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Facile Peripheral Modification of N-Confused Porphyrin

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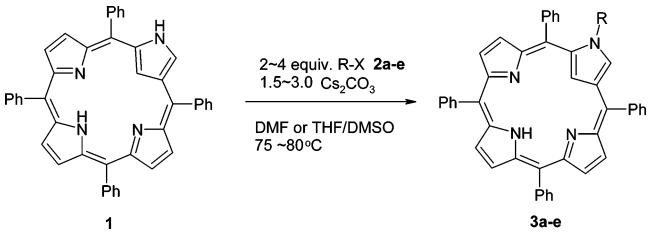
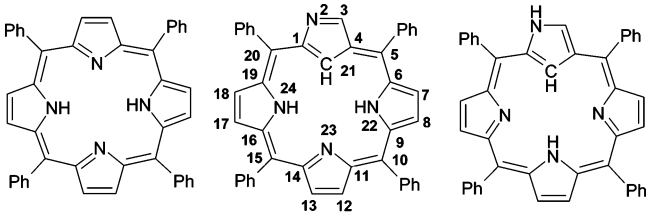


1 **3a-e**

An improved methodology for the N-alkylation of the porphyrin isomer N-confused porphyrin is presented. The combination of polar solvent conditions and the use of the base Cs_2CO_3 affords externally modified products in high yield without separation difficulties and without the use of large excesses of alkylating reagent. The further transformation and metalation of these products provides opportunities for the construction of metalloenzyme model complexes, peptide adducts, and chromophore assemblies.

In the model chemistry of the heme proteins, there has long been a focus on the functionalization of the periphery of synthetic porphyrins. The most classic of such modified rings is the picket fence porphyrin, which possesses a quartet of sterically bulky groups around the outside of the macrocycle.[1] This steric bulk results in the reversible binding of dioxygen in the iron adduct, and this observation has spurred the development of the peripheral organic chemistry of porphine.[2] For example, the cytochrome *c* oxidase work of Karlin and co-workers involves a tetraphenyl porphyrin modified with an appended copper-binding ligand.[3] However, efforts in this area are compounded by the difficulties associated with generating such free base porphyrins[4] or the separations of mixtures of asymmetric macrocycles.[5]



TPP **1i** **1e**

FIGURE 1. Structures of normal 5,10,15,20-tetraphenylporphyrin (**TPP**), the internal tautomer of NCTPP free base (**1i**), and the external tautomer of NCTPP free base (**1e**).

We have lately presented work on the synthesis, photophysics, and metalation of the porphyrin isomer N-confused porphyrin (NCP) (Figure 1).[6] This macrocycle exhibits chemistry that is significantly different from its normal porphyrin parent. One notable characteristic of this species is that the nitrogen atom at the periphery of the ring presents a tempting target for functionalization. The modification of this position has been examined, most simply with methyl iodide, resulting in an external *N*-methylated NCP.[7] Since then, there has been additional work on the modification of metalated NCPs,[8] but the functionalization of free base NCPs remains largely unexplored.[9] Recently, Chmielewski reported the alkylation of NCP with a dibenzyl bromide,[9b] thus opening up the possibility of using NCPs in larger covalent assemblies. We have been working along similar lines trying to functionalize the external nitrogen with various electrophiles.

In this paper, we present an investigation into the functionalization of the external nitrogen of free base NCP using various alkylating agents. Under the optimized conditions, high yields

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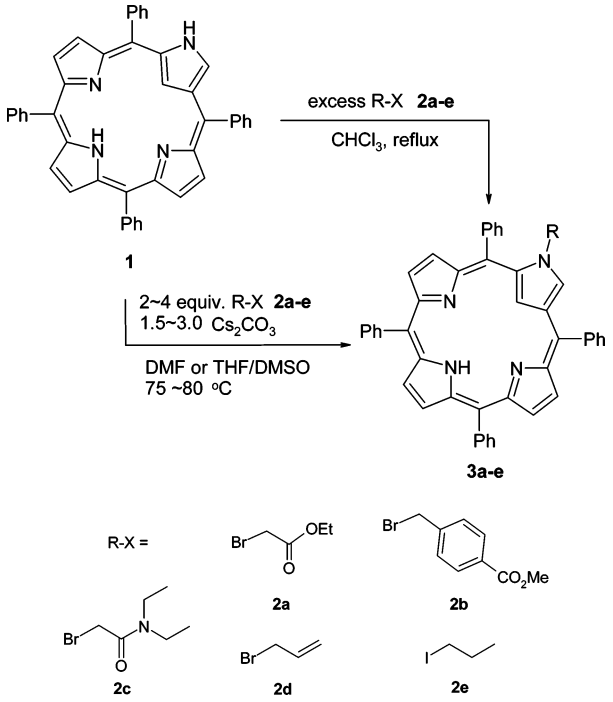
SCHEME 1. Synthesis of Externally N-Alkylated NCTPPs



