Kinetic Study of *meso*-Tetraphenylporphyrin Synthesis Under Microwave Irradiation

Rodrigo De Paula, Maria A.F. Faustino, Diana C.G.A. Pinto, Maria G.P.M.S. Neves, José A.S. Cavaleiro*

University of Aveiro, Department of Chemistry, Campus Santiago. 3810-193, Aveiro-Portugal, Tel.: +351 234 370 717 ; Fax: +351 234 370 084 ; e-mail : jcavaleiro@ua.pt

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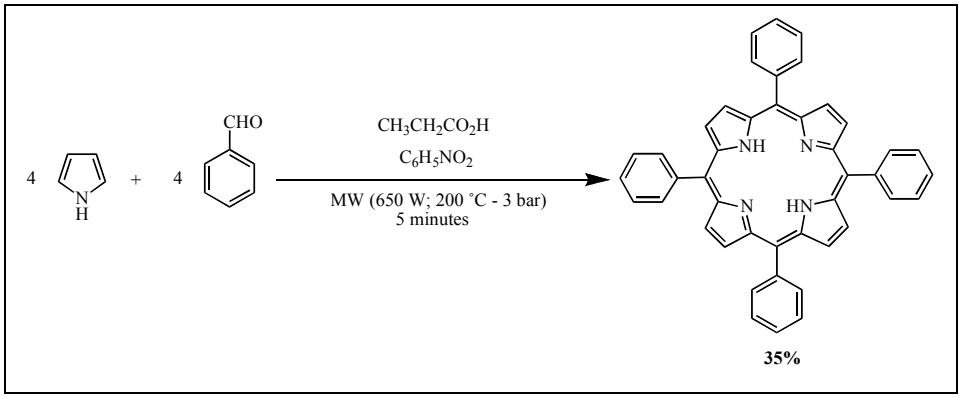

A typical synthesis of *meso*-tetraphenylporphyrin was carried out from condensation of pyrrole with benzaldehyde in acidic medium under microwave irradiation. A batch of tests were carried out and a systematic evaluation of organic acid, reactant concentration, microwave power, time of reaction, presence of added oxidant at normal pressure conditions and in closed vessels system, allowed us to find a good set of conditions within the range of study. The best result was achieved in only 5 minutes of irradiation showing a great reduction in reaction time and reaching yields higher than those mentioned in literature for the synthesis under classical synthetic heating method.

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INTRODUCTION

Several reports on the use of microwave (MW) heating to accelerate organic chemical transformations have appeared two decades ago involving the use of a domestic microwave oven; since then, the use of MW irradiation in organic synthesis has been increasing annually, offering a promising alternative for conventional heating sources [1-3]. It seems that the reason for the observed rate enhancements is a purely thermal/kinetic effect which is a consequence of the high reaction temperatures that can be rapidly attained when irradiating materials in a microwave field [4]. MW irradiation produces efficient internal heating by direct coupling of MW energy with molecules being present in the reaction mixture. Such procedure usually reduces reaction times, avoids side reactions, increases the yields and improves reproducibility [5,6].

As far as porphyrin synthesis is concerned, certain publications describing the use of MW irradiations can be found [7,8]; in some cases, domestic MW ovens have been used. However uncontrolled MW heating in such ovens involves non-continuous pulsed irradiation without proper control of reaction temperature or pressure. If the rate-enhancements are due to thermal effects, then one needs to accurately control the temperature. Other studies about reproducibility have shown that the results obtained in domestic MW devices are not reliable due to the lack of reproducibility [1,2]. Indeed, such domestic devices have on-off switches that do not allow keeping a constant energy power. For reliable and reproducible procedures it has been established that MW synthesis in dedicated devices should be considered.

It is well known that the role of porphyrins in biological functions such as photosynthesis, catalytic oxidative transformations, transportation and storage of molecular oxygen has been greatly assisted by studies using synthetic models like *m*eso-tetraarylporphyrins. The potentiality of this type of porphyrins in a great number of scientific fields (*e.g.*, medicine, catalysis and in the production of new electronic materials) is also well established. The lack of functionalization of such type of macrocycles is being overcome by intensive work developed by several research groups and reported in excellent reviews [11-15].

Macrocycle reactivity studies in addition to all those potential applications point out that an easy and efficient access to the starting porphyrin is required. The most common synthetic methods leading to *meso*-tetraphenyl-porphyrin (TPP) being used worldwide are summarized in Table 1 [16]. Others methods derived from those shown

Table 1

Experimental conditions for the most common methods in *meso*-tetraphenylporphyrin synthesis*.

