# Isocyanate as a Versatile Synthon for Modular Synthesis of Functionalized Porphyrins

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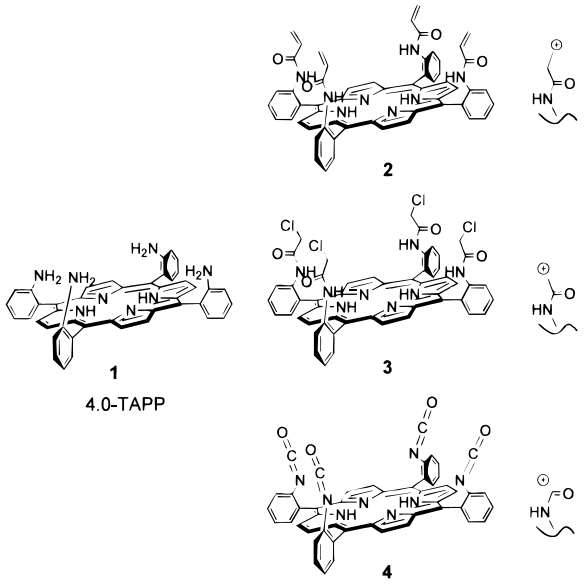
A lot has been learned about the functions and mechanisms of hemeproteins by studying the chemistry of *meso*-tetraarylporphyrin-derived model compounds.[1] The fact that the members of this large protein class manifest a wide range of diverse biochemical functions but share the same prosthetic group, iron protoporphyrin, suggests that the superstructure of each protein is critical in determining its specific biochemical behavior.[2] The key, therefore, to developing a deeper understanding of hemeprotein functions is to study a range of porphyrins with different steric and coordination environments around the heme center. To this end, it is important to have powerful techniques for attaching superstructures to porphyrins. In previous publications, we reported the Michael acceptor and chloroacetamido synthetic methods.[3,4] Functionalization of the readily available 4.0-tetrakis(*o*-aminophenyl)porphine (4.0-TAPP, **1**) with acryloyl or chloroacetyl chloride furnished the tetra-Michael acceptor **2** or tetrachloroacetamidoporphyrin **3** (Chart 1). These transformations reverse the polarity of the amino picket by converting the weak aniline nucleophiles to either of two modest electrophiles. These techniques greatly facilitate the incorporation of superstructures over an aminoporphyrin template since they expand the range of potential derivatizing agents to aliphatic amines and other nucleophiles.[5]

Herein, we present a new general strategy that further extends this work by providing access to a larger range of nucleophilic derivatizing agents, including alcohols and aromatic amines. The critical step transforms the aniline groups of TAPP into highly reactive isocyanato groups forming the intermediate TIPP (**4**) (tetrakis(*o*-isocyanatophenyl)porphine). This resultant porphyrin can, in turn, be derivatized with almost any nucleophile. This new method is also an important extension of the Michael acceptor and chloroacetamido methods, since it gives rise to functionalized porphyrins with one-carbon linkers. In contrast, the Michael acceptor and chloroacetamido methods yield tethers that are three and two carbons long, respectively. The three methods can be used in conjunction to vary the length of a tail or the tightness of a strap or cap (Scheme 1, the structures on the far right are schematic designations of the corresponding synthons).

**Chart 1**




Isocyanate and isothiocyanate precursors have been extensively used in the preparation of peptide analogues and other bioactive compounds.[6] There are a few isolated examples of urea-functionalized porphyrins.[7] However, until now, no general method has been reported for the construction of urea-linked superstructured porphyrins.

Our critical discovery was that, under mild conditions, triphosgene can be used to convert the four amino groups of TAPP to isocyanato groups. This generates the useful new intermediate, TIPP, which can be derivatized with a nearly unlimited range of functional groups, giving us the freedom to prepare sophisticated superstructures that may more accurately mimic natural hemeprotein structures.

Any aminoporphyrin may be used. For example, reaction of α,α,α,α-tetrakis(*o*-aminophenyl)porphine (4.0-TAPP, **1**) (1.0 mmol) with 4/3 equiv of triphosgene and 8 equiv of $Et_3N$ at 0 °C in $CH_2Cl_2$ (200 mL) gives α,α,α,α-tetrakis(*o*-isocyanatophenyl)porphine **4** (4.0-TIPP). The product shows a strong IR band at 2260 $cm^{-1}$, indicating the presence of the cumulative double bond of N═C═O, rather than a carbamoyl chloride.

