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Efficient Microwave-Assisted Synthesis of Amine-Substituted Tetrakis(pentafluorophenyl)porphyrin

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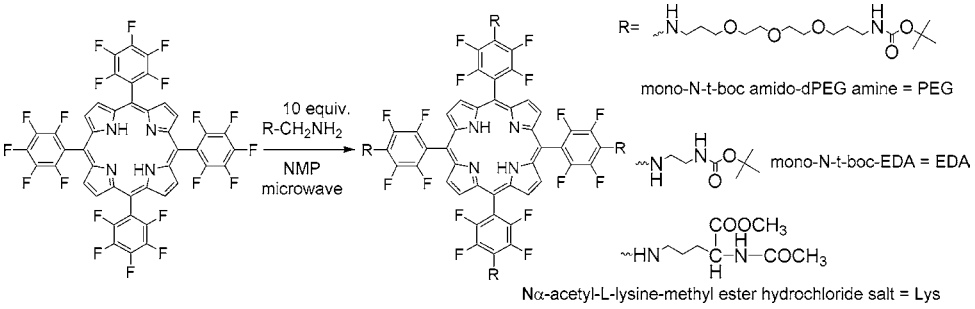
ABSTRACT



We report an efficient and rapid means for the synthesis of tetrakis(pentafluorophenyl)porphyrin ($TPPF_{20}$) derivatives by microwave irradiation in an environmentally acceptable solvent. The selective displacement of the *para*-fluorine groups in $TPPF_{20}$ by primary amines occurs in yields between 70 and 95%. This method demonstrates that $TPPF_{20}$ is an ideal platform for the rapid formation of porphyrin conjugates for therapeutic, catalytic, and other applications.

Applications of porphyrin derivatives range from catalysts,[1] materials, and devices[2] to photodynamic therapeutic agents (PDT)[3] because of their rich photochemistry and redox chemistry. However, most applications require modification of the porphyrin macrocycle to allow attachment of additional substituents with various other functionalities.

Microwave-assisted reactions have become increasingly important in chemical synthesis in the last 20 years due to the advantages they provide over conventional heating methods.[4] Significant reduction in reaction times, side reactions, increased yields, ease of purification, and minimization of the amount of solvent used are only a few of these desirable qualities.[5] Shorter reaction times (usually <15 min) allow rapid investigation into new methodologies and reaction optimization. Microwave-assisted reactions are believed to facilitate polarization of the substrates thereby promoting the reactions.[6]

We previously demonstrated a solvent-free[7] porphyrin synthesis, and solid-supported reactions minimize the amount

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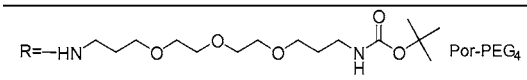
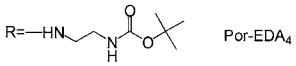
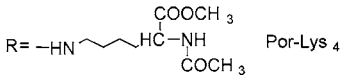
Table 1. Comparison of Conventional vs Microwave Heating in the Synthesis of Protected Porphyrin Derivatives[a]

porphyrin derivative	solvent	conventional heating[b]	yield	microwave irradiation	yield
	NMP	2 days	~50%	12 min	94 ± 1%
	NMP	1 day	~50%	10 min	94 ± 2%
	NMP	20 h	72%	30 min	77 ± 5%

[a] Reaction conditions: 5.1 μmol of $TPPF_{20}$ and 10 equiv of amine in 100 μL of *N*-methylpyrrolidone were irradiated for the times indicated at 2 min intervals. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography. [b] In an oil bath maintained at 60−70 °C.

of subsequent purification.[8] In view of the significant need for rapid synthesis of porphyrin derivatives—especially for therapeutic applications—we present methods for the facile preparation of porphyrin derivatives around a core platform of 5,10,15,20-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin ($TPPF_{20}$). As a demonstration of the method, a variety of amphipathic moieties are grafted onto the core for evaluation as photodynamic therapeutic (PDT) agents.