	Porphyrin Synthetic Methods		
	Rothemund	Adler	Lindsey
Solvent	Pyridine	(I) Propionic acid (II) Acetic acid	Dichloromethane Chloroform
Temperature	220 °C	(I) 141 °C (II) 120 °C	25 °C
Catalyst	-	Same as solvent	TFA BF_3.etherate BF_3.etherate/ethanol
Oxidant	-	O_2	DDQ or p-chloranil
Reactant concentration	3.6 mol.dm^{-3}	0.3 – 1.0 mol.dm^{-3}	0.001 – 0.1 mol.dm^{-3}
Time of reaction	48 h	0.5 – 1.0 h	1 h
Procedure	One step	One step	Two steps
Purification (work up)	Crystal separation	Filtration	Chromatography**
Yield	< 10%	~ 20%	Up to 40%
Method range	Restrict	Medium	Large

*Adapted from [16]; ** The yield is calculated by either UV-Visible spectrum or HPLC.

in Table 1 can be found in literature but without great advantage [17,18].

Following our interest [19-22] on the use of Microwave Assisted Organic Synthesis we decided to study the synthesis of TPP, using the Adler *et al.* conditions, but under MW irradiation. It was aimed to look for how the acid used, the power applied, the reaction time, the reactants concentration and lastly, how the closed vessels system can affect the yield in the synthesis of TPP. This porphyrin was chosen because it is the most simple one and it is being used in a wide range of chemical studies mainly related to the reactivity and functionalization of the macrocycle [23-30].

RESULTS AND DISCUSSION

MW heating at normal pressure. As it is mentioned in Table 1, Adler and co-workers have found that the best conditions for the condensation of pyrrole with benzaldehyde requires the use of boiling acetic or propionic acids; in propionic acid TPP usually precipitates in the reaction medium and the crystals can be collected by filtration.

As it was mentioned above we have selected the reaction conditions developed by Adler and coworkers (Table 1) to carry out the condensation reaction between pyrrole and benzaldehyde. Their studies showed that the best results were obtained when the condensation reaction is performed in the presence of acetic acid or propionic acid. Much poorer results were reported when longer chain organic acids like butyric acid or mixtures of those acids with toluene or benzene were used [16]. Under those conditions the organic acid being used acts as the solvent and the catalyst.

Those authors in their original method observed that in propionic acid TPP usually precipitates in the reaction medium, thus making the work up less tedious. [16,31-33].

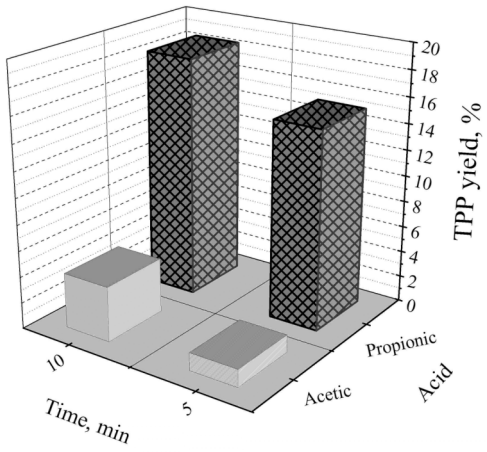


Figure 1. Effect of acid on the TPP yield under 650 W irradiation during 5 and 10 minutes at reflux.

These facts prompted us to look for the effect of these two acids on the yield of TPP under microwave irradiation at normal pressure. These reactions were carried out using both reagents in a concentration of 0.20 mol.dm^{-3}, which is close to the one reported by Adler, and an irradiation power of 650 W. The yields were determined after 5 and 10 minutes of irradiation and the results obtained are shown in Fig. 1. It can be observed that in acetic acid the yields are extremely low when compared with those obtained in propionic acid, even when the reaction is extended for 10 minutes.

Presumably, due to the bigger pKa and dielectric constants of acetic acid [34], there is more polymerization

when using this acid in comparison with the case using propionic acid. As a result we have selected propionic acid as the solvent for further optimization studies.

To check the power value selected (650 W) and so the energy amount applied to the reaction, it was decided to perform other experiments using the conditions reported above, but irradiating with different MW powers. As depicted in Figure 2, the power of 650 W provides the best yield in such synthesis independently of how long the reaction is irradiated (5 or 10 minutes). Nevertheless, in the 10 minutes irradiation case, irradiations with 650 W or 700 W gave rise to similar yields. Also with 650 W irradiations, at longer times, no improvement was reached (Figure 2).

