Experiment 11

Stereochemistry of Alkene Additions: Addition of Bromine to trans-Stilbene

Reading: Handbook for Organic Chemistry Lab, sections on Writing Lab Reports (Chapter 4), Reflux (Chapter 16) and Green Chemistry (Handbook Supplement on website). Organic Chemistry by Marc Loudon, 6th ed., pp. 184-186 (5.2A); 203-217 (5.6); 306-308 (7.8A); 309-313 (7.8C); 1233-1238 (24.2, Fischer Projections).

When chlorine or bromine is added to cycloalkenes, two products are theoretically possible: a *trans* product and a *cis* product (Figure 11-1).

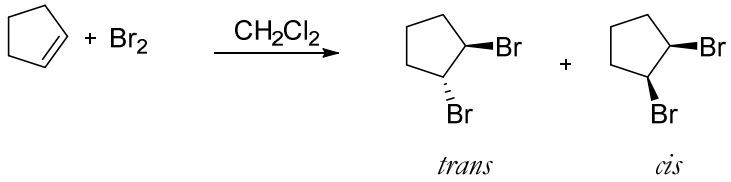


Figure 11-1: Two theoretically possible outcomes of bromine addition.

When this reaction takes place in the laboratory, only the *trans* product is isolated. The reaction is therefore stereoselective, because one of several possible products is preferentially formed. This is because halogens usually react with alkenes via an electrophilic addition mechanism involving a bromonium ion intermediate, which leads to *anti*-addition.

Step 1: Reaction of cyclopentene with bromine to form a bromonium ion intermediate (Figure 11-2).

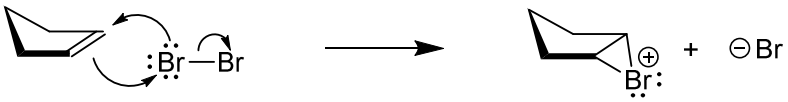


Figure 11-2: The first step of bromine addition involves the formation of a bromonium ring intermediate.

Step 2: Nucleophilic attack of bromide anion on the bromonium ion on the *anti*-face on either of the two carbons (Figure 11-3).

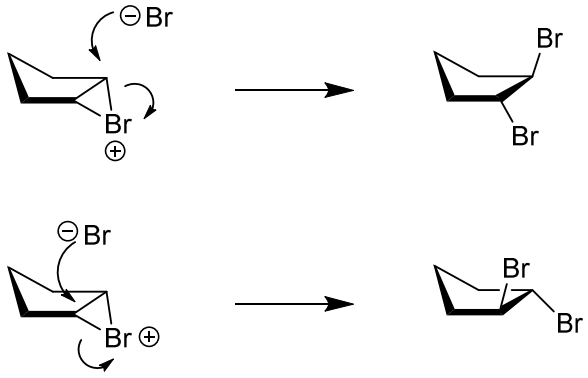
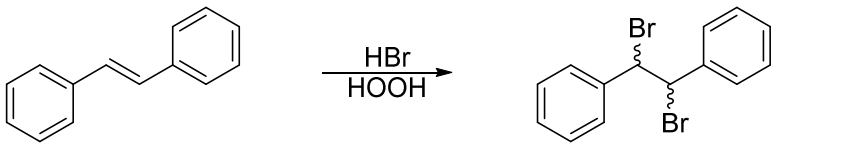


Figure 11-3: The second step involves the bromonium ring being broken open by an attacking halide ion.

In this experiment you will brominate *trans*-stilbene, but you will not add elemental bromine (Br_2) directly to the reaction mixture. Instead, you will generate it *in situ* from 47% hydrobromic acid and 30% hydrogen peroxide. (Whenever a reagent is created within the reaction flask instead of added to it, it is said to be created *in situ* or on-site.) The overall reaction is shown in Figure 11-4. The squiggly bonds drawn in the reaction product denote the presence of stereocenters of an unknown configuration (i.e., R or S is not known).



trans-Stilbene 1,2-dibromo-1,2-diphenylethane

Figure 11-4: The overall reaction you will perform.

