Experiment 4: Stereochemical Analysis of the Reduction of Benzil

Department of Chemistry, University of Ottawa, 10 Marie Curie Priv, Ottawa, Ontario, K1N6N5

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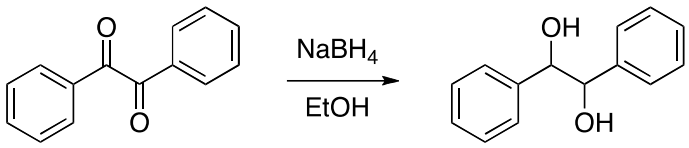
ABSTRACT



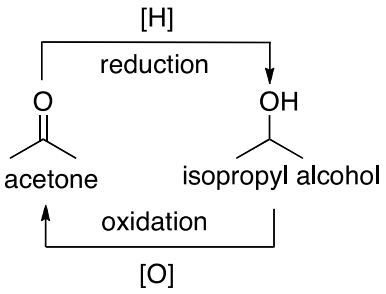
The carbonyl group of benzil will be reduced in this experiment.

Introduction

Oxidation-reduction reactions play a pivotal role in chemical transformations. The controlled oxidation of glucose into carbon dioxide is the primary means of producing energy in living things and provides the key raw materials for life-sustaining processes. In plants, carbon dioxide and water are reduced into glucose and oxygen using the energy provided by the sun.

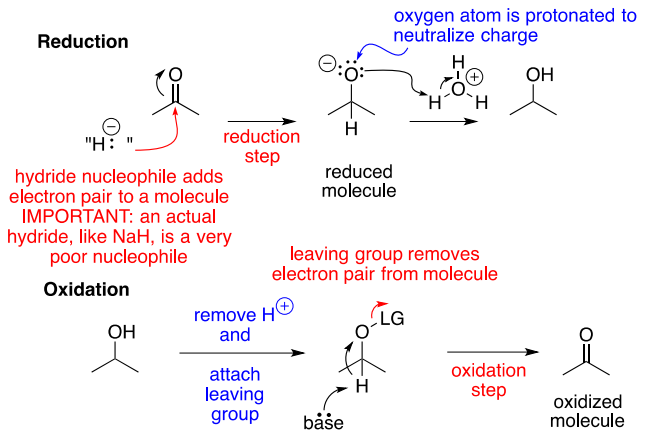
In the basic definition of oxidation and reduction, a substance that is oxidized loses electrons, while a substance that is reduced gains electrons. In organic chemistry, oxidation and reduction are often defined in other terms, related to the gain or loss of hydrogen atoms by a molecule. During oxidation, the number of hydrogen atoms on a molecule normally decreases. Conversely, adding hydrogen atoms to a molecule constitutes a reduction. In the example shown below, acetone can be reduced to give isopropyl alcohol. Because this involves the addition of hydrogen atoms to the molecule, the symbol [H] is used to denote a reduction process. Isopropyl alcohol can be converted into acetone by removing hydrogens in an oxidation process and in this case the symbol [O] is used.

Figure 1. Oxidation and reduction



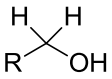
Mechanistically, many reductions involve the interaction of nucleophiles with electrophilic π bonds. Nucleophiles are electron pair donors, and so the addition of a nucleophile to a π bond will increase the number of electrons in a functional group thereby producing a reduction. Oxidation reactions normally occur when π bonds are formed by the loss of a leaving group through elimination. The leaving group removes a pair of electrons from the molecule thereby oxidizing the functional group.

Figure 2. Organic reduction and oxidation



Alkanes represent the lowest oxidation state that organic molecules can attain. The introduction of heteroatoms increases the oxidation state of a molecule, as does the removal of hydrogen atoms to make π bonds (electrons are removed). As shown below, the oxidation state of a functional group increases systematically as this is done.

