Achieving selectivity in porphyrin bromination through a DoE-driven optimization under continuous flow conditions

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Received: 9 October 2020 / Accepted: 24 November 2020 / Published online: 14 December 2020
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Abstract
The post-functionalization of porphyrins through the bromination in β position of the pyrrolic rings is a relevant transformation because the resulting bromoderivatives are useful synthons to covalently link a variety of chemical architectures to a porphyrin ring. However, single bromination of porphyrins is a challenging reaction for the abundance of reactive β-pyrrolic positions in the aromatic macrocycle. We herein report a synthetic procedure for the efficient preparation of 2-bromo-5,10,15,20-tetraphenylporphyrin (1) under continuous flow conditions. The use of flow technology allows to reach an accurate control over critical reaction parameters such as temperature and reaction time. Furthermore, by performing the optimization process through a statistical DoE (Design of Experiment) approach, these parameters could be properly adjusted with a limited number of experiments. This process led us to a better understanding of the relevant factors that govern porphyrins monobromination and to obtain compound 1 with an unprecedented 80% yield.

Keywords Bromination · Porphyrin synthesis · Design of experiment · Continuous flow

Introduction
Porphyrins and related compounds are a class of macrocycles that play a leading role in catalysis, [1–3] molecular recognition, [4–6] energy conversion [7] and photomedicine. [8, 9] Their remarkable optical and electrochemical properties can be modulated by a careful choice of peripheral substituents or by metatation of the inner core. Covalent linking of porphyrins to a wide variety of systems, such as carbon nanostuctures [10] or biopolymers, [11–13] is commonly exploited to obtain functional materials. Peripheral functionalization may also be used to create light harvesting systems [14]. For instance, zinc porphyrins substituted at the β-pyrrolic position with groups bearing an extended π-system are known as a highly performing class of photosensitizers employed for Grätzel solar cells. [15] A convenient synthetic route to these compounds relies in the derivatization of meso-tetraaryl porphyrins through a two-step process in which the initial monobromination of a pyrrole moiety is followed by a cross-coupling reaction to achieve the desired functionalization. [16] Porphyrins mono-bromination is a reaction with an inherent poor selectivity for the simultaneous presence of eight available pyrrolic positions. Also, purification is an important issue, because the chromatographic separation of monobromo porphyrins from the starting material and/or from polybrominated adducts is hampered by their very similar retention factors. This often translates into a limited isolated yield for the monoadduct. For this reason, some authors propose the direct use the unpurified bromoporphyrins for further synthet-ic steps [17] since the final functionalized porphyrins is easier to separate, although this means a consistent production of waste materials.

In view to develop the synthesis of precisely designed porphyrins through scalable and sustainable methodologies, we implemented the bromination step with flow chemistry technology. [18] In particular, the improved mixing efficiency and heat transfer can be beneficial to the reaction selectivity. [19]
For instance, the selective mono-bromination at the benzylic position of substituted toluene species was successfully achieved under continuous flow conditions. [20–22]. Despite the potential of continuous flow processing there are, to the best of our knowledge, only a few reports on their use for porphyrin synthesis. [23, 24] Even more surprisingly, there are no reports concerning continuous flow post-synthetic functionalizations of porphyrins.

In order to maximize the mono-bromination selectivity, it is necessary to finely tune the key reaction parameters; however, an accurate control of temperature and reaction time is difficult to achieve in batch systems. Up to now, the best results were achieved by a very slow addition of the brominating agent to the starting porphyrin that gave the monobromo derivative in 78% isolated yield on a 60 mg scale. However, the same value dropped to 64% when the reaction was carried out on a gram-scale. [25] On the other hand, continuous flow processes can be efficiently scaled up in an effortless way or with minimal changes in the reaction settings.

We investigated the selectivity in porphyrin monobromination by means of flow chemistry with the aid of the DoE statistical approach. DoE allows to optimize a reaction by modelling the response (e.g. yield) across the multiple variation of the relevant factors within a given “reaction space”. [26] This approach stands in contrast with the more popular OVAT (one variable at a time) strategy. However, the significant advantages in employing a DoE methodology can be found in the limited number of experiments required to reach the final result and in the reliable optimum conditions derived from the statistical model. [27, 28] Moreover, DoE provide useful information by quantifying the effect of the variation of single factors, or factors combinations, on the product yield. Thanks to this underexploited strategy, we could identify the key reaction parameters, increasing the yield of 2-bromo-5,10,15,20-tetraphenylporphyrin (1) up to 80%.

**Results and discussion**

The single bromination at the pyrrolic β-position of meso-tetraphenyl porphyrin (2) is generally carried out with NBS as the halogen source (Scheme 1). The inherent difficulties of this transformation were discussed above and consist in a delicate balance between the efficient conversion of the starting material and the generation of polybrominated byproducts.

