

Combination of X-ray Diffraction and Specific Rotation to Unequivocally Characterize Carvone Semicarbazone Derivatives

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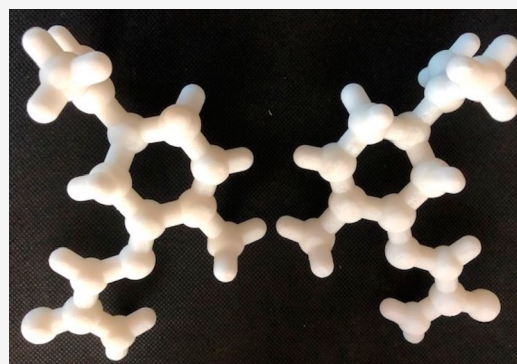


Article Recommendations



Supporting Information

ABSTRACT: Single-crystal X-ray structures, melting points, and students' specific rotation results on carvone semicarbazone derivatives are presented with experimental details. Critical parameters are identified to ensure the success of the experiment. Procedures developed here were tested in a laboratory course, consisting of approximately 70 students over three semesters. This experiment teaches undergraduate students important new instrumental methodology for characterizing a sample, allowing students to gain skills from hands-on experience using modern analytical instrumentation, and analyzing data to achieve a conclusion.



KEYWORDS: Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Laboratory Instruction, Safety/Hazards, Computer-Based Learning, Hands-On Learning/Manipulatives, Chirality/Optical Activity, Diastereomers, X-ray Crystallography

INTRODUCTION

The MIT Undergraduate Teaching curriculum uses lab classes to teach students new skills needed for more advanced work in research laboratories. This concept has been expanded to include X-ray diffraction. Course 5.310 Laboratory Chemistry: a one semester course with five experiments each allotted four 4 h lab days. In addition, there are 17 lectures, each 50 min long, covering the historical and theoretical background on each experiment. This includes one lecture on X-ray diffraction to help the students understand the diffraction experiment.

S(+)-Carvone from caraway oil and *R*(-)-carvone from spearmint oil have been isolated using preparative gas chromatography, steam-distillation of caraway seeds, liquid chromatography, column chromatography, and vacuum distillation.^{1–6} In this experiment, vacuum distillation is used to remove the major impurity *R*(+)-limonene (Figure 1).⁷ Techniques are presented to eliminate the foaming problems reported by Murov et al.⁴ The purities of the distillates were checked by gas chromatography and infrared spectrometry.

The *S*(+)-carvone or *R*(-)-carvone obtained is converted to a solid semicarbazone derivative to remove any traces of limonene (Figure 2).^{7–11}

Because of the restricted rotation about the C=N bond, two possible diastereomers could form (Figure 2). Melting point determination helps to distinguish between α and β diastereomers. Only little relevant information is available in the literature. It was reported that the β isomer is preferred under low temperature reaction conditions and can convert to the α isomer on heating at 170–175 °C.^{9,11} The diastereomer

identity was determined by measuring melting points of the semicarbazone crystals and confirming the carvone semicarbazone diastereomer via single-crystal X-ray diffraction.

Polarimetry was used to determine the specific rotation (\pm) of the semicarbazone derivative. The exact rotation is proportional to the amount of optically active material present. In searching the literature with SciFinder, there appears to be very limited published data on the specific rotation of the carvone semicarbazones; some of the data appears to be low quality and/or inaccurate.^{9,12} This paper presents student data representing multiple trials that establish accurate specific rotation angles for these important carvone semicarbazone derivatives. Polarimetry is able to tell us the sign of the rotation (+ or -) but not the (*R* or *S*) absolute configuration; consequently, it did not distinguish between enantiomers. Single-crystal X-ray diffraction was used to determine the absolute configuration.

