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Synthesis of non-aggregating chlorins and isobacteriochlorins from *meso*-tetrakis(pentafluorophenyl)porphyrin: a study using 1,3-dipolar cycloadditions under mild conditions

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ABSTRACT

The 1,3-dipolar cycloaddition of *meso*-tetrakis(pentafluorophenyl)porphyrin and its nickel complex, with the bulky azomethine ylide dipole was studied under mild conditions, and yielded chlorin and isobacteriochlorin derivatives self-prevented from aggregation. The reactions were performed at room temperature or 0 °C, and we were able to establish a set of reaction conditions to obtain only the chlorin or the isobacteriochlorin. These compounds were evaluated in solution, and no aggregation was observed at less than 25 mM (~30 mg mL^{-1}) using ^1H NMR experiments.

Introduction

Porphyrinoid compounds (Fig. 1) have attracted increasing attention due to the wide range of applications that these compounds present, and for the synthetic challenges of obtaining compounds with improved photophysical properties.[1–5]

Reductions or similar transformations at the porphyrin core are important to furnish chlorins and bacteriochlorins, that show useful photophysical properties for a number of applications, such as PDT treatments.[2,3,6–9] Cycloaddition reactions are also a powerful tool for obtaining these derivatives, since they allow the formation of new carbon–carbon bonds and inhibit re-oxidation reactions leading back to the porphyrin core. In the case of the Diels–Alder reaction, porphyrins can react as dienes or dienophiles to obtain chlorin derivatives.[10–13] Another interesting approach is the use of 1,3-dipolar cycloadditions reactions. Cavaleiro's laboratory has explored the reactivity of *meso*-tetrakis(pentafluorophenyl)porphyrin (**TPFPP**) to act as a dipolarophile with azomethine ylides.[14] These authors reported the synthesis of chlorin and isobacteriochlorin derivatives under such methodology. However, the bacteriochlorins were only obtained when the preformed chlorin was used as substrate, under the same reaction conditions.[11,15–18] In all cases, the highly reactive dipole is generated by treating an aldehyde and an amino acid, with a decarboxylation step, in toluene or chlorobenzene, at reflux temperatures, and with an excess of more than 100 equiv of the dipole precursors. This is necessary because the dipole is partially decomposed under these conditions.

It has been reported that the same kind of dipoles can be generated starting from different precursors, and using milder reaction conditions, lower temperatures, and less equivalents of dipole precursor.[19,20] The use of a Bronsted acid, commonly TFA, is necessary to promote the conversion of the dipole precursor to the 1,3-dipole. We envisioned the application of such a 1,3-dipolar cycloaddition to a porphyrin system, thus obtaining much milder reaction conditions and better selectivity. We have attempted to control the products formed in the reaction, by tuning the temperature and equivalents of dipole precursor. In addition, we also propose to

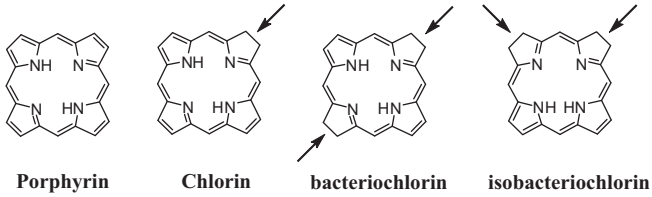

Figure 1. Core structures of a porphyrin and derivatives.

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produce low aggregation compounds by the use of the bulky benzyl azomethine ylide as the 1,3-dipole, which should avoid aggregation in solution.

Results and discussions

The dipole precursor **1** was prepared from benzylamine and (chloromethyl)trimethylsilane, followed by reaction with aqueous formaldehyde in methanol.[17]

Initially, we used porphyrin **3** (**TPFPP**) as the dipolarophile, and depending upon the reaction conditions three different products were obtained. One of these exhibited a visible spectrum which is characteristic for chlorin **5**, and for the other two we detected the typical bands of isobacteriochlorins, corresponding to a mixture of compounds **7** and **9** (Scheme 1). The compounds **5** and **7** were isolated and characterized by ^{1}H NMR and UV–vis analyses (Figs. S12-S13, S57 and S59—Supporting information); compound **9** was isolated as a trace product, and characterized only by UV–vis spectra (Fig. S61—Supporting information). However, a number of non-porphyrinoid impurities remained after exhaustive purification steps, involving column chromatography and preparative thin layer chromatography. As a consequence, only very small amounts of pure chlorin **5** and the other derivatives were obtained. In all these experiments no bacteriochlorin derivatives could be detected.