Compound **4** is highly moisture sensitive. Only moderate yields were obtained by regular column chromatography, probably due to reaction with water and other nucleophilic species present in silica gel. Purification on predried alumina under a nitrogen atmosphere allowed isolation of 87% pure TIPP; however, in situ reaction of a nucleophile with this sensitive intermediate gave a much higher yield of the resulting product, indicating that conversion of TAPP to TIPP is nearly quantitative. Reactions with nucleophiles

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(2) (a) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978/79; Vol. 1−7. (b) Battersby, A. R. *Science* **1994**, *264*, 1551. (c) Collman, J. P. *Inorg. Chem.* **1997**, *36*, 5145.
(3) Collman, J. P.; Zhang, X.; Herrmann, P. C.; Uffelman, E. S.; Boitrel, B.; Straumanis, A.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 2681. Collman, J. P.; Herrmann, P. C.; Fu, L.; Eberspacher, T. A.; Eubanks, M.; Boitrel, B.; Hayoz, P.; Zhang, X.; Brauman, J. I.; Day, V. W. *J. Am. Chem. Soc.* **1997**, *119*, 3481.
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(5) Previously, strong electrophiles such as acid chlorides had exclusively been used for derivatization of TAPP. Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427. Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. Mansuy, D.; Battioni, P.; Renaud, J.-P.; Guerin, P. *J. Chem. Soc., Chem. Commun.* **1985**, 155. Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. Collman, J. P.; Zhang, X.; Lee, V. J. Brauman, J. I. *J. Chem. Soc., Chem. Commun.* **1992**, 1647.
(6) Edwards, P. D.; Foster, D. L. D.; Owen, L. N.; Pringle, M. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2397. Buntain, I. G.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3175.
(7) One previous urea-linked porphyrin system was made via a porphyrin isocyanate; however, the use of phosgene and harsh conditions limited its applications: Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; LaMar, G. N.; Del Gaudio, J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182. The several other known urea-functionalized porphyrins were made by combining aminoporphyrins with the few stable aromatic isocyanates: Jagessar, R. C.; Burns, D. H. *Chem. Commun.* **1997**, 1685.

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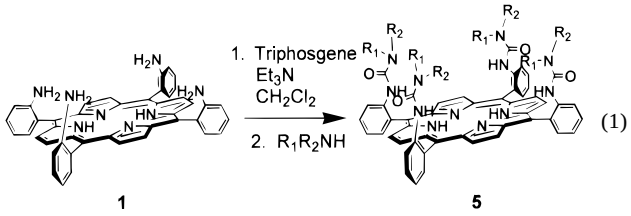
**Table 1. Preparation of Urea-Functionalized Porphyrins[a]**

| entry | $R_1$ | $R_2$ | 5 | yield[b] (%) |
|---|---|---|---|---|
| 1 | $PhCH(CH_3)$ | H | **5a** | 96 |
| 2 | $R_1R_2NH$ = piperidine | | **5b** | 94 |
| 3 | *i*-Pr | *i*-Pr | **5c** | 91 |
| 4 | $ImCH_2CH_2$ | H | **5d** | 92 |
| 5[c] | $HO_2CCH(CH_3)$ | H | **5e** | 89 |
| 6[d] | Ph | H | **5f** | 66 |

[a] Reaction conditions. See ref 8. [b] Isolated yield. [c] The reaction was carried out using alanine sodium salt (4 equiv) and (*n*-Bu)$_4$NBr (0.3 equiv) in THF. [d] 10 equiv aniline was used, and the reaction time was 24 h.

are best carried out in one pot without isolating the isocyanate intermediate (eq 1).[8]

