The Microscale Laboratory

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Synthesis of *Meso*-Octamethylporphyrinogen: An Undergraduate Laboratory Mini-Scale Experiment in Organic Heterocyclic Chemistry[1]

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Porphyrins and related macrocycles are vital biomolecules present in systems that convert light into chemical energy, transport oxygen, and regulate electron transport at the cellular level *(1).* Porphyrins are also of importance in modern heterocyclic chemistry *(2, 3),* optics *(4),* sensor materials *(5),* and medicine *(6–8).* A large number of excellent books and articles covering all aspects of porphyrin chemistry are available. This is naturally reflected at the educational level. In this *Journal* a number of articles have been published on porphyrins, covering the identification and isolation from natural sources *(9–13),* chemical and physical characterization *(14–16),* and their synthesis or that of their precursors *(17–19).*

Despite the existence of a large number of synthetic pathways to tetrapyrrolic macrocycles, reported laboratory activities offer only simple, one-pot syntheses that lead directly to the porphyrin without special concern to its intermediates. This may be due to a desire for clear, simple experiments in the belief that the chemistry of porphyrin precursors is too complex for most undergraduates. Consequently, a lot of information on these hetero-macrocycles is left out of the undergraduate curriculum. A good example is the case of the important class of the porphyrinogens, which are not usually described in the experiments presented in the classroom. Because porphyrinogens are porphyrin precursors, their formation is a major determinant of the efficiency of the porphyrin synthesis. Thus the kinetic and thermodynamic factors that influence porphyrinogen formation deserved an intense study in the past, either in vivo, where porphyrinogen formation is determinant on the understanding of the biochemical basis of heme-related metabolic problems, or in vitro, where the favorability of the pyrrole cyclization over the linear polymer formation represents a source of interesting discussions on the relationship of thermodynamic versus kinetic control in the reaction mechanism *(20–30).*

Besides their importance in porphyrin chemistry, porphyrinogens, also known as calix[4]pyrroles, are excellent chelating agents for binding anionic and neutral molecules, host materials for inclusion crystals and compounds for metal complexation with a growing importance in the medical, analytical, and chemical sensor areas *(31–46).*

Porphyrinogens resulting from the condensation of pyrrole with aldehydes are quite labile owing to the presence of hydrogen atoms at the meso positions. These make the macrocycle very susceptible to oxidation. In contrast, porphyrinogens resulting from the condensation of pyrrole and ketones are very stable compounds, making them attractive targets for undergraduate experiments in heterocyclic chemistry. An excellent example of a stable porphyrinogen is *meso*-octamethylporphyrinogen (Figure 1) also known as "acetonepyrrole", whose synthesis by acid condensation of pyrrole and acetone was reported by Baeyer in 1886 and subsequently improved by others *(47–49).*

In the case of the acid polymerization of pyrrole with acetone we find one of the most favorable cases of cyclization among the known examples of macrocycle formation in solution. The growing pyrrole chain intermediates in the pyrrole/acetone polymerization have the necessary conformations to favor the tetrapyrrolic macrocycle over the polypyrroles, making *meso*-octamethylporphyrinogen the major product.

Our synthesis of *meso*-octamethylporphyrinogen involves a mini-scale preparation and uses acetone as reactant and also as solvent. The first aspect minimizes the problems with the heat formed and allows an exothermic reaction without special risks. The second leads to precipitation of the product as it is formed, avoiding extraction procedures. This approach results in a product of almost analytical grade directly from the reaction medium. The preparation of *meso*-octamethylporphyrinogen is in this way a simple procedure, suitable for

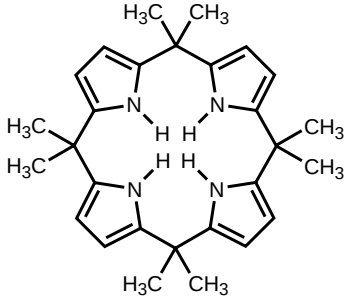

Figure 1. Structure of 5,5,10,10,15,15,20,20-octamethylporphyrinogen.

a 4-hour class. In our experience, students enjoy this easy preparation of a large macrocycle in high yields, in a one-pot reaction, in a few minutes, without any template adjuvant!

Experimental Procedure

A 250-mL round-bottom flask equipped with a magnetic stirring bar, a condenser, and an addition funnel are placed in an ice bath. Pyrrole (1 mL; 15 mmol) and acetone (5 mL) are added to the flask and the solution is cooled for 10 minutes. Meanwhile concentrated HCl (0.5 mL) is added the addition funnel. After cooling, the solution is slowly stirred and the HCl is added dropwise (approximately one drop/second) into the acetone solution. The colorless solution turns brown and shows a moderate effervescence that is followed by the rapid precipitation of acetonepyrrole as a white solid. After precipitation occurs, the HCl addition is stopped, but stirring is continued for 4–5 minutes. The solid is filtered, washed with cold acetone (15–20 mL), and the acetonepyrrole is dried at 40 °C for 30 minutes. Yields near 60% are usually obtained.

The residues of acetone and pyrrole should be stored in an appropriate labeled container for recycling. The acid residues should be carefully neutralized with a saturated solution of hydrogen carbonate and then disposed of down the drain accompanied by water flush.

Hazards

There are no special hazards to report in this experiment beyond the standard handling of organic compounds. Concentrated hydrochloric acid is corrosive. Contact with the skin and eyes can cause severe burns. Inhalation of vapors can cause coughing, choking, inflammation of the nose, throat, and upper respiratory tract, and in severe cases, pulmonary edema, circulatory failure, and death. Acetone is flammable. Contact can cause irritation to the eyes, nose, and respiratory tract. Pyrrole is flammable and is irritating to the eyes, nose, and respiratory tract. It is harmful if swallowed. Octamethylporphyrinogen is irritating to the eyes, respiratory tract and skin. Caution must be taken when adding the HCl as heat released in the exothermic reaction easily makes the acetone reflux. All experiments should be performed in an efficient fume hood, wearing safety glasses and gloves.

Conclusion

The preparation of *meso*-octamethylporphyrinogen, by the acid-catalyzed condensation of pyrrole and acetone, to afford in one step, directly from the reaction medium, a nearly analytical-grade sample of a large macrocycle is an excellent instructional experiment for the organic synthesis laboratory. Students gain experience in organic synthesis and increase their perception that, when the nature of the reagents is adequate, it is possible to construct elaborate structures from simple compounds. Due to the similarity of *meso*-octamethylporphyrinogen with the important heme and chlorophyll macrocycles, this work may act as a bridge between the concepts of simple organic reactions and complex biological processes.

[w]Supplemental Material

Detailed student procedures, postlab questions and answers, instructors notes with comments on the experiment, reagent and product's CAS number and R/S phrases, elemental analysis, MS, ^{1}H NMR, ^{13}C NMR, and FTIR spectra are available in this issue of *JCE Online*.

Note

1. This article is dedicated to Sebastião J. Formosinho on the occasion of his 60th birthday.

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