Communications

The Chloroacetamido Group as a New Linker for the Synthesis of Hemoprotein Analogues

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Received January 17, 1997

Previously, we reported a general method[2] for appending a Michael acceptor functionality to the *o*-amino mesophenyl pickets of TAPP (**1**).[3] Before the advent of this Michael acceptor method, derivatization of TAPP was almost exclusively limited to acid chlorides. Now, via Michael acceptor porphyrin **2**, TAPP can be derivatized with a wide range of nucleophiles including primary and secondary monoamines, diamines, triamines, and tetraamines. This advance has greatly increased the utility of readily synthesized TAPP as a synthon for heme protein model compounds.[4]

Herein we describe a new strategy that further increases the utility of **1** by providing an alternative to the aforementioned congruent multiple Michael addition method (Scheme 1). Our new strategy involves addition of chloroacetyl chloride (instead of acryloyl chloride) to TAPP. The result is a porphyrin (**4**) analogous to **2**, but with chloroacetamide pickets in place of Michael acceptor pickets. Many of the amine caps that undergo congruent multiple Michael addition also react with the chloroacetamide porphyrin **4** in a series of congruent S_N2 reactions. It is important to note that a chloroacetamide porphyrin-derived compound has linkers that are one carbon shorter than the linkers of the analogous Michael acceptor porphyrin-derived compound. This allows us to choose one method or the other and control the length of a picket, or the tightness of a cap over the porphyrin ring.[5]

Porphyrins **6**−**8** and **10** and **11** demonstrate the scope of this method by utilizing a tetraamine, a triamine, and a monoamine. Porphyrin **6** is made by reaction of cyclam with **4**. It is identical to the cyclam-capped porphyrin (derived from **2**) except that each link between cyclam and the porphyrin is one carbon shorter. Reaction of **4** with triazacyclononane or triazacyclododecane results in **7** or **8**, which are tighter versions of our triaza-capped porphyrins. The triaza macrocycles are known to bind copper, making this family of porphyrins excellent candidates for bimetallic iron-copper cytochrome c oxidase (CcO) model studies.[6] Use of either the Michael acceptor or the chloroacetamido linker allows variation of the critical distance separating the two metals. Porphyrin **11** is made by reaction of **10**[7] with 3-(aminomethyl)-pyridine. Here we deliver an internal axial ligand via one-point covalent attachment to the single chloro picket that was not used for attachment of the triaza copper ligand moity. NMR of **11** shows the pyridine protons shifted dramatically upfield due to the porphyrin ring current effect. This indicates that the pyridine is fixed directly under the porphyrin plane and is best explained by a coordinate bond between the pyridine nitrogen and zinc.[8] Especially in light of the known low affinity of pyridine for zinc, this is a powerful demonstration of this technique for facilitating binding of an axial ligand to a metal.

Finally, we report the results of a one-pot reaction between TAPP and both acryloyl chloride and chloroacetyl chloride. By this method we have prepared **3**, a porphyrin with three chloro acetamide pickets and one Michael acceptor picket. The difference in reactivity between the two types of pickets allows us to selectively functionalize one type of picket, leaving the other for derivatization in a later step. For example: condensation of **3** with triazacyclononane under conditions that do not allow Michael addition leads exclusively to **5**, a useful intermediate in route to synthesis of tailed compounds similar to **11**.

In conclusion, we developed a new method for synthesis of biomimetic heme models and synthesized an array of compounds that are useful in our myoglobin and cytochrome c oxidase model studies. The power of this new method is greatly enhanced by our ability to use it in conjunction with the previously described congruent multiple Michael addition method: either to probe the effects of varying the length of the links between super-

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(2) 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.

(3) TAPP = 5,10,15,20-tetrakis(*o*-aminophenyl)porphyrin.

(4) (a) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, 261, 1404. (b) Collman, J. P.; Fu, L.; Herrmann, P. C.; Zhang, X. *Science* **1997**, 275, 949.

(5) From myoglobin and cytochrome c oxidase model studies, it is known that the cavity dimension and size of the binding pocket and the distance between two metals of the activity site are very critical.

