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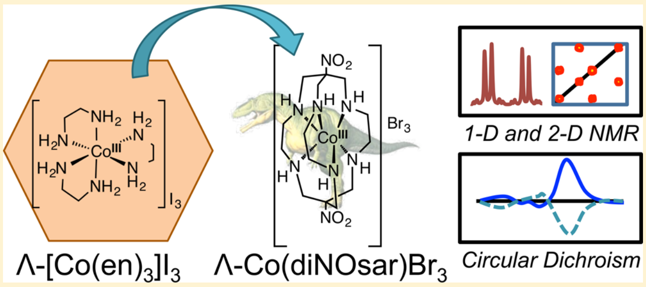
Improved Syntheses and Expanded Analyses of the Enantiomerically Enriched Chiral Cobalt Complexes Co(en)$_3$I$_3$ and Co(diNOsar)Br$_3$

Michael J. McClellan[†] and Marion E. Cass*

Department of Chemistry, Carleton College, Northfield, Minnesota 55057, United States

Ⓢ *Supporting Information*

ABSTRACT: This communication is a collection of additions and modifications to two previously published classic inorganic synthesis laboratory experiments. The experimental protocol for the synthesis and isolation of enantiomerically enriched Λ-(or Δ-)Co(en)$_3$I$_3$ has been modified to increase reproducibility, yield, and enantiomeric excess. A computational component including molecular visualizations, model building, and energy minimization may be added to teach about the conformers that are formed as a result of λ and δ twists of the ligands. Modification of a second experiment for the synthesis of a Sargeson encapsulation product (Λ-(or Δ-)Co(diNOsar)-Br$_3$) from enantiomerically enriched Λ-(or Δ-)Co(en)$_3$I$_3$ includes advanced undergraduate analytical techniques including COSY, HMQC (or HETCOR), and NOESY NMR experiments, molecular visualizations, and CD spectroscopy for the characterization of products. Synthesis of a deuterated d^{12}-Co(diNOsar)Br$_3$ (which facilitates NMR assignments) is also described.

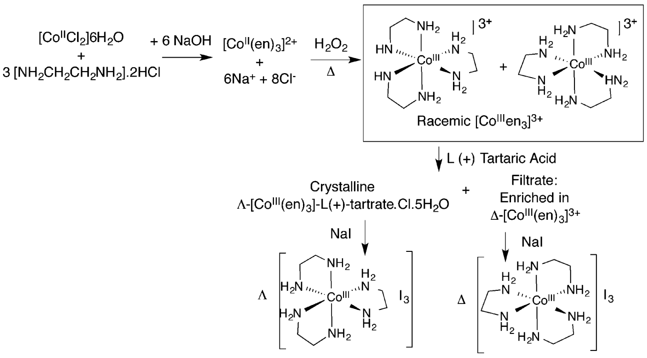


KEYWORDS: *Upper Division Undergraduate, Inorganic Chemistry, Hands-On Learning/Manipulatives, Computer-Based Learning, Asymmetric Synthesis, Chirality/Optical Activity, Coordination Compounds, Group Theory/Symmetry, Molecular Modeling, NMR Spectroscopy*

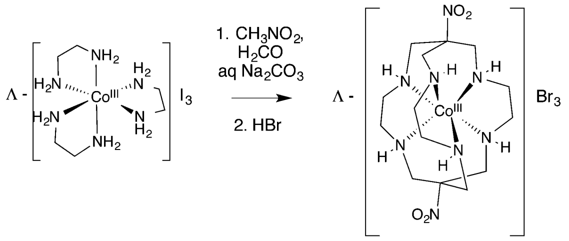
■ INTRODUCTION

The synthesis and isolation of enantiomerically enriched Λ-Co(en)$_3$I$_3$ (en = ethylenediamine, $NH_2CH_2CH_2NH_2$) by crystallization with a chiral resolving agent (and subsequent isolation of its enantiomer Δ-Co(en)$_3$I$_3$ from the filtrate) is a classic experiment[1] that has undergone at least one update to utilize less-toxic reagents (Scheme I).[2] This experiment can be extended by taking the Λ-Co(en)$_3$I$_3$ product forward to one of two Sargeson encapsulated products with retention of absolute configuration about the metal center.[2−4] The encapsulation product that has given the best yields for our undergraduate students (Scheme II) is Λ-(or Δ-)Co(diNOsar)Br$_3$ (diNOsar = dinitrosarcophagine, or 1,8-dinitro-3,6,10,13,16,19-hexaazabicyclo-(6,6,6)icosane).[3]