You may be asking, why not simply use elemental bromine for this reaction, instead of generating it *in situ*? The reason is that elemental bromine is quite hazardous – it causes severe burns when it comes in contact with the skin and its vapor irritates the eyes, nose and throat. Even if it is dispensed as a solution in DCM (as it was done during the previous version of this experiment performed in the labs at CU), bromine burns are still a serious concern. Generating small amounts of bromine *in situ* makes the reaction considerably safer. In addition, the reagents used to generate bromine are soluble in alcohols. This allows the replacement of DCM as a solvent with ethanol, which is less toxic and easier to deal with as chemical waste. The replacement of reagents and solvents with more environmentally-friendly options is a major goal of green chemistry.

Very often, when HBr and HOOH are present in a reaction scheme we anticipate the anti-Markovnikov addition across the double bond, which we can attribute to the peroxide effect. In the case of *trans*-stilbene, however, the double bond is highly stabilized through the extended π conjugation with the aromatic rings, resulting in high bond dissociation energy. The corresponding free radical mechanism of addition is endothermic and therefore does not act as the primary mechanism for addition, but moves directly to the radical termination step. Subsequently, elemental bromine is formed directly in solution more quickly than anti-Markovnikov addition can occur (Figure 11-5).

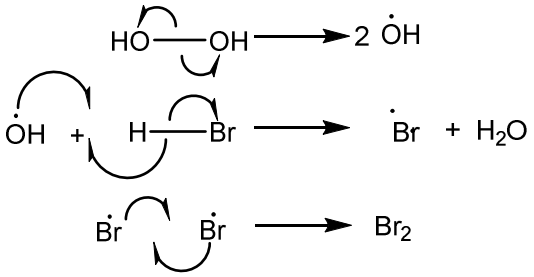


Figure 11-5: The radical mechanism for Br_2 formation.

Once elemental bromine is present, the reaction proceeds via the bromonium ion intermediate, and therefore the addition must be anti. The product is named using *threo* and *erythro* nomenclature, which is explained below. The *erythro* and *threo* products each have a different melting point, therefore you must determine whether anti addition gives the *erythro* or the *threo* isomer before you come to lab. To do this, fill out the worksheet at the end of the Procedure section for this lab. Your molecular model set will be particularly useful in completion of the worksheet.

Because you will prepare a new compound by a chemical reaction, this is a preparative lab, so your prelab will be slightly different from the technique prelabs you have done up until now. The two main differences are that you will have to calculate theoretical yield (refer to your Handbook), and you will have to include a mechanism for this reaction in your prelab. Since you are using an excess of hydrogen peroxide and hydrobromic acid, your limiting reagent will be stilbene.

Fischer Projections and *Threo/Erythro* Nomenclature

Fischer projections were invented to show stereochemistry in an organized way on carbohydrates. They were created by German carbohydrate chemist and 1902 Nobel Prize winner, Emil Fischer. To create a Fischer projection, arrange the tetrahedral carbon so that the vertical bonds at the chiral center point away from you and the horizontal bonds point towards you (Figure 11-6). This means that a Fischer projection still means the same thing if rotated by 180°, but not 90°, since this would involve swapping bold and dashed bonds. If there are multiple stereocenters along the parent chain (the backbone), arrange them vertically.

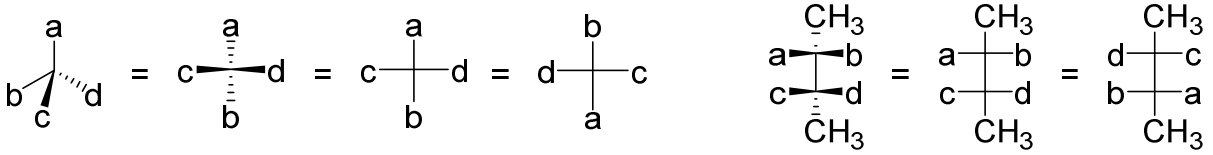


Figure 11-6: Some examples of Fischer projections.