Thus, we decided to test the use of the Ni(II) complex **4** as substrate,[21] and this approach has afforded much better results. With Ni(II)–TPFPP (**4**), it was possible to obtain the products with no impurities after one column and one preparative TLC (CH_2Cl_2/hexanes, 7:3). Table 1 summarizes all these results for the reactions between **4** and **1**, at 25 °C and 2 h reaction time.

The use of 5–10 equiv of **1** leads to the recovery of starting material **4**, and chlorin **6** in low yields. Under these conditions, the formation of isobacteriochlorin **8** was observed just as traces or not observed at all. For intermediate conditions (15–25 equiv of **1**), a mixture of all three compounds was obtained. Finally, using 30 equiv of dipole precursor **1**, we observed the total consumption of **4**, and the isobacteriochlorin **8** was isolated as the major product in 65.5% yield. When dipole precursor **1** was used in more than 10 equiv, we observed the formation of a second isobacteriochorin **10**, always as traces.

Table 1
Yields in the reaction of **4** and **1**, with TFA, at 25 °C[a–d,22]

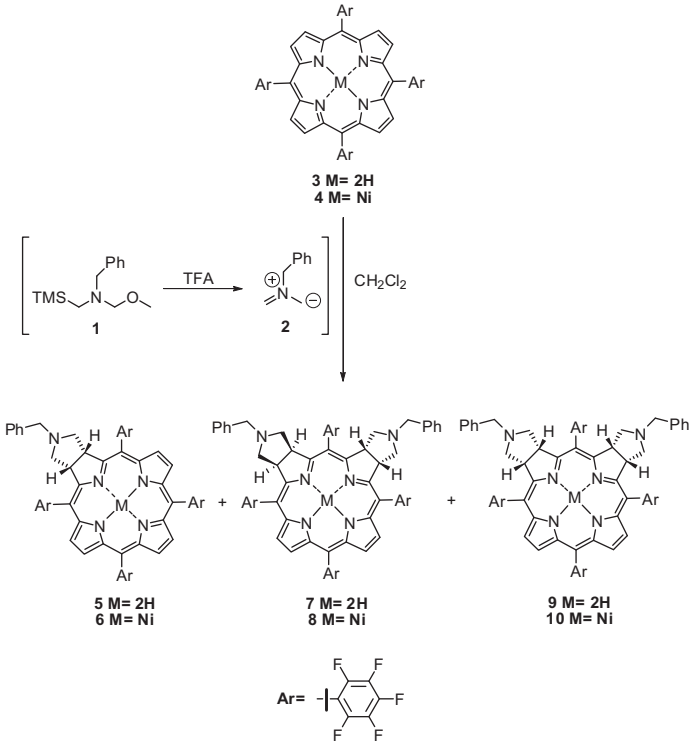
Entry	Equiv of **1**	Recovered **4** (%)	Product **6** (%)	**8** (%)
1	5	80.3	10.0	—
2	10	63.0	22.4	Traces
3	15	53.0	36.6	5.3
4	20	46.0	40.0	6.1
5	25	36.6	45.8	12.4
6	30	—	Traces	65.5

[a] In all experiments 30 mg (29.1 μmol) of porphyrin **4** was used.
[b] Anhydrous CH_2Cl_2 was used as the solvent and the final volume for all the reactions was 7.5 mL.
[c] 2 Equiv of TFA was used in all the reactions.
[d] Reaction time was 2 h in all cases.

We also performed some reaction tests at 0 °C, and in these conditions a very low conversion rate of **4** was observed after 2 h. When 50 equiv of **1** was employed, only the chlorin **6** was obtained in 16.8% yield and most of the starting materials were recovered (76.0%). Using smaller quantities of dipole precursor insignificant amounts of chlorin **6** and recovery of starting compound took place.

All the reactions described in Table 1 were performed starting from 30 mg (29.1 μmol) of **4** at the concentration of 3.9 mM. We also performed some tests starting with 10 mg (9.7 μmol) of **4** and maintaining the same concentration, but we found some difficulties to reproduce the yields because of the small scale.

Compounds **6** and **8** were fully characterized using ^{1}H, ^{13}C, and 2D NMR analyses (see Supporting information), as well as HRMS



Scheme 1. Cycloadducts from **3** or **4** under mild conditions.