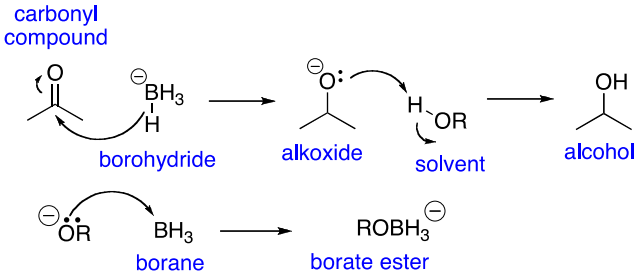
Table 1. Oxidation states.

Alkane		Least oxidized
Alcohol		
Aldehyde		
Carboxylic Acid		Most oxidized

Reagents that carry out oxidations or reductions are often called "agents". A reducing agent will reduce a molecule; an oxidizing agent will oxidize a molecule. A commonly used reducing agent (species that is oxidized while reducing another substance) is sodium borohydride ($NaBH_4$). This molecule behaves as both a nucleophile and reducing agent. It is a reducing agent because it is a good source of nucleophilic hydride (H^-) ions, and thus adds hydrogens and electrons to electrophiles. Because BH_4^- has four available hydride units, one $NaBH_4$ molecule is capable of reducing four functional groups. $NaBH_4$ is usually added in excess when performing small-scale reactions. When reducing on large scale, this stoichiometry is altered for safety reasons and to reduce cost and waste.

The widely used mechanism for the reduction of a carbonyl group using sodium borohydride is presented in Scheme 1. You should be aware that this is an approximation of the actual mechanism (discussed later). The key step in this reaction is the transfer of a hydride unit from the borohydride to the carbonyl group. Following the nucleophilic addition of the hydride ion, the negatively charged oxygen in the alkoxide that is produced forms an O-H bond by removing a proton from a molecule of solvent. The alkoxide that results reacts with the borane byproduct forming a borate ester (more on this below).

Scheme 1. Simplified mechanism of the reduction of a ketone.

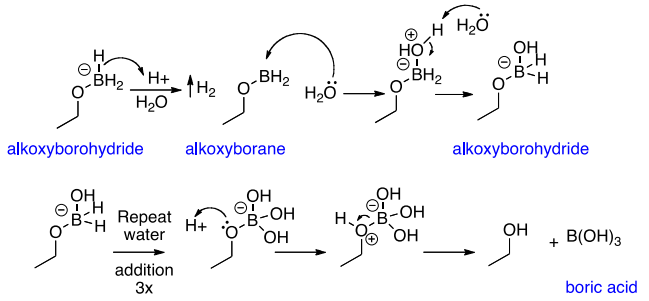


Once all of the carbonyl molecules have been reduced, an acid or base work-up is often performed. The workup is a process that is done to stop (or quench) a reaction, and to facilitate the purification of the desired product.

The first goal of the $NaBH_4$ workup is to destroy any excess $NaBH_4$ that may remain. This ensures that the subsequent steps will be safe. The second goal of the workup is to purify the desired product of the reaction.

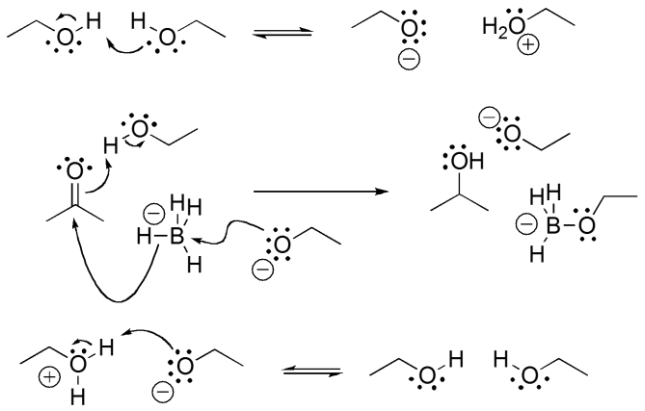
The purpose of acid or base in the $NaBH_4$ workup is to catalyze the hydrolysis of the borate ester into the water-soluble boric acid or tetrahydroxyborate anion. This facilitates the isolation and purification of the product, which is not normally soluble in water. The mechanism of this reaction is shown in Scheme 2 below. When acid and water are added, any remaining hydrides will react very quickly with the added acid producing hydrogen gas. This can sometimes be a violent reaction and so the addition of acid during the workup phase must be done carefully. Water will react with the resulting borane to fill its octet producing an intermediate that loses a proton to form a mixed borate ester. The loss of H^+ from this intermediate implies that acid is a catalyst in the process – it is not consumed in the reaction. Once the hydrides have been replaced by water, the resulting borate ester will be hydrolyzed by water to form boric acid and release the solvent alcohol.

