Synthesis of *meso* substituted porphyrins in air without solvents or catalysts

Charles M. Drain* and Xianchang Gong

Department of Chemistry, Hunter College of the City University of New York, 695 Park Avenue, New York, NY 10021, USA

***meso*-Tetraarylporphyrins are synthesized from pyrrole and aryl aldehydes cleanly and efficiently in one step without solvents or catalysts by reactions at temperatures 10–15 °C above the boiling point of the starting aldehydes using air as oxidant.**

The remarkably diverse photo-, electro- and bio-chemical properties of the porphyrins continue to attract the attention of researchers even after well over a hundred years. In this century porphyrin research has gone from Hans Fischer's pioneering synthesis of hemin in the 1920s,[1] to their use as redox catalysts,[2] molecular electronic devices[3] and photodynamic therapy agents. In order to exploit their chemistry and fine tune their properties, a variety of synthetic methods have been developed for non-natural porphyrins, especially for the *meso* tetrasubstituted porphyrins.[4–8] We have developed a simple way to synthesize many *meso* substituted porphyrins without solvents, catalysts or man-made oxidants, and the reaction is complete in minutes. This is the synthesis of porphyrins at high temperatures and/or in the gas phase.

Previous syntheses using pyrrole and aromatic aldehydes are typified by the Ruthemund sealed-tube anaerobic reaction in pyridine at 200 °C (*ca.* 5% yield),[4] the Adler–Longo reaction in propionic or acetic acid under aerobic conditions (10–30% yield),[5] the MacDonald coupling of dipyrroles (10–20% yield)[6] and most recently the Lindsey, anaerobic condensation to form the porphyrinogen followed by oxidation to the porphyrin (10–60% yield).[7] The rapid appearance of water and what is now known to be the porphyrinogen[8] in a pseudo zero-order reaction in the Adler–Longo method, the equilibrium conditions of the Lindsey method, and the stability of the porphyrin to high temperatures of the Rothemund method, led us to attempt porphyrin synthesis at high temperatures and in the gas phase.

Although solventless mixtures of the pyrrole and aldehyde rapidly heated to > 200 °C form the corresponding porphyrins,[9] better yields but similar side product distributions are observed by mixing the two reagents in the gas phase at the same temperature.† Whether the porphyrin is formed entirely in the gas phase is unknown at present, but a brown–purple vapour is observed within *ca.* 2 s of adding the pyrrole to gaseous aldehyde, and a blue–black tar begins to condense on the sides of the reaction vessel soon afterwards. In the rapid heating experiments, porphyrins condense at the top of the reaction vessel, which is below the reaction temperature, with the same purity as that found in the bottom containing the original solution.

High temperature gas phase conditions allow for the rapid aldehyde–pyrrole condensation, for the removal of water from the proximity of the intermediate and for an increase in the rate of oxidation by dioxygen. This latter reaction is proposed to be the rate limiting step in the Adler–Longo method.[5] Examination of yield and products *versus* time indicates that oxidation of the porphyrinogen, or its intermediates, occurs very rapidly, since we detect no porphyrinogen and no chlorin in the UV–VIS spectra (Fig. 1) even after reaction times of a few seconds. Anaerobic reaction conditions result in very low porphyrin yields and only traces of porphyrinogen, indicating the crucial role of dioxygen in trapping the porphyrin products. Studies show that the reaction temperature must be above the boiling point of benzaldehyde to result in yields of *meso*-tetraphenylporphyrin (TPP) greater than a few percent, but the yield levels off by 210 °C. That the rapid removal of water from the condensing porphyrin (intermediates) is one key to these reaction conditions is shown by the decreased yield (*ca.* 12%) when a 5 : 1 water : aldehyde mixture is used.[10] Consistent with the known chemistry of aryl aldehydes, benzaldehyde can serve as an oxidant, since greater than 20% yields are obtained in experiments where the ratio of benzaldehyde to pyrrole is 3 : 1 and the amount of dioxygen is limiting. Catalytic amounts (< 5 mol%) of HCl or NH_3 block porphyrin formation almost entirely, but washing the reaction vessel with 1.0 M HCl or KOH and thorough drying has no effect. TFA diminishes the formation of TPP, but increases the yield of tetramesitylporphyrin from trace amounts to about 7% for reasons still under investigation.

This method is general enough to make a wide variety of *meso* substituted porphyrins in yields ranging from 7 to 23% (not optimized) (Table 1). For those reactions using aldehydes that have boiling points greater than *ca.* 250 °C at 1 atm, where the pyrrole begins to decompose too rapidly, a thin film of the melted or liquid aldehyde is coated into the reaction vessel sides at *ca.* 220 °C before the pyrrole is injected. Thus a 15% yield of tetrakis(4′-*tert*-butylphenyl)porphyrin are obtained.

