Experiment 5

Optical Resolution of 1,2-Diaminocyclohexane

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PURPOSE OF THE EXPERIMENT

Separate an enantiopure compound, (*R*,*R*)-1,2-diaminocyclohexane from *racemic* and *meso* mixture of 1,2-diaminocyclohexane by forming diastereomeric complexes with L-tartaric acid.

BACKGROUND INFORMATION

Vicinal diamines (or 1,2-diamines) are one of the most widely used building blocks for making catalysts and drugs (Figure 1a). Among vicinal diamines, 1,2-diaminocyclohexane (DACH) is the most popular chiral diamine due to its availability from commercial sources (Figure 1a). Thus, chiral DACH is used for making stereoselective catalysts such as Jacobsen's catalyst or making bioacitive drugs such as eloxatin (Figure 1b).

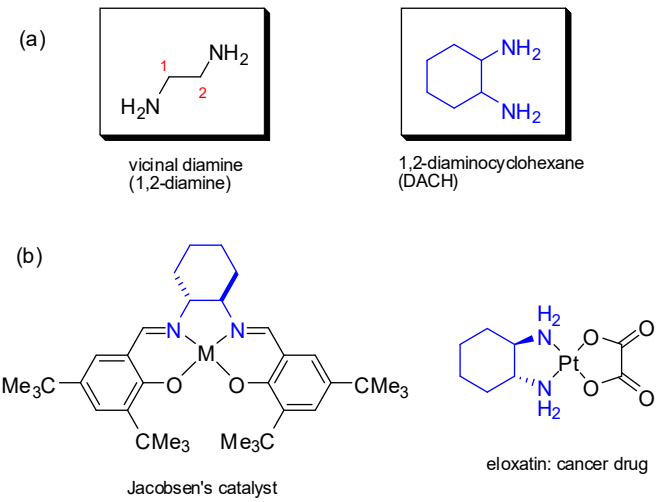


Figure 1. (a) Chiral Vicinal Diamine structure and 1,2-diamino-cyclohexane. (b) Jacobsen's catalyst and eloxatin

1,2-Diaminocyclohexane (DACH) is produced in a industrial process for making nylon-66. Nylon are synthetic polymers which are prepared by a condensation reaction between diamine and dicarboxylic acid. For making nylon-66, hexamethylenediamine (1,6-diaminohexane) and adipic acid are used. While preparing hexamethylenediamine by the reduction of 1,4-dicyanobutane, DACH is produced as a side product (Figure 2).

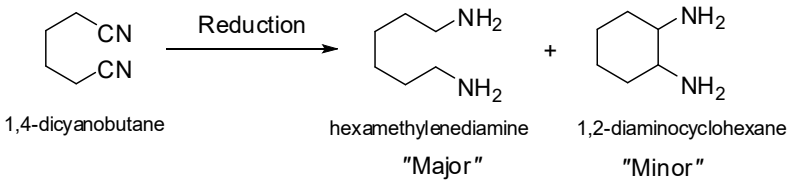


Figure 2. Industrial Production of hexamethylenediamine

1,2-Diaminocyclohexane (DACH) prepared from the industrial process is a 1:1 mixture of *cis*- and *trans*-stereoisomers. *Cis*- and *trans*-DACH are diasteromers, which exhibit different physical properties (Figure 3). As shown in Figure 3, there is a plane of symmetry in the *cis*-DACH. Thus, *cis*-DACH is a achiral, *meso* compound. However, *trans*-DACH consists of two enantiomers in (*R*,*R*) and (*S*,*S*) forms (Figure 3).

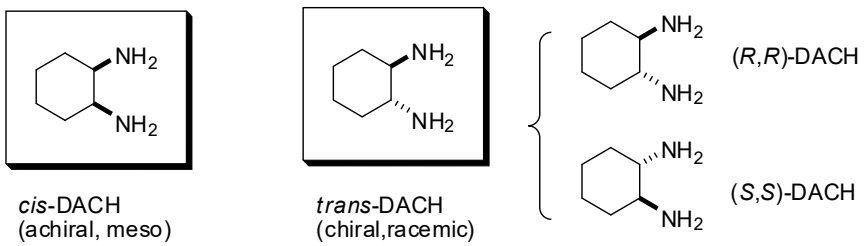
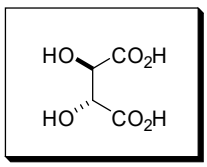


Figure 3. *Cis*- and *trans*-DACH

There are currently many methods to obtain optically active compounds. These methods include asymmetric synthesis, use of chiral building blocks, and optical resolution. In recent years, there has been rapid improvements in asymmetric synthesis, with many reports of success.