Scheme 2. Acidic Mechanism of Borate Ester Hydrolysis



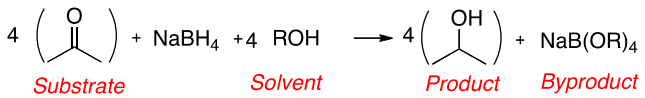
Sodium borohydride is soluble in many organic solvents, however reductions with this reagent require the presence of a protic solvent such as water or alcohol. The reason for this is that the protic solvent actually participates in the reaction mechanism,[1] which is shown in Scheme 3 below. In this mechanism, two molecules of solvent participate in each hydride transfer. Just like in the simplified mechanism above, borohydride provides a nucleophilic hydride to reduce the carbonyl-containing compound. However, the presence of a protic solvent increases the activity of BH_4^- significantly. Protic solvents are in equilibrium with their alkoxide forms, and the reaction begins when a small amount of alkoxide forms as part of the normal acid/base equilibrium that exists in the bulk solvent (top equation). The alkoxide is nucleophilic and donates electrons to a molecule of BH_4^- to form an oxygen-boron bond This process increases the nucleophilicity of the borohydride, causing it to donate a hydride nucleophile to the carbonyl group. While this happens, the oxygen of the carbonyl gains electrons from the fracturing π bond, and uses this electron excess to form a bond with an H^+ taken from another molecule of solvent. All of these bond-forming and bond-breaking events happen simultaneously, and produce the product of the reaction along with a molecule of borate ester (middle equation). The alkoxide formed by this sequence then reforms a molecule of alcohol through the normal acid/base equilibrium.

Scheme 3. Full Mechanism of Sodium Borohydride Reduction in Protic Solvent



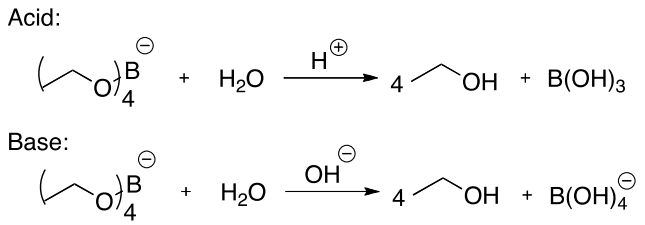
The borate ester that is formed possesses three active hydrides that can reduce additional carbonyls. When all of the hydrides are consumed following four reductions, a full borate ester and four molecules of the reduced alcohol are produced. The overall equation for this process is shown in Scheme 4.

Scheme 4. Overall stoichiometry for borohydride reduction.



The borate ester byproduct of this reaction is a jelly-like solid that is sometimes difficult to remove from the desired product. For this reason, acid or base is often added at the end of a $NaBH_4$ reaction to convert this byproduct into boric acid. Boric acid and tetrahydroborate dissolve easily in water, making them much easier to separate from the organic materials present. This makes the desired product much easier to purify. The overall equations for the hydrolysis of borate ester into boric acid are shown below in Scheme 5.

Scheme 5. Equations for the conversion of borate esters to boric acid and tetrahydroxyborate.