of adducts have been obtained. In addition, these new macrocycles can be metalated using our established metal carbonyl methods.[6g−k] The resultant compounds can then be used to covalently couple molecules to the periphery of NCP for the generation of novel model complexes and light-harvesting arrays.[3,10]

In an effort to synthesize an externally N-alkylated NCP with the potential for further functionalization, ethyl bromoacetate **2a** was chosen as the alkylating reagent. Following the protocol for N-methylation of NCP,[7] the reaction of free base N-confused tetraphenylporphyrin (NCTPP) **1** with a large excess of **2a** was carried out in $CHCl_3$ under refluxing conditions, resulting in a yield of 46% of NCTPP-ethyl acetate **3a** (Scheme 1). The formation of **3a** from **1** was clearly evident from the analysis of the ^{1}H NMR spectrum of **3a** ($CDCl_3$): the triplet at 1.17 ppm, quartet at 4.04 ppm, and singlet at 4.43 ppm showed that the electrophile had been attached to the 2-nitrogen position.

TABLE 1. N-Alkylations of Free Base NCTPP 1

entry	substrate[a]	ratio of reactants **1**:Cs_2CO_3:**2a**−**e**	reaction time (h)	% yield
1	**2a**	1:0:90	16	46
2	**2a**	1:1.5:2.0	2	45
3	**2a**	1:1.5:2.0	2	52
4	**2a**	1:3.0:4.0	2	96
5	**2b**	1:0:5.0	30	38
6	**2b**	1:1.5:2.0	2	43
7	**2c**	1:3.0:4.0	20	69
8[b]	**2d**	1:0:1160	24	45
9	**2d**	1:3.0:4.0	6	61
10	**2e**	1:3.0:4.0	16	80

[a] In entries 1 and 5, reaction solvent was $CHCl_3$ and no base was used in the reaction; in entry 2, the solvent is DMF; in entries 3, 4, 6, 7, 9, and 10, solvent is THF/DMSO; in entries 1 and 4 the reaction was conducted at the 0.7 mmol scale, whereas in the other reactions the scale was 0.1 mmol. [b] In entry 8, 5 mL of allylbromide was mixed with 0.05 mmol of NCP and no extra solvent was involved.

Similar to other modified analogues,[7,9] the aromaticity of **3a** is weaker than that of its parent **1**, since the aromatic region moves back to 7−8.2 ppm from 7−9 ppm, and the internal CH and NH upshift significantly from −5.0 and −2.42 ppm to 1.66 and 4.16 ppm, respectively (Figure 2). The product was of high purity and formed crystals suitable for X-ray diffraction analysis (vide infra).

Similarly, when a large excess of methyl-4-(bromomethyl)-benzoate **2b** or allylbromide **2d** was reacted with **1**, the corresponding N-alkylated products were also obtained in 38% and 45% yields, respectively (Table 1, entry 5 and 8). However, these conditions have drawbacks: First, a large excess of alkylating reagent is required, and at times separation of the excess reagent can be difficult or tedious. Also, the use of an excess of alkylating reagent often affords additional decomposition products.