Optical resolution is the method of separating enantiomers from racemates. Optical resolution is widely used as it is an easy and practical method. One of the most common optical resolution methods utilizes diastereomers which are obtained from the reaction of racemic compounds and an optical resolving agents. The differences of physical properties between diastereomers is used to separate diastereomers.



L-tartaric acid

In order to separate *cis*- and *trans*-DACH, we will use L-tartaric acid, as a resolving agent. When L-tartaric acid is added to a mixture of *cis*- and *trans*-DACH, 1:1 complexes of L-tartaric acid and DACH are formed by proton transfer (Figure 4). As a result, DACH-L-tartaric acid complexes become three diastereomeric mixtures. Interestingly, the "matched" complex of (*R*,*R*)-DACH and L-tartaric acid complex, is much less soluble in water than "mismatched" complex of (*S*,*S*)-DACH and L-tartaric acid complex or *meso*-DACH and L-tartaric acid complex. Thus only

(*R*,*R*)-DACH-L-tartaric acid complex came out from an aqueous solution as a white crystal leaving other two complexes in the solution.

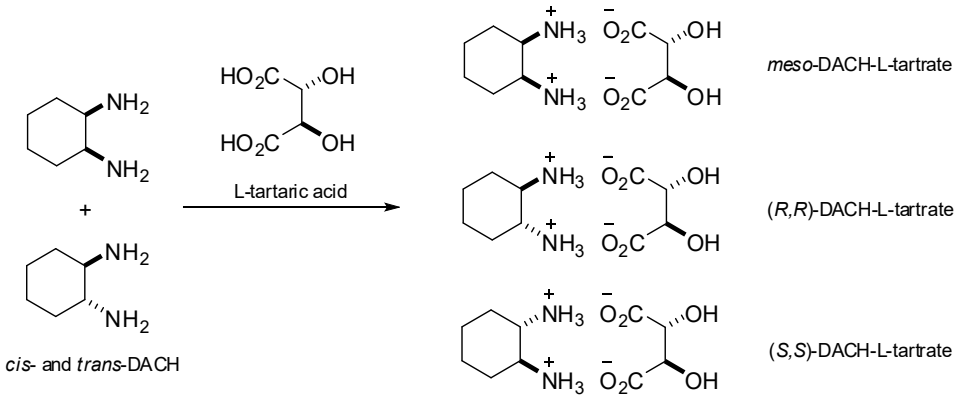


Figure 4. Formation of three diastereomeric complexes between *cis*- and *trans*-DACH and L-tartaric acid

It is also known that L-tartaric acid forms *trans*-DACH-L-tartrate complex more tightly than *cis*-DACH-L-tartrate complex. Thus, to a mixture of *cis*- and *trans*-DACH, L-tartaric acid can be added by exact molar amount of *trans*-DACH and acetic acid can be added to make *cis*-DACH-acetic acid complex (Figure 5). In this experiment, we will use 1 equivalent of L-tartaric acid and 2 equivalent of acetic acid to resolve 1:1 mixture of *cis*- and *trans*-DACH. Finally (*R*,*R*)-DACH-L-tartrate will be isolated.

