

Photosensitizers for photodynamic therapy: One-pot heterogeneous catalytic transfer reduction of porphyrins

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ABSTRACT

A number of new porphyrin-based photosensitizers have been developed for Photodynamic Therapy (PDT) in recent years. Chlorins, which are a reduced form of porphyrins, show better potential of application since they have a stronger absorption band on the red region of the visible spectrum and, hence, a deeper penetration into tissues. We found that by using heterogeneous catalytic transfer reduction (CTR), *meso*-tetraphenylporphyrin (TPP) could be hydrogenated, although in modest yields, to *meso*-tetraphenylchlorin (TPC) in a single reaction step. Best reaction conditions were attained using formic acid or sodium phosphinate/water as hydrogen donors, tetrahydrofuran (THF) or toluene as solvent and 10% palladium on charcoal as catalyst.

KEY WORDS: Catalytic transfer reduction, hydrogenation, *meso*-tetraphenylchlorin, *meso*-tetraphenylporphyrin, photosensitizers

Porphyrins have a variety of applications^[1-4] and, for this reason, their synthesis and modification is an expanding area. An example is the reduction of the pyrrole ring to produce chlorins and bacteriochlorins.^[5-9]

Porphyrins and their reduced derivatives are the most popular photosensitizers for Photodynamic Therapy (PDT). A number of new porphyrin-based photosensitizers have been developed for PDT in recent years, including chlorins, bacteriochlorins and purpurins.^[10,11] Porphyrins can be prepared in good yield from pyrrole-aldehyde condensation^[12] and, therefore, the common method for chlorin synthesis is by diimide reduction proposed by Withlook in the sixties.^[13] In spite of some recent advances,^[14,15] this methodology presents some difficulties in product isolation and chlorins are generally obtained in

moderate to poor yields. It would be convenient to find simpler procedures which originate better chlorin yields and at same time reduce the workup difficulties.

Catalytic transfer reduction in heterogeneous medium has proven to be an efficient method (specific and selective, under mild conditions) in the reduction of a variety of compounds.^[16,17] We wish to report our efforts to achieve the transformation of a porphyrin (*meso*-tetraphenylporphyrin or TPP) **1** to the corresponding chlorin (*meso*-tetraphenylchlorin or TPC) **2** in a single step using catalytic transfer reduction (CTR) with 10% palladium on charcoal as catalyst and formic acid or sodium phosphinate as hydrogen donors [Scheme 1].

Material and Methods

Reagents and equipment

Reagents were of reagent grade and solvents were of HPLC grade. TPC was purchased from Porphyrin Systems (Lübeck, Germany) and 10% palladium on charcoal was from Aldrich (St. Louis, MO, USA). TPP was synthesized by standard procedures from pyrrole and benzaldehyde^[12] and was metallated by refluxing

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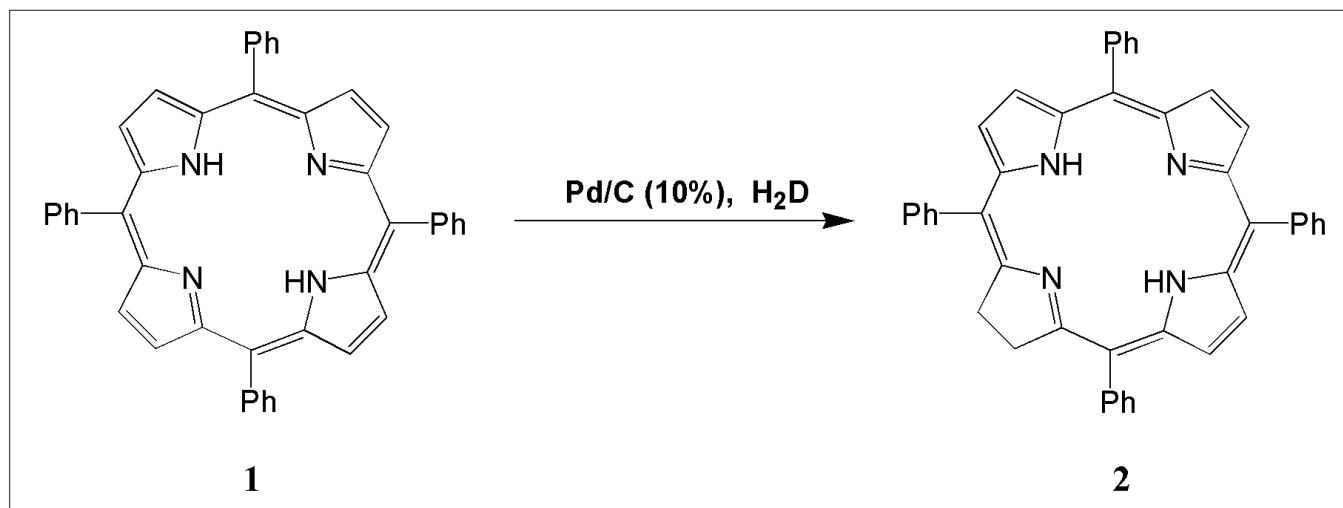
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Scheme 1: Catalytic transfer reduction of *meso*-tetraphenylporphyrin 1 to *meso*-tetraphenylchlorin 2, over palladium on charcoal with a hydrogen donor, H₂D