1. (a) Brown, H.C.; Mead, E.J.; Rao, B.G.S. *J. Am. Chem. Soc.* **1955**, *77*, 6209. (b) Wigfield, D.C.; Gowland, F.W. *J. Org. Chem.* **1977**, *42*, 1108. (c) Wigfield, D.C.; Gowland, F.W. *Can. J. Chem.* **1978**, *56*, 786

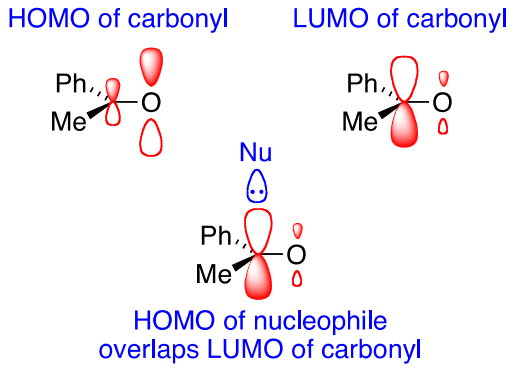
The nature of the alcohol solvent has a strong influence on the rate of $NaBH_4$ reactions. $NaBH_4$ reacts very quickly in water or methanol, but reacts much more slowly in isopropanol or tert-butanol (why?).

Stereochemistry

Reducing a carbonyl group to an alcohol converts an sp^2 hybridized carbon into an sp^3 hybridized one. If the two groups on the carbonyl carbon are different, the newly formed sp^3 carbon will be stereogenic.

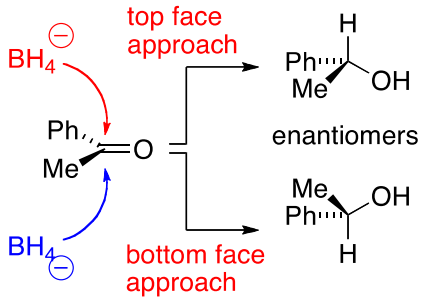
Reducing a ketone with two different substituents such as acetophenone with $NaBH_4$ produces a racemic mixture of products. When $NaBH_4$ reacts with the carbonyl group, the filled σ orbital of the B-H bond (HOMO – Highest Occupied Molecular Orbital) interacts with an empty orbital on the carbonyl (LUMO). The LUMO (Lowest Unoccupied Molecular Orbital) on a carbonyl group is the π* orbital. This orbital is located above and below the plane that is defined by the atoms of the carbonyl group (scheme 6).

Scheme 6. Orbital interactions control the stereochemistry of carbonyl reduction.



The only way that the HOMO of the nucleophile can interact with the LUMO of the electrophile is if the nucleophile approaches perpendicular to the plane of the carbonyl atoms. This approach is toward one face of the carbonyl. Approach of the nucleophile to the top of the carbonyl produces one enantiomer; approach to the bottom face generates the other enantiomer. The π* orbital is located both above and below the plane of these atoms, and therefore there is an equal probability that the nucleophile can approach from either the top face or the bottom face of the carbonyl (Scheme 7).

Scheme 7. Top and bottom face approach produces equal mixture of enantiomers.

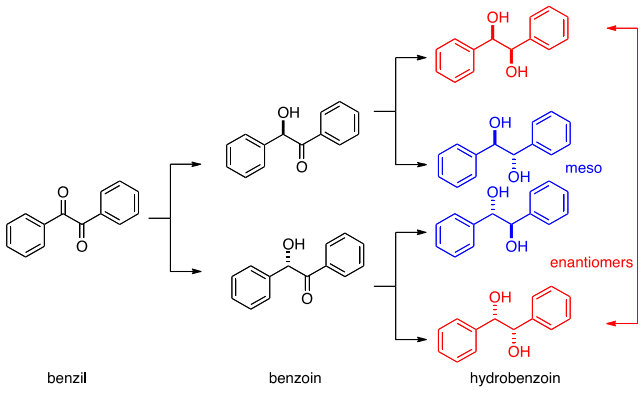


The reaction in this experiment converts a starting material (benzil) that has no stereocenters, into a product (benzoin) containing two stereogenic carbons. This means that the complete reaction can generate a maximum of four stereoisomers.

The BH_4^- nucleophile reduces one carbonyl at a time. When this nucleophile approaches the first carbonyl, there is an equal probability of top face and bottom face approach. This results in an equal mixture of both possible configurations of the alcohol in the hydrobenzoin intermediate, making this material racemic.

