efficacy in cisplatin-resistant cell lines. Square planar Pt(II) complexes that contain mixed *cis*-amine/ammine or *cis*-pyridyl/ammine motifs are of interest as both potential novel chemotherapeutic Pt(II) complexes and as intermediates for promising chemotherapeutic drugs such as satraplatin. An example of a Pt(II) complex with a *cis*-amine/ammine motif is shown in Figure 1. The trans effect can be very useful in the development of methodologies for the selective synthesis of the desired *cis* isomer.

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# Figure 1. *cis*-[Pt(NH3)(NH­2C6H11)Cl2] (NH2C6H11 = cyclohexylamine)

# As a group, define the trans effect, and explain what properties of a ligand cause it to have a strong trans effect.

# Which ligand has the stronger trans effect, NH3 or Cl-? Draw a reaction coordinate diagram that compare dissociation of the ligand trans to the ammine versus dissociation of a ligand trans to one of the chloride ligands.

# One way to synthesize *cis-*ammine/amine Pt(II) complexes is by beginning with [Pt(NH3)Cl3]−. The synthesis of *cis*-[Pt(NH3)(NH­2C6H11)Cl2] was described by Giandomenico *et al.* in 1995.2 In this synthesis, shown below in Scheme 1, the mixed-halo complex 2 is first isolated, and then converted to the dichloride complex 3 by formation of the aqua species with silver nitrate, followed by precipitation with HCl. Would this isomer of complex 2 be predicted to form based on the trans effect? Why is this geometry in complex 2 necessary for formation of *cis*-[Pt(NH3)(NH­2C6H11)Cl2]?

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# Scheme 1. Synthesis of *cis*-[Pt(NH3)(NH­2C6H11)Cl2].2

# A second synthetic route for the synthesis of *cis-*ammine/amine Pt(II) complexes is shown in Scheme 2 below. It involves the formation *cis-*[Pt(NH2C6H11)2I2], followed by formationof either *cis* or *trans* iodo-bridged platinum-amine dimers, [Pt(NH2C6H11)I(μ-I)]2 (complexes 6 and 7 in Scheme 2), which can then be cleaved to give *cis-*[Pt(NH3)(NH2C6H11)I2] (complex 8). In scheme 2, would this isomer of complex 5 be predicted based on the *trans* effect? If not, what are other reasons that the *cis* isomer would form rather than the *trans* isomer?

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# Scheme 2. Alternative route for the synthesis of *cis*-[Pt(NH3)(NH­2C6H11)Cl2].1

# A second synthetic route for the synthesis of *cis-*ammine/amine Pt(II) complexes involves the formation of either *cis* or *trans* iodo-bridged platinum-amine dimers, [Pt(NH2C6H11)I(μ-I)]2, which can then be cleaved to give *cis-*[Pt(NH3)(NH2C6H11)I2]. *Cis-* and *trans-*[Pt(NH2C6H11)I(μ-I)]2 are shown in Figure 2 below. Johnstone and Lippard propose a step-wise mechanism for the cleavage of *trans*- or *cis*-[Pt(NH2C6H11)I(μ-I)]2, with NH3, which is shown in Figure 7 of “Improvements in the synthesis and understanding of the iodo-bridged intermediate en route to the Pt(IV) prodrug satraplatin.”1 Explain why cleavage of both the *trans* and *cis* isomers of [Pt(NH2C6H11)I(μ-I)]2 with NH3 lead to the formation of *cis-*[Pt(NH3)(NH2C6H11)I2].

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# ­Figure 2. *Trans-* (left) and *cis-* (right) [Pt(NH2C6H11)I(μ-I)]2.

# The trans influence refers to the impact of a ligand on the length of the bond trans to it in the ground state of a complex. Is the trans influence a thermodynamic parameter or a kinetic parameter?

# According to the trans influence, ligands that are trans to ligands that are better sigma donors or pi acceptors will tend to have longer metal-ligand bond distances than ligands that are trans to ligands that are weaker sigma donors or pi acceptors. In the crystal structure of *trans-*[Pt(NH2C6H11)I(μ-I)]2obtained by the authors, the bond distance between the Pt and the bridging iodide ligand is 2.5439(2) Ǻ when the iodide is trans to the amine at that Pt center, and 2.5947(2) Ǻ when the bridging iodide ligand is trans to the terminal iodide ligand. Is this what you would expect based on the trans influence?

# Timothy C. Johnstone and Stephen C. Lippard, *Inorganica Chimica Acta,* Volume 424, 1 January 2015, Pages 254–259.

# Christen M. Giandomenico *et al.* *Inorganic Chemistry* 1995, 34, 1015-1021.