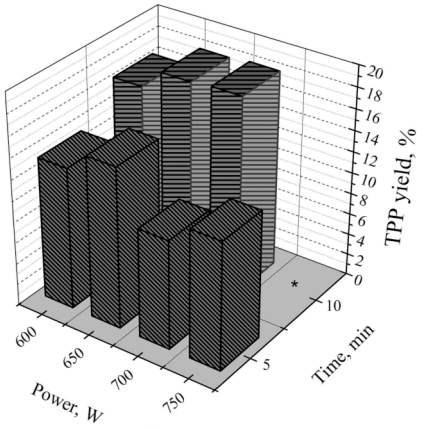


Figure 2. Effect of reaction time and energy applied on the TPP yield. *The experiment for 10 minutes at 750 W was not run due to abnormal heating.

The concentration effect was also a parameter to be evaluated. These studies were carried out using the two, 0.1 and 0.4 mol.dm^{-3} reagents concentrations. The vessels were irradiated during 5 and 10 min at 650 W. Figure 3 summarizes the results obtained under the reaction conditions selected.

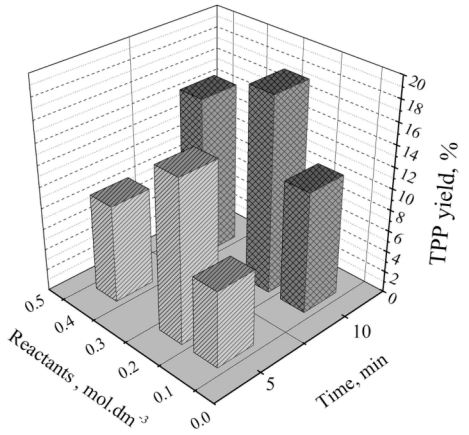


Figure 3. Relationship between reactants concentration and time of reaction on the yield of TPP, under 650 W power irradiation.

The obtained results indicate that the best yields of TPP (15-18%) can be achieved with a 650 W power irradiation during 5 or 10 minutes, having a concentration of 0.20 mol.dm^{-3} for both reagents.

The presence of chlorin as a by-product is known for a long time [35,36]. It usually occurs in 5% amounts [37] and can be oxidized by DDQ as it is mentioned in Table 1. A good alternative for such oxidation relies on the use of nitrobenzene in the reaction mixture [38]. Due to its dielectric constant and high boiling point, nitrobenzene has good features for MW irradiation [34]. Fig. 4 shows the heating profile obtained in a typical experiment in MW under reflux. Temperatures above the boiling point of the solution are obtained faster in the presence of nitrobenzene.

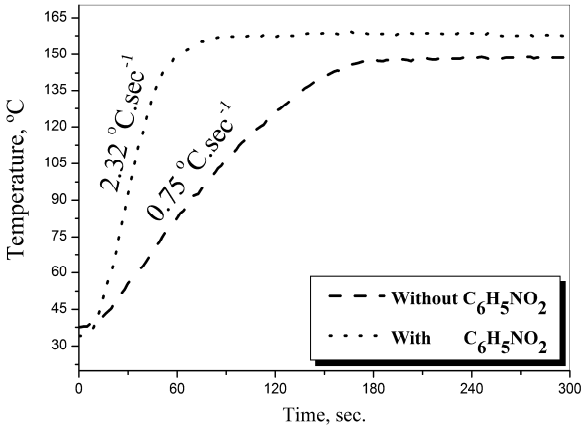


Figure 4. Heating profile (MW 650 W) obtained in reaction carried out with and without nitrobenzene under normal pressure glass reactor. Conditions: 20 mL solvent (only propionic acid or the mixture propionic acid/nitrobenzene 13:7), with pyrrole and benzaldehyde at a concentration of 0.20 mol.dm^{-3}.

An experiment under these "oxidative" conditions allowed us to obtain in a slightly better yield (20%) a chlorin-free TPP after 5 minutes of MW irradiation. This result led us to evaluate the nitrobenzene oxidizing effect under pressurized system, using the mixture propionic acid/nitrobenzene (13:7).

