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Appending a Tris-imidazole Ligand with a Tyr^{244} Mimic on the Distal Face of Bromoacetamidoporphyrin

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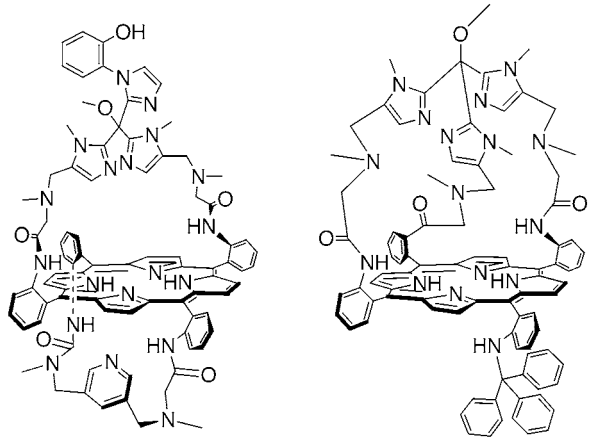
ABSTRACT



Bromoacetamidoporphyrin is a convenient synthon for the attachment of distal superstructures at room temperature in good yields. New models are presented that contain a tris-imidazole distal ligand set bound to the porphyrin in either a binary or trinary fashion. More importantly, one distal imidazole is cross-linked to a phenol mimicking Tyr^{244}, making this model the closest structural analogue yet reported of the metal free cytochrome *c* oxidase (CcO) active site.

Structural characterization of cytochrome *c* oxidase (C*c*O) active sites[1−2a−c] has led to significant progress in the design and synthesis of close structural C*c*O analogues. Several linkers have been attached to amino-porphyrin **1** to perform the tethering of the distal superstructure:[3a−c] Michael acceptor porphyrins (**2**),[3d−e] chloroacetamidoporphyrins (**3**),[3e−g] and isocyanatoporphyrins (**4**).[3h] Some, such as **4**, are moisture-sensitive or have been used with moisture-sensitive compounds such as the acyl chloride superstructures in reaction with **1**. On the other hand, **2** and **3** are very stable in air, but heating is required for them to react, which induces significant rotation, lowering the yields and preventing recovery of the unreacted starting material. A new derivatization of porphyrin anilines is presented to obtain bromoacetamidoporphyrin synthon **5** offering a compromise between reactivity and moisture sensitivity.

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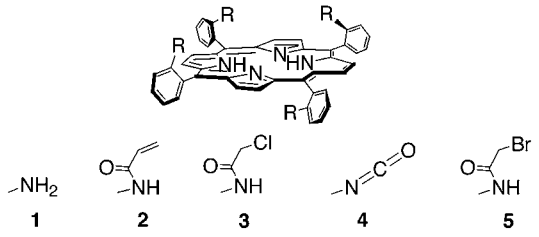
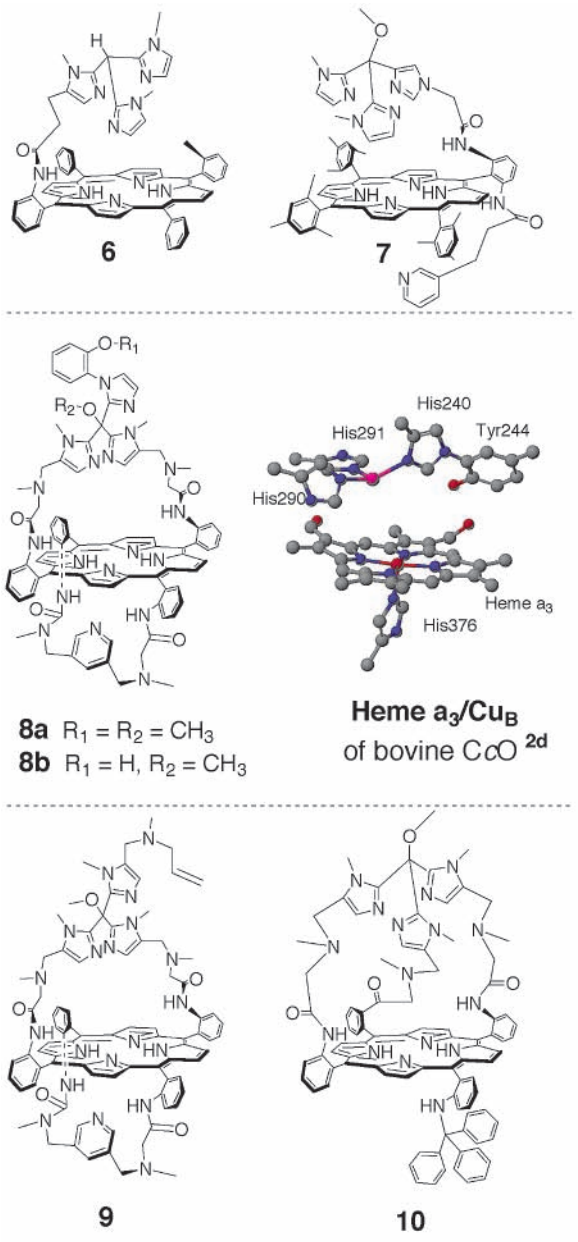


