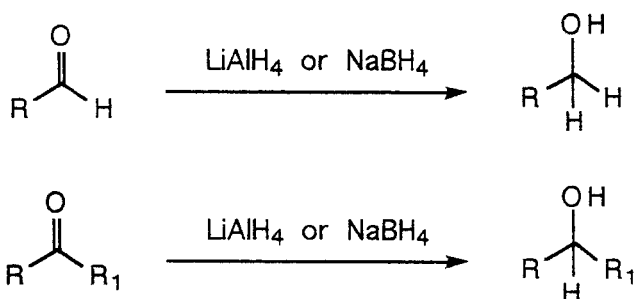


EXPERIMENT 25

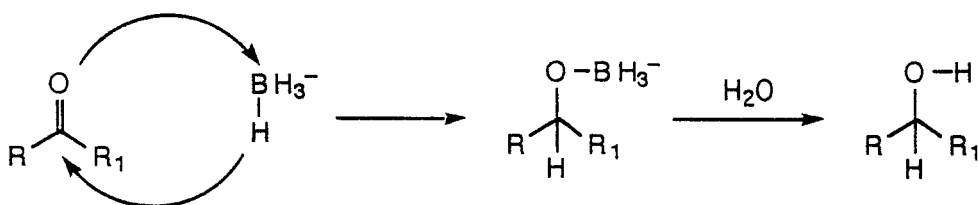
SODIUM BOROHYDRIDE REDUCTION OF BENZIL and DETERMINATION OF ACETONIDE STEREOCHEMISTRY BY ^1H NMR

Reduction of Aldehydes and Ketones with Metal Hydrides

The reduction of aldehydes and ketones to alcohols can be accomplished by a variety of methods, including catalytic hydrogenation and reducing metals such as sodium in alcohol. The most common reagents for this purpose are the complex metal hydrides, particularly lithium aluminum hydride (LiAlH_4) and sodium borohydride (NaBH_4). These reagents serve as sources of hydride ion (H^-) and reduce aldehydes to primary alcohols and ketones to secondary alcohols.

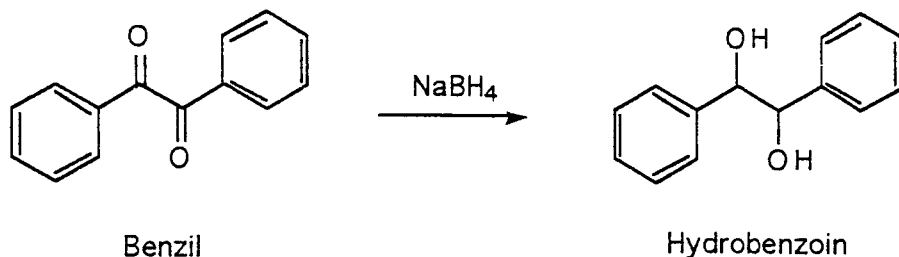


Of the two reagents, LiAlH_4 is more powerful (it will reduce acids, esters, and amides as well), more expensive, and must be used in aprotic solvents like ethers. NaBH_4 is commonly used in water or simple alcohols and is the usual choice for reducing aldehydes and ketones. It transfers a hydride from the borohydride anion to the electrophilic carbonyl carbon. All four hydrogen atoms of BH_4^- can be transferred in this way. The initially formed tetraalkylborate salt decomposes in water or dilute acid to give the alcohol product.



A. Sodium Borohydride Reduction of Benzil

In the first part of this experiment the use of sodium borohydride is illustrated in the reduction of the diketone benzil. This short preparation demonstrates the speed and simplicity of this valuable reducing agent.



Physical Constants

	mol. wt. (g/mole)	mp (°C)
Benzil	210.22	94-95
Sodium borohydride	37.83	400 d.
Hydrobenzoin (<i>S,S</i> or <i>R,R</i>)	214.27	148.5-149.5
Hydrobenzoin (<i>meso</i>)	214.27	137-139
Hydrobenzoin (racemic)	214.27	122-123

Experimental Procedure

Note: These directions are given for a reaction scale designed to provide sufficient product to serve as the starting material for part B. If only part A is assigned, the reaction can be scaled down to one-third, or even further to the microscale directions given subsequently.

Dissolve 1.5 g of benzil in 15 mL of absolute ethanol in a 125-mL Erlenmeyer flask by gentle warming and swirling (or magnetic stirring). Add 300 mg of sodium borohydride in small portions over 3-4 minutes. Record any observations: gas evolution, heat evolution, color changes, etc. Continue swirling or stirring the flask for another 15 minutes. Cautiously add 30 mL of water, cool the flask in an ice bath, and with continued stirring, carefully add concentrated HCl dropwise, with stirring (**Caution: Foaming may occur!**) until foaming ceases. Add an additional 10 mL of water and continue stirring for 15 minutes.

Collect the precipitate by suction filtration. Wash it with three 25-mL portions of cold water and allow it to air dry. A typical yield is about 1.0 g with a melting point of 135-136 °C. (If desired, the solid can be recrystallized from acetone-petroleum ether, raising the melting point to 136-137 °C). Weigh the dry product, calculate the percent yield, and determine its melting point.

Experimental Procedure (microscale)

Dissolve 50 mg of benzil in 0.5 mL of ethanol in a 5-mL reaction vial, and cool the vial in an ice bath. Remove the vial from the ice bath and add 10 mg of sodium borohydride, swirling the vial to mix the contents. Swirl the vial periodically while the reaction continues for ten minutes. Note any observations: gas evolution, heat evolution, color changes, etc.