Closed vessel systems. In previous optimization studies all experiments were run at reflux temperature (155 – 160 ºC) and normal pressure (Figure 4). The closed vessels system can bring temperatures above those from the solution boiling point, thus originating pressure values higher than the normal one. The potential effect on the TPP yield was then evaluated under these new conditions, mainly considering the effects of reactants' concentration, irradiation time (2.5, 5.0 and 7.5 minutes) and temperature.

It should be mentioned that it was assumed that the reaction follows a *pseudo*-zero-order kinetics (equation 1), as it was determined before by Longo and co-workers [32].

$$[TPP] = [TPP]_0 + kt \qquad \text{equation 1}$$

where *[TPP]* represents the molar concentration at a given time; *k* is the *pseudo*-zero-order rate constant and *t*, the time, given in minutes. For *t=0*, we can consider $[TPP]_0=0$.

The rate constant estimation can be seen in Figure 5. The diluted condition (0.10 mol.dm^{-3}) is not attractive since a low rate constant was found and a longer reaction time is then required for synthesis. With the 0.40 mol.dm^{-3} concentration the rate constant value is slightly smaller than the value obtained when a concentration of 0.20 mol.dm^{-3} was used; the latter brings a higher TPP yield and a higher rate constant [39].

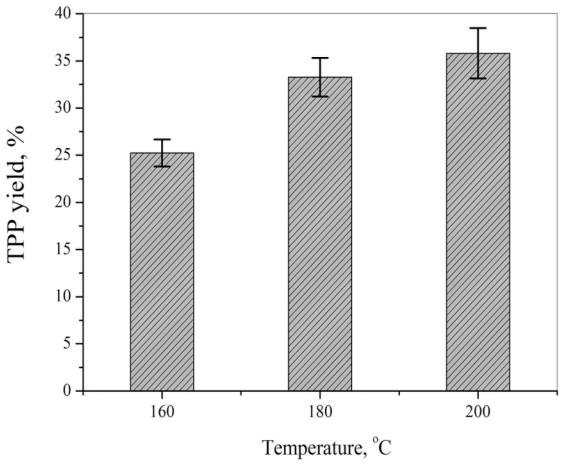
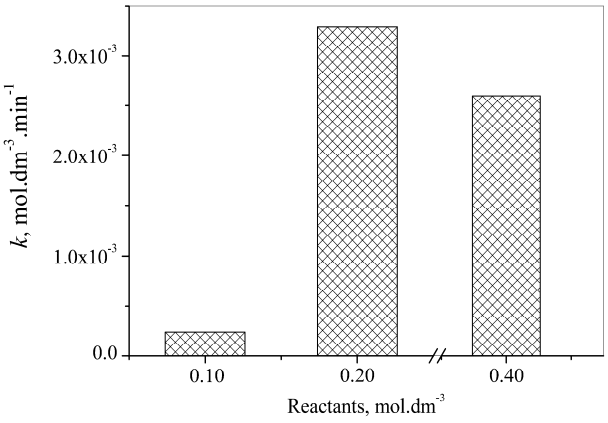


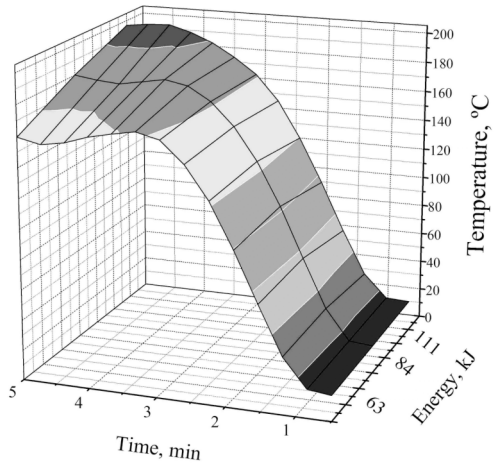
Figure 5. Results obtained for kinetic analysis of TPP synthesis under MW irradiation in closed vessels showing the *pseudo*-zero order rate constant obtained. Conditions: 20 mL of a mixture propionic acid/nitrobenzene (13:7), 0.20 mol.dm^{-3} reactants concentration and 650 W of MW power.

To evaluate how higher temperatures than those due to reflux can affect the TPP yield, a batch of reactions were carried out at the same time and under the same conditions.

Figure 6-A shows the yield obtained under the chosen temperature values while Fig. 6-B presents the heating profile for TPP synthesis in the studied temperature range.