(MALDI-TOF). For compound **6**, we observed the presence of two broad triplets at 2.51 and 3.01 ppm, corresponding to the methylene groups of the pyrrolidine ring, as well as a broad signal at 4.86 ppm corresponding to the hydrogens of the ring junction. A sharp singlet for the methylene hydrogens of the benzyl group is also observed at 3.45 ppm, and all the eleven aromatic hydrogens can be found between 7.13 and 8.35 ppm. No signals were observed at the negative region of the spectrum, demonstrating that the metal was not removed during the cycloaddition reaction. In the case of compound **8** four triplets (2.20 ppm, 2.29 ppm, 2.66 ppm, 2.84 ppm) were observed corresponding to the four methylene groups of the two pyrrolidine rings. Also, we observed a singlet at 3.40 ppm corresponding to the methylene groups of the benzyl groups, and a multiplet between 4.24 and 4.39 ppm corresponding to the hydrogens of the ring junctions. All the fourteen aromatic hydrogens were observed between 7.09 and 7.68 ppm.

The relative stereochemistry of isobacteriochlorin **8** was determined by ^{19}F NMR analysis. In the spectrum, there are 4 signals (−135.66 ppm, −135.10 ppm, −138.06 ppm, and −138.22 ppm), corresponding to the *o*-F atoms of the pentafluorophenyl substituents. Only a *trans* relative configuration between the two pyrrolidine rings can allow such a pattern, due to the higher symmetry of **8** (Fig. 2). For the *cis* isomer **10**, 6 signals should be expected since it is less symmetric. This analysis is based upon previous publications from Cavaleiro's laboratory.[11] Planning on future PDT studies, we have successfully removed nickel from compounds **6** and **8** (see Supporting information) by using CH_2Cl_2 and H_2SO_4. Here we have demonstrated that metallation is a very important approach to access the *mono* and bis adducts, and that there is no difficulty to obtain metal free derivatives for potential uses in PDT studies.

Aggregation studies

We have demonstrated in recent publications that porphyrinoids presenting a 'L-shape' structure, are self-prevented from aggregation in solution.[23–25] The presence of bulky moieties in a perpendicular orientation to the porphyrinoid core prevents the occurrence of π-stacking interactions, and thus the occurrence of molecular aggregates. We have demonstrated the lack of aggregation for chlorin **6** and isobacteriochlorin **8** using ^1H NMR analysis (Fig. 2 and Fig. S60 in the Supporting information), as aggregation in solution directly affects the aromatic ring anisotropy, resulting in variations in the chemical shift (0.1–0.5 ppm), and also drastic loss of signal resolution. It is also known that the probability of formation of aggregates increases along with the concentration,