We are currently examining the complex balance between temperature, pressure and concentrations of all three reactants in order to maximize the yield and gain a deeper understanding of the reaction mechanism and thermodynamics. Porphyrin formation is believed to be driven by enthalpic changes[9] and the macrocycle is preferred over the polymer for entropic reasons (ΔH −212 kcal mol^{-1}, ΔG −166 kcal mol^{-1}, and ΔS −153 e.u.).[7–9] If this data is correct, then the favourable ΔG is dominated by the entropy term, and cooler temperatures should favour porphyrin formation. However, the porphyrin yield increases with temperature up to *ca.* 250 °C, thus under these conditions the high temperature gas phase formation of porphyrins represents a kinetically controlled reaction dominated by the reactivity of dioxygen—as the oxidation studies suggest. The glass walls of the vial do not directly participate in

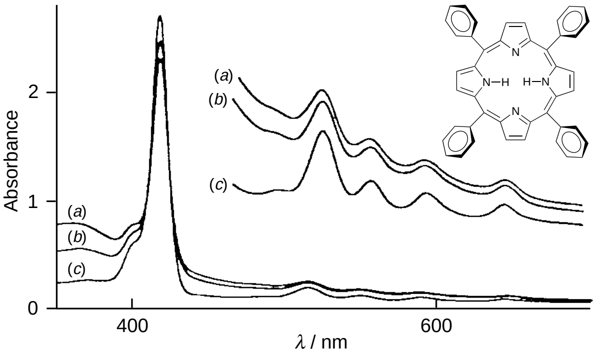
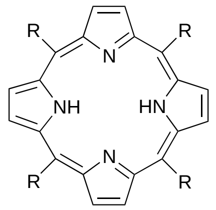


Fig. 1 Unpurified $CHCl_3$ rinses from two gas phase reactions: (*a*) a 3 : 1 and (*b*) a 1 : 1 ratio of benzaldehyde to pyrrole are compared to (*c*) the UV–VIS absorption spectra of known pure H_2TTP from a large gas phase reaction, showing the purity of the soluble materials and the lack of dipyrromethanes and chlorins in the product mixture. The inset absorbance scale is ×10.

Table 1 Isolated, unoptimized yields of porphyrin derivatives



R	Yield (%)[a]
Ph	23
4-MeC$_6$H$_4$	20
4-Pr^{i}C$_6$H$_4$	12
4-Bu^{t}C$_6$H$_4$	15
4-ClC$_6$H$_4$	10
4-MeOC$_6$H$_4$	20
4-MeSC$_6$H$_4$	10
Mes[b]	7
C$_5$H$_{11}$	1–2
4-Pyridyl	10[c]

[a] ± 3%. [b] 5 mol% TFA added to reaction. [c] 25 mol% Zn(Ac)$_2$ added to reaction.

the reaction since control experiments, whereby glass wool is inserted into the reaction vial or the vial has been silanated, show similar yields and reactivities. We are further investigating the possibilities of surface catalysis.

Our results show that the commercially important *meso* arylporphyrins may be synthesized without catalysts or solvent, and using only dioxygen as an oxidant. The polymeric byproducts are insoluble, so washing the reaction vessel with minimal amounts of solvent followed by a short silica gel column results in pure porphyrin. Dioxygen is a key requirement for porphyrin synthesis under these conditions. While the unoptimized 7–23% isolated yields resulting from our high temperature gas phase method are typically not as good as the Lindsey method and on a par with the Adler–Longo and MacDonald methods, the great advantages of this method are its simplicity and minimal waste production. Purification is generally easier since there is virtually no chlorin formation and the tarry byproducts are less soluble than other byproducts from other procedures. We have been able to scale up this method for the synthesis of 0.1–0.3 g of several porphyrins using a glass tube wrapped with heating tape (or in a zone refining furnace) whereby the aldehyde is slowly injected at one end, and the pyrrole is slowly added at the other end, of a 1.5 × 60 cm tube closed with glass wool to allow sufficient dioxygen for the reaction. The product is removed with 100–200 ml CHCl$_3$ and a very short silica gel column yields pure material. Thus, this method is quite amenable for industrial-type reactors.

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Footnotes and References

* E-mail: cdrain@shiva.hunter.cuny.edu

† Synthesis of *meso*-tetraphenylporphyrin is used as an example. A 5 ml vial is closed by a cap fitted with a rubber septum, placed in a temperature controlled sand bath and heated to *ca.* 200 °C, at which time benzaldehyde (10 µl, 0.1 mM) is injected into the system. After a few minutes, when the aldehyde is in the gas phase, 1 equiv. of pyrrole is injected slowly into the vial. (Alternatively both reagents can be placed in the vial, stirred and placed in the sand bath, but the yields are 25–30% lower.) The vial is kept at *ca.* 200 °C for another 15 min. Rinsing the reaction vessel sparingly with CH$_2$Cl$_2$ or CHCl$_3$ removes most of the porphyrin in *ca.* 80% purity as measured by UV–VIS spectroscopy,[7] while the remaining insoluble material contains < 1% of the porphyrin yield. Isolated yields are listed in Table 1. All compounds had satisfactory ^{1}H NMR, UV–VIS and FAB mass spectra. **Caution**: the rapid formation of gases and the flash point of all compounds should be considered. Under these conditions there is some benzaldehyde decomposition, and little decomposition of the pyrrole.

‡ A plethora of methods result in spectroscopically detectable quantities of porphyrins, including gamma ray irradiation, supercritical fluids, very high pressures, DC plasmas and fluidized bed reactors (ref. 9).

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