(A)



(B)

Figure 6. (A)-TPP yields and selected temperature values (at 650 W initial power). The standard deviation is 2.7%; (B)-profile obtained for TPP synthesis under closed vessel system. Conditions: 20 mL propionic acid/nitrobenzene (13:7), 0.20 mol.dm^{-3} of reactants concentration during 5 min. in closed vessels.

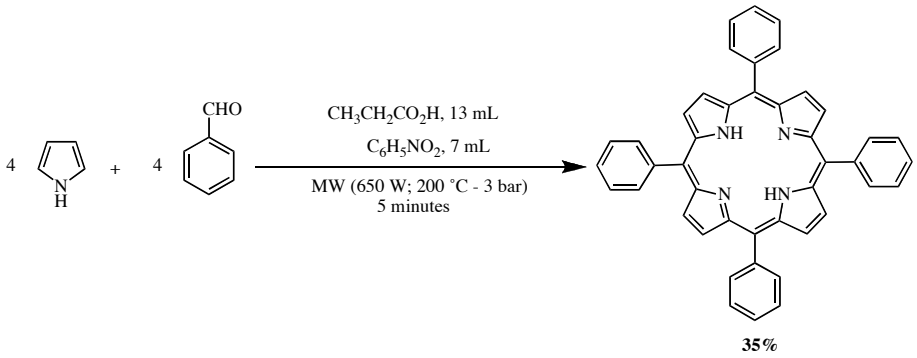
The best TPP yield found was 35% (±2.7%) at 200 °C (as shown in Figure 6-A). When reaching this temperature value, the internal pressure also increased, achieving a maximum value of 3 bar. Based on these results the general view for chlorin-free TPP synthesis could be rewritten as shown in Scheme I.

These results prompted us to find some physical-chemistry parameters for TPP synthesis under MW irradiation and to explain the effect attributed to the MW acceleration in the synthesis when compared with the oil-bath heating method.

Microwave effect. As postulated by several authors [6,10,40], the effect provided by MW irradiation goes beyond achieving the temperature in less time. The different way for heating the system can affect the

Scheme I

Schematic view to TPP synthesis under our synthetic conditions.



physical-chemistry parameters. Based on the results shown in Fig. 6, we could estimate the rate constant and activation energy for porphyrin synthesis.

Our tests for estimating the rate constant for TPP synthesis (Figure 5) took into consideration what was previously described by Longo [32] (reaction proceeding in a *pseudo*-zero order kinetics).

The increment observed in our studies under microwave irradiation can be explained through an increment on the rate constant for the reaction; this can be illustrated by the Arrhenius theory [10,4] (equation 2)

$$\ln k = \ln A - E_a/RT \qquad \text{equation 2}$$

where k is the *pseudo*-zero order rate constant given in $mol.dm^{-3}.min^{-1}$; A is the collision frequency in mol per unit time; E_a is the activation energy given in Joule and R is the ideal gas constant.

Using the results shown in Figure 6-A the activation energy for such reaction under microwave irradiation can be obtained.

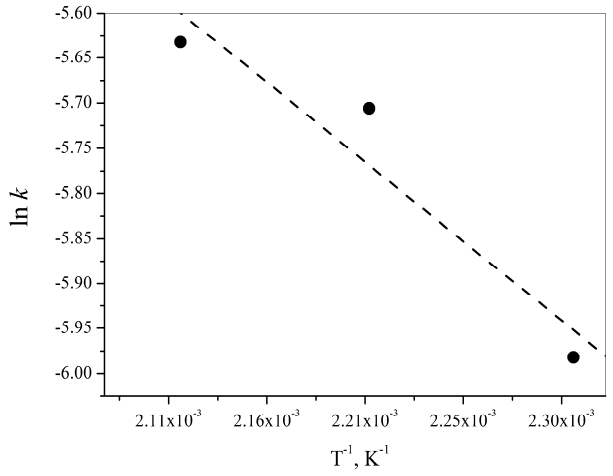


Figure 7. Correlation between rate constant and the inverse of temperature obtained by kinetic measurements from 160 to 200 ºC. The experimental Arrhenius function found was $ln\ k = -1798.7.T^{-1} - 1.7987$; $R^2 = 0.91$.

From Figure 7 the activation energy found for TPP synthesis under MW is 14.9 kJ. This value is smaller than 58.5 kJ, the one obtained by Longo *et al*. [32], for the same porphyrin.