Since the stability of the Cu complex in the tris-imidazole pocket might be an issue,[4] and tris-imidazolyl methane gives stable complexes with copper(I) ions,[5] Naruta et al.[6a] and Collman et al.[6b] synthesized a new family of active-site models with **6** and **7**, in which a tris-imidazolyl moiety is covalently linked to the porphyrin. However, this linkage to the porphyrin was attached at only one position, which allowed the triimidazole ligand to rotate. To obviate this problem, a new family of cytochrome *c* oxidase models has been developed (models **8**−**10**). In models **8** and **9**, the distal tris-imidazole moiety and the proximal base are cross-trans-linked to the $\alpha\beta\alpha\beta$-porphyrin atropisomer in a binary fashion reminiscent of previous porphyrin designs,[7a−d] whereas in model **10**, the former is linked in a trinary fashion to the $\alpha\alpha\alpha\beta$-porphyrin. A phenol moiety that our previous models lacked has been covalently linked to one distal imidazole in model **8b**. It mimics the Tyr^{244} residue, which is thought to play a key role in the $4H^+/4e^-$ reduction of O_2[8a−e] and which has been the subject of studies based on non-heme models.[8f−j] Model **8b** is a more representative model of the C*c*O active site because all key groups are present: porphyrin, proximal base, three distal imidazoles, and one imidazole linked to a phenol residue. In model **9**, an amine remains protected and after deprotection may be used as a synthon for modifying the superstructure.

Several synthetic routes were investigated for the preparation of the pyridine-diamine building block **16** (Scheme 1). Following a previously reported procedure[9a] with some modifications, 3,5-pyridine-dicarboxylic acid was converted into the diacyl chloride **17**, which was further reduced by lithium tri-*tert*-butoxyaluminum hydride to afford the dialdehyde **18** in 28% yield.[9a] To avoid the use of hydride in the preparation of **18**, **17** was converted into the pyridine-bis-3,5(*p*-toluenesulfonylhydrazide) **19** in 82% yield.

This underwent a McFayden−Stevens reaction by treatment with Na_2CO_3 to afford **18** in 25% yield. A simpler approach employed a Riley oxidation of 3,5-dimethyl pyridine yielding **18** in 20% yield. Pyridine dicarbinol **20** was oxidized to **18** in 32% yield by treatment with MnO_2. $LiAlH_4$ reduction of pyridine diester **21a**,**b** led to **20** in poor yields, contrary to previous reports.[9b−e,7c] However, the polymer-supported borohydride reduction of **17**, previously reported by Ley for the reduction of pyridine acyl chloride species,[9d]



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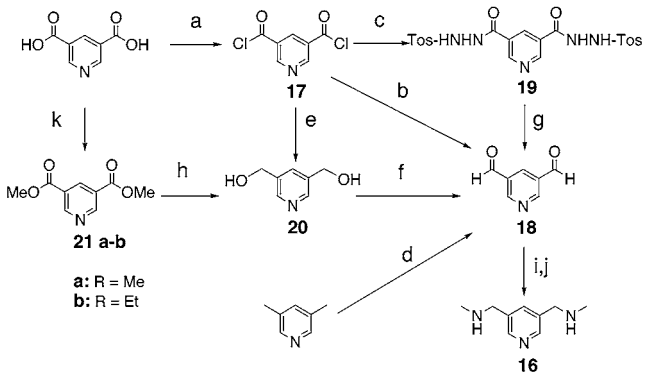
Scheme 1[a]