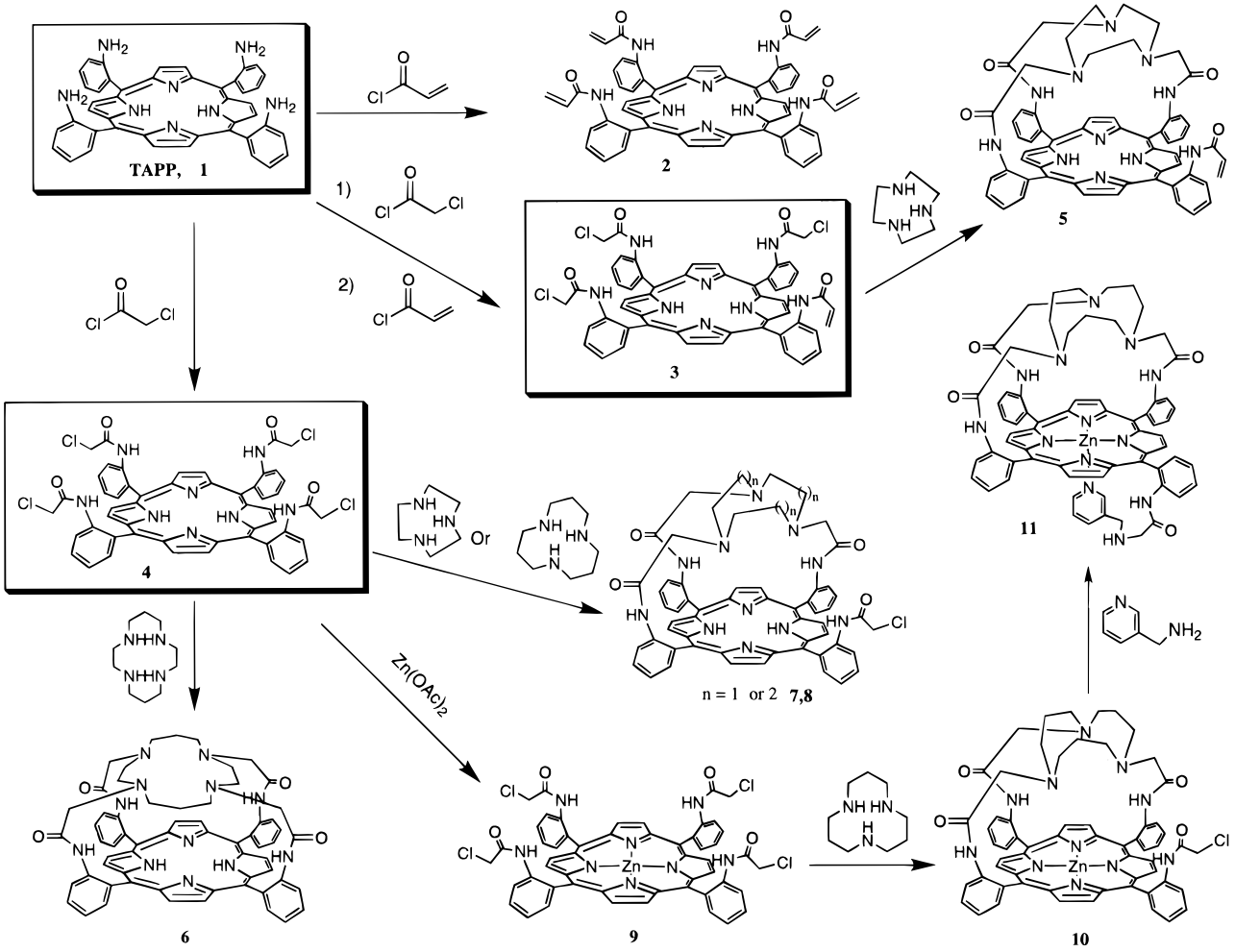
(6) (a) Collman, J. P.; Herrmann, P. C.; Boitrel, B.; Zhang, X.; Eberspacher, T. A.; Fu, L. *J. Am. Chem. Soc.* **1994**, *116*, 9783. (b) Collman, J. P.; Herrmann, P. C.; Fu, L.; Eberspacher, T. A.; Eubanks, M.; Boitrel, B.; Hayoz, P.; Zhang, X.; Brauman, J. I.; Day, V. *J. Am. Chem. Soc.*, in press.

(7) **10** is made from **9** instead of by direct metalation of **8** to avoid the problem of inadvertent metalation of the triaza cap.

(8) ^{1}H NMR of **11** included in Supporting Information.

S0022-3263(97)00097-2 CCC: $14.00

Scheme 1



structure and porphyrin, or to add a nucleophile specifically to certain pickets and not to others by controlling the reaction conditions.

Acknowledgment. We thank the NIH (Grant 5R37 GM-17880-26) and the NSF (Grant CHE9123187-A4) for financial support. We also thank the Mass Spectrometry Facility, University of California, San Francisco, supported by the NIH (Grants RR 04112 and RR 01614).

Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**11** (6 pages).

JO970097G