In 1956, X-ray diffraction studies were first demonstrated as a valuable technique for characterizing essential oils and their derivatives.¹³ X-ray powder diffraction data on a variety of semicarbazone carbonyl type compounds including carvone

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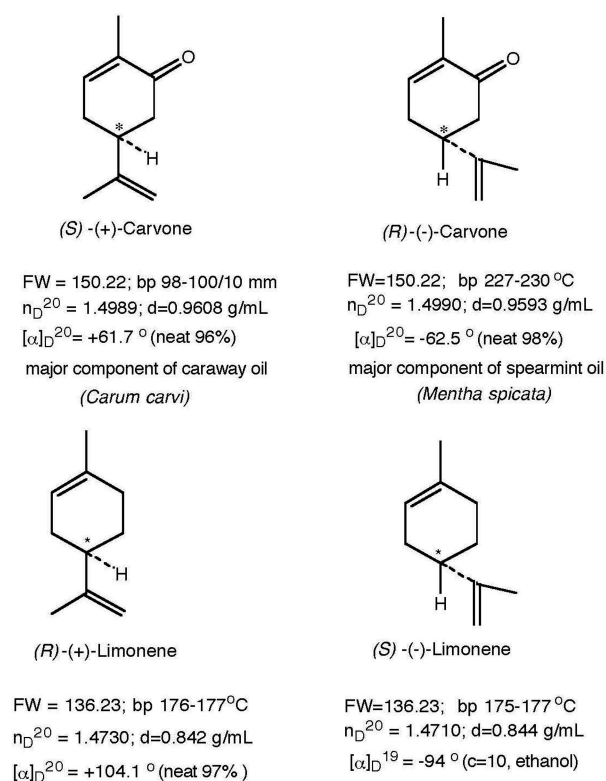


Figure 1. Carvone and limonene chemical structures (* denotes chiral center).⁷

were published by Meranger et al.¹⁴ Recently, the incorporation of single-crystal X-ray diffraction into the undergraduate chemistry curriculum has since proven itself in terms of the pedagogical value and benefits to students.^{15–20} Despite the obvious benefits, the technique has not been adopted widely, primarily due to the expense of installing and maintaining the instrumentation needed. This experiment could become a virtual reality in the absence of equipment (see instructor [Supporting Information](#)). The goal of this experiment is to

introduce single-crystal X-ray diffraction into the undergraduate curriculum exposing nonmajors (sophomores, juniors, and seniors) to an advanced analytical method in examining an important class of essential oil derivatives, the carvone semicarbazones. Furthermore, it is important that these nonmajors are able to visualize and manipulate their results, learn what a crystal is, and learn that diffraction is something observable. This experiment represents the first attempt to use single-crystal X-ray diffraction to differentiate between two important types of carvone semicarbazone diastereomers.

Students synthesized their carvone semicarbazone crystals. X-ray diffraction allowed students to obtain the three-dimensional structure, confirming the molecules' absolute configuration in addition to the α or β diastereomer (Figure 2). Prior to this experiment, no single-crystal X-ray diffraction data for semicarbazone derivatives of carvone, of particular value to essential oil chemists, have been deposited with the Cambridge Structure Database.²¹ Prior to this, most published protocols have yielded microcrystalline samples not suitable for single-crystal X-ray diffraction. This experiment presents a new recrystallization protocol for obtaining X-ray quality single crystals on carvone semicarbazone derivatives. This protocol could be adopted and modified to work for other difficult crystal recrystallizations.

EXPERIMENTAL PROCEDURE

Vacuum Distillation of Carvone and/or Spearmint Oil

Experimental details may be found in the [Supporting Information](#) instructor notes.

Gas Chromatography Analysis of Distillation Products

Experimental details may be found in the [Supporting Information](#) instructor notes.

IR Spectroscopy Analysis of Distillation Products

Experimental details may be found in the [Supporting Information](#) instructor notes.

