The Trans Effect: A Guided-Inquiry Experiment for Upper-Division Inorganic Chemistry

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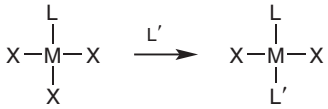
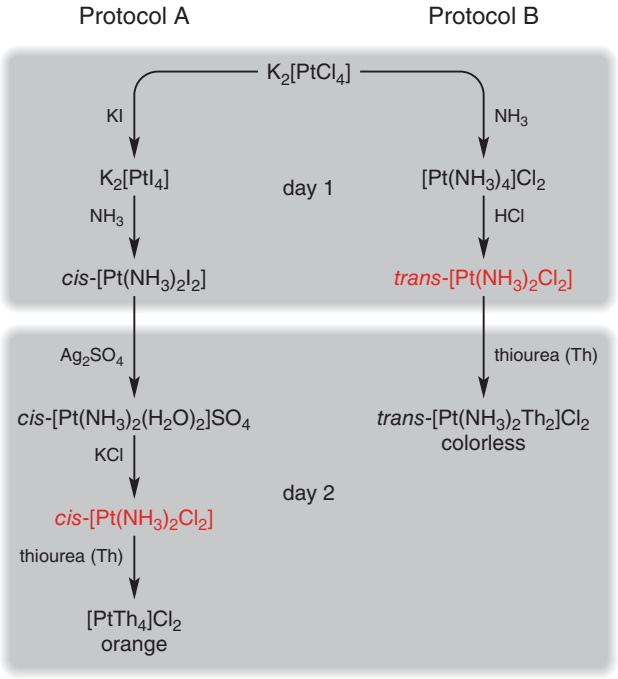
Few guided-inquiry laboratories for upper-division inorganic chemistry exist in the literature, with the focus instead being on traditional experiments in which students are directed to follow a procedure, and the results verify concepts already presented *(1–3)*. While traditional experiments dealing with isomers of coordination complexes are plentiful in this *Journal (4–19)*, we describe a guided-inquiry laboratory in which students synthesize the cis and trans isomers of a square-planar platinum(II) complex and are guided to develop the *trans effect* concept. The cis isomer, *cis*-diamminedichloroplatinum(II), *cis*-$Pt(NH_3)_2Cl_2$ or cisplatin, is a chemotherapeutic that is used to treat a variety of cancers *(20–26)*. The cis geometry of cisplatin is important to the mechanism of anticancer activity, as cisplatin's geometric isomer, transplatin, is not viable as a chemotherapeutic *(26)*. This experiment gives students technical experience in microscale inorganic synthesis and stereochemical analysis while teaching them about coordination chemistry and the importance of metals in medicine. This experiment may be appropriate for students in inorganic chemistry, bioinorganic chemistry, or medicinal chemistry.



Scheme I. Ligand L is a stronger trans director than X. Therefore, incoming ligand L′ adds trans to L.



Scheme II. The synthetic protocols for cisplatin (left) and transplatin (right).

Overview of Procedure

The cis or trans isomers of $Pt(NH_3)_2Cl_2$ can be preferentially synthesized by taking advantage of the trans effect. This effect describes the ability of certain ligands to promote substitution at a position trans to themselves in coordination complexes with square-planar or octahedral geometries owing to the electronic properties of the ligands *(27–29)*. Therefore, ligands can be ranked by their ability to direct trans substitution (Scheme I). In this experiment the trans effect is used to control product geometry by systematically introducing ligands to a platinum center in the appropriate sequence.

An overview of the synthetic protocols for cisplatin and transplatin is shown in Scheme II. The microscale protocols for both isomers were adapted from the literature *(9, 30, 31)*. Each synthetic protocol begins with the same starting salt, potassium tetrachloroplatinate. The synthetic portion of the experiment requires two, three-hour lab periods. Product geometry is determined on day two using a colorimetric thiourea test *(32)*. The laboratory may also be expanded to incorporate instrumental methods of analysis (i.e., capillary electrophoresis) and would be well suited for universities following the integrated laboratory model (see the online material) *(33, 34)*.

This experiment is designed to employ a guided-inquiry approach to introduce the target concept of the trans effect. Each set of two students is assigned one protocol to synthesize $Pt(NH_3)_2Cl_2$ without being told whether they are making the cis (protocol A) or the trans (protocol B) isomer. The geometry is not verified until the end of day two. Although students are provided synthetic protocols, the procedures and results combined serve as the exploration phase *(35)*. By answering focus questions in groups of four (two students from each protocol, see the online material), students compare and contrast the protocols to predict which factors may lead to the formation of cisplatin or transplatin. After product geometry is determined using thiourea, students revisit their predictions to determine accuracy. The focus questions are designed to address both the concept invention and application phases of guided-inquiry learning *(35)*. Ultimately, students are guided to answer the following conceptual question: What are factors that lead to trans-substitution versus cis-substitution in square-planar transition-metal complexes?

Hazards

Some of the chemicals used in this experiment require care in handling and their use should be restricted to fume hoods: thiourea (potential carcinogen), hydrochloric acid (corrosive), potassium tetrachloroplatinate (hazardous), cisplatin (hazard-

ous: irritant especially if ingested or inhaled, repeated exposure may cause chronic health effects), transplatin (hazardous), ethanol (flammable), and diethyl ether (flammable). Silver sulfate is light-sensitive and may be protected by wrapping containers with aluminum foil. Gloves and eye protection should be worn at all times.

Results and Discussion

This experiment has been performed for the past two semesters in a bioinorganic chemistry laboratory course. The class is composed primarily of biochemistry majors, and the enrollment ranges from 10–16 students. Our experience has shown that students can successfully complete this experiment in two lab periods, confirming the reproducibility of the synthetic protocols. A third lab period proves useful for group discussion to compile knowledge, discuss results, and address any misconceptions.