The two enantiomers have identical physical properties and behave like one compound. When the second carbonyl is reduced, the reaction produces diastereomers.

Scheme 8. Sequential reductions produce diastereomers.



The final benzoin products in which the two OH groups are *syn* to each other are enantiomers. These two products are formed in equal amounts (racemic mixture). Because this diastereomer is present as an equal mixture of *d* and *l* forms, the product is referred to as the *dl* isomer.

The two benzoin products with *anti*-stereochemistry are actually the same and so represent a *meso* compound. The *meso* and *dl* compounds are diastereomers of each other, and therefore have different physical and chemical properties. For example they have different R_f values on TLC.

The transition states of the reductions of hydrobenzoin into the diastereomeric benzoins are themselves diastereomers and have different energies. This means that the rates of conversion of hydrobenzoin into *syn* or *anti* diastereomers are different. This will produce a mixture that will be enriched in one of these isomers. In this experiment, you will use TLC to identify the stereoisomers present in your reduction process.

Recrystallization

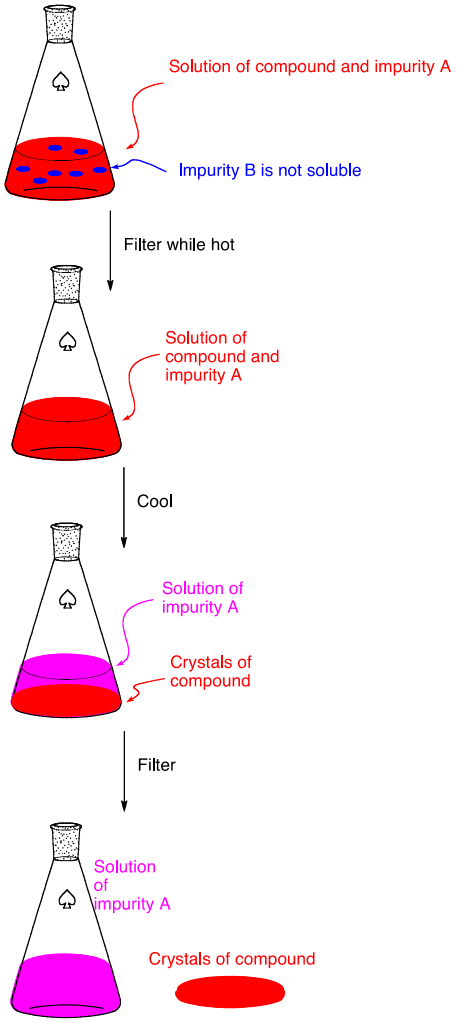
Recrystallization is an important method of purifying organic compounds. Its use in the research lab has declined somewhat, however recrystallization is still the best way to obtain ultra-pure samples of organic materials, and to purify large quantities. Recrystallization is used extensively in industry because it is scalable – it works with 10 milligrams or 10 megagrams of material. Most pharmaceuticals are manufactured using recrystallizations to purify intermediates and final products.

Recrystallization makes use of the differential solubility of the compound to be purified in hot and cold solvents. The process consists of dissolving the impure material in hot solvent, filtering the solution to remove impurities, allowing the desired compound to crystallize by cooling, and finally recovering the crystals. In practice, recrystallization requires that the substance has undergone some kind of preliminary purification. The technique will not work well if it is done with very impure material.

In recrystallization (Scheme 9), the material to be purified is dissolved in a minimum of hot solvent. This will dissolve some impurities and not others. Those impurities that do not dissolve (dust for example) can be filtered off while the solution is hot. It is common, however, to skip this initial filtration.

The hot solution is then allowed to cool causing the desired compound to crystallize while leaving impurities behind in solution. The crystals can be recovered by filtration.

Scheme 9. General strategy for recrystallization



Solvent. The most important factor in recrystallization is the solvent. Choosing a solvent requires experience, but there are guidelines that can be followed to help make a reasonable choice.