it (2 mg in 15 mL of dry dimethylformamide (DMF)) with 15 mg of anhydrous palladium(II) chloride for 30 min.^[18,19] The catalyst was filtered off by Chromafil RC-20/25 disks (Machery-Nagel, Düren, Germany). Absorbances were measured on a UV-Vis spectrophotometer (Varian Cary 50 Bio) and reaction mixture analysis was carried on an HPLC (Agilent 1100) with RP-18 LiChrospher column (250×4 mm, 5 μm) and diode array UV-Vis detector and isocratic acetonitrile/THF (9:1, V/V) as eluent. Conversions were obtained from the peak areas at 419 nm in the HPLC chromatograms, after calibration using authentic samples of TPP and TPC. Retention times (*t_r*) were the following: chlorin 6.7 min, porphyrin 7.2 min, and Pd(II)-TPP 9.4 min.

Isotherms

Ten milliliters of 2.40 μM solution of TPP in THF was stirred at 25°C for 1 h, with the amounts of catalyst ranging from 27 to 750 mg. The catalyst was filtered and the solution absorbance was measured at 416 nm. The same procedure was repeated using toluene.

Catalytic transfer reduction with formic acid

As an example, 10 mL of 0.1 mM solution of TPP in toluene was stirred with 1 mL of 0.26 M toluene solution of formic acid, 0.4 mL of triethylamine and 50 mg of catalyst at 50°C. At intervals, samples were withdrawn, filtered and injected on the HPLC.

Catalytic transfer reduction with aqueous phosphinate

As an example, 10 mL of 0.1 mM solution of TPP in toluene and 5 mL of aqueous 5 mM solution of sodium phosphinate (25 eq) were refluxed in the presence of 50 mg of catalyst. Analysis was carried as previously.

Results and Discussion

Although CTR presents practical advantages, it requires very

fine tuning of several experimental parameters – solvents, donors, catalysts – in order to render the process efficient. Key features in our approach are (i) the establishment of conditions to quantitatively analyze reaction progress with identification of side products, (ii) the study of adsorption isotherms, which are crucial in any heterogeneously catalyzed reaction, in order to predict which conditions are more likely to produce the best results, and (iii) screening and adjustment of hydrogen donors and other conditions to optimize yields.

UV/vis is broadly used to monitor the reaction progress in porphyrin chemistry, but mainly due to spectral similarities of the involved species, HPLC with diode array detection proved to be a more reliable quantitative methodology, with many reports on its application to the above compounds existing in the literature.^[20-23] Therefore, some efforts were devoted to the establishment of elution conditions.

In the measurement of the adsorption of porphyrins onto the catalyst, various solutions of known concentration of porphyrin were stirred with different amounts of the catalyst, under controlled conditions, and the decrease in porphyrin concentration was monitored by UV/vis [Figure 1].