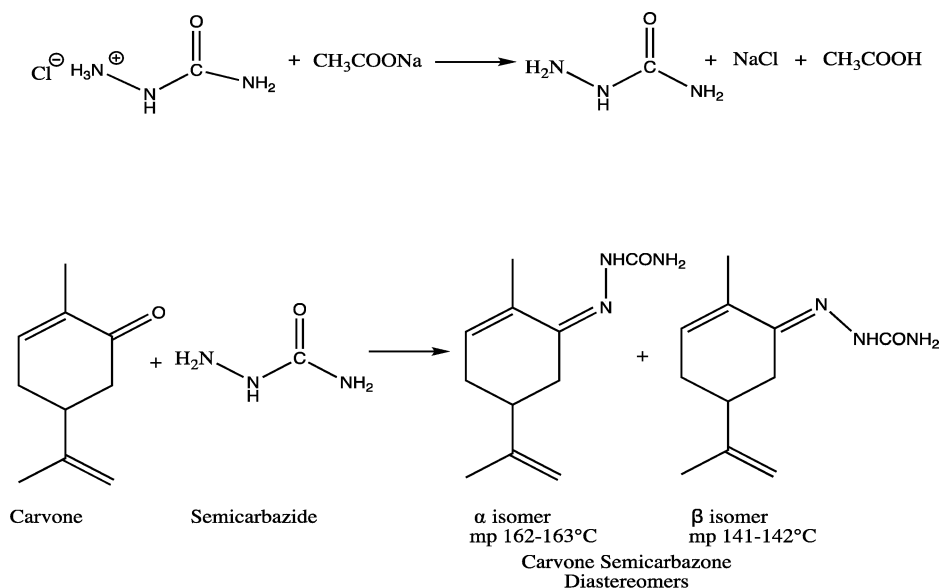


Figure 2. Synthesis of carvone semicarbazone derivative.

Table 1. Crystal Data and Structure Refinement for (S)-(+)- and (R)-(-)-Carvone Semicarbazone, β Isomers

	(S)-(+)-carvone semicarbazone	(R)-(-)-carvone semicarbazone
empirical formula	C ₁₁ H ₁₇ N ₃ O	C ₁₁ H ₁₇ N ₃ O
fw	207.27	207.27
cryst size (mm ³)	0.310 × 0.120 × 0.050	0.450 × 0.280 × 0.125
cryst syst	monoclinic	monoclinic
space group	P2 ₁	P2 ₁
unit cell dimensions (Å, deg)	a = 9.2050(4), α = 90 b = 19.6760(8), β = 98.027(2) c = 9.5245(4), γ = 90	a = 9.2133(3), α = 90 b = 19.6895(7), β = 98.1143(10) c = 9.5206(3), γ = 90
V (Å ³)	1708.15(12)	1709.80(10)
Z	6	6
calcd density (Mg/m ³)	1.209	1.208
Θ range for data collection (deg)	4.494–67.713	4.491–74.452
index ranges	–10 ≤ h ≤ 11, –23 ≤ k ≤ 23, –11 ≤ l ≤ 11	–11 ≤ h ≤ 11, –24 ≤ k ≤ 24, –11 ≤ l ≤ 11
reflns collected	55,933	129,767
indep reflns	6,092 [R _{int} = 0.0391]	6,979 [R _{int} = 0.0281]
completeness	99.3%	100.0%
data/restraints/params	6,092/10/439	6,979/10/439
GOF on F ²	1.035	1.069
final R indices [I > 2 σ (I)]	R1 = 0.0294, wR2 = 0.0768	R1 = 0.0247, wR2 = 0.0647
R indices (all data)	R1 = 0.0303, wR2 = 0.0775	R1 = 0.0247, wR2 = 0.0648
absolute structure param	0.05(5)	0.014(18)
largest diff peak and hole (e Å ^{–3})	0.183 and –0.123	0.121 and –0.186