After ten minutes, carefully add 0.5 mL of water to the vial (**Caution:** *Foaming may occur!*). Carefully heat the solution to its boiling point on a hot plate, remove the vial from the heat source, and add hot water dropwise until the solution just remains cloudy; about 1 mL will be required. Set the vial aside to cool; the product should crystallize as shiny flakes as the solution cools.

When the mixture has reached room temperature, cool the vial in an ice bath to complete crystallization. Collect the diol by suction filtration on a Hirsch funnel, wash it with a small amount of cold water, and allow it to dry in air. Weigh the dry product, calculate the percent yield, and determine the melting point.

Questions

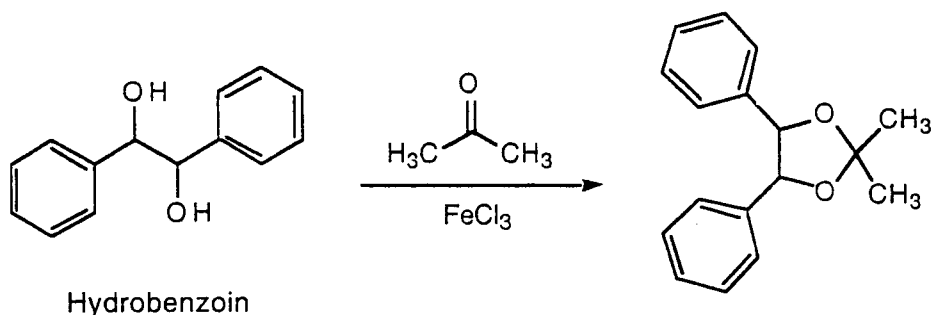
1. Reduction of just one of the carbonyl groups of benzil gives a compound called benzoin. Draw its structure and give the IUPAC names of benzil, benzoin, and hydrobenzoin.
2. Calculate the weight of sodium borohydride needed to reduce 1.00 g of benzil to hydrobenzoin.

Part B. Formation of Hydrobenzoin Acetonide and Determination of its Stereochemistry by ^1H NMR

The hydrobenzoin prepared in part A has two identical asymmetric centers. How many stereoisomers with this constitution are possible? The answer for any compound possessing two identical asymmetric centers (*cf.* tartaric acid) is **three**: a pair of enantiomers, the (R,R) and (S,S) isomers, and an achiral (R,S) *meso* isomer that possesses a plane of symmetry. In principle, the sodium borohydride reduction of benzil could give all three stereoisomers. The (R,R) and (S,S) enantiomers would necessarily be formed in equal amounts, and therefore we might expect a mixture containing two separable forms, the *meso* isomer and the *racemate* (50:50 mixture of enantiomers).

Actually, the reduction in part A appears to give almost exclusively one of these products. The reduction is not stereochemically random, but rather the first asymmetric center that forms appears to influence the creation of the second asymmetric center. So how can we determine which product was produced, the racemate or the *meso* compound? The table of Physical Constants in part A lists different melting points for the racemate and the *meso* compound, so determination of the melting point might answer our question. But how did the people who made the table know which isomer was which, i.e., what is the *conclusive proof* of stereochemical assignment?

In this part we will provide conclusive proof of the stereochemistry of the product by preparing the acetonide of hydrobenzoin and examining its ¹H NMR spectrum. An acetonide is a cyclic ketal prepared from acetone and either a 1,2- or a 1,3-diol. Our procedure uses anhydrous ferric chloride as a Lewis acid catalyst for the preparation of the acetonide.



Experimental Procedure¹

Note: For the acetonide preparation to be successful, it is essential that *all reagents and apparatus must be thoroughly dry*. The hydrobenzoin prepared in part A should be allowed to air dry at least overnight, or dried in a drying oven. The ferric chloride used must be anhydrous FeCl₃, and the acetone must be anhydrous reagent-grade acetone, not wash acetone. The flask and condenser must be dry.

A mixture of 1.0 g of hydrobenzoin from part A and 0.3 g of anhydrous ferric chloride in 30 mL of anhydrous acetone is heated under reflux (boiling chip) for 20 minutes. After cooling, the mixture is diluted with 10 mL of 10% aqueous potassium carbonate and 50 mL of water, then extracted with two 20-mL portions of dichloromethane. The combined organic extracts are washed with 25 mL of water, dried over anhydrous sodium sulfate, and concentrated.

¹Rowland, A., *J. Chem. Educ.* 1983, 60, 1084.

The oily residue is dissolved in 15 mL of boiling petroleum ether (bp 30-60 °C), filtered hot to remove any insoluble diol, and the filtrate is concentrated to a volume of 3-4 mL. Cooling in an ice bath and scratching initiates crystallization of chunky white crystals. These are filtered and washed with a little cold petroleum ether. A typical yield is 500-800 mg, mp 57-59 °C.

¹H NMR Spectrum

Your instructor may ask you to record the ¹H NMR spectrum of your acetonide, if you have been trained to operate the NMR spectrometer; otherwise the spectrum will be provided to you. Locate the signals for the methyl groups. How many signals do you expect to see for each of the stereoisomers? How many are actually present?

Questions

1. Write a mechanism for the formation of the acetonide.
2. In the acetonide, are the phenyl groups *cis* or *trans*? Explain clearly how the NMR spectrum permits an unambiguous answer to this question.
3. Based on your answer to Question 2, is the hydrobenzoin from part A the *meso*-isomer or the racemic form? Draw a Newman projection showing the stereochemistry you assigned to the hydrobenzoin.