As a prelab assignment, students are asked to predict the possible platinum-containing products of the reaction shown in Scheme III. They are also asked to indicate which would be the major product and to explain their reasoning for this selection. Students are able to predict the cis and trans geometric isomers, and they usually argue that the major product will be the trans isomer owing to the steric hindrance of the NH_3 groups.

Guided-Inquiry Approach: Exploration

In the experiment, protocol A begins by reacting potassium tetrachloroplatinate with potassium iodide to replace the chlorides in the coordination sphere of the platinum. The solution of $[PtI_4]^{2-}$ is then filtered and aqueous NH_3 is added to the filtrate to precipitate *cis*-$Pt(NH_3)_2I_2$. The cis product results owing to the trans-directing ability of the iodide ligands (Scheme IV). The replacement of the chlorides with iodides prior to reacting with ammonia is necessary because iodide is a stronger trans director compared to chloride. This step ensures the formation of pure *cis*-$Pt(NH_3)_2I_2$. Ultimately, the need to introduce iodide in place of chloride allows students to rank the two halide ligands in terms of their trans-directing ability ($I^- > Cl^-$).

In the following lab period, *cis*-$Pt(NH_3)_2I_2$ is reacted with aqueous silver sulfate to replace the iodides through precipitation. The chloride ions are then reintroduced to obtain *cis*-$Pt(NH_3)_2Cl_2$. It should be noted that the chloride anions add to the platinum in a cis fashion, replacing the two waters. This cis substitution does not follow the trans-directing ligand series cited in the literature *(27–29)*. However, cis substitution can be explained using the relative lability of water compared to NH_3, which makes water a better leaving group *(36–38)*. Students can establish their ligand trans-directing series in lieu of this step because they are not asked to include water in their series. Students who discover this anomaly may find it interesting to learn that cis chloride hydrolysis is important to cisplatin's therapeutic mechanism *(39–41)*.

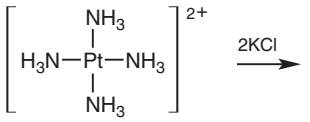
In protocol B, for the synthesis of transplatin, the chlorides of potassium tetrachloroplatinate are replaced using excess NH_3 to yield $[Pt(NH_3)_4]^{2+}$. Then, hydrochloric acid is added to the solution and the volume is reduced until *trans*-$Pt(NH_3)_2Cl_2$ precipitates. Multiple crops of product may need to be isolated through repeated precipitation, which requires the second laboratory period (see the online material). Ultimately students can rank NH_3 and Cl^- in terms of their trans-directing ability ($Cl^- > NH_3$) by focusing on the sequence of ligand replacement steps. Then, by combining the data from both synthetic protocols, the following trans-directing ligand series is established: $I^- > Cl^- > NH_3$.

Guided-Inquiry Approach: Concept Invention

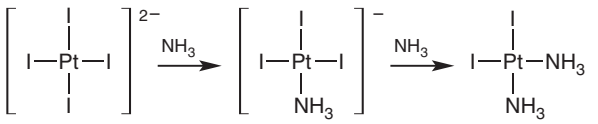
Focus questions are used to guide students towards establishing this ligand series and answering the conceptual question (see the online material). Daily assignments are turned in before students leave lab so the instructor can assess learning and serve as a better guide. For example, at the end of day one students are asked to compare and contrast the reaction conditions of each synthetic protocol (temperature, time, sequence of reagents, etc.) and to predict possible reasons for these differences. One difference to note is the higher temperature required during protocol B compared to protocol A (88 and 70 °C, respectively). In our experience, students relate differences in temperature to chemical kinetics and hypothesize that the product of protocol B is slower to form and requires a higher temperature to increase reaction rate. Students also recognize that sources of chloride and NH_3 ligands are present in both synthetic protocols but that iodide is only present in protocol A. Students may begin to relate differences in the sequence of ligand substitution to product geometry.

During day two of both synthetic protocols, product geometry is determined using a colorimetric thiourea test *(32)*. Focus questions instruct students to use their knowledge of product geometry to work backwards through each synthetic protocol determining all reaction intermediates. Students are also instructed to revisit their answers to the questions from day one to reevaluate their predictions. This process encourages students to relate complex geometry to the sequence of ligand substitution around the platinum center. By the end of day two, students are prompted to propose possible explanations for the geometry of each product.

After turning in the day two assignment, students are provided with their final lab report handout. Questions 1, 2, and 3 on this handout cement the trans effect concept invention (see the online material). Through the use of focus questions, students are able to answer the conceptual question, demonstrating their understanding of the target concept.



Scheme III. The prelab assignment; students are asked to predict the products.



Scheme IV. Iodide is a stronger trans director than NH_3, which leads to the formation of the cis product.

Guided-Inquiry Approach: Applications

In the lab report handout, Questions 4, 6, and 7 serve as the application phase of guided inquiry. These questions require students to extend their ligand series to include bromide, which is not used in the experiment. This helps students recognize that the ligand series is tied to periodic trends and can be expanded to include other species. Students are also asked to propose protocols for the synthesis of cis and trans isomers of an octahedral metal complex, thereby applying their knowledge to new situations. In addition, the questions highlight the importance of geometry to the therapeutic mechanism of cisplatin, giving the experiment more relevance.

Conclusion

This experiment successfully guides students to construct the trans effect concept. Based on positive student feedback, we plan to incorporate additional laboratories of this type into our curriculum. We will work to convert traditional experiments into guided-inquiry experiments with a focus on concepts important to upper-division inorganic chemistry.

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