The most important consideration is solubility. The substance to be purified should have high solubility in the solvent at elevated temperatures and low solubility at low temperature. Solvents can be screened by placing a small sample of the compound to be crystallized (~50 mg) in a test tube and shaking it with about 0.5 mL of the solvent. If the compound dissolves it is too soluble in that solvent for a good crystallization. If the sample does not dissolve, heat the solvent to the boiling point. If necessary add small portions of solvent, maintaining boiling, until the sample dissolves. If more than 3 mL of solvent is required to do this, the substance is probably not soluble enough in that solvent. If the sample dissolves using less than 3 mL of solvent, then the solvent is a good candidate and you can proceed.

The solvating power towards impurities must also be considered. The solvent should readily dissolve the impurities, or not dissolve them at all. If the impurities are

soluble, they will remain in solution as the crystals of the desired compound are forming. Filtration will give the desired compound and leave the impurities behind in solution. If the impurities are insoluble, once the desired compound has dissolved in the hot solvent the solution can be filtered while still hot thus removing those impurities.

Finally, the solvent should be easy to remove from the crystal. Small amounts of solvent stick to crystals after filtering. This normally is removed by "drying" the crystals, usually under reduced pressure. Basically this means that either the solvent must be volatile, or it must be easily washed away with a second, more volatile solvent.

The choice of solvent can be made based on the principle of "like dissolves like". For example, if you are recrystallizing a polar compound, you will most likely need a polar solvent. Common solvents for crystallization are listed below in order of decreasing polarity.[2] The boiling point of the solvent must also be considered. If the boiling point of the solvent is higher than the melting point of your compound, you will likely have problems with "oiling out". As the hot solution cools, the compound becomes insoluble in the solvent. If this happens above the melting point of the compound, the material will separate as a liquid (called an oil) and not as a solid. The oil will sometimes solidify on standing, but because this solid is not formed from a solution the purity will usually be low (impurities are often soluble in the oil and are trapped when it solidifies).

Solvent	Boiling Point (°C)
Water	100
Methanol	65
Ethanol	78
Acetone	56
Ethyl Acetate	78
Chloroform	61
Methylene Chloride	40
Benzene	80
Toluene	110
Carbon Tetrachloride	77
Petroleum ether (ligroin)	Varies

Crystal Formation. Besides the nature of the solvent, cooling rate has the highest impact on the success of the technique. Rapid cooling tends to produce impure material as the crystals simply grow around pockets of solvent and impurities. Slow cooling is best. As the solution cools crystals begin to form. Once these small crystals are available, molecules move out of solution and onto the surface of the crystals joining the lattice in an ordered way. Occasionally a molecule will pack imperfectly onto the crystal lattice. Equilibrium conditions (slow cooling) allow these imperfectly packed molecules to re-dissolve thus "fixing" the crystal defects and preventing the formation of solvent pockets.

This mechanism "selects" the proper molecules. As the whole process is random, occasionally an impurity molecule becomes incorporated into the crystal. These impurity molecules usually will not "fit" the crystal lattice and so will readily re-dissolve, provided that cooling is slow enough so that the defect does not become covered in additional molecules. In other words, defects correct themselves if the crystal growth is in equilibrium with the solution. Slow crystallization, from an undisturbed solution, will provide the purest crystals.

Oiling out. Sometimes compounds separate from solution as liquids. When this happens, a two-phase mixture is formed. The process is called oiling out, and happens when the compound has a low melting point or when the molecular structure makes crystal formation difficult. Oiling out can sometimes be avoided by choosing a solvent with a low boiling point, or by cooling the solution very slowly. If this is not possible, try "scratching" or "seeding" the mixture as it cools. Scratching the walls of the flask with a glass rod produces small defects in the glass around which crystals can grow. Seeding involves adding a small crystal of the desired compound. This serves as a nucleus or "seed" around which larger crystals can form. Seed crystals can be obtained by evaporating a small amount of your solution on a watch glass.

If oiling out cannot be prevented, you can allow the oil to solidify, then filter this solid from the solution. Sometimes this removes enough impurities so that a second recrystallization will be successful.

