

Experiment 12

STEREOCHEMISTRY OF BROMINE ADDITION

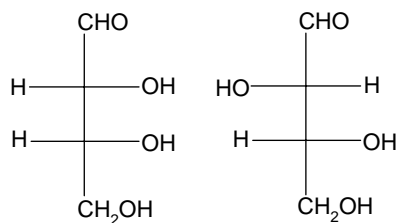
Text Topics

Stereochemistry including anti-addition and diastereomers, dropwise addition.

Discussion

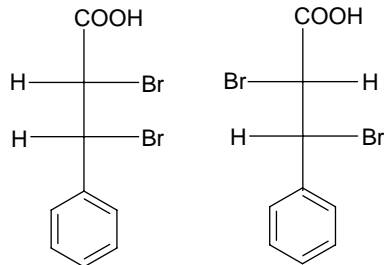
The idea that the positions of the four atoms bonded to a tetravalent carbon could be oriented in a tetrahedral fashion around the carbon was an astounding and significant advance in the field of organic chemistry. Two chemists, J. H. van't Hoff and J. Achille Le Bel independently published this idea within a short time period in 1874. This idea enabled chemists to understand the concept of non-superimposable mirror images that is of vital importance in the understanding of stereochemistry and its role in organic and biological chemistry. In today's experiment, bromine will be added to the double bond in cinnamic acid. As a result of the addition, two stereogenic carbons are created. By determining the relative orientations about the two carbons, you should be able to gain insight into the mechanism of the reaction.

Assuming the reaction occurs, there are three possible scenarios. The two bromines could add from the same side or syn addition, opposite sides or anti addition or a mixture of both. The possible products are the diastereomers *erythro*-2,3-dibromo-3-phenylpropanoic acid [a mixture of (2*R*,3*S*)-2,3-dibromo-3-phenylpropanoic acid and (2*S*,3*R*)-2,3-dibromo-3-phenylpropanoic acid] and *threo*-2,3-dibromo-3-phenylpropanoic acid [a mixture of (2*R*,3*R*)-2,3-dibromo-3-phenylpropanoic acid and (2*S*,3*S*)-2,3-dibromo-3-phenylpropanoic acid]. The terms *erythro* and *threo* are derived from structural comparisons to the sugars erythrose and threose as can be seen from an accompanying Fischer projections. This terminology is subject to some ambiguity and has largely been replaced by the unambiguous use of the Cahn-Ingold-Prelog R-S system.



D-erythrose

D-threose



erythro dibromide

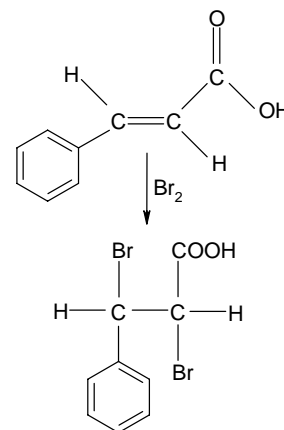
threo dibromide

Fig. 12-1



J. H. van't Hoff
J. Achille Le Bel

Fig. 12-2



Note that the enantiomers of the erythro and threo dibromides are not illustrated. For this addition reaction, formation of either the erythro or the threo will be accompanied by formation of an equal amount of the enantiomer of each. It will be your responsibility to demonstrate with illustrations which pair of enantiomers should result from syn addition and which pair from anti addition. You should show that syn and/or anti addition leads to a 50/50 mixture of enantiomers. The melting point of your product should enable you to determine whether the product is a racemic mixture of the erythro or the threo stereoisomers or a mixture of diastereomers. From this information, you should be able to conclude whether the reaction proceeded by syn or anti addition or a mixture of both.

<u>compound</u>	<u>melting point (°C)</u>
<i>erythro</i> -2,3-dibromo-3-phenylpropanoic acid	204
<i>threo</i> -2,3-dibromo-3-phenylpropanoic acid	95

Safety is always the first concern in the organic chemistry laboratory. Option 1 in the Procedure Section uses a bromine solution. Option 2 reduces the hazards somewhat by using pyridinium tribromide as the brominating agent. Perform the option designated by your instructor. Regardless of the procedure used, it is important to understand the hazards and the care that should be exercised when using a bromine solution. In the **Prelaboratory Preparation** section, you will be asked to look up the inhalation hazard of bromine and other hazardous vapors. Although the bromine LD₅₀ (lethal dose 50 percent kill - oral rat - 2.6 g/kg) seems to indicate a low degree of oral toxicity in rats, the LD_{Lo} (lowest published lethal concentration) for humans when taken orally is only 14 mg/kg. This means that as little as about 1 gram taken orally can be lethal to a human. This also points out that the LD₅₀ values (oral rat) are not necessarily a valid indication of the danger to humans. In this case, the lethal dose could be about 1000 times less than the value indicated by the LD₅₀ for rats.

