Microwave Synthesis of Tetraphenylporphyrin

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Chemical Concepts  
Electrophilic aromatic substitution; visible spectroscopy

Green Chemistry Topics  
Solventless, solid-supported synthesis; microwave heating of reaction mixtures; more benign solvent systems for chromatography

Introduction  

Porphyins or hemes (iron-containing porphyrins) are important molecules in biological systems. For example, they are responsible for the oxygen-carrying action of hemoglobin, are essential electron relay stations in the electron transport chain important in metabolism, and form part of the light-harvesting antennae (in the form of chlorophyll) in photosynthesis. These are only a few of the many roles that porphyrins play in biology. Porphyrins are essential to life as we know it. Understandably, chemists have long been interested in the challenge of synthesizing these important but often complex molecules.

Nearly all syntheses of porphyrins involve electrophilic aromatic substitution, in which an electrophile replaces (substitutes for) a hydrogen substituent on an aromatic ring (Scheme 1). In the present experiment, you will prepare a porphyrin, tetraphenylporphyrin (TPP), from pyrrole and benzaldehyde. The carbon framework of the porphyrin is assembled through eight electrophilic substitutions between benzaldehyde and pyrrole (Scheme 2). The product of these substitution reactions is called a porphyrinogen—it has saturated methine groups separating the pyrrole fragments in the macrocycle. Oxidation of the porphyrinogen yields a porphyrin. The porphyrin itself is an 18-electron aromatic compound.

Traditionally, porphyrin syntheses have been carried out in corrosive, high-boiling solvents, such as propionic acid, or in large volumes of a halogenated solvent containing a corrosive Lewis acid catalyst. In many cases, toxic oxidizing compounds are used to convert the porphyrinogen to porphyrin.

Scheme 1. Electrophilic aromatic substitution on pyrrole.

In this experiment, you will use solventless reaction conditions—benzaldehyde and pyrrole react with each other while adsorbed on a solid support (silica gel). Microwave irradiation is used instead of thermal heating as a means of promoting the reaction between the two starting materials. When microwaves are used as an energy source, the temperature increases rapidly because the entire sample is heated simultaneously. With conductive heating methods, the reaction vessel must first be heated and energy transferred to the sample. Consequently, reactions promoted by microwave irradiation can occur in a fraction of the time required for reactions promoted by conventional heating methods (1).
Scheme 2. Assembly of the porphyrin ring structure by eight sequential electrophilic aromatic substitution reactions.

Oxidation of the presumed porphyrinogen intermediate produces the porphyrin product. The product is collected by removing it from silica gel and purifying it by column chromatography. Traditionally, porphyrins are purified by column chromatography, often using chlorinated solvents such as methylene chloride or chloroform. In this experiment, a safer solvent mixture (hexanes and ethyl acetate) is used as the chromatography solvent.

Note: The procedure as reported here provides porphyrin product in approximately 85% purity as determined by relative \(^1\)H NMR integration. The major impurity can be seen in the NMR spectrum as a broad multiplet around 7.3 ppm. The impurity does not affect the UV-visible spectrum of the porphyrin product nor does it affect your ability to use the product in the experiments described below or in the next laboratory exercise, Metallation of Tetraphenylporphyrin (page 32).

Prelab Questions

1. Read the sections in your laboratory manual regarding techniques for column chromatography, thin-layer chromatography (TLC), visible spectroscopy, and rotary evaporator usage.
2. In your notebook, write the balanced reactions for the synthesis.
3. Prepare a table of reagent and product molecular weights, target masses, target mole%, and theoretical eld.
4. Read over the preparations, and write your plan of attack in your notebook. You may choose a narrative description that paraphrases the procedure given below or perhaps a flowchart illustrating the procedures you will use.
5. Draw two additional resonance structures for the intermediate shown in Scheme 1.
Chemicals and Equipment

Benzaldehyde
Pyrole
25-mL Erlenmeyer flask
Silica gel
Pyrex watch glass
Ethyl acetate
Methylene chloride
Thin-layer chromatography plate
Hexanes
Glass wool or glass floss
Sand
Glass column
Triethylamine
Microwave oven

Experimental Procedure

SAFETY PRECAUTIONS

Avoid inhalation of benzaldehyde as some benzaldehydes are suspected mutagens. Ethyl acetate, hexanes, and acetone are flammable, so avoid exposing them to flames or heat sources. Avoid inhalation of silica gel.