Scheme I. Synthesis and Resolution of Λ-Co(en)$_3$I$_3$



Scheme II. Synthesis of Λ-Co(diNOsar)Br$_3$



The following communication is our collection of what we view as the best contributions (both new and previously published, and stemming from both pedagogical and research sources) that help create a great experiment for teaching concepts about the coordination chemistry of chiral metal complexes. We readily acknowledge that this contribution is neither entirely new chemistry nor entirely new pedagogy, but it represents one package of ideas for a wonderfully rich experiment for undergraduate students. With the additions and modifications described herein, our students spend four weeks

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on this set of two experiments. Typically we have two lab sections of eight students (four teams per section), close to a perfect number of teams to contribute data about a specific isomer or partially deuterated analog to the class as a whole. If we have fewer students, we provide data from previous years for those compounds not synthesized. In this paper, we address two sets of modifications we have tested with our students at Carleton.

Modifications to the Synthesis and Resolution of the Optical Isomers of $Co(en)_3^{3+}$

For this experiment we have made the following five modifications:

1. We modified the published 1999 synthetic procedure (Scheme I) for Λ-$Co(en)_3I_3$ to increase the reproducibility, improve the yields, and give higher %ee products.
2. Different teams of students are given the option of using either L-(+)-tartaric acid or D-(−)-tartaric acid as a resolving agent to get preferential enantioselective crystallization of the Λ or Δ $Co(en)_3^{3+}$ ion, respectively.
3. Three-dimensional visualizations (and models if desired) are provided to teach assignment of Λ and Δ absolute configurations at the metal center and λ and δ ligand twists.
4. These 3D visualizations are also used to examine the different conformers (within each set of absolute configurations Λ or Δ). All four conformers for Λ-$Co(en)_3^{3+}$ are known and X-ray crystal structures are published in the Cambridge Crystallographic Data Centre (CCDC). The Λ-δδδ-$Co(en)_3^{3+}$, Λ-δδλ-$Co(en)_3^{3+}$, Λ-δλλ-$Co(en)_3^{3+}$, Λ-λλλ-$Co(en)_3^{3+}$ structures can be visually compared. If desired, a computational component of the experiment can be added to determine the relative energy differences and statistical populations of these conformers.
5. The ramifications of having four easily accessible conformers on the appearance of the ^{1}H NMR spectrum can then be discussed with students.

Modifications to the Experiment for the Synthesis of [(Λ or Δ)-Co(diNOsar)]Br_3

The following four steps were added to more fully evaluate the structure of the [Co(diNOsar)]Br_3 product (synthesized as outlined in Scheme II).

1. Two-dimensional NMR techniques (COSY, HMQC or HETCOR, and NOESY) are used to examine the structure of the (Λ or Δ)-Co(diNOsar)Br_3 product (Scheme II) and its partially deuterated analogs.
2. The ^{1}H NMR spectrum of Λ-$Co(en)_3I_3$ is compared to that of Λ-Co(diNOsar)Br_3 to highlight the contrasting structural implications.
3. Three-dimensional visualizations were created to help students assign the chemically equivalent protons and magnetically inequivalent protons in the product.
4. Circular dichroism (CD) spectroscopy is then used to examine the enantiomeric excesses of the products and to further explore the features (not observed) in the optical spectroscopy. A discussion of the published literature on the CD spectroscopy of Λ-$Co(en)_3^{3+}$ (single crystal and solution) and Λ-$Co(diNOsar)^{3+}$ is illuminating.

RESULTS AND DISCUSSION

Improvements in the Procedure for the Synthesis and Resolution of Λ and Δ-$Co(en)_3^{3+}$

In 1999 the third edition of *Synthesis and Technique in Inorganic Chemistry: A Laboratory Manual*[2] by Gregory Girolami, Thomas Rauchfuss and Robert Angelici was published with a new synthetic procedure in the classic experiment "Optical Resolution of $Co(en)_3^{3+}$" (outlined in Scheme I). Over the years of carrying out this procedure with Carleton undergraduates, we found that although this procedure removed barium tartrate as a chiral resolving agent used in the earlier editions[1] (therefore eliminating the use of the toxic heavy metal barium) students' yields and enantiomeric excesses (%ee) were hugely variable.[5a] Careful experimentation allowed us to determine that if we monitored and controlled the pH of the reaction solution during two crucial steps, and reintroduced one recrystallization step included in the earlier edition,[1] we obtained reasonable and reproducible yields and enantiomeric excesses of Λ-(or Δ-)$Co(en)_3I_3$.[5b] Our modified synthetic procedure can be found in the Supporting Information files. We have also shared these suggested revisions with Professors Girolami and Rauchfuss for future editions of their text.