In previous work,[8g,9] bases such as Na_2CO_3, K_2CO_3 or *t*-BuOK were used to promote the N-alkylation of NCP or its metal complexes. This results in the need for a smaller excess of alkylating reagent. For example, recently Chmielewski and co-workers showed that only a 3-fold excess with 2 equiv of base could afford a decent yield (55%) of a benzyl-alkylated NCTTP product.[9b] While the above-described procedure has been successful with certain reactions, it was found that these conditions were not universal for all alkylating reagents. For

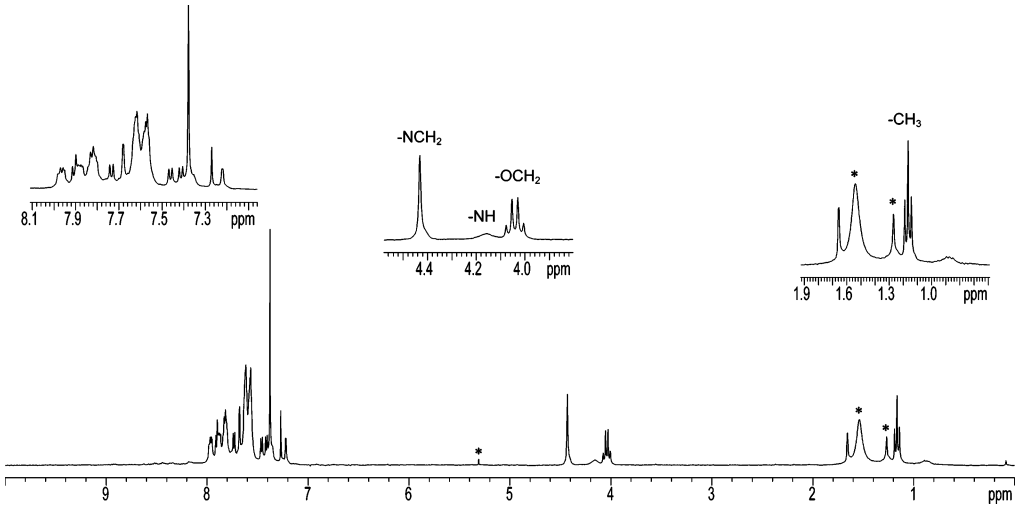


FIGURE 2. ^{1}H NMR of **3a** (300 MHz, $CDCl_3$). Asterisk (∗) marks solvent and solvent impurities.

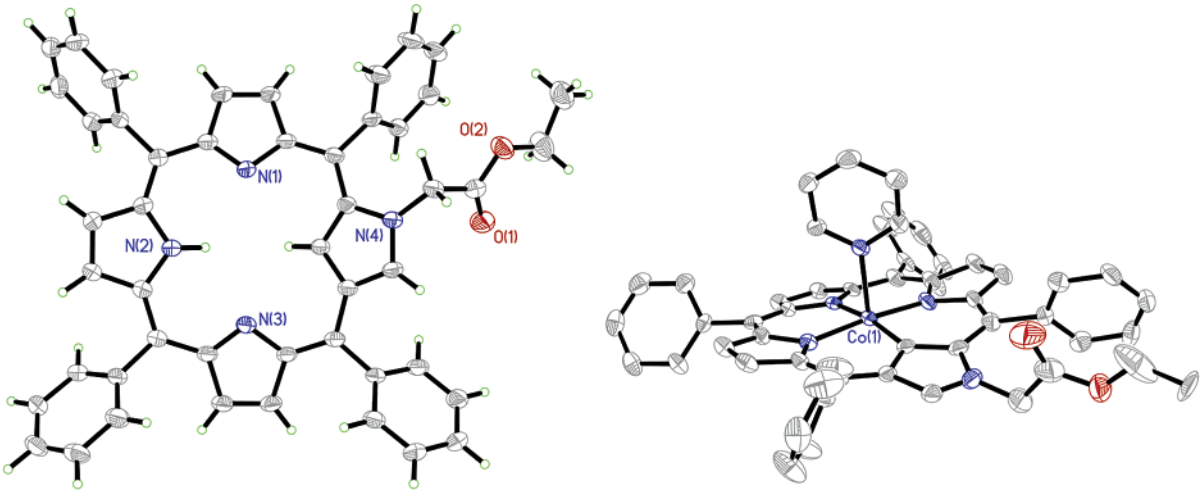
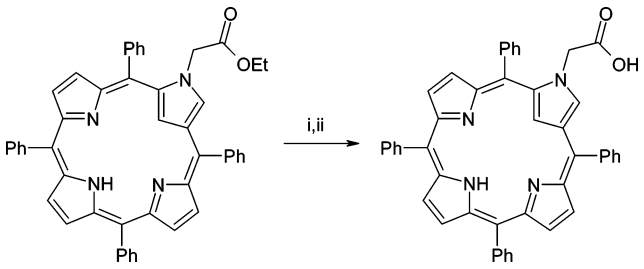


FIGURE 3. X-ray structures with 50% thermal ellipsoids for **3a** (a) and Co-**3a** (b) Hydrogen atoms have been omitted for clarity in the cobalt structure.