Synthesis of Semicarbazone

A 0.5 g (4.5 mmol) portion of semicarbazide hydrochloride and 0.8 g of sodium acetate trihydrate were dissolved in a 13 mm × 100 mm test tube with 4 mL of distilled water and 7 mL of ethanol. Then, 0.5 mL (0.48 g, 3.2 mmol) of carvone was added. The test tube was stoppered and vigorously shaken to complete the dissolving process. The stopper was removed and a boiling chip added. The test tube was placed into an 80–90 °C water bath for 30 min. The test tube stopper was turned upside down while heating, to prevent pressure from building up. Ethanol was added as needed, to ensure homogeneity. After 30 min, the test tube was removed from the bath, and 3 mL of water was added slowly. After cooling, the contents of the test tube were transferred to a 125 mL Erlenmeyer flask. The test tube was rinsed with water and ethanol as needed, and the washings were added to the flask. The Erlenmeyer flask was placed into an 80 mm × 40 mm crystallizing dish, half filled with water, and heated on a hot plate; ethanol was added as needed, until the precipitate dissolved and the solution was clear. The flask and water bath were then heated to remove excess solvent, until the first sign of cloudiness. Then, the flask and water bath were removed from the heat and placed into a desk drawer until the next lab period. Needlelike crystals were collected via vacuum filtration, with a small Hirsch funnel, washed with cold milli-Q water, and left to air-dry.

Melting Point Determination

The melting point of the dried semicarbazone derivative was determined with an Afon DMP100 melting point device and recorded.

Measurement of Optical Rotation via Polarimetry

A 3% (w/v) solution was created upon addition of 0.3008 ± 0.0001 g of semicarbazone to 10.0 ± 0.1 mL of ethanol in a 25 mL Erlenmeyer flask. The semicarbazone was dissolved in the ethanol by gentle, indirect warming on a sand bath, set up in an 80 mm × 40 mm crystallizing dish with constant swirling. A 1.5% (w/v) solution also works well, if not enough derivative is

available. The solution was added to a 1 dm polarimeter cell, free of any particulate matter, air bubbles, and cloudiness. The observed optical rotations were recorded on a Rudolph Research Analytical Autopol IV polarimeter at 20 °C.

X-ray Diffraction

Low-temperature diffraction data were collected on a Bruker-AXS X8 Kappa Duo diffractometer coupled to either a Photon 2 CPAD detector or an APEX2 CCD detector using Cu K α radiation (λ = 1.54178 Å) from an I μ S microsource, performing ϕ - and ω -scans. Data reduction was carried out with the program SAINT,²² and semi-empirical absorption correction based on equivalents was performed with the program SADABS.²³ Structures were solved by dual-space methods using SHELXT²⁴ and refined against F² on all data by full-matrix least-squares with SHELXL-2017²⁵, following established refinement strategies.²⁶ All non-hydrogen atoms were refined anisotropically. All carbon-bound hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. Coordinates for the hydrogen atoms connected to nitrogen were taken from the difference Fourier synthesis, and those hydrogen atoms were subsequently refined semi-freely with the help of distance restraints on the N–H distances (target value 0.91(2) Å). The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U_{eq} value of the atoms they are linked to (1.5 times for methyl groups). Details of the data quality and a summary of the residual values of the refinements are listed in Table 1.

HAZARDS

General lab safety procedures should be followed throughout this experiment, including mandatory eye protection (goggles), skin protection (gloves), clothing protection (lab coats), and proper disposal guidelines for all chemicals. S(+)-Carvone is 400× more toxic than R(-)-carvone. Limonene is a toxic monoterpene wetting agent, used in the manufacture of resins. Semicarbazide hydrochloride is a cancer suspect, potential

mutagen, and is toxic to mucous membranes. Repeated or prolonged exposure can produce target organ damage. Sodium acetate is an irritant to the skin and eyes; inhalation may cause coughing and a sore throat.

RESULTS AND DISCUSSION

X-ray Diffraction

All analyzed samples of semicarbazone crystallized in the monoclinic, chiral space group $P2_1$, with three semicarbazone molecules per asymmetric unit. The two forms, $S(+)$ - and $R(-)$ -semicarbazone, were found to be perfectly isostructural, except, of course, for the handedness of the structure. Each semicarbazone molecule has three N–H functions which dominate the supramolecular arrangement. The three independent molecules are linked together via four N–H \cdots O hydrogen bonds, as shown in Figure 3. Those trimeric building