These differences occur due to thermodynamic factors; when the solvent and the reactants absorb energy, the molecules can be aligned with the electromagnetic field produced by MW. When this takes place, the reactant molecules are best organized within the solvent cage. That phenomenon does the activation energy of the transition state to be reduced and consequently the entropy [4]. In Table 2, we show the data reported by Longo *et al.* [32] with our entropy value, obtained by using the same approach as described in [41]

Table 2

Entropy change in TPP synthesis under MW irradiation [42].

Condition	**-T ΔS, kJ**
Oil-bath (Longo condition)	4.18
MW (experimental result)	3.93

CONCLUSION

We describe here the microwave effect on the TPP synthesis. The time saving and a good yield for TPP indicates that MW can be used as an efficient alternative energy source. Our best results were obtained using a reactant concentration equals 0.20 $mol.dm^{-3}$, propionic acid (13 mL) and nitrobenzene (7 mL) mixture in only 5 minutes under a power of 650 W at pressurized system (up to 3 bar; 200 ºC). An extension of these conditions to the synthesis of several other *meso*-tetraarylporphyrins is being carried out.

EXPERIMENTAL

The microwave device (Milestone Inc.) operates at fixed frequency (2450 MHz) in multimode (run up to 12 flask simultaneously). The equipment can control the temperature (up to 250 ºC) and the pressure (up to 55 bar) in a range of power values from 0 to 1000 Watts (steps in 10 W).

Pyrrole was purchased from Aldrich and was distilled before use. Benzaldehyde was used as received (Riedel-de-Häen). Acetic and propionic acids were purchased from Sigma-Aldrich and nitrobenzene was from Acros.

Unless other conditions are specified, a typical TPP synthesis was carried out by putting into a normal pressure glass reactor, pyrrole (0.280 mL, 4 mmoles), benzaldehyde (0.410 mL, 4 mmoles) and propionic acid (20 mL) as solvent. In the cases where acetic acid was tested, the same amount (20 mL) was employed as solvent. In experiments where nitrobenzene was used, the volumes of acid and nitrobenzene were, respectively, 13 mL and 7 mL. The reactions were carried out usually for 5 or 10 minutes (sometimes in 7.5 min) under a specified MW power. Once the reaction was completed, the mixture was cooled down and methanol was added to promote the porphyrin crystallization. The TPP crystals were collected by filtration. Recrystallization was made in chloroform/methanol. The experiments for the established conditions were carried out at least, three times each one in order to verify the reproducibility; the yields were the mean values obtained in those experiments.

The structure of the porphyrinic material was confirmed by comparing the UV-Vis and ^{1}H-NMR spectra with those described in literature. UV-vis ($CHCl_3$): λ, nm (log ε) 418 (5.65), 515 (4.25), 550 (3.87), 589 (3.74), 646 nm (3.58). ^{1}H NMR (300 MHz; deuteriochloroform): δ_H, ppm -2.78 (2H, s, pyrrole NH), 7.71-7.78 (12H, m, Hm-, Hp-Ph), 8.18-8.23 (8H, m, Ho-Ph), 8.84 (8H, s, pyrrole-H).

The kinetic measurements were performed under 650 W irradiation power and the higher temperature achieved was 200 ºC. The reaction was stopped at different intervals (2.5, 5.0 and 7.5 min). The yield for each time was calculated after work up and crystallization as mentioned above. For rate constant estimation, the zero-order approximation was considered from the TPP formation. The activation energy values were found by following the Arrhenius theory; experiments were done by fixing a given temperature value and the heating was achieved using 650 W as initial power. The energy was cut off when matching the set up temperature. For these experiments the temperature values chosen were 160, 180 and 200 ºC.

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[39] In the experiments for the rate constant estimations, six vessels were irradiated at the same time. The irradiation was stopped every 2.5 minutes and then 2 vessels were withdrawn from the MW cavity; the other ones left behind were irradiated again. This procedure was repeated until the final time (7.5 min.) was reached. At 2.5 minutes,

the final slope of the MW heating curve was achieved, but only a small amount of porphyrin was formed; at 5.0 minutes the reaction continues to be heated; at this time the reaction is complete because almost no difference in TPP yield can be observed between the two 5.0 and 7.5 minute heating times.

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[42] In the transition state, we have a state function given by $\Delta^{\neq}G = \Delta^{\neq}H - T.\Delta^{\neq}S$, where G is the Gibbs energy, H the enthalpy and S the entropy in the transition state. At this point, we can consider $Ea \approx \Delta^{\neq}G$ and $\Delta^{\neq}H = Ea - R.T$, according the Eyring theory.