Removing impurities. Steps must be taken to remove impurities before inducing crystal formation. In the case of insoluble materials and dust, the solution is filtered just after the product has dissolved. When doing this, it is important to keep the solution hot as it is filtered. Add a small amount of extra solvent just before filtering and heat the funnel you will use. You can pre-heat a funnel by placing it on top of your boiling flask. The hot solvent vapors will often do the job. Choose a short stem funnel (a powder funnel is a good choice) or use vacuum filtration. Hot filtering usually works best with porous filter paper (Whatman #1). If your material crystallizes in the funnel, try heating the receiving flask or washing the funnel with some hot solvent.

Crude materials often contain colored impurities. The vast majority of organic solids are white, but most reactions generate small amounts of aromatic, colored impurities as side products. These compounds can be removed by using decolorizing carbon (also called Norit or charcoal). The decolorizing carbon adsorbs these impurities and removes them from solution. The decolorizing carbon is added to the hot solution and is then filtered off while the solution is still hot. It is important to use a small amount of decolorizing carbon as using too much may remove some of the desired product.

[2] Ethyl ether is sometimes used for recrystallization, but it is generally a poor choice. Ether is very flammable, has a low boiling point and tends to creep up the walls of glassware and deposit materials after evaporation. Some of the older literature recommends the use of isopropyl ether. This is a very dangerous solvent that has no place in a modern lab.

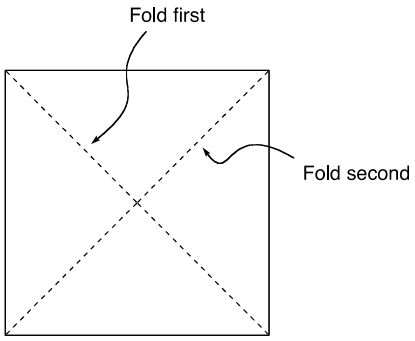
Mixed Solvent Recrystallizations. Sometimes a single solvent will not give an effective recrystallization. In cases like these, you can use a mixed solvent or solvent pair. A solvent pair consists of two *miscible* liquids, one in which the compound readily dissolves and one in which it does not. The compound is dissolved in the minimum amount of hot solvent in which it is soluble. This is usually done by adding some of the "good" solvent (in which the compound is soluble), heating to the boiling point and then adding additional solvent slowly until the compound just dissolves. The second solvent (in which the compound is insoluble) is then slowly added until the solution becomes turbid (cloudy). This addition is done while the mixture is boiling. A few drops of the first solvent are then added until the solution again becomes clear. The flask is then removed from heat and allowed to cool.

Additional crops. Recrystallization does not remove all of the compound from solution. The liquid that remains after filtration may still contain a significant amount of material. This liquid is called the *mother liquor* (because it is the solution that gave birth to the crystals). In many cases additional material can be recovered from the mother liquor by evaporating some or all of the solvent and performing a second recrystallization. The crystals that are obtained in this manner are called the *second crop*. The first crop of crystals normally has the highest purity and so crops are usually not combined unless both crops are of similar purity.

The Experiment

Part A

1. Accurately measure 1 g of benzil using a folded piece of weighing paper and place the compound in a 50 mL Erlenmeyer flask.