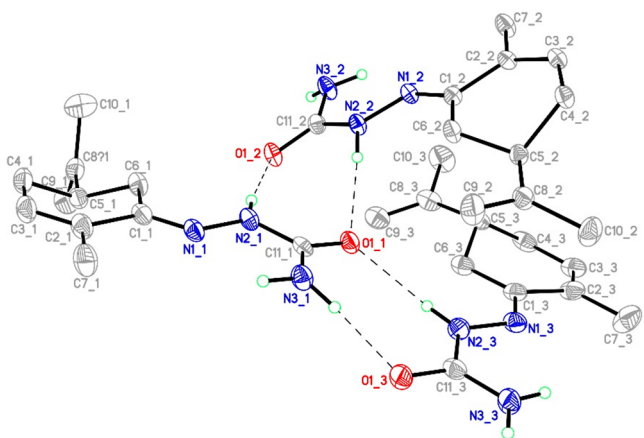


Figure 3. Thermal ellipsoid representation at the 50% probability level for the contents of the asymmetric unit in the structure of $R(-)$ -semicarbazone. The number after the underscore in the atom names serves to identify and distinguish the three individual crystallographically independent molecules. Hydrogen bonds are drawn as thin dashed lines; carbon-bound hydrogen atoms omitted for clarity.

blocks are linked into infinite helical chains extending along the crystallographic y -axis via two additional N–H \cdots O hydrogen bonds (Figure 4). This leaves three N–H functions unused, one per crystallographically independent molecule, and indeed, those three N–H donors are not involved in meaningful interactions. All hydrogen bonds, including C–H \cdots O interactions, are specified in Tables 2 and 3.

The molecule at hand is chiral, and for all analyzed crystals, the absolute structures could be determined unequivocally on the basis of the resonant scattering signal (see Table 1). The Flack- x parameters as calculated by the Parsons method²⁷ refined to zero within three standard uncertainties for all determined structures, and the results from optical rotation experiments could be confirmed in all cases.

Over the course of 1.5 years, well over a dozen data sets were collected, and the corresponding structures of $R(-)$ - and $S(+)$ -semicarbazone were determined. For the sake of brevity, two structures from the year 2017 were selected, and the figures and tables here correspond to those two representative structures.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC

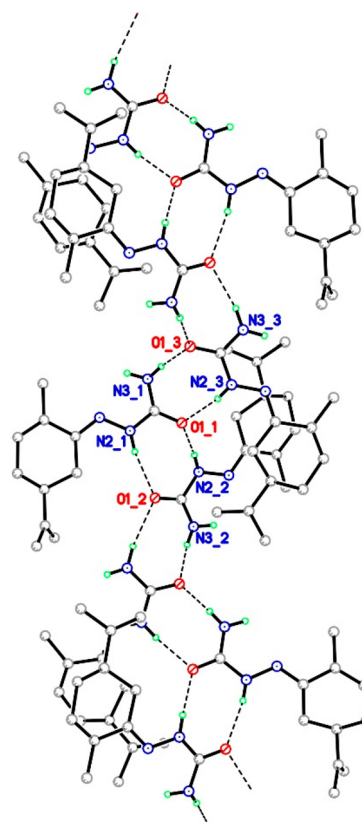


Figure 4. Trimers shown in Figure 3 are linked into infinite helical chains extending along the crystallographic y -axis. The three semicarbazone molecules above the central trimer are generated by symmetry operation $-x, -1/2 + y, 1 - z$, the three molecules below by $-x, 1/2 + y, 1 - z$. The “unused” N–H functions are clearly visible in this figure. Hydrogen bonds are drawn as thin dashed lines; carbon-bound hydrogen atoms are omitted for clarity.

Table 2. Hydrogen Bonds for (S)-(+)-Carvone Semicarbazone, β Isomer

D–H \cdots A ^a	$d(\text{D–H})$	$d(\text{H}\cdots\text{A})$	$d(\text{D}\cdots\text{A})$	$\angle(\text{DHA})$
N21–H21 \cdots O12	0.90(2)	2.11(2)	2.992(2)	167(2)
N31–H3A1 \cdots O13	0.91(2)	1.97(2)	2.868(2)	169(2)
C61–H6B1 \cdots O12	0.99	2.66	3.394(2)	131.4
N22–H22 \cdots O11	0.90(2)	2.05(2)	2.926(2)	164(2)
N32–H3A2 \cdots O13 ⁱ	0.90(2)	2.05(2)	2.937(2)	168(2)
C62–H6B2 \cdots O11	0.99	2.32	3.301(2)	172.7
N23–H23 \cdots O11	0.89(2)	2.15(2)	3.012(2)	164(2)
N33–H3A3 \cdots O12 ⁱⁱ	0.91(2)	2.22(2)	3.113(2)	168(3)
C63–H6B3 \cdots O11	0.99	2.44	3.372(2)	157.0