We started this study by considering the conventional batchwise synthesis with two different protocols reported in the literature. The parent methodology reported by Callot [29] consists in refluxing a chloroform solution containing NBS and compound 2. Zhang et al. improved this procedure by using pyridine as an additive and a slow addition of an NBS excess. [25] To the best of our knowledge, the latter is the strategy that gives the highest yield (78%). We repeated the Zhang methodology by a dropwise addition over 3.5 h of an NBS solution in chloroform to a refluxing chloroform/pyridine mixture containing 2. After quenching the reaction, HPLC analysis of the crude mixture showed a composition of 72% of 1, 5% unreacted 2 and 23% of a mixture of dibrominated porphyrins, confirming the literature data. On the other hand, we observed also a consistent amount of dibrominated byproducts, reasonably due to excess NBS (3 equivalents with respect to 2). Since the presence of polybrominated porphyrins hampers the purification of monobromo derivative, the additive-free Callot approach was pursued under continuous-flow conditions.

To this end, we used a Vapourtec R-Series modular flow system (the set-up is illustrated in the Supporting Information), in which two chloroform streams, containing 2 and NBS respectively, were mixed and flowed through a heated coil reactor. An in-line back-pressure regulating valve (BPR) allowed us to carry out the bromination at a temperature significantly higher than the chloroform boiling point. The reaction mixture was collected in a stirred flask containing an aqueous Na2CO3/Na2S2O3 solution to quench unreacted NBS before HPLC analysis. This automated and reproducible flow system prompted us to perform reaction parameters screening and optimization by using the DoE approach. For this purpose, a set of experiments is planned following a given design, then the results are fitted in a mathematical model to predict the conditions for yield maximization. This approach is particularly convenient for the monobromination of compound 2, with the aim to find the sweet spot where an efficient conversion of the starting porphyrin occurs without an excessive formation of polybrominated byproducts.

In order to build the factorial design, three reaction parameters were chosen to be optimized; namely, temperature (T), residence time (Rt) and NBS equivalents (eq). Afterwards, the upper and lower limits of the three factors must be set in order to individuate the reaction space for the DoE analysis. To this

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**Scheme 1** Porphyrin 2 bromination with NBS

![Scheme 1 Porphyrin 2 bromination with NBS](image-url)
aim, we performed some preliminary tests (see Supporting Information). At first, we investigated the reactions with a low residence time (10 min), the temperature ranging from 60 °C (close to chloroform boiling point at ambient pressure) to 150 °C (the upper temperature limit of the employed reaction system) and a stoichiometric amount of NBS (1 equivalent). We started to observe an appreciable 25% conversion of the starting material when two streams of chloroform containing 2 and NBS respectively were mixed at 100 °C. By setting the temperature up to 140 °C the conversion increased to 60–70% but also the formation of polybrominated products was detected to a major extent (>10%). Also increasing the NBS amount up to 3 equivalents was detrimental to the monobromination selectivity even at mild conditions (100 °C and 10 min residence time, see Supporting Information), in contrast with the reported Zhang methodology.

With this preliminary information, the three factors T, Rt and NBS equivalents were set in the respective ranges of 100–140 °C, 10–40 min and 1–2 equivalents. Once the factors levels were assessed, we could proceed to the DoE optimization by building a full factorial design of 11 experiments composed by eight corner points and three center points (Entries 1–11 of Table 1). As observed in the preliminary experiments, a high reaction temperature ensures a higher conversion of the starting material but we observed a drop in selectivity with respect to the reactions carried out at low T. Interestingly, the experiments performed at the center points conditions (Table 1, Entries 9–11) already exhibit a yield in the desired product comparable to the one reported by Zhang et al. The resulting yield in the mono-brominated product 1 was considered as the response parameter. By using the Minitab Statistical Software, the experimental data were fitted into a model through a multiple linear regression.

The data fitting gave an $R^2$ of 0.999; thus, the model can nicely explain the response variation. The coded coefficients for the parameters in the regression equation are represented in Fig. 1 and were all found statistically significant with a confidence interval of 0.95. The most influential contribution to porphyrin 1 yield variation were given by Rt and the two-way interaction between T and Rt. It is worth to mention that a poor influence was acknowledged to the NBS amount in the range between 1 and 2 equivalents. Each one of the three factors (T, Rt, eq) has a positive coefficient, but negative effects were found for all two-ways interactions (T*Rt, eq*Rt and eq*T). For instance, this points out that while a longer residence time can lead to a better yield in porphyrin 1, the simultaneous increase of both T and Rt has a negative impact.