Previously reported $TPPF_{20}$ derivatives were typically synthesized in refluxing DMF with a large excess of the amine or thiol reagents;[9] however, the yields were relatively poor, and the substitution was sometimes incomplete. Better yields, ~90%, are obtained by using thiol reagents and stirring for ~12 h at room temperature in DMF with a stoichiometric amount of dialkylamine.[3a,c] To decrease the reaction time, improve yields, and employ a greener solvent, we developed a synthesis using microwave irradiation (MW) in *N*-methylpyrrolidone.

A diverse array of primary amines were chosen to demonstrate the method: poly(ethylene glycol)s (PEGs) are relevant to drug design and delivery as they enable the facile uptake of drugs into cells;[10] polylysine derivatives because these moieties are known to impart selectivity toward cancer cells; and polyamines because these impart both cancer cell selectivity and cell permeability. The functional groups other than the intended amine are *t*-boc protected.

Reaction of 5−10 mg (5.1 or 10.2 μmol) of $TPPF_{20}$ with 10 equiv of a primary amine in 1−2 mL of *N*-methylpyrrolidone (NMP) at 60−70 °C overnight leads to mixtures of six different $TPPF_{20}$ derivatives. However, the same amounts of porphyrin and amine in 100 μL of NMP and 10 min MW irradiation yields only the tetra-substituted products. The reaction time was dramatically reduced (see Table 1 and abstract). The nucleophilic aromatic substitution of the *para*-fluoro group by primary amines takes 10−30 min in this procedure compared to 1−2 days with conventional heating.[9c] A significant added advantage for the MW reaction is that it tolerates functional groups that can decompose under extended heating.

The improved yields of the tetra-substituted derivatives are concomitant with the reduced amounts of incompletely reacted products. Also, prolonged heating in DMF results in the fragmenting of the PEG moieties (data not shown). A 95% yield of the Por-PEG_4 product indicates that each reaction on the porphyrin proceeds with ~99% efficiency. In general, the protected acids are used because these are more soluble in NMP and are found to result in greater yields. The deprotection of these groups is readily accomplished using literature procedures. For the EDA and the PEG, the amide esters are cleaved using HCl in MeOH. For the Lys derivative, 6 N HCl is used to cleave both the acetamide and methyl ester groups.

These conditions are specific for *para*-fluoride substitution by primary amines because under similar reaction conditions secondary amines exhibit no reactivity. Refluxing of $TPPF_{20}$ in DMF is known to yield dimethylamino substitution on the para position, thus previous methods require temperatures <60 °C and extended reaction times. When 5 mg of $TPPF_{20}$ in DMF is heated in the microwave for 10 min, several dimethylamino derivatives are observed. Procedures in other solvents, such as toluene, DMSO, and morpholine, generally result in low reactivity or significantly diminished yields compared to NMP.

All porphyrins were characterized by electrospray ionization mass spectrometry (ESI−MS, see Supporting Information). For all porphyrins, the parent [M + H^+] was seen and in some cases the sodium adduct was seen. The electronic absorption spectra of the porphyrins were characterized at 1 μM concentrations and were found to be typical for nonaggregated porphyrins. Substitution of the electron-withdrawing fluorine with the electron-donating amine results in a 7−9 nm red shift in the Soret. Table 2 summarizes the

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Table 2. ESI−MS, UV−Vis, and Emission Data of Protected Porphyrin Derivatives

derivative	mass[a]	UV−vis[b]	emission[b]
$TPPF_{20}$	975	406, 502 (536, sh), 580 (634, sh)	640, 707
Por-PEG_4	2176	418, 509, 545, 586, 643	652, 714
Por-EDA_4	1535	417, 508, 543, 585, 644	647, 713
Por-Lys_4	1703	419, 509, 545 587, 649	652, 711

[a] $[M + H]^+$. [b] Absorption and emission in methanol.

UV−visible spectra of these porphyrins in methanol. All the derivatives show similar spectra, including the B band or Soret band at 417−419 nm and the Q-band at 508−509 nm together with three vibronic bands at 543−545, 585−587, and 643−649 nm. A singlet for the pyrrole H in the ^{1}H NMR indicates the presence of the four para substituents, whereas incomplete substitution results in multiplets for this proton.