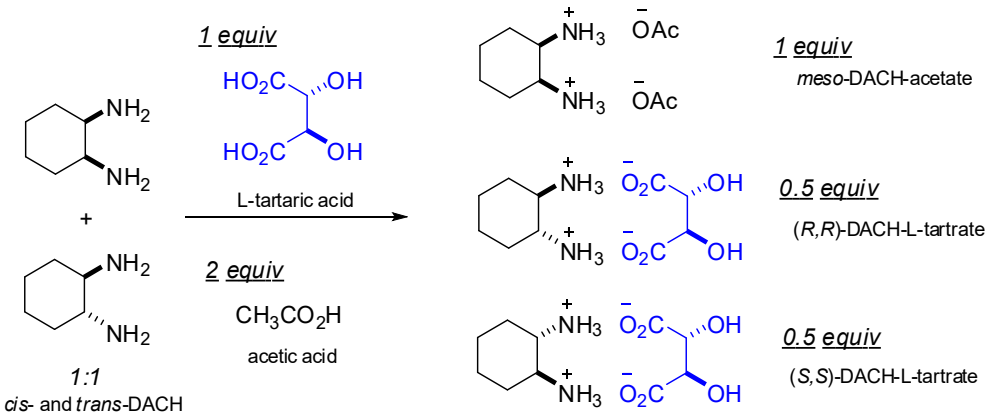


Figure 5. Resolution of DACH by L-tartaric acid and acetic acid

EXPERIMENT **Optical resolution of *cis*- and *trans*-DACH by L-tartaric acid.**

Reagents and Properties

substance	*quantity*	*molar mass* (*g/mol*)	mmol†	*mp* (*°C*)	bp (*°C*)	*density* (*g/mL*)
acetic acid	2.54 mL	60.05	44.4		117-118	1.05
1,2-diaminocyclohexane mixture of *cis* and *trans*	5.00 mL	114.19	40.4			0.931
L-tartaric acid	3.15 g	150.08	21.0	170-172		
water, distilled	14 mL					
methanol						
saturated $NaHCO_3$ solution		84.07g				

PROCEDURE

Caution: Wear lab coats and safety goggles at all times while in the lab. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Wearing contact lens is strictly prohibited.

1. Setting Up the Reaction

Caution: Acetic acid is corrosive and flammable. Handle acetic acid in a *fume hood*.

Prepare 100 mL round-bottom flask (RBF) equipped a magnetic stir bar. Weigh L-tartaric acid and transfer it into the RBF. Add water and dissolve L-tartaric acid by gently stirring the mixture. Place a thermometer in the solution but avoid contact with the stir bar. Record the initial temperature of the aqueous solution.

After dissolving L-tartaric acid completely, add 1,2-diamino-cyclohexane slowly into the solution. Record the temperature after adding 1,2-diaminocyclohexane.

With a *vigorous stirring*, add acetic acid ***dropwise*** into the solution. During the addition, the solution temperature shouldn't exceed 95 °C. If the solution is too hot, slow the addition of acetic acid. When the addition is completed, record the final temperature of the solution, turn off the stirring, and remove the thermometer.

2. Isolating (*R*,*R*)-1,2-diamino-cyclohexane L-tartrate

Allow the RBF to cool to room temperature. Then, put the RBF into an ice bath for 30 min. In the mean time, prepare about 10 mL of ice-cooled distilled water.

Collect the white crystals by vacuum filtration. Using ice-cooled water (5 – 10 mL), wash the crystals on the funnel. Then, wash the crystals with methanol 2-3 times until the crystals become white. By passing air, allow the crystals to dry on the funnel for at least 10 min.

Transfer the product to a watch glass or a beaker, and dry the product in an oven (~ 90°C) for at least 1 h until the product becomes light powder. Measure the amount of the product.

3. Regeneration of Free Amine and NMR Spectroscopy

Isolated product with salt form is hard to be analyzed by NMR technique intactly. Pour 500 mg or more of product to 20ml of ethyl acetate and stir for a second. Transfer the mixture to 100 ml size separatory funnel and pour 10 ml of saturated $NaHCO_3$ solution. Block the open side of funnel with appropriate stopper and work-up by shaking funnel. (Be careful of the gas generated during the work-up procedure.) When the solution becomes homogeneous and no more gas is generated, separate two layers. Transfer the organic phase to a 50 ml beaker. And repeat the work-up procedure with residual water solution and 15ml of ethyl acetate. After that, dry the combined organic solution over $MgSO_4$. Filter the solution and remove solvent through rotatory evaporator.

Add 0.5~1 ml of $CDCl_3$ to dried product and conduct an NMR analysis under TA's guidance.

Post-Laboratory Questions

1. What is the method we used for optical resolution? Explain the principle in detail.
2. Through procedure, we stirred reaction mixture vigorously for reasons. What are the reasons and why do they happen?
3. Suggest other example of substances that can be seperated by the method we used.
4. Which compound is isolated in this method? How can we isolate the others?
5. In this experiment, we did not confirm enantiopurity of (R,R)-DACH-L-tartrate. Propose possible methods to determine the enantiopurity of (R,R)-DACH-L-tartrate.

Pre-Laboratory Questions

1. Write the types of isomers and explain.
2. Which type of isomeric relationship is for 1) cis/trans-DACH and 2) (*R,R*)/(*S,S*)-DACH?
3. Suggest one example of chiral organometalic catalyst and related reaction with vicinal diamine structure (do not use the manual).
4. Is there any other method for optical resolution except the one used in this experiment?
5. Draw the reaction scheme for nylon-66 synthesis.