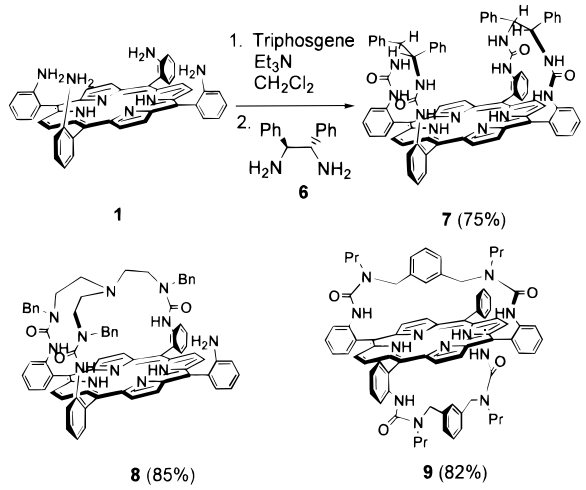


(1)

As shown in Table 1, the reaction of different aliphatic amines with TIPP gave, in uniformly high yields, superstructured porphyrins that demonstrate a variety of interesting properties. Entries 4 and 5 show that amine addition reactions selectively occur in competition with other nucleophilic functional groups such as imidazole or carboxyl. The multifunctional amino compounds histamine and alanine undergo clean amine addition to afford the urea-functionalized porphyrins **5d** and **5e**,[9] which feature cation- and anion-binding pocket superstructures, respectively. Porphyrins **5a** and **5e** demonstrate that the high yields and mild conditions of this reaction are suitable for efficient addition of chiral moieties to a porphyrin (entries 1 and 5). Note that aniline (entry 6) reacts more slowly and gives lower yields than aliphatic amines; however, an overall 66% yield for four successive additions of aniline to TIPP indicates that reaction with each isocyanato picket is still more than 90% efficient.

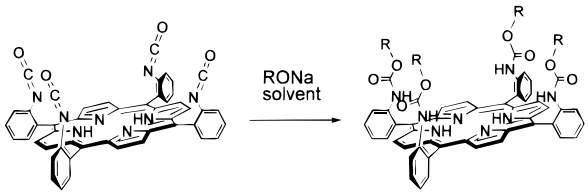
Combining the use of di- or triamines and different atropisomers of TAPP, one can prepare porphyrins with sophisticated superstructures that manifest a wide variety of cavity dimensions and chiral environments. When 2 equiv diamine **6** in $CH_2Cl_2$ is added via syringe pump to a solution

**Scheme 1**




of 4.0-TIPP, **7** is obtained in high yield. Little polymeric or oligomeric byproduct is formed, indicating a high selectivity for intramolecular isocyanato−amino coupling. This property allows the construction of complicated strapped and capped superstructures and is furthur exemplified by the efficient synthesis of the porphyrins shown in Scheme 1.

Other nucleophiles, such as phenolate and alcoholate, also react with isocyanate intermediates to give carbamate-functionalized porphyrins (eq 2). In these cases, the carbamate groups serve not only as structural linkers but also as protective groups that may be removed subsequently.



(2)

In summary, we have developed a general, high-yielding method to prepare isocyanato-functionalized porphyrins from readily available starting materials. The efficient coupling of isocyanate with a wide range of nucleophiles makes this a versatile method for attaching superstructures to porphyrins. Application of these reactions to the synthesis of structural and functional models of hemeprotein active sites will be the subject of continuing research.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **4**, **5a**−**f**, **7**−**9**, and **10a**,**b** (23 pages).

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(8) A typical procedure is examplified with **5b**. To a stirred solution of 4.0-TAPP (67 mg, 0.10 mmol) and $Et_3N$ (89 mg, 0.88 mmol) in $CH_2Cl_2$ (50 mL) was added triphosgene (39 mg, 0.13 mmol) under $N_2$. The reaction mixture was stirred at room temperature for 1 h, after which time piperidine (43 mg, 0.50 mmol) was added and stirring continued for another 1 h. The solvent was removed by rotavap, and the residue was chromatographed on silica gel column (eluent: $MeOH/CH_2Cl_2$ = 1/100) to give **5b** (94%).

(9) Alanine and its sodium salt gave poor yields under standard conditions due to their low solubilities in $CH_2Cl_2$. Optimized conditions use alanine sodium salt in the presence of a catalytic amount of tetrabutylammonium bromide to react with TIPP in THF.