The X-ray crystal structure of the Por-EDA_4 derivative was elucidated (Figure 1). This derivative was crystallized

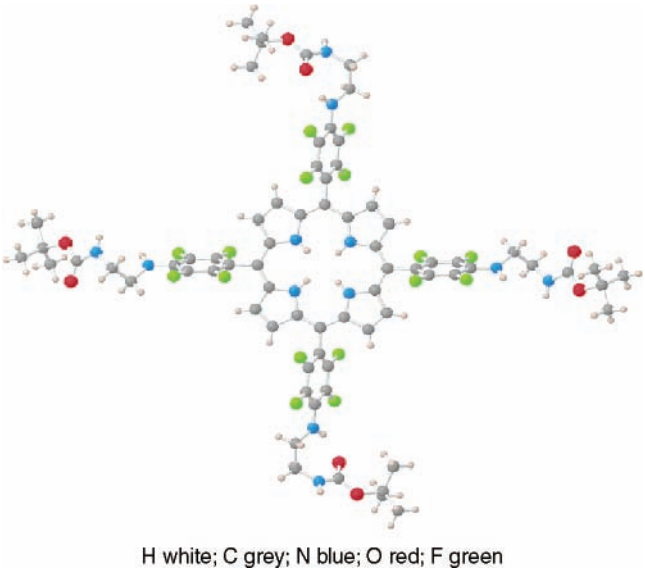

Figure 1. X-ray crystal structure of Por-EDA_4.

from layered hexane over toluene at room temperature over several weeks. There are two different EDA conformations, bent and extended; the bent conformation is organized by an intramolecular H-bond. The most interesting aspect of the structure is that it forms a two-dimensional lattice (Figure 2) organized by intermolecular N−H···O═C hydrogen bonds. The bent EDA moieties form a cyclic structure mediated by intramolecular hydrogen bonds. The extended EDA moieties on opposite sides of the porphyrin H-bond to the bent EDA moieties on adjacent porphyrins. (See packing diagram Figure 2.) There is a surprising lack of porphyrin π-stacking in the crystal structure, and the layers are organized by dispersion and packing forces. The intramolecular and intermolecular hydrogen-bonding motifs were not expected and may explain the aggregation of these compounds at unexpectedly low concentrations.

One of the immediate goals for these porphyrin derivatives is to evaluate their uptake into cancer cells. Thus, the solubility of these protected derivatives in an aqueous cell culture medium (Dulbecco's modified eagle medium without phenol red or phosphate-buffered saline) must be considered. The absorption spectra of Por-EDA_4 in this medium show a red shift and substantial broadening of the Soret band, from 417 to 431 nm (Supporting Information), and similar spectral changes are observed for the other derivatives. These changes in the electronic spectra are indicative of aggregate formation.

The fluorescence emission of these derivatives in methanol and aqueous solvents was also recorded. For Por-EDA_4 in methanol, excitation at 417 nm in the Soret band resulted in a strong fluorescence emission at 647−652 nm with a Stokes shift of 7−12 nm, which is typical of porphyrins. In the cell culture medium, the ground-state spectra are red shifted by 6−10 nm, thus there is a similar red shift in the emission bands (Table 2).

On the basis of the above results for primary amines, we hypothesized that combinatorial libraries of porphyrins can be created by this method as long as the individual reagents react with the $TPPF_{20}$ with similar rates and efficiencies. As a proof-of-principle experiment, a 1:1:1 mixture of the three amine reagents was used in a solution-phase combinatorial reaction. The total amount of the three primary amines was present in the reaction at the same 10:1 ratio with the porphyrin as used above. Statistically, this should yield 21 compounds, but ESI−MS analysis indicated incomplete reactivity as a significant number of compounds with one or more unsubstituted fluorines were observed. Sequential addition of the less reactive amine followed by the more reactive amines also yields inconsistent results.