The factorial design revealed the most influential parameters for the maximization of the monobromination yield. However, the software detected the presence of curvatures in the response surface. Therefore, the prediction of the optimal reaction conditions would be inaccurate if simply based on a linear model. In order to better describe the yield variance, a

| Entry | Run | Factor 1 T (°C) | Factor 2 Rt (min) | Factor 3 eq | Conversiona (%) | Response 1 Yielda (%) | Response 2 Selectivityb (%) |
|-------|-----|----------------|------------------|------------|-----------------|------------------------|---------------------------|
| 1     | corner points | 100 | 10 | 1.0 | 25 | 21 | 82 |
| 2     |      | 100 | 10 | 2.0 | 32 | 30 | 94 |
| 3     |      | 100 | 40 | 1.0 | 70 | 68 | 97 |
| 4     |      | 100 | 40 | 2.0 | 83 | 73 | 88 |
| 5     |      | 140 | 10 | 1.0 | 57 | 54 | 96 |
| 6     |      | 140 | 10 | 2.0 | 72 | 62 | 86 |
| 7     |      | 140 | 40 | 1.0 | 60 | 52 | 86 |
| 8     |      | 140 | 40 | 2.0 | 99 | 45 | 45 |
| 9     | center points | 120 | 25 | 1.5 | 85 | 77 | 91 |
| 10    |      | 120 | 25 | 1.5 | 88 | 77 | 87 |
| 11    |      | 120 | 25 | 1.5 | 82 | 78 | 95 |
| 12    | axial points | 120 | 40 | 1.5 | 94 | 75 | 80 |
| 13    |      | 120 | 10 | 1.5 | 35 | 34 | 99 |
| 14    |      | 140 | 25 | 1.5 | 82 | 69 | 84 |
| 15    |      | 100 | 25 | 1.5 | 55 | 49 | 91 |
| 16    |      | 120 | 25 | 1.0 | 68 | 67 | 99 |
| 17    |      | 120 | 25 | 2.0 | 82 | 75 | 92 |
| 18    | optimized conditions | 119 | 30.6 | 1.5 | 93 ± 0.4c | 80 ± 1.2c | 86 ± 3.6c |

*Table 1* Experiments performed for the response optimization.

aDetermined by HPLC. bRatio between yield and conversion. cAverage values over three identical runs.
more detailed central composite design (CCD) (Fig. 2) was constructed by adding six additional experiments as axial points (Table 1 entries 12–17) to the previous design. The so-obtained data were fitted through a multiple quadratic regression. The new model fitted reasonably with the experimental data and gave an $R^2$ of 0.919. The coefficients obtained from the quadratic regression are represented in Fig. 3. Considering a confidence interval of 0.95, the coefficients associated with the NBS equivalents parameter was found not statistically significant and therefore excluded from the quadratic model. The central value of 1.5 NBS equivalents was kept constant while $T$ and $R_t$ were adjusted in order to maximize the $I$ yield. The results of the prediction based on this model are pictured in the yield contour plot in Fig. 4a.

A similar CCD analysis was performed also considering the selectivity values reported in Table 1 as the response factor (the results of the multiple quadratic regression are reported in detail in the Supporting information). A plot of the predicted selectivity based on $R_t$ and $T$ variation with a constant number of NBS equivalents of 1.5 is represented in Fig. 4b. The comparison of the yield and selectivity plots reveals that the respective maxima are located in different areas. In fact, it appears that the selectivity is maximized either at high residence time and low temperature or vice versa. On the other hand, the yield plot in Fig. 4a shows a well-defined area (marked in dark blue in the plot) that indicates the optimal $R_t$ and $T$ values where the monobromination yield is over 75%. As observed in Fig. 4b, the predicted selectivity for the same $R_t$ and $T$ values is still high and ranges between 85 and 90%. The optimal settings predicted in the contour plot in Fig. 4a were therefore employed to investigate the monobromination of 2. Three runs were performed (Table 1 entry 18) at these conditions obtaining an average yield in 1 of 80%, while compound 2 and dibrominated side-products were detected at 7% and 13% respectively.

With the optimized conditions in hand, the reaction was performed on a 150 mg scale, which is a size comparable to the typical amounts of porphyrin compound usually employed for post-synthetic functionalization reactions in research laboratories. The HPLC analysis of the chloroform solution collected at the outlet of the flow system gave an 82% yield in porphyrin 1 and therefore a productivity of 22 mg/h was obtained by using a 10 mL coil reactor. After chromatographic purification, the desired pure product was isolated in a 73% yield.