At the site: <http://www.cdc.gov/niosh/idlh/7726956.html>, it has been reported that 10 ppm and above cause such severe upper respiratory irritation that exposures will not be voluntarily borne [MCA 1968]. Also, it has been reported that 0.75 ppm caused no symptoms in 6 hours. Further, 4 ppm has been recommended as the maximum concentration allowable for 0.5 to 1 hour, with 40 to 60 ppm dangerous for brief exposures. It has also been stated that respiratory damage occurs at 10 ppm. It has been reported that 1.7 to 3.5 ppm produces severe choking, 4.5 to 9 ppm is extremely dangerous, and 30 ppm would prove fatal in a short time.

Because of the significant hazard posed by bromine, all work with bromine should be performed in a well-functioning hood with the doors down as far as possible. The bottle containing the bromine solution should never leave the hood and the containers it is transferred to should not leave the hood until after the bromine has been completely reacted.

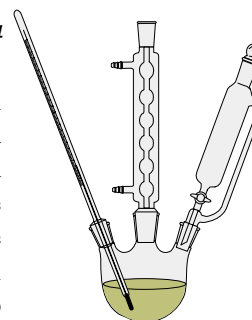
Fig. 12-3



Technique

Rather than add two reactants together all at once, higher yields are often achieved when one of the reactants is added slowly to the other. This is accomplished with an apparatus like the one to the right equipped with a pressure compensated dropping funnel. The rate of addition of the second reactant can be controlled with the stopcock on the dropping funnel. The tube which extends from near the top of the funnel to below the stopcock enables the user to stopper the funnel without creation of a vacuum as the reactant is added. For your apparatus, you will probably have to use a separatory funnel and frequently remove the stopper as the reactant is added. An

Fig. 12-4



alternative is to install a drying tube in the top of the separatory funnel. In the apparatus illustrated, a reflux condenser has been included so that the solution can be refluxed during the addition. Actually, many reactions that use this type of apparatus are exothermic and refluxing occurs without the addition of heat from an external source.

Procedure

Option 1: Use of bromine solution. Because of the potential hazards of bromine, the reaction must be carried out in the hood. (Note: While the amounts given below afford excellent results, it should be possible to halve or even quarter the amounts and still obtain satisfactory results. If hood space is limited, it might be necessary to work with a partner on this experiment.) Set up an apparatus similar to the one above using a 50 mL round bottom flask for the reactor. It is satisfactory to substitute a 50 mL single necked flask with a Claisen adapter to accommodate the condenser and dropping funnel. The thermometer while desirable is not necessary. Mount the flask on a heater-stirrer unit (if available) in a crystallizing dish or beaker containing water and add a magnetic stirring bar to the flask. Add 1.0 g of cinnamic acid and 5 mL of glacial acetic acid to the round bottom flask. Charge the separatory funnel with 10 mL of a 0.67 M bromine solution in acetic acid. Heat the crystallizing dish or beaker until the water is at about 50°C. With the stirrer going, add the bromine solution in a dropwise fashion. The cinnamic acid should dissolve and the bromine color should disappear as the bromine is added. After addition is complete, continue to maintain the mixture at 50°C for an additional 10 minutes. If the orange color persists, add cyclohexene dropwise until a light yellow is achieved.

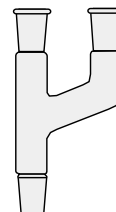


Fig. 12-5

Transfer the reaction mixture to an Erlenmeyer flask and cool in an ice bath until the temperature goes below 5°C. If crystallization does not occur, scratch the sides of the flask with a glass rod. If crystallization still does not occur, add about 20 mL of water to the mixture. Collect the solid using vacuum filtration on a Hirsch funnel or a very small Büchner funnel. Recrystallize about 3/4 of the product from 50% aqueous ethanol. After the sample is dry, weigh it, determine the % recovery from the recrystallization, the % yield of the reaction and the melting range of the impure and recrystallized product, the product structure and the mechanism of the reaction.