To convert a normal skeletal structure to a Fischer projection, arrange the molecule's backbone so that all the bends are curving around in the same direction, rather than alternating in a zigzag. (The molecule itself doesn't necessarily bend into this conformation in reality; this is just a standardized way of showing it.) You will probably have to rotate every alternating carbon around 180° to do this, which means that which means that the bold and dashed bonds will appear to interchange on these carbons, although the absolute configuration (R or S) should remain the same. Once the backbone is curled up, you can look down on the molecule from outside the curve. In Figure 11-7, all the groups which are on bold bonds in the curled-up structure end up pointing to the left in the Fisher projection.

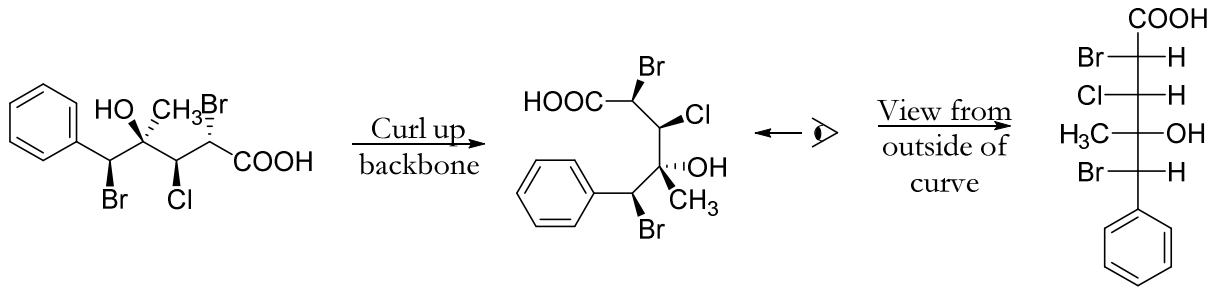


Figure 11-7: Converting a structural formula to a Fischer projection.

Compounds with only two stereocenters can be named *erythro* or *threo*, based on their similarity to the sugars erythrose and threose (Figure 11-8). If the substituents are both on the same side when the molecule is drawn as a Fischer projection, it is designated as an *erythro* compound; if they are on opposite sides, it is designated as a *threo* compound.

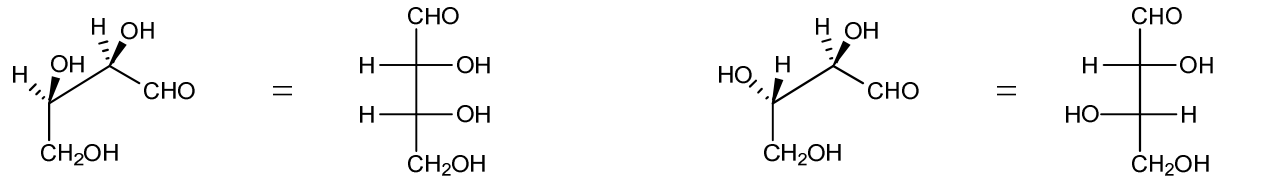
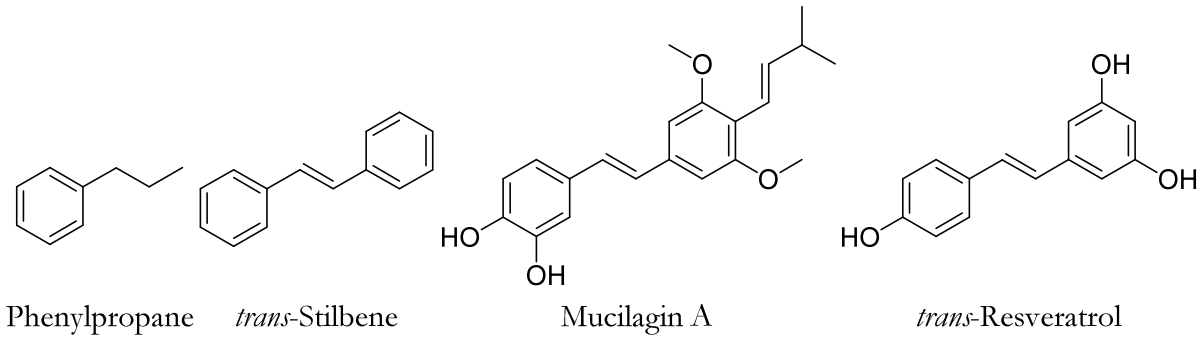