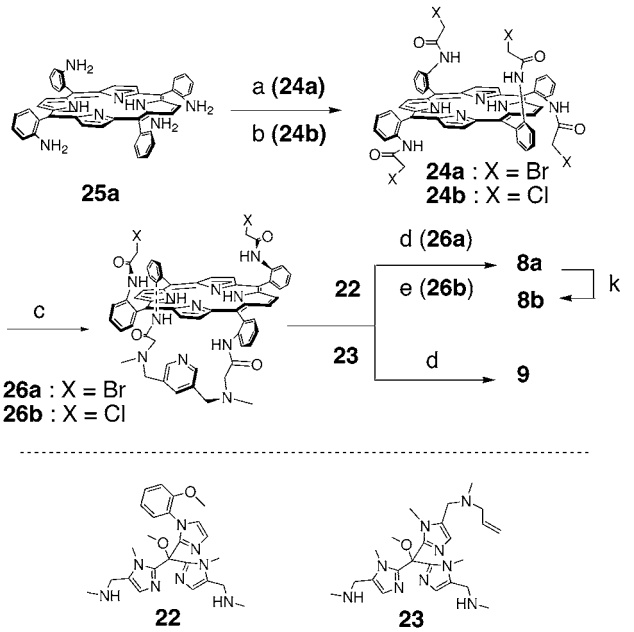


[a] Reagents and conditions: (a) $SOCl_2$, DMF cat., toluene, 110 °C, 95%; (b) $(t\text{-BuO})_3AlH$, THF, −78 → 0 °C, 28%; (c) $TsNHNH_2$, CH_2Cl_2/C_6H_5N, 40 °C, 82%; (d) SeO_2, dioxane−water, 80 °C, 12 h, 20%; (e) polymer$-N^+Me_3BH_4^-$, CH_2Cl_2, 0 °C, 30 min, 43%; (f) MnO_2, CH_2Cl_2, rt, 2 h, 32%; (g) K_2CO_3, glycol, 150 °C, 5 min, 25%; (h) $LiAlH_4$, THF, −78 → 0 °C, 5−10%; (i) CH_3NH_2, CH_3OH, rt, 16 h, 50%; (j) $NaBH_4$, CH_3OH, 10 min, 50%; (k) ROH, H_2SO_4, 80 °C, 3 h, 80%.

yielded **20** in 43% yield. Diimination of **18** by treatment in methylamine followed by reduction with $NaBH_4$ afforded the desired diamine pyridine **16** in 65% yield.

Preparation of $\alpha\beta\alpha\beta$-models **8** and **9** was achieved by S_N2 reaction of bis-secondary amine straps **16**, **22**, and **23** with a tetrahalogenoacetamidoporphyrin **24a**,**b** (Scheme 2). The sequence was chosen to introduce the pyridine tail **16** first, followed by the tris-imidazole ligand **22** or **23** because the purification of imidazole-containing porphyrins is always tedious. The previously reported chloroacetamidoporphyrin TClPP **3** [3e,f] required halogen exchange and heating (45−60 °C) for 18−72 h to be condensed with secondary amines in ca. 40% yield.[3c] But a control reaction showed that $\alpha\beta\alpha\beta$-TClPP **25b** refluxed in acetone (55 °C) for 6 h led to 50% rotation. Therefore, the preparation of bromoacetamido-type porphyrins **24a**,**c**,**e** was carried out since Br is a better leaving group for S_N2 reactions and should allow milder reactions. Tetra(bromoacetamido)-porphyrin **24a** ($\alpha\beta\alpha\beta$-TBrPP) is obtained in 86% yield by addition of bromoacetyl bromide to $\alpha\beta\alpha\beta$-tetraaminophenyl-porphyrin synthon **25a**. A short reaction time and low temperature are required; otherwise, side-products form. Preparation from a pure TAPP-atropisomer was preferred over a mixture of TAPP-atropisomer because separation of TBrPP-atropisomers have closer R_f values than TAPP, making them more difficult to separate. Subsequent reaction of **24a** and diamine **16** proceeded at room temperature, affording **26** in 45% yield, with no observed rotation. The same reaction run with TClPP **24b** led to 14% of **26b** after a reaction time of several weeks at room temperature and 23% yield when the reaction was carried out at 50 °C. The subsequent reaction of **26a** with tris-imidazole dipodal ligands **22**[8c] and **23** proceeded at room temperature and led to **8** and **9** in 40 and 35% yields, respectively. Longer reaction times led to a drop in yield of **8** and **9** together with other unidentified fractions, presumably arising from S_N2 nucleophilic attack of the unprotected