In conclusion, we reported a continuous flow methodology for the selective monobromination of meso-tetraphenylporphyrin. A combined approach with an automated flow reactor and a DoE-driven optimization allowed us to enhance the compound 1 productivity with respect to the reported methodologies. This achievement relied in the precise control of the key parameters (such as the temperature and residence time) given by a continuous flow system and in their fine-tuning thanks to the statistical data treatment. With respect to the best existing methodology, this brought to a moderate improvement in the monobromination yield to 80% but other major advancements were achieved. Beside the intrinsic enhanced safety of using an aggressive brominating agent in a controlled environment, we reported a consistent decrease of the reaction time (30 min residence time versus 3.5 h of dropwise
addition) and consumption of NBS (1.5 equivalents versus 3.0 equivalents).

**Experimental**

**Materials and methods** All reagents and solvents were commercially available and used as received. All reaction in continuous flow were carried out on a Vapourtec R-Series Flow Chemistry System, using PFA tubing (ID 1.0 mm) and a heated mixer reactor with a PFA coil of 10 mL volume. Setting of the reaction parameters and sample collection were performed using the Flow Commander software. HPLC analyses were performed on a Shimadzu LC-2010C-HT instrument equipped with a Phenomenex Gemini 3 μ C18 column. DoE analysis of the data was performed using Minitab 17 Statistical Software. NMR spectra were recorded at 301 K on a Bruker Avance-300 MHz. The 1H NMR spectra were referenced to the residual protiated impurity of CDCl3 (7.26 ppm). Electrospray ionization mass spectrometry analysis was carried out on an Agilent Technologies LC/MSD Trap SL AGILENT instrument in positive mode with acetonitrile as mobile phase.

**Synthesis of porphyrin 1 in batch conditions** The reaction was carried out following a reported procedure. [24] 61.7 mg (0.10 mmol) of porphyrin 2 were dissolved in chloroform (60 mL). Pyridine (1 mL) was added and the mixture was heated to reflux. A solution of NBS (53.7 mg, 0.30 mmol) in chloroform (60 mL) was added dropwise over 3.5 h. After additional 30 min of refluxing, the reaction mixture was quenched with acetone (30 mL). The HPLC analysis gave a composition of the reaction mixture as follows: 72% porphyrin 1, 5% porphyrin 2. The missing mass balance was assigned to a mixture of dibrominated porphyrin isomers.

**Procedure for the DoE bromination experiments in continuous flow** The flow reactions were performed using bottled reagent solutions. A stock chloroform solution of porphyrin 2 (0.004 M) was prepared. An NBS solution in chloroform was freshly prepared each day and shielded from light with an aluminum foil. The concentration of the NBS solution depended on the number of NBS equivalents necessary for a given reaction (e.g. 0.006 M solution when 1.5 equivalents were required). For each trial, 5 mL of the porphyrin solution and 5 mL of the NBS solution were withdrawn and mixed in a T-junction and flowed through a 10 mL internal volume coil reactor at the required temperature and flow rate. Reaction sampling was performed when the reagents concentration reached a steady state according to the dispersion model elaborated by the Flow Commander software. The samples were...
collected in vials containing a stirred 0.01 M aqueous solution of Na₂CO₃ and Na₂S₂O₃ to quench unreacted NBS. The reaction mixture composition was determined by HPLC analysis.

**Continuous flow synthesis of porphyrin 1 on a 150 mg scale**  
Following the above described general procedure, a 0.004 M chloroform solution of porphyrin 2 and a 0.006 M chloroform solution of NBS were mixed and flowed through the coil reactor at 118 °C with a residence time of 30.6 min. 130 mL of the resulting reaction mixture were collected at the reactor outcome and quenched in a stirred 0.01 M aqueous solution of Na₂CO₃ and Na₂S₂O₃ (100 mL). The organic layer was separated, washed with water (100 mL), dried over Na₂SO₄ and evaporated to dryness. Porphyrin 1 was purified by flash chromatography on silica using 8:2 hexane/dichloromethane as eluent. A dark violet solid was obtained (128 mg, 73%). NMR data are in accord with those reported in the literature, ¹H NMR (300 MHz, CDCl₃) δ: 8.94–8.80 (m, 5H, Hβ), 8.77 (s, 2Hβ), 8.25–8.17 (m, 6H, Hα), 8.10 (d, J = 6.8 Hz, 2H, Hα), 7.85–7.68 (m, 12 H, Hα), –2.84 (s, 2H, NH). ESI-MS(+) m/z: 693 [M + 1].

**Supplementary Information**  
The online version contains supplementary material available at https://doi.org/10.1007/s41981-020-00131-4.

**Acknowledgments**  
Open access funding provided by Università degli Studi di Padova within the CRUI-CARE Agreement. Financial support is gratefully acknowledged to Italian Ministry of Education, University and Research through the NExuS – Department of Excellence Program.

**Compliance with ethical standards**

**Declarations**  
The authors declare there is no conflict of interest.

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