SCHEME 2. Hydrolysis of NCP Derivative 3a[a]



[a] Reagents and conditions: (i) LiOH, THF/H_2O, reflux; (ii) acidification.

example, 3 equiv of **2b** were reacted with **1** in the presence of 1.5 equiv of K_2CO_3 as the base in toluene. However, after 18 h of refluxing, little product formation was detected. This led us to investigate and optimize the conditions for the alkylation of the external nitrogen of **1**, such that a variety of alkylating reagents could be appended onto the macrocyle. In addition, we sought to carry out these reactions with the free base, such that we could use the modified macrocyles in later metalation chemistry.

Some insight into the optimal reaction conditions was gained by considering the tautomerization of the macrocycle in its alkylation chemistry. As observed by Furuta and later confirmed in our laboratory, **1** exhibits two tautomers depending on the polarity of the solvent (Figure 1, **1i** and **1e**).[11,6l] With regard to the alkylation of the peripheral nitrogen, the enamine-type tautomer (**1e**) in the polar solvent should be more reactive than the imine-type tautomer (**1i**). As a result, we believe that alkylations in a polar solvent, such as DMF, should favor the more reactive form and possibly afford more product than those carried out in nonpolar media. In addition, polar solvents will solubilize basic salts better than solvents such as toluene, which produces a biphasic reaction with K_2CO_3. We chose Cs_2CO_3 as the base because it exhibits increased solubility and basicity relative to K_2CO_3. When **1** (0.1 mmol) was combined with 2 equiv of ethyl bromoacetate **2a** in the presence of 1.5 equiv of Cs_2CO_3 in DMF at 75−80 °C for 2 h, the reaction solution afforded 45% of the expected product **3a** (Table 1, entry 2). In an effort to avoid the use of high-boiling DMF, THF was examined as a possible solvent. In THF, the reaction is slow and only affords a small amount of product. However, after ~4% DMSO (v/v) was added to the THF solution, the reaction was complete in 1 h and afforded 52% (Table 1, entry 3). Moreover, increasing the ratio of Cs_2CO_3 to 3.0 equiv and ethyl bromoacetate to 4.0 equiv greatly improved the reaction yield of **3a** to 96% (Table 1, entry 4).

Following this result, three additional reagents for N-alkylation of **1** were examined. Promising results were quickly obtained without further optimization (Table 1, entry 6, 7, 9) and indicate that THF/DMSO conditions should be broadly applicable to a variety of alkylating reagents. Entries 1−9 in Table 1 all involve halides activated by adjacent functionality. To test whether NCP would react with halides other than methyl iodide or functionality-activated halides, we chose to examine iodopropane. Entry 10 in the table shows the result with this reagent; although the reaction takes more time than the others in the table, the yield of product is exceptionally high for a porphyrin functionalization reaction (80%). With the successful generation of compound **3a**, we can readily hydrolyze it for further functionalization of the periphery of NCP (Scheme 2). The ester can be cleaved by using LiOH as the base in THF/H_2O, and the acid produced via acidification with HCl.

In addition, peripherally functionalized NCPs can be metalated by using previously established techniques.[6g−k] The reaction of compound **3a** with $Co_2(CO)_8$ produces a cobalt NCP, and recrystallization from pyridine affords X-ray quality crystals of Co(NCTPP−AcOEt)py **Co-3a**. The crystal structure of **3a** prior to metalation (Figure 3a) shows the presence of two protons in the center of the macrocycle, similar to the structure of the exterior tautomer **1e**.[11] The structure of the metalation product (Figure 3b) correlates with an oxidation state assignment of Co(II) based on the interior protonation state of the free base, the coordination number of the metal, and the axial ligand bond

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length.[6h] The successful metalation of **3a** bodes well for the construction of NCP-based metalloporphyrin model complexes.