In summary, protected amine conjugates of tetrakis(pentafluorophenyl)porphyrin with poly(ethylene glycol), ethylenediamine, and lysine groups were synthesized by microwave irradiation. The protocol described allows for significant reduction in reaction times yet results in high yields and limits byproduct formation compared to earlier reports.[11] The procedure uses commercially available reagents at ca. 10-fold greater concentrations in an environmentally friendly solvent. In general, the MW method works for primary nucleophiles significantly better than secondary and better for amines than for sulfides.[11]

In future studies, the prepared protected and deprotected porphyrin conjugates will be assessed for their photodynamic efficiency using MDA-MB-231 cancer cells. The crystal

(11) **General Procedure for the Preparation of Amine Derivatives of $TPPF_{20}$ by Microwave Irradiation**. Into a 3.4 mL vial were added 5 mg of 5,10,15,20-tetrakispentafluorophenylporphyrin (5.1 μmol) and 10 equiv of mono-*N*-^{t}boc EDA (Quanta BioDesign) in NMP (0.1 mL). The closed vial was irradiated using a domestic microwave oven (1100 W, Samsung MW4250W) at 2 min intervals until no starting material was visualized by TLC (10 min). After the vial was cooled, the solvent (NMP) was removed in vacuo. The reaction mixture was purified on a silica gel prep TLC plate (hexane/ethyl acetate/methanol, 2:1.5:0.5). The porphyrin was redissolved in methanol and evaporated under reduced pressure to afford >90% yield.

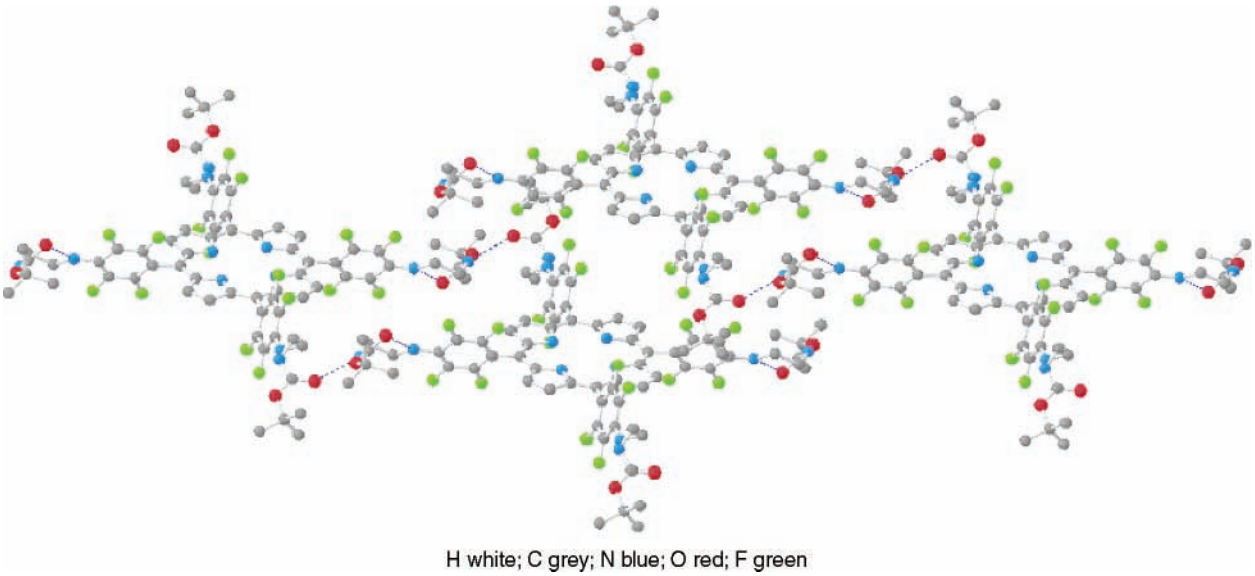

Figure 2. X-ray crystal packing structure of Por-EDA$_4$ illustrating the inter- and intramolecular H-bonding.

structure indicates that these types of porphyrins may self-organize into photonic materials.

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Supporting Information Available: Experimental procedures and full spectral data for new compounds and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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