Scheme 2[a]



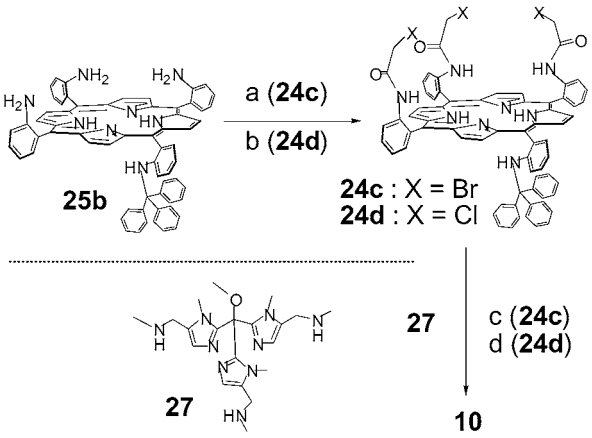
[a] Reagents and conditions: (a) bromoacetyl bromide, THF, $Et_2NC_6H_4$, 0 °C, 2 min, 86%; (b) chloroacetyl chloride, CH_2Cl_2, 15 min, rt, 80%; (c) **16**, THF, $Et_2NC_6H_4$, rt, 36 h (45% (**26a**)) or 4 weeks (14% (**26b**)), or 60 °C (25% (**26b**)); (d) THF, $Et_2NC_6H_4$, rt, 36 h, **22** (40% (**8**)) or **23** (35% (**9**)); (e) NaI, acetone, 50 °C, 16 h, then step d, 8%; (f) BBr_3, CH_2Cl_2, −78 °C, 30 min, then 0 °C, 1 h, 40%.

imidazolic nitrogen on the bromomethylene of unreacted **24a** as pointed out earlier with imidazol acyl chlorides.[3b]

As expected, a gain in reactivity is obtained with TBrPP. Reaction times were slightly shorter than with TClPP, but no heating was required, which allowed recovery of the starting porphyrin; also, the yields of products were slightly increased. TBrPP is not as moisture sensitive as the very reactive isocyanatoporphyrin **4**: this strategy represents a compromise between sufficient reactivity and convenience of handling. Unreacted **24a** did not suffer from rotation or hydrolysis during the reaction and workup, which is normally an issue when dealing with valuable porphyrin synthons such as **26a** in the synthesis of **8a** or **9**. TBrPP **24a** is stable when stored at 4 °C, whereas dibromoacetamidopyridine-strapped porphyrin **26a** was slowly converted into several unidentified porphyrins of higher polarity. Similarly, the preparation of α_3[bromoacetamido]-β-[trityl]-porphyrin α_3BrβTr **24c** (Scheme 3) from α_3[amino]-β-[trityl]-porphyrin **25b**[3f] was achieved in 55% yield. A 40-fold excess of base was required to keep trityl cleavage to a minimum. α_3BrβTr Synthon **24c** was stable at room temperature in solution for hours. Reaction of tripodal ligand tris-imidazole-tris-secondary amine **27**[8f] with **24c** led to $\alpha\alpha\alpha\beta$-model **10** in 28% yield together with several unidentified side products. When starting from **24d**, prior halogen exchange was required and the isolated yield of **10** was only 6.5%.