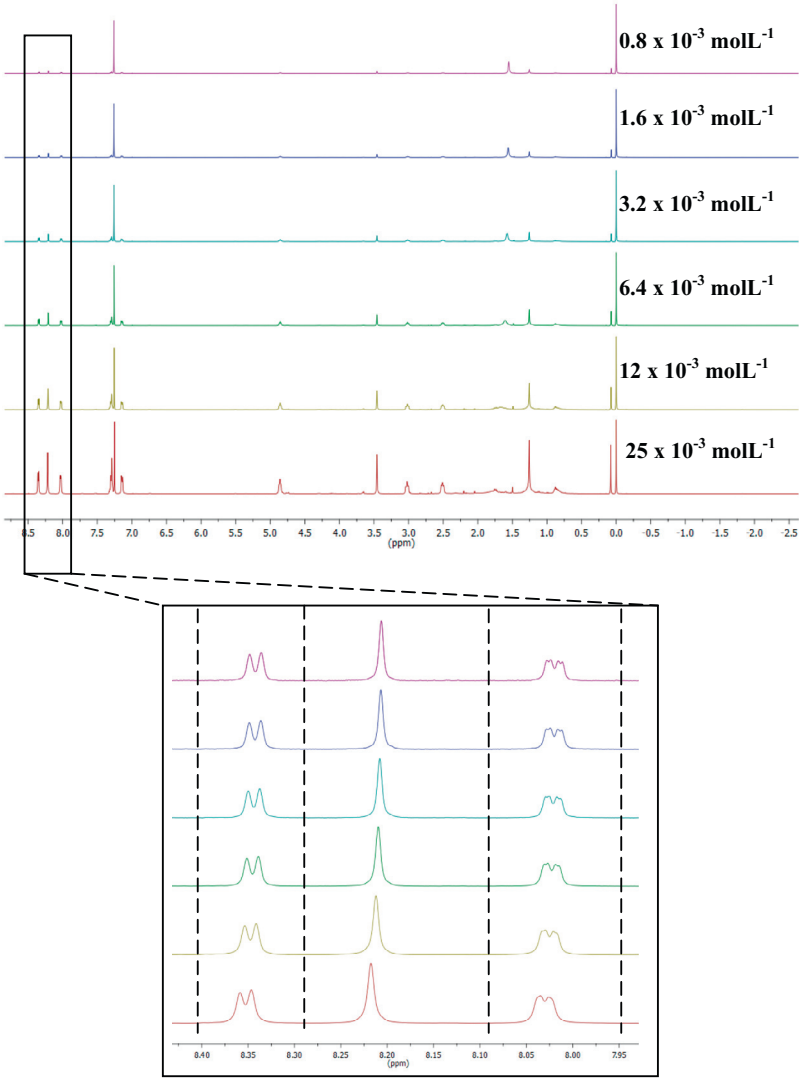


Figure 2. ^1H NMR aggregation study for chlorin **6** in $CDCl_3$.

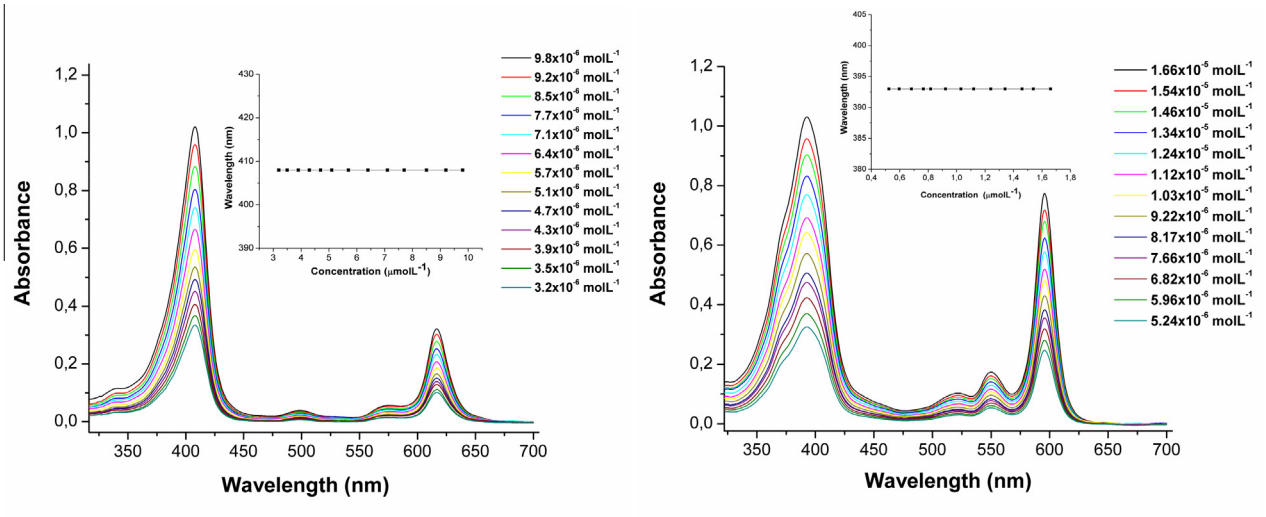


Figure 3. UV–vis aggregation study for chlorin **6** (left) and isobacteriochlorin **8** (right) in $CHCl_3$.

especially above 4 mM.[20] For compounds **6** and **8** even at 25 mM, aggregation was not substantially observed.

Complementary UV–vis studies were also carried out for compounds **6** and **8** (Fig. 3), and the results are in agreement with the NMR data. In UV–vis studies the concentrations are obviously much lower than in the ^{1}H NMR analyses, but confirm that compounds **6** and **8** possess a low-aggregation character in the solution, as can be observed by the linearity of the wavelength versus the concentration (insets at Fig. 3).

Conclusions

We have prepared chlorin and isobacteriochlorin derivatives **5** to **8**, under mild and improved conditions by using the 1,3-dipolar cycloaddition reaction. These products are self-prevented from aggregation in solution, proving the relevance of the studies developed here.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.049.