^aSymmetry transformations used to generate equivalent atoms: (i) $-x + 2, y - 1/2, -z + 1$; (ii) $-x + 2, y + 1/2, -z + 1$.

1958609–1958610. Copies of the data can be obtained free of charge from <https://www.ccdc.cam.ac.uk/>.

Specific Rotation and Melting Point

Representative student results of approximately 70 students were collected over three semesters and are presented here as a class average \pm standard error of the mean.

For (S)-(+)-1-methyl-4-isopropenyl-cyclohexen-(1)-on-(6)-semicarbazone (ETHOH = ethanol)

Table 3. Hydrogen Bonds for (R)-(-)-Carvone Semicarbazone, β Isomer

D-H...A ^a	d(D-H)	d(H...A)	d(D...A)	\angle (DHA)
N21-H21...O12	0.877(18)	2.125(18)	2.9898(16)	168.5(18)
N31-H3A1...O13	0.911(18)	1.970(18)	2.8691(18)	168.5(19)
C61-H6A1...O12	0.99	2.65	3.3965(18)	131.9
N22-H22...O11	0.893(17)	2.047(17)	2.9265(16)	167.8(17)
N32-H3A2...O13 ⁱ	0.894(18)	2.067(18)	2.9382(17)	164.6(18)
C62-H6A2...O11	0.99	2.32	3.3022(17)	172.6
N23-H23...O11	0.870(18)	2.164(18)	3.0144(17)	165.7(18)
N33-H3A3...O12 ⁱⁱ	0.902(18)	2.232(19)	3.1144(17)	166.0(19)
C63-H6A3...O11	0.99	2.44	3.3717(18)	157.0

^aSymmetry transformations used to generate equivalent atoms: $-x, y + 1/2, -z + 1$; $-x, y - 1/2, -z + 1$.

$$\alpha_D^{20} = +145.5^\circ \pm 1.1^\circ (c = 0.030, \text{ETHOH})$$

$$\text{MP} = 139.3\text{--}141.3^\circ\text{C}$$

For (R)-(-)-1-methyl-4-isopropenyl-cyclohexen-(1)-on-(6)-semicarbazone

$$\alpha_D^{20} = -146.0^\circ \pm 1.0^\circ (c = 0.030, \text{ETHOH})$$

$$\text{MP} = 138.7\text{--}141.6^\circ\text{C}$$

The resulting semicarbazone was determined to have an average specific rotation of $+145.5^\circ \pm 1.1^\circ$, or $-146.0^\circ \pm 1.0^\circ$, identifying the derivative as either the (S) or (R) isomer and, thus, the original essential oil as caraway seed oil or spearmint oil. The experience was meaningful: Each student prepared their own polarimeter samples, transferred them into clean polarimeter tubes, and had a hands-on experience operating the polarimeter to obtain the optical rotation of the semicarbazone derivatives. Approximately 20% of students' results for the specific rotations were slightly above or below the standard deviation for 70 determinations. Poor sample preparation was the main cause, including not dissolving all of the crystals by warming the sample, when preparing the polarimeter sample for analysis. Students learned quickly that the measurements obtained were only as valid as the care spent

on preparing the samples. Overall, the experiment was successful, and the uncertainty in the mean was reduced significantly on the basis of the large number of samplings. Polarimetry provided the students with information on chirality, since the rotation of polarized light allowed the students to distinguish between enantiomers based on the original samples.