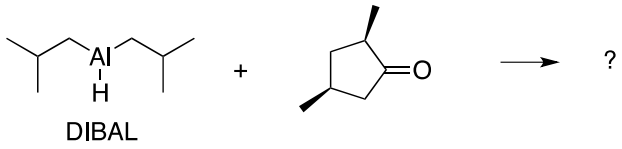
   To fold weighing paper, fold along one diagonal. Open the crease and fold along the second diagonal. Opening this crease produces a bowl shaped weighing paper.
2. **Carefully** place a magnetic stir bar in the flask. To do this tilt the flask to one side and **gently** slide the stir bar into the flask.
3. Clamp the flask over a magnetic stir plate. Add approximately 5 mL dichloromethane and then 5 mL of ethanol. Stir until fully dissolved. Place an empty ice bath underneath the flask. Add ice and then water to the ice bath. Stir for 5 minutes. (If you are using the rectangular ice bath, use an L bar to ensure that the flask sits close to the stir plate).
4. Add 0.3 g of sodium borohydride in three equal portions to the reaction flask, waiting approximately 2 minutes between additions. Continue stirring for 10 minutes. The mixture should lose its original yellow colour.
5. Remove the ice bath and stir your solution while allowing it to warm to room temperature (10 minutes).
6. Take a TLC of the reaction mixture to determine if the reaction is complete. The TLC plate should have three lanes: reference (benzil, dissolved in dichloromethane), co-spot, and the reaction mixture. Use 1:9 EtOAc:Hexanes as the eluent.
7. While your reaction is running (step 5), warm 50 mL of water. To do this, place the water in a second Erlenmeyer flask along with a stir bar. Place the flask on a hotplate, and heat to 80 °C while swirling occasionally.
8. Once your TLC shows that the reaction is complete, pour approximately 10 mL of hot water into your reaction mixture. Transfer the *reaction* mixture into a clean Erlenmeyer flask and place it on a hotplate, swirling occasionally as the mixture heats. The solution should clear and turn pale yellow. Continue swirling until the intense bubbling stops (5 minutes).
9. Add an additional 20 mL of hot water to the reaction mixture. Stir while heating for approximately 10 minutes. The mixture should gently boil during this time.
10. Remove the flask from heat and allow it to cool undisturbed until it reaches room temperature.
11. Collect the crystals that form using gravity filtration. Wash the crystals with a small amount of cold water. Then, use a suction filtration set up to dry your crystals. (see experiment 3 for suction filtration set up). Maintain suction for approximately 5 minutes to dry the crystals.
12. Determine the mass of the product and your percent yield. Perform a TLC of the final product (1:9 EtOAc:Hexanes). To spot your plate, place a few crystals in a small vial and dissolve by adding a few drops of CH_2Cl_2.

Part B

13. Using your model kit, build a representative model for each of the benzoin products. Place your student card (or another photo ID) next to your model and take a photo; include these photos with your report.
14. In your lab report, include a scheme analysing the relative stereochemistry of the 4 benzoin products, indicating which pairs are enantiomers which pairs are diastereomers, identify any meso compounds *etc*. In your scheme, label each isomer as *R,R*; *S,S*; *R,S*; or *S,R*.

Questions

1. "A compound can *oil out* if the boiling point of the recrystallization solvent is higher than the melting point of the compound". Is this statement true or false? Explain your answer.
2. The solubility of a compound is 35.6 g/100 mL at 25ºC and 39.1 g/100 mL at 108ºC. If a saturated solution of the compound at 108ºC is allowed to slowly cool to 25ºC, what is the maximum yield of solid crystals that can be obtained?
3. A student dissolves 80 mg of a crude product in 4.5 mL (the minimum required) of methanol at 25 °C. She cools the solution in an ice bath and obtains crystals. The crystals are recovered by filtration and rinsed with 0.5 mL of ice-cold methanol. After drying, the weight of the crystals is 5 mg. Why was the recovery so poor? What could she do to improve the process?
4. When butanoic acid reacts with sodium borohydride, 1-butanol is not obtained. However, bubbling is still observed and heat is produced.
    a. Why is 1-butanol not obtained?
    b. What is the product of this reaction?
5. The reagent below is diisobutylaluminum hydride, or DIBAL. Like sodium borohydride, it is a source of nucleophilic hydride. Predict the configurations of each stereocentre in the product of the following reaction (with appropriate work-up) and provide a



DIBAL

justification for your choice. Unlike $NaBH_4$, reductions performed with DIBAL require equimolar amounts of DIBAL and substrate. Can you explain this difference?

Report Notes

Refer to the instructions early in the lab manual regarding the preparation of reports. Be sure to explain all the steps of your experiment, paying attention to the workup/purification. Add mechanisms as necessary. Based on your understanding of the reaction mechanism, predict and explain the major and minor products of the reaction.