Option 2: Use of pyridinium tribromide. Set up a reflux condenser with a 25 mL round bottom boiling flask equipped with a magnetic stirrer or boiling chips and a heat source such as a heating mantle. Transfer 0.25 grams of cinnamic acid, 0.60 grams of pyridinium tribromide and 5 mL of acetic acid to the boiling flask. Gently reflux the mixture preferably with magnetic stirring for about 15 minutes. After allowing the mixture to cool, add 5 mL of 5% sodium thiosulfate to the mixture. Cool in an ice bath and vacuum filter using a Hirsch funnel or a small Büchner funnel. Wash the flask and the collected solid a few times with about 5 mL of ice water. Allow the collected solid to dry (preferably until the next lab period). Determine the experimental and percent yields, the melting range of the product, the product structure and the mechanism of the reaction.

Please note that we are not sure the pyridinium tribromide reaction was successful. In our hands, the product had the right melting point but the nmr had a mysterious peak at 6.5 δ , the integration was not correct and lacked evidence of the presence of an acid. A reported nmr for the correct product is at: http://www.bama.ua.edu/~blacksto/CH237/spectra/exp2_product_NMR.pdf

References

McKenzie, L. C.; Huffman, L. M.; Hutchison, J. E. *J. Chem. Educ.*, **2005**, *82*, 306.

Option 1 - Lehman, J. W. *Operational Organic Chemistry: A Laboratory Course*, 2nd, Prentice Hall, **1988**, 191-199.

Mohrig, J. R., Hammond, C. N., Morrill, T. C., Neckers, D. C., *Experimental Organic Chemistry*, Freeman, **1998**, 98-103.

Option 2 - Julian, J. <http://comenius.susqu.edu/bi/201/02/julian/chemproducts/bromalkenes.pdf> (accessed in November, 2010).

Prelaboratory Preparation - *Experiment 12*

First, be sure to list all the goals of the experiment. At the sites below,

<http://www.cdc.gov/niosh/idlh/7726956.html>

<http://www.stanford.edu/dept/EHS/prod/researchlab/lab/tgo/tgodata.html>

http://www.denison.edu/offices/security/safety_page_bromine.html

look up the rat LC₅₀ values for bromine, carbon monoxide, chlorine, hydrogen chloride, hydrogen sulfide and phosgene. Using the comments on bromine toxicity reported earlier, the LC₅₀ values and information you have found on the Internet, report on the precautions you should take when working with bromine. Be sure to report the meaning of a rat LC₅₀ value.

For the reaction you will run in this experiment, determine which reagent is the limiting reagent and calculate the theoretical yield (note that for option 2, the pyridinium tribromide is only 90% pure). Carefully write the mechanisms for syn and anti additions and show which pair of enantiomers should be formed (erythro or threo) depending on the stereochemistry of the addition. Locate this type of addition reaction on the *Reaction-Map of Organic Chemistry* in **Appendix C** and include the reaction number in your report.

Observations

Report all relevant observations including, masses and melting ranges.

Conclusions

This section should include the following:

1. Were the goals of the experiment achieved? Explain your answer.
2. Which pair of enantiomers was formed or was it a mixture? Explain your answer.
3. Based on the answer to #2, what was the mechanism of the reaction?
4. How confident are you that your answer to #3 can be applied to other bromination reactions? Explain your answer.
5. According to the reference, McGahey, L. *J. Chem. Ed.*, **1990**, *67*, 554-555, bromination of *trans*-anethole and *trans*-1-phenylpropene yields 65% and 85% erythro respectively. Suggest a reason for the difference in % erythro for these two compounds.
5. How could the percent yield and recoveries have been improved?
6. Pyridinium tribromide apparently acts as a source of bromine in its solutions. Write a reaction for this process.
7. Ethylene is emitted by fruits and its presence increases the ripening rate of fruit. To decrease the ripening rate of fruits, commercially available bags are available that it is claimed remove the emitted ethylene and lengthen the shelf life of fruit stored in the bags. Suggest materials that could be incorporated into plastic bags that might remove emitted ethylene. Be sure to consider safety issues associated with the plastic additives.