Mix 0.43 mL of benzaldehyde and 0.5 mL of pyrole in a 25-mL Erlenmeyer flask. Once the reactants are thoroughly mixed, add 0.03 g of silica gel, stopper the flask, and mix well until the silica gel is evenly and completely covered with the reactant mixture.

Place the flask containing the reaction mixture in the microwave oven (a standard 1000-W model works well), cover it with a Pyrex watch glass, and heat it for 10 min in five 2-min intervals. Using several shorter heating intervals reduces overheating of the microwave oven.

Once the reaction is complete, allow the mixture to cool to room temperature, then add approximately 15 mL of ethyl acetate. Filter the solution to remove the silica gel, then remove the ethyl acetate using a rotatory evaporator. Prepare a chromatography sample by extracting the residue with 1 mL of methylene chloride.

Thin-Layer Chromatography

TLC of the product mixture is performed on silica TLC plates using a 7:1 hexane:acetone mobile phase. Tetraphenylporphyrin will appear as the leading spot on the silica plate ($R_f = 0.46$). $R_f$ is the ratio of the distance the spot travels from the point of origin to the distance the solvent travels. The remaining impurities appear as a broad band with an $R_f$ range of 0.6–0.8.

Column Chromatography

Prepare a silica gel column in a glass column (3–5 cm i.d.) fitted with a Teflon stopcock. Use a glass frit or a layer of glass wool covered with a 2-cm layer of sand to provide a flat base for pouring the silica column. Prepare a slurry with 6.5–8.5 g of silica gel in the mobile phase (50 mL of 7:1 hexane:acetone), resulting in a column height of ~32–40 cm.

Then place a 2-cm layer of sand on the top of the settled silica gel to protect the top surface of the column. Carefully load the entire 1-mL solution of the product mixture in methylene chloride on the top of the column, and elute until the solvent level has reached the top of the sand. Elute the column with 7:1 hexane:acetone at a flow rate of ~50 drops/min until the leading purple TPP band elutes. No other bands precede the TPP band, and the entire sample should be collected in ~7–8 mL of solvent after about 20–25 min.

Note: Save three drops of the lead fraction for the next laboratory exercise, Metalation of Tetraphenylporphyrin (page 32).

Greener Approaches to Undergraduate Chemistry Experiments
Visible Spectroscopy

Prepare visible spectroscopy samples by placing 1–2 drops of the highly colored TPP solution collected during column chromatography in a scintillation vial and diluting to 4 mL with additional 7:1 hexanes:ethyl acetate. Add a few drops of triethylamine to the solution to maintain the free-base form of the porphyrin. The absorption spectrum of TPP shows a strong absorbance at 420 nm along with four weaker absorbances at 510, 550, 590, and 645 nm.

Cleanup

Place the chromatography fractions (remember to save three drops for the metallation experiment) in the halogenated waste container. Once the solvent has evaporated, place the silica gel in the solid waste container.

Postlab Questions

1. Report your isolated yield and percent yield for the synthesis.
2. Label your UV-visible spectrum, including the wavelength and absorbance of each peak as well as your name and sample identification. Attach the spectrum to your report.
3. Compare the “greenness” of the conventional preparation with that of microwave synthesis.
4. Assuming the preparation given to you for this lab provides a 5% yield, how much pyrrole, benzaldehyde, and silica gel would you need to prepare 100 mg of TPP? Assume that the reaction scales linearly.
5. Assign the peaks in the 1H NMR spectrum of TPP in Figure 1. Explain why the peak at ~2.7 ppm occurs at that chemical shift.

![Figure 1. 1H NMR spectrum of TPP.](image)

Greer Assessment and Opportunities for Improvement

Although this preparation offers several advantages over traditional methods, there is usually room for improving the safety and leveraging the environmental impact of any method. The most obvious areas for improvement in this experiment involve developing syntheses that use more benign benzaldehyde derivatives and that reduce solvent usage during chromatography. Elimination of the chromatography step is not an option because one of the primary goals of the experiment is to teach column chromatography methods.

Another possible extension involves the synthesis and 1H NMR analysis of orthosubstituted tetraphenylporphyrins. The NMR spectroscopy is especially interesting in this case because of atropisomerism (2), and it provides a platform for teaching and discussing more
advanced topics in spectroscopy, such as observing temperature-dependent phenomena and measuring rates of interconversion by line-broadening methods. The porphyrin product can also be used to construct functioning solar cells according to a procedure published in the recent literature (3).

REFERENCES

EXPERIMENT DEVELOPMENT NOTE
This experiment was adapted from the original report of Petit et al. (4) for use in the University of Oregon’s organic chemistry teaching labs.