We also found that a fun and simple variation on the experiment was to allow half the class to use commercially available D-(−)-tartaric acid as the chiral resolving agent (rather than the standard L-(+)-tartaric acid) so that half of the class produced the Δ-$Co(en)_3I_3$ as the major product of their syntheses. The challenge in the laboratory is to encourage everyone to carefully label the products. There are many orange powders that must be labeled with some combination of Δ, D, δ, *d*, (+), Λ, L, *l*, λ, and (−); it can be dizzying at times. A further confounding factor is that L-(+)-tartaric acid was also historically called *d*-tartaric acid [*d* for (+) = dextrorotary (see notes in the Supporting Information)]. In order to facilitate successful isolation of the correct products, students must be systematic and precise in their use of symbols for assignment of stereochemistry.

Additional Analyses of the Λ and Δ-$Co(en)_3^{3+}$ Structures

Before continuing to the synthesis of the Sargeson encapsulated product, students carry out standard characterization techniques on their $Co(en)_3^{3+}$ products; determining the %ee by measuring optical rotation and analyzing the molecular structure by taking ^{1}H NMR and ^{13}C NMR spectra. Students also set aside a small portion (10−20 mg) of their product for later spectroscopic analysis performed simultaneously with the analysis of Co(diNOsar)Br_3. At this point in the experiment, we pause to discuss symmetry and chirality in metal complexes, the assignment of the absolute configuration of the stereochemistry around the metal center, and the possible conformers created by the λ and δ ligand twists within the complex. The four conformers of the Λ form of $Co(en)_3^{3+}$ are shown in Figure 1. Three-dimensional interactive visualizations written with JSmol[6] commands are available to facilitate teaching the assignment of Λ and Δ absolute configurations and λ and δ ligand twists (see "The Structure and Symmetry of the Metal Tris Chelates"[7]) and visualizations created specifically for this experiment show the Λ and Δ forms of $Co(en)_3^{3+}$, Λ and Δ forms of $Co(diNOsar)^{3+}$, and the four conformers of Λ-$Co(en)_3^{3+}$ (see "Visualizations for the Advanced Inorganic Chemistry Laboratory at Carleton College").[8]

A computational component can be added at this point in the experiment to teach about the conformers within each set

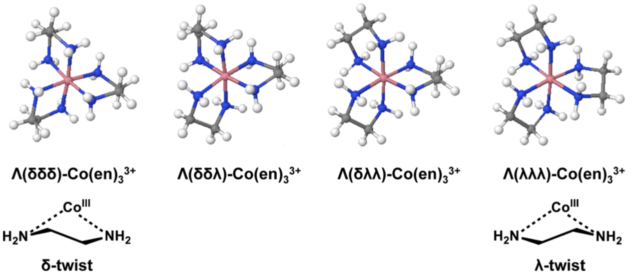

Figure 1. Four conformers resulting from ligand twists for the Λ-Co(en)$_3$$^{3+}$ complex.

of resolved products (Λ or Δ) and to shed light on the observed NMR spectroscopy. All four conformers of Λ-Co(en)$_3$$^{3+}$ (as well as all four conformers of Δ-Co(en)$_3$$^{3+}$) are structurally well defined and many X-ray crystal structures have been posted by the Cambridge Crystallographic Data Centre (CCDC).[9] These structures can be used as input files to calculate the relative energy difference between the four conformers within each Λ and Δ set. Learning to search the CCDC is a worthwhile exercise and searching for the different isomers is excellent practice in assigning absolute chirality at the metal center and recognizing the different ligand twists. The relative energies of the four conformers (through comparison of energy minimization calculations) can be used in a Boltzmann distribution population analysis to think about the distribution of isomers found in solution. We note that a full version of our computational assignment has been published on the online Virtual Inorganic Pedagogical Electronic Resource (VIPEr) Web site.[10] In addition we note that this exercise was inspired by a similar exercise published by F. Coleman on the eight isomers of the isostructural Ni(en)$_3$$^{2+}$ cation.[11]