In conclusion, the method that can functionalize the NCP through N-alkylation has been optimized. By choosing THF/4% DMSO as solvent and Cs_2CO_3 as the base, a variety of modified NCPs can be produced in high yield without using a large excess of reagent or base. The resultant products can be readily isolated via chromatographic methods and can be subsequently used in further organic transformations or metalation reactions. Currently, this method is being expanded for further modification of NCP with amino acids, chromophores, and metal binding ligands.

Experimental Section

General Procedure for the Synthesis of N-Alkylated N-Confused Porphyrin 3a−e. Procedure 1. In a flame-dried 50 mL two-neck round-bottom flask under nitrogen was dissolved 430 mg (0.7 mmol) of NCTPP (**1**) in 10 mL $CHCl_3$, and 2 mL of ethylbromoacetate was added to this solution, which was stirred and refluxed for 16 h. The reaction mixture was cooled to room temperature, and solvent was evaporated under vacuum. The residue was purified by flash chromatography on a basic alumina column (activity III). Starting from benzene and gradually increasing polarity by changing the ratio of benzene/CH_2Cl_2 from 100/0 to 20/80, the elute was collected and checked by TLC (alumina plate). Green colored product fractions were combined together, followed by removal of solvent to afford 228 mg (46.5%) of the NCP-ethyl acetate (**3a**). Crystals of NCP-ethyl acetate suitable for X-ray crystal structure analysis were obtained from a slow diffusion of MeOH into a CH_2Cl_2 solution.

Procedure 2. In a flame-dried 50 mL two-neck round-bottom flask under nitrogen was dissolved 430 mg (0.7 mmol) of NCTPP (**1**) in 20 mL THF and 0.8 mL of DMSO mixture, and 684 mg (2.1 mmol) of Cs_2CO_3 and 0.31 mL (2.8 mmol) of ethylbromoacetate were added. The reaction mixture was stirred and heated to reflux for 2 h. After the TLC was checked and no NCTPP reactant was left, the reaction mixture was allowed to cool to room temperature and the solid was filtered off. Following removal of the solvent, the residue was purified by flash chromatography on a neutral alumina gel column (activity III). Decomposition impurities and a small amount of unreacted NCTPP were eluted with benzene/hexanes solvent (80:20 v/v), and product was eluted with benzene/CH_2Cl_2 (95:5 v/v). After the TLC plate was checked, the pure product fractions were collected and solvent was removed to give 470 mg (96%) of the NCP-ethyl acetate (**3a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98−7.95 (m, 2H), 7.92−7.87 (m, 3H), 7.84−7.80 (m, 3H), 7.73 (d, J = 4.6 Hz, 1H), 7.68 (bs, 2H), 7.62−7.57 (m, 10H), 7.46 (d, J = 4.6 Hz, 1H), 7.41 (d, J = 4.6 Hz, 1H), 7.38 (bs, 3H), 7.2 (b, 1H), 4.43 (s, 2H), 4.16 (b, 1H), 4.04 (q, J = 7.1 Hz, 2H), 1.66 (s, 1H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 164.3, 163.7, 155.1, 154.2, 144.1, 143.7, 141.8, 141.7, 141.3, 140.3, 136.8, 136.2, 135.3, 135.0, 134.5, 133.7, 133.5, 133.4, 133.1, 132.3, 131.8, 131.3, 131.2, 130.8, 129.7, 129.4, 128.5, 128.1, 128.0, 127.5, 127.4, 127.0, 125.0, 116.0, 115.5, 106.0, 61.7, 51.1, 14.2. UV−vis(CH_2Cl_2): λ_{max} (ϵ) 361 (45375), 446 (128000), 661 (11375), 716 (15250). MS (ESI) calcd for $C_{48}H_{37}N_4O_2$ ($[M + H]^+$) 701.8, found 701.2. HRMS (ESI) calcd for $C_{48}H_{37}N_4O_2$ ($[M + H]^+$) 701.2916, found 701.2901.

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Supporting Information Available: Synthetic procedures and characterization for compounds **3a**−**e** and X-ray crystallographic tables for compounds **3a** and its cobalt complex (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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