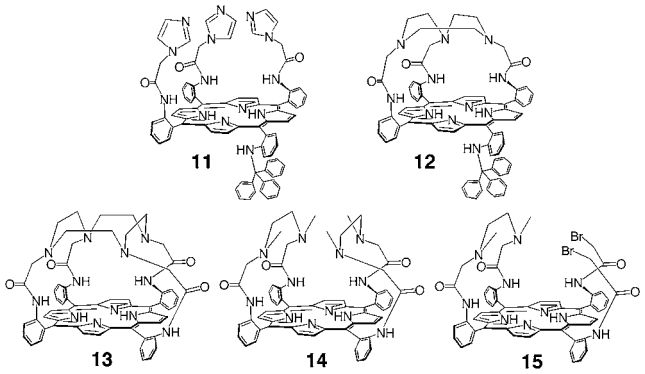
Previously reported condensations were also run with the new bromoacetamido linker. Tris-imidazole-picket-β-trityl-

Scheme 3[a]



[a] Reagents and conditions: (a) bromoacetyl bromide, THF, $Et_2NC_6H_4$, 0 °C, 2 min, 86%; (b) chloroacetyl chloride, CH_2Cl_2, 15 min, rt, 70%; (c) **27**, THF, $Et_2NC_6H_4$, rt, 36 h, 28%; (d) NaI, acetone, 50 °C, 16 h, then step c, 6.5%.

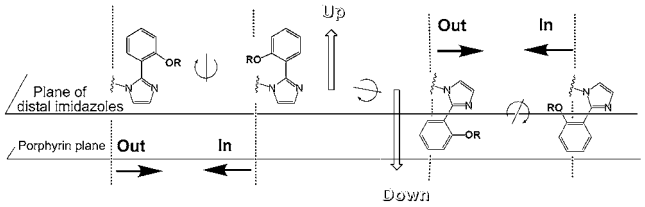
porphyrin **11**[3f] was obtained in 40% yields by reaction of **24c** with cyanoethyl-protected imidazole[3f] followed by treatment with sodium methylate. Capping of α_3- and α_4-porphyrins α_3BrβTr **24c** and $\alpha\alpha\alpha\alpha$-TBrPP **24e** with triazacyclononane and cyclen led to porphyrins **12** and **13** in 43−50% yield.



Also, mono- and bis-strapped α_4-porphyrins **14** and **15**, respectively, were obtained by reaction of **24e** with dimethylethylenediamine. Contrary to **24c** and **26a**, **15** is less stable in solution, as unidentified polar fractions appeared after several hours, presumably from nucleophilic attack of the poorly hindered tertiary amine on the bromomethylene picket. Also, in capped and strapped porphyrins **12**−**15**, there is only one methylene per acetamido picket in contrast to previously capped and strapped porphyrins, where two methylenes per acetamido picket are present.[3d−f] This is an issue when considering Fe/Cu distances in the metalated models.

The tris-imidazole strapped and capped models **8**−**10** are more polar than tris-imidazole picket porphyrins. With respect to chloroacetamido-type porphyrins, the new bromoacetamidoporphyrins display the following physical and spectroscopic characteristics: lower solubility in common organic solvents, smaller R_f values, and halogeno-methylene ^{1}H NMR signals downfield-shifted (by 0.24 ppm) with bromine. **8a** has theoretically several isomers: the phenoxy-imidazole moiety can rotate along the C−N axis giving two possible isomers, one with the moiety *up*, the other with the moiety *down*. The phenoxy moiety can also rotate along the C(imidazole)−C(phenyl) bond: two extreme positions might be considered, inside (*in*) or outside (*out*) together with other intermediate positions. This is another kind of rotational isomer taking place on porphyrin at the superstructure and not at the *meso*-phenyl rings.

Scheme 4



Interconversion was slow enough at room temperature to attempt chromatographic separation, but because of the similar polarity of the atropisomers, only one atropisomer could be purified. As for the other fractions, the same peak at *m*/*z* 1464.5 was found, and broad ^{1}H NMR peaks were obtained. Interconversion was much faster above 30−40 °C, which is reminiscent of the rotation of *meso*-amino pickets previously reported,[3a] which did not allow the use of high-temperature NMR with **8a**,**b**. With the more polar compound **8b**, obtained by BBr_3 treatment of **8a**, isomers were not even detected on TLC.

In conclusion, a new generation of models is reported where capped and strapped tris-imidazole porphyrins offer greater stability and no rotation of distal Cu complexes. One of them is the closest structural analogue yet reported of the metal free C*c*O. The bromoacetamido linker is efficient in attaching a variety of distal tris-imidazole superstructures. It offers a compromise between high reactivity and convenience in handling.

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Supporting Information Available: Experimental procedures and characterization data for new compounds **8**−**10**, **12**, **14**−**16**, **19**, **23**−**24**, and **26a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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