Synthesis of Λ or Δ-Co(diNOsar)Br$_3$

After students have isolated the Λ and Δ form of Co(en)$_3$I$_3$, they convert one or both of their enantiomers to Λ-(or Δ-) Co(diNOsar)Br$_3$ by the experimental procedure outlined in Scheme II (for the Λ enantiomer) that was published in *J. Chem. Educ.* in 1985.[3]

A variation on this experiment is to allow one group to synthesize a d^{12}-Co(diNOsar)Br$_3$ product by substituting d^2-formaldehyde (commercially available) for formaldehyde. It is useful to have this deuterated product to facilitate the assignment of protons and carbons in the final NMR analyses.

2D NMR on the Λ or Δ-Co(diNOsar)Br$_3$ Products

To further characterize the Λ or Δ-Co(diNOsar)Br$_3$ products students perform HMQC (Heteronuclear Multiple Quantum Coherence is a more sensitive NMR experiment which gives the same information as HETCOR), COSY and NOESY 2D NMR experiments. The NMR spectra are beautifully resolved, unlike those of Co(en)$_3$$^{3+}$, because the Λ-(or Δ-)Co-(diNOsar)$^{3+}$ complex is locked into a single conformation by the newly added nitro-group-containing caps; Λ-*δδδ*-Co-(diNOsar)$^{3+}$ or Δ-*λλλ*-Co(diNOsar)$^{3+}$. The COSY and HMQC spectra of Λ-Co(diNOsar)$^{3+}$ and Λ-d^{12}-Co(diNOsar)-Br$_3$ are shown in Figure 2.

The identification of groups of chemically inequivalent protons and carbon atoms observed in the ^{1}H NMR, ^{13}C NMR, HMQC, and COSY spectra of Λ-(or Δ-)Co(diNOsar) is straightforward; however, mapping out those sets onto the 3D structure of the molecule and differentiating between the cap and ethylene bridge protons is more challenging. For students to ascertain chemical and magnetic equivalence or inequivalence, we have developed interactive 3D visualizations[8] and a guided tutorial (found in the Supporting Information) to facilitate making these assignments. To differentiate between cap and bridge protons, evidence of magnetic inequivalence can be seen in the proton NMR spectrum; however, Carleton students have synthesized both the Λ and Δ-d^{12}-Co-(diNOsar)$^{3+}$ products using d^2-formaldehyde in the reaction outlined in Scheme II in order to unambiguously distinguish between the these sets of protons. Examination of the published mechanism for the reaction[3] allows students to use their NMR data to distinguish between the cap and ethylene bridge protons and carbons. Using the NOESY spectrum (Figure 3) and a final guided visualization,[8] students can unambiguously assign all of the individual protons within geminal pairs.

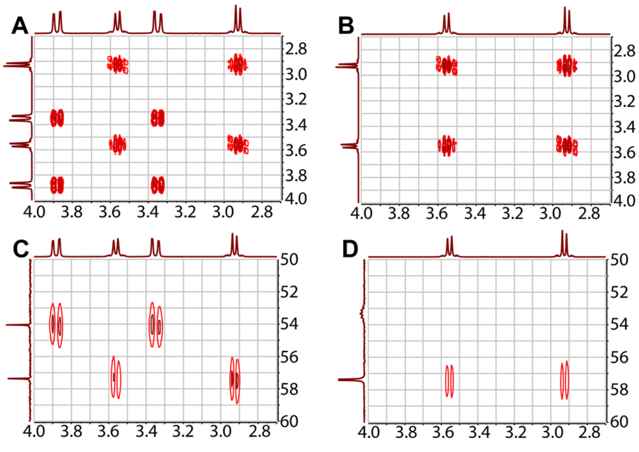

Figure 2. Top: COSY spectrum of Λ-Co(diNOsar)$^{3+}$ (A) and Λ-d^{12}-Co(diNOsar)Br$_3$ (B). Bottom: HMQC spectrum of Λ-Co(diNOsar)$^{3+}$ (C) and Λ-d^{12}-Co(diNOsar)Br$_3$ (D). NMR experiments were run with students on a Bruker AVANCE III 400 MHz High Performance Digital NMR Spectrometer at Carleton College. Samples were prepared in D$_2$O with acetone reference.