Initial attempts to reduce TPP were made using formic acid as hydrogen donor and THF or toluene as solvents. Reaction proceeded reasonably fast, reaching a steady state in approximately 20 min. Conversions to the desired product TPC were below 40% [Figure 2] along with the formation of metalloporphyrin Pd(II)-TPP (not quantified) and trace amounts of bacteriochlorin and isobacteriochlorin. The metalloporphyrin is formed by complexation of Pd²⁺ ions present on the catalyst, in spite of the reducing conditions, and was identified by comparison with an authentic sample. The latter compounds are due to reduction of the formed chlorin 2, and were identified simply from their visible spectra characteristic bands. Although the preparation of an authentic sample of Pd(II)-TPC was attempted, the product of reaction between

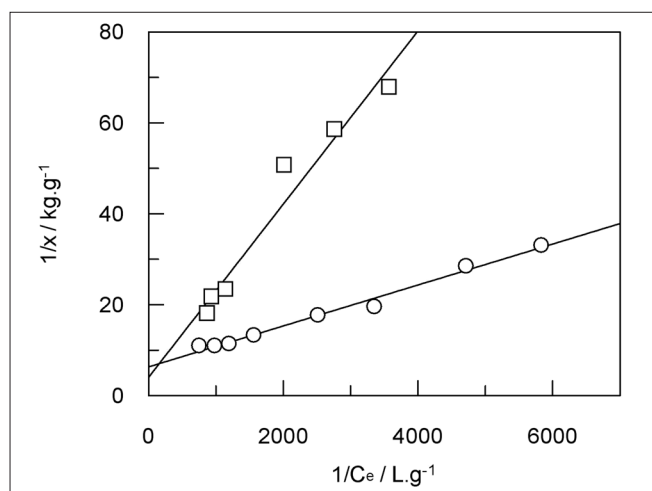


Figure 1: Linear plots of the Langmuir adsorption isotherms for THF (o) and toluene (□) TPP solutions on 10% palladium over charcoal

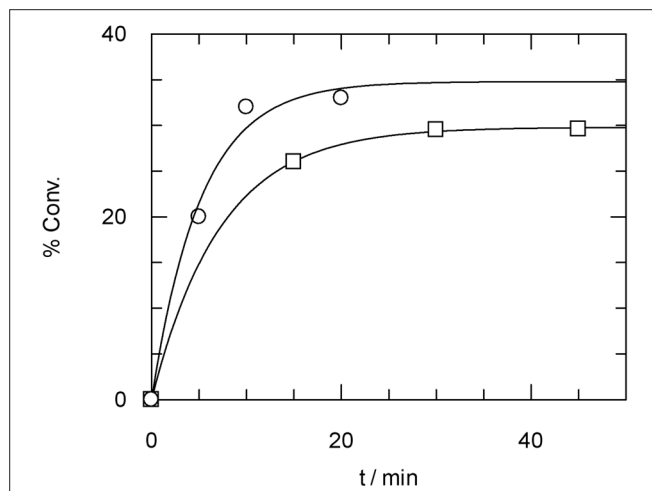


Figure 2: Percent conversion (reduction) of TPP with time, in toluene, with formic acid (o) and with aqueous solution of sodium phosphinate (□)

TPC and PdCl₂ exhibited the same t_r and visible spectrum as Pd(II)-TPP, probably due to oxidation during the reflux and, therefore, the possibility of its formation cannot be discarded.

In the second approach, a biphasic system consisting of a toluene solution of TPP and an aqueous solution of sodium phosphinate was used. Product distribution was found to be dependent on donor concentration: when 25 equivalents of the latter were used, the desired product TPC was obtained in nearly 40% yield; for other substrate:donor ratios (1:5, 1:15, 1:35, 1:50 and 1:100), an unidentified product was formed ($t_r = 4.9$ min). In all cases, the metalloporphyrin was observed, but none of the other side products were obtained.

A plausible explanation for the stagnation of hydrogenation below 50% conversion is catalyst poisoning by the product, as although a double bond was reduced, most of the system responsible for the adsorption remained untouched, preventing product desorption.

Further work will be required to tackle this problem, but so far, it has been demonstrated that TPP could be reduced to TPC in a single step, although in moderate yields, using either (i) formic acid as hydrogen donor in a THF or toluene solution or (ii) a biphasic system of aqueous sodium phosphinate and toluene as solvent for the substrate, and 10% palladium on charcoal as catalyst.

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