Figure 11-8: Erythrose and threose.

For this particular experiment, **the *threo* product has a melting point of 100-102°C and the *erythro* product has a melting point of 240-242°C**, although the *erythro* product will decompose at its melting point. The worksheet included at the end of this experiment is designed to guide you through predicting which product is expected for this reaction. There will not be a prelab quiz for this experiment. Instead, fill out and hand in the worksheet when you arrive at your lab.

Stilbene and Its Derivatives

Stilbene is a chemical compound that forms the backbone of the stilbenoid class of antioxidants (Figure 11-9). These natural products are found in a variety of plants. Stilbenoids are members of the family of phenylpropanoids, aromatic compounds based on a phenylpropane skeleton. The stilbenoids are hydroxylated forms of the stilbene backbone. Many stilbenoid compounds are natural products associated with plants such as peanuts (mucilagin A) and grapes (resveratrol). Plants biosynthesize stilbenoids as a defensive mechanism to protect them from fungal invasion. This potent chemical activity gives rise to many pharmacological uses especially in regards to treatment and prevention of cancer.



Phenylpropane *trans*-Stilbene Mucilagin A *trans*-Resveratrol

Figure 11-9: Stilbene and many other compounds are based on the structure of phenylpropane.

Safety Precautions

Hydrobromic acid (47%) is corrosive; avoid contact and inhalation of vapors. Hydrogen peroxide (30%) is a strong oxidizer, can cause burns if it comes in contact with skin, and it is toxic. Wear protective clothes and gloves and avoid inhaling vapors. Run this and all other reactions in your student hood. Clean up any spills immediately.

Procedure

This experiment will be done individually.

In this reaction, concentrated aqueous hydrogen bromide and hydrogen peroxide are added to a stirring solution of *trans*-stilbene in ethanol while heating under reflux. The reagents you use will generate a small amount of bromine *in situ*. Since acetone reacts with bromine (in fact, it creates a lachrymator which releases fumes that will irritate your eyes), be sure your reaction glassware has no traces of acetone in it when you start adding reagents. If you need to clean your glassware before you begin, you should rinse it with ethanol, not acetone.

Start by placing 0.002 moles (2 mmoles) of *trans*-stilbene and 10 mL of ethanol in a 50 mL round bottom flask. Add a stir bar and place the flask on your stirring hotplate. Fit the flask with a reflux condenser as shown below in Figure 11-10.

Heat the contents of the flask to boiling. Adjust the hotplate setting so that the solvent vapors condense about halfway up the condenser; this is called the "reflux level". When the mixture is refluxing properly, slowly add 0.8 mL of the concentrated hydrobromic acid to the flask. This is easily accomplished by using a Pasteur pipet and counting the drops added directly to the top of the condenser. A good rule of thumb is that one drop is approximately 0.05 mL. Add dropwise 0.3 mL of the 30% hydrogen peroxide to the reaction mixture. The initial colorless mixture will change to a dark golden yellow. Continue heating your reaction at reflux for an additional 20 minutes until the yellow color fades and the mixture becomes a cloudy white.