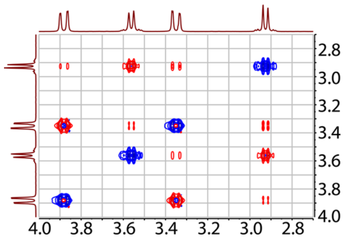

Figure 3. NOESY spectrum of Λ-Co(diNOsar)$^{3+}$ in D$_2$O (acetone reference).

Circular Dichroism (CD) to Determine %ee

One of the truly interesting aspects of this experiment comes from taking CD spectra of the Λ- and Δ-Co(en)$_3$$^{3+}$ and the Λ- and Δ-Co(diNOsar)$^{3+}$ products. We use CD rather than polarimetry at this point due to its beautiful high precision spectra, sensitivity, and pedagogical value in teaching advanced analytical and inorganic topics to undergraduate students. *The most striking (and initially disturbing) observation when we record the CD data is that the Λ-Co(diNOsar)Br$_3$ product and the Λ-Co(en)$_3$I$_3$ starting material from which it is produced show opposite sign of the molar ellipticity of the major absorption centered near 490 nm* (see Figure 4).

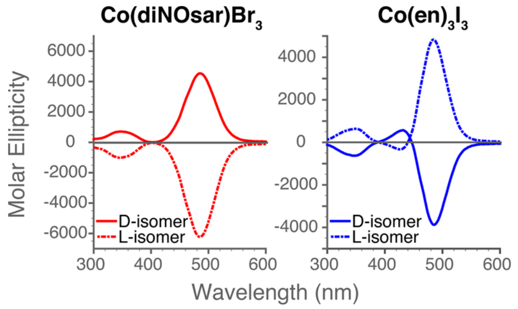

Figure 4. Left: CD Spectrum of Λ-Co(diNOsar)$^{3+}$ (dashed red line) overlaid with the CD Spectrum of Δ-Co(diNOsar)$^{3+}$ (solid red line). Right: CD Spectrum of Λ-Co(en)$_3^{3+}$ (dashed blue line) overlaid with the CD Spectrum of Δ-Co(en)$_3^{3+}$ (solid blue line). Spectra were recorded by Carleton Students on a Jasco J-810 CD Spectrometer in the laboratory of Dr. Frank Prendergast of the Mayo Clinic, Rochester, MN.

Typically, this would lead researchers to conclude that the two structurally similar compounds have opposite absolute configuration. On the contrary, the reaction proceeds with retention of configuration as expected. A published study of the single crystal CD spectroscopy on [Λ-Co(en)$_3$]Cl$_3$·NaCl·6H$_2$O allows students to understand why the CD spectra show opposite sign of the rotation of polarized light for the same absolute configuration at the metal center.[12] A discussion of the argument is presented in our Supporting Information. The equations for calculation of enantiomeric excess from the intensity of the CD signal at a given wavelength[13] relative to published literature values for samples of known optically pure Λ-Co(en)$_3^{3+}$ and Λ-Co(diNOsar)$^{3+}$ products[14] can also be found in our Supporting Information.

■ CONCLUSION

Through the introduction of more sophisticated and extensive spectroscopic characterization, computational analysis and molecular visualizations we have taken two classic coordination chemistry syntheses and expanded the pedagogical breadth of the combined laboratory experiment. Small modifications to the published synthetic procedure have enabled students to achieve reasonable yields and higher enantiomeric purity for the Co(en)$_3^{3+}$ product, key to their success in the subsequent synthesis of Λ-(or Δ-)Co(diNOsar)Br$_3$. With these new additions, we expand our pedagogy in the inorganic curriculum to include circular dichroism and more advanced topics in electronic spectroscopy. In addition, this experiment revisits and reinforces topics seen earlier in the undergraduate curriculum, such as chemical equivalence, magnetic inequivlence, molecular modeling and statistical thermodynamic population analysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Modifications to the Published Procedures, Instructor Notes, Guided Tutorials, and Student Handouts can be found in the Supporting Information Files. The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00140..

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mcass@carleton.edu.

Present Address

†Department of Earth, Atmospheric, and Planetary Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States.

Notes

The authors declare no competing financial interest.

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(5) (a) Prior to optimization, tabulation of student data over 4 years: yields ranged from 3% to 80%, averaging 30%; enantiomeric excess values ranged from 50−70%. (b) After optimization for three years of student data, yields ranging from 50% to 90% averaging 70%; enantiomeric excess values ranged from 70−96%.

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