After taking into account approximately 70 determinations, the melting points of the semicarbazone derivatives of 139.3–141.3 °C for (S)-semicarbazone and 138.7–141.6 °C for (R)-semicarbazone fell into a narrow range, indicating reasonable purity of the product. The mp range was only slightly lower than the literature value of 141–142 °C for the β isomer, compared to 162–163 °C for the α isomer; thus, the semicarbazone derivatives were identified as the β isomer. However, about 17% of students had melting point ranges below 140 °C. In addition, two students' melting points significantly exceeded 142 °C which brought out the possibility of the α isomer's existence. Nevertheless, X-ray diffraction confirmed these two samples to be β isomers. Therefore, this could be another interesting study later on. The slightly lower melting points indicate the presence of impurities, or crystals that may not have been fully dried. Students learned that thoroughly cleaning glassware including any dirty stir bars before a reaction is critical in controlling impurities that could easily contaminate their products.

On the last day of the essential oils lab, students visited the MIT X-ray Diffraction Facility with their X-ray quality crystals. Students observed how selected crystals were chosen and how samples were prepared and, finally, watched a demonstration of the process and uses of X-ray crystallography which produced a structure for the semicarbazone crystals. Students used the X-ray crystal structures (Figure 5) to determine the chirality of the original carvone. In single-crystal X-ray structure determination, the X-ray beam interacts with the electrons in the crystal, giving rise to a diffraction pattern consisting of discrete spots. Those spots, taken together, can be understood as the Fourier transform of the three-dimensional electron density function. Consequently, back-transformation leads to an electron density map in which maxima correspond to atomic positions. Therefore, the result of an X-ray diffraction study is a three-dimensional molecular structure on the atomic level. The semicarbazone crystal structures showed the -NHCONH_2 group oriented across the $\text{C}=\text{N}$ bond, trans



Figure 5. Representative student results are presented in this paper: Structures of (S)-(+)-carvone semicarbazone, β isomer (left), and (R)-(-)-carvone semicarbazone, β isomer (right).

from the methyl group (Figures 5). This orientation results in less steric interaction between the -NHCONH_2 group and the methyl group, which favors the lower melting point β isomer, compared to that of the α isomer.

CONCLUSION

After derivatization of an unknown essential oil, the resulting carvone was purified and analyzed to determine the stereochemistry and, thus, identify the oil as either caraway seed oil or spearmint oil. Through resonant scattering, X-ray diffraction allowed determination of the absolute structure and, therefore, the absolute configuration of the molecules. Using this method, the chirality of the original carvone as $S(+)$ or $R(-)$ was confirmed. The melting points were measured, and specific rotations of the semicarbazones were determined via polarimetry. The specific rotation of the $(S)-(+)$ -semicarbazone was found to be $+145.5^\circ \pm 1.1^\circ$, with a melting point of $139.3\text{--}141.3^\circ\text{C}$, and for the $(R)-(-)$ -semicarbazone it was $-146.0^\circ \pm 1.0^\circ$, with a melting point of $138.7\text{--}141.6^\circ\text{C}$. X-ray diffraction confirmed the absolute configuration of the enantiomer and supports the results obtained in the polarimetry analysis. The X-ray diffraction results also confirmed the results from the melting point analysis. On the basis of the experimental conditions used here, the structure was found to be the β isomer of carvone semicarbazone. Including X-ray diffraction into undergraduate education exposes students to an advanced analytical method. This kind of exposure prepares students for what lays ahead. Student online subject evaluations from 2017 to 2019 ranked the essential oil lab second out of five laboratories with an overall student satisfaction rating of 4.2–4.4 out of 5.0.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.0c00074>.

Essential oil experiment with instructor and student notes, CAS numbers of all chemicals used including suppliers, CIF and RES files for both $(S)-(+)$ -carvone semicarbazone β isomer and $(R)-(-)$ -carvone semicarbazone β isomer as well as RTF files containing the tables with data refinement, instructor notes on how to download the free program MERCURY at the (CCDC) Cambridge Crystallography Data Center, and short summary on X-ray diffraction (ZIP)

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Notes

The authors declare no competing financial interest.

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