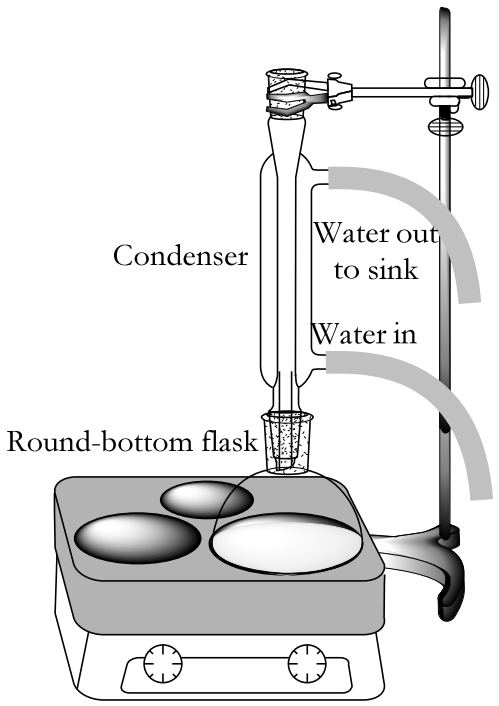


Figure 11-10: The reflux setup you will use for this reaction.

While the reaction is at reflux, clean an NMR tube with acetone and allow it to dry.

After 20 minutes, remove the flask from the heating mantle and allow it to cool to room temperature. Checking with pH paper, carefully adjust the pH of the solution to pH 5 to 7 through the addition of saturated aqueous sodium bicarbonate, $NaHCO_3$. This may take very little volume to accomplish.

Once the pH has been adjusted, continue the cooling of the reaction mixture in an ice bath to crystallize additional product out of solution. Collect the solid that forms through vacuum filtration; a careful wash with cold ethanol can be used to remove trace impurities. Determine the melting point and yield of your product, and submit a sample of your product for NMR analysis in $CDCl_3$.

Wastes

Organic Waste: All residual solvent

Recovery Jar: Product

Solid Chemical Waste: Used melting point capillaries, and pipets.

Lab Report

Your conclusions should include:

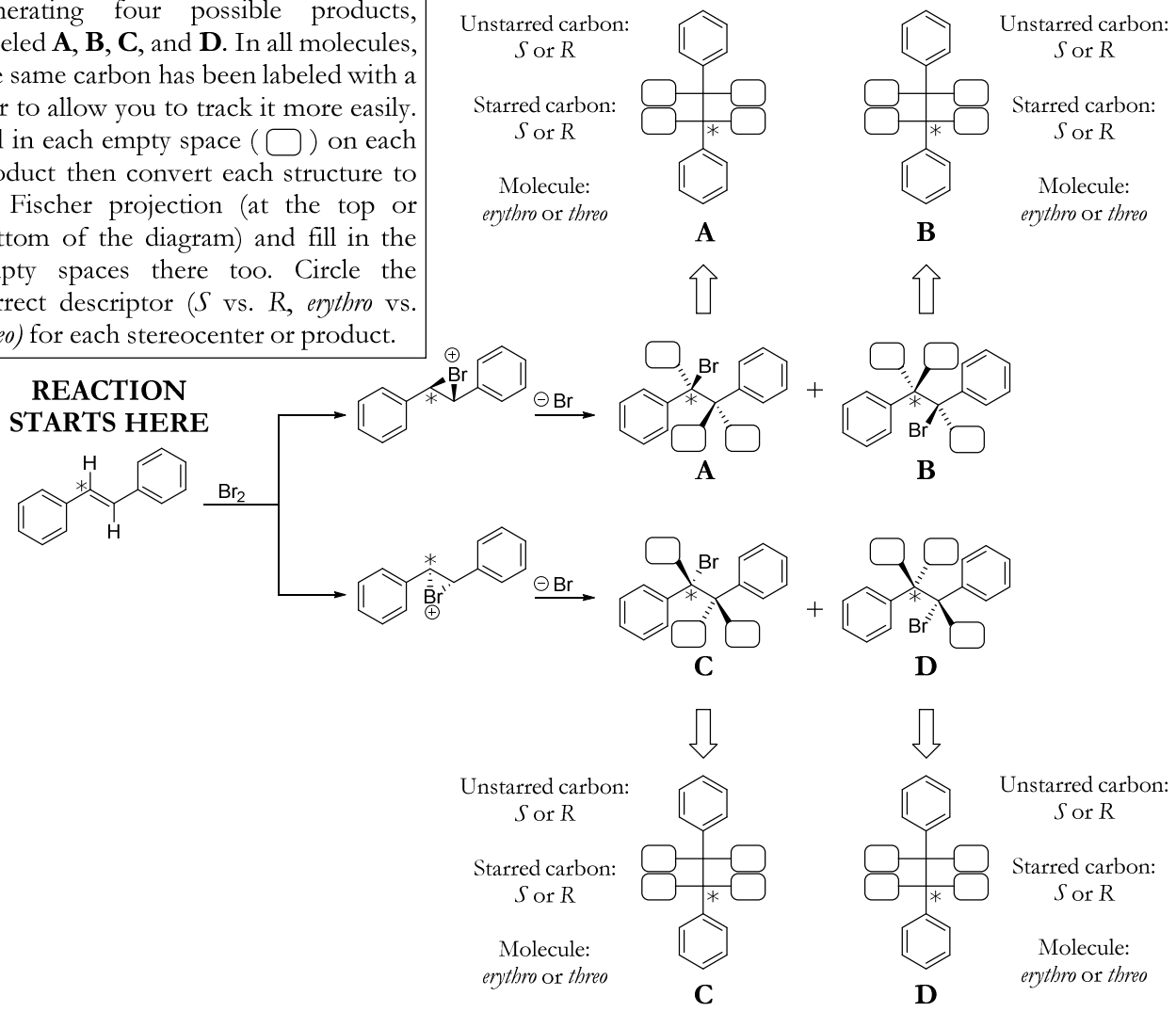
- Analysis of your NMR. Is your product just the expected dibromo compound, or are there any byproducts? Is there any stilbene left? If so, how much? The SDBS literature spectrum for the product was not taken in the same solvent that you used, so the two nonaromatic protons will appear in a slightly different location than they do in the literature (around 5.4 ppm).
- Yield and melting point.
- Based on melting point, did you isolate the *erythro* or the *threo* isomer? What does this tell you about the literature mechanism?

Name_____

Stereochemistry of Alkene Additions Worksheet

Follow the directions to fill in the structures of all possible products below. When you are converting each product to its Fischer projection, remember to use the method shown in **Error! Reference source not found.** above. Using your molecular modeling kit will also be very helpful – you can build each product, then rotate around the middle bond of the molecule to show how it would look in a Fisher projection. (10 points for completed reaction scheme)

Directions: The diagram below shows a reaction beginning on the left, and generating four possible products, labeled **A**, **B**, **C**, and **D**. In all molecules, the same carbon has been labeled with a star to allow you to track it more easily. Fill in each empty space (▢) on each product then convert each structure to its Fischer projection (at the top or bottom of the diagram) and fill in the empty spaces there too. Circle the correct descriptor (*S* vs. *R*, *erythro* vs. *threo)* for each stereocenter or product.



Based on your results for this diagram, answer the questions on the back of this page. (2 pts per question)

1) What is the relationship between the products (enantiomers, diastereomers or identical)?

Products	**Relationship**	**Products**	**Relationship**
A & B		A & C	
C & D		A & D	
B & D		B & C	

2) What melting point do you expect for your product(s)?

3) What would be indicated by a melting point that is similar to one expected in the literature, but lower?

4) Though the major product expected is produced through a bromonium ion intermediate, evaluate the reaction conditions and propose other side reactions that may occur. (Hint: remember that hydrobromic acid is added to stilbene first, and then hydrogen peroxide is added afterwards. What reaction would occur if stilbene and HBr reacted with each other, with no other molecules involved?)

5) What substance is responsible for the golden yellow color you should see in your flask when you have added all the reagents? (Hint: what reagent are you hoping to generate *in situ*? What color is it when concentrated? What color is it likely to be when it's more dilute?)