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22. *Representative procedure for the synthesis of chlorin **6** and isobacteriochlorin **8**:* To a mixture containing 7.5 mL of anhydrous CH_2Cl_2 and 30 mg of porphyrin **4** (29.1 μmol) at 25 °C and under argon atmosphere were added compound **1** (molar equiv depending on the experiment) and trifluoroacetic acid (TFA) (58.2 μmol). After 2 h, the reaction was extracted with a saturated solution of $NaHCO_3$ (20 mL) and dichloromethane (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at 40 °C. Purifications were performed by silica flash column chromatography using CH_2Cl_2/Hexanes (7:3) as eluent and then by preparative TLC using the same eluent.
*Compound **6**:*
^{1}H NMR: ($CDCl_3$, 400.15 MHz) δ (ppm): 2.51 (br t, 2H, *J* = 7.0 Hz), 3.01 (br t, 2H, *J* = 8.4 Hz), 3.45 (s, 2H), 4.89–4.82 (m, 2H), 7.30–7.13 (m, 5H), 8.35–8.02 (m, 6H). ^{13}C NMR: ($CDCl_3$, 100.4 MHz) δ (ppm): 49.5, 59.4, 60.1, 95.5, 106.9, 114.0, 114.2, 114.4, 127.6, 128.0, 128.4, 128.7, 129.0, 133.0, 136.2, 136.7, 137.4, 138.9, 139.3, 140.4, 140.8, 143.3, 143.9, 144.7, 146.3, 147.0, 147.1, 157.0.
^{19}F NMR: ($CDCl_3$, 376.52 MHz) δ (ppm): −161.3 to −161.1 (m, 4F), −160.8 (t, 2F, *J* = 22.1 Hz), −159,9 (t, 2F, *J* = 22.1 Hz), −151.8 (t, 2F, *J* = 22.1 Hz), −151.5 (t, 2F, *J* = 22.1 Hz), −137.4 to −137.1 (m, 6F), −134.8 (d, 2F, *J* = 22.1 Hz). HRMS (MALDI-TOF): calcd for $[M+H]^+$, $C_{53}H_{20}F_{20}N_5Ni^+$, 1164.0747; found: 1164.0729.
*Compound **8**:*
^{1}H NMR: ($CDCl_3$, 400.15 MHz) δ (ppm): 2.13 (br t, 2H, *J* = 7.7 Hz), 2.22 (br t, 2H, *J* = 7.7 Hz), 2.59 (br t, 2H, *J* = 8.1 Hz), 2.77 (br t, 2H, *J* = 8.1 Hz), 3.32 (s, 4H), 4.25–4.17 (m, 4H), 7.04–7.01 (m, 5H), 7.20–7.17 (m, 7H), 7.64 (br s, 2H). ^{13}C NMR: ($CDCl_3$, 100.4 MHz) δ (ppm): 47.0, 50.1, 59.2, 59.7, 60.4, 91.6, 98.3, 112.6, 113.4, 113.6, 113.7, 114.0, 114.2, 121.7, 127.5, 128.4, 128.9, 129.0, 135.7, 136.7, 137.4, 139.2, 140.4, 143.0, 143.5, 143.9, 144.3, 144.7, 146.0, 146.4, 146.9, 147.1, 151.8, 164.0. ^{19}F NMR: ($CDCl_3$, 376.52 MHz) δ (ppm): −161.4 (dt, 2F, *J* = 22.4 Hz, *J* = 7.5 Hz), −161.0 (dt, 2F, *J* = 22.4 Hz, *J* = 7.5 Hz), −160.3 (dt, 2F, *J* = 22.4 Hz, *J* = 7.5 Hz), −159.3 (dt, 2F, *J* = 22.4 Hz, *J* = 7.5 Hz), −152.6 (t, 1F,

J = 22.4 Hz), −152.3 (t, 2F, J = 22.4 Hz), −150.7 (t, 1F, J = 22.4 Hz), −138.2 (dd, 2F, J = 22.4 Hz, J = 7.5 Hz), −138.1 (dd, 2F, J = 22.4 Hz, J = 7.5 Hz), −135.0 (dd, 2F, J = 22.4 Hz, J = 7.5 Hz), −134.7 (dd, 2F, J = 22.4 Hz, J = 7.5 Hz). HRMS (MALDI-TOF): calcd for $[M+H]^+$, $C_{62}H_{31}F_{20}N_6Ni^+$, 1297.1639; found: 1297.1671.

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