Competitive Reaction of Axial Ligands during Biomimetic Oxygenations

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Nitrogenous bases have commonly been employed as axial ligands for metalloporphyrins in biomimetic model compounds and catalytic oxygenation chemistry. The addition of bases such as pyridines or imidazoles to metalloporphyrin-catalyzed hydrocarbon oxidation reactions is known to affect catalyst selectivity and turnover rate; this effect has been correlated with the electron-donor ability of the ligand. We have found that the role of pyridine in these reactions is far more involved than that of a simple axial ligand: pyridine is a competitive substrate and is converted in high yield to the *N*-oxide. Subsequently, both of these species act as ligands to the metal center. Thus, catalytic systems containing oxidizable pyridines involve complex equilibria with multiple forms of ligated catalyst, and kinetic results should be interpreted with caution. Alternatives to free pyridine were tested, including a pyridine "tail" which is covalently attached to the porphyrin.

Introduction

Metalloporphyrins have long been employed as models of heme proteins,[1−10] and the use of nitrogenous bases as axial ligands in these metalloporphyrin systems has extensive historic precedent. Originally, these ligands were applied in biomimetic chemistry as substitutes for the axial cysteine thiolate (P-450) or histidine imidazole (horseradish peroxidase, hemoglobin, myoglobin, cytochrome *c* oxidase) in the natural metalloproteins. In metalloporphyrin systems which were designed to imitate the oxygenation function of cytochrome P-450, the reported benefits of nitrogenous bases included improvements in the reactivities and selectivities of the catalysts, as well as protection against the formation of μ-oxo dimers ((por)M−O−M(por)).

Marked improvements in selectivities and turnover rates have resulted from the addition of nitrogenous ligands such as pyridines or imidazoles to metalloporphyrin-mediated epoxidations of olefins.[11−13] In particular, manganese-based catalyst systems are much improved by the use of such ligands.[14−21] Nitrogenous ligands are reported to lengthen and weaken the M−O bond in the oxidized form of the catalyst by donating electron density into the M−O antibonding orbital, which can account for the improved reactivity.[22−27] Yields based on oxidant consumed, however, typically have been low, especially for less reactive substrates (vide infra).[24,28−36]

In monofaced model oxygen-binding and selective hydrocarbon oxidation catalysts, bulky axial ligands were required in order to block the open, nonselective face of the metalloporphyrin[11,13,37] and to prevent the formation of μ-oxo dimers. Flat,

(1) Sono, M.; Roach, M. P.; Coulter, E. D.; Dawson, J. H. *Chem. Rev.* **1996**, *96*, 2841−2887.
(2) Ogoshi, H.; Mizutani, T. *Compr. Supramol. Chem.* **1996**, *4*, 337−385.
(3) Momenteau, M. *Perspect. Supramol. Chem.* **1996**, *3*, 155−223.
(4) Chorghade, M. S.; Dezaro, D. A.; Hill, D. R.; Lee, E. C.; Pariza, R.; Andersen, J. V.; Hansen, K. T.; Dolphin, D. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2867−2870.
(5) Gunter, M. J.; Turner, P. *Coord. Chem. Rev.* **1991**, *108*, 115−161.
(6) Dawson, J. H.; Sono, M. *Chem. Rev.* **1987**, *87*, 1255−1276.
(7) Murayama, H.; Inoue, S. *Kagaku (Kyoto)* **1985**, *40*, 480−1.
(8) Baldwin, J. E.; Perlmutter, P. *Top. Curr. Chem.* **1984**, *121*, 181−220.
(9) Groves, J. T.; Nemo, T. E. *NATO Adv. Study Inst. Ser., Ser. C* **1983**, *100*, 329−341.
(10) Dolphin, D.; James, B. R. *ACS Symp. Ser.* **1983**, *211*, 99−115.
(11) Collman, J. P.; Brauman, J. I.; Fitzgerald, J. P.; Hampton, P. D.; Naruta, Y.; Michida, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 47−57.
(12) Gross, Z.; Ini, S. *J. Org. Chem.* **1997**, *62*, 5514−5521.
(13) Naruta, Y.; Maruyama, K. *Tetrahedron Lett.* **1987**, *28*, 4553−4556.
(14) Baciocchi, E.; Boschi, T.; Galli, C.; Lapi, A.; Tagliatesta, P. *Tetrahedron* **1997**, *53*, 4497−4502.
(15) Mohajer, D.; Tangestaninejad, S. *Tetrahedron Lett.* **1994**, *35*, 945−948.
(16) Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 1313−1317.
(17) Halterman, R. L.; Jan, S. T. *J. Org. Chem.* **1991**, *56*, 5253−5254.
(18) Mansuy, D. *Pure Appl. Chem.* **1987**, *59*, 759−770.
(19) Battioni, J. P.; Dupre, D.; Mansuy, D. *J. Organomet. Chem.* **1987**, *328*, 173−184.
(20) Guilmet, E.; Meunier, B. *Tetrahedron Lett.* **1982**, *23*, 2449−2452.
(21) Guilmet, E.; Meunier, B. *Nouv. J. Chim.* **1982**, *6*, 511−513.
(22) Jorgensen, K. A.; Swanstrom, P. *Acta Chem. Scand.* **1989**, *43*, 822−824.
(23) Gold, A.; Jayaraj, K.; Doppelt, P.; Weiss, R.; Chottard, G.; Bill, E.; Ding, X.; Trautwein, A. X. *J. Am. Chem. Soc.* **1988**, *110*, 5756−5761.
(24) Gunter, M. J.; Turner, P. *J. Mol. Catal.* **1991**, *66*, 121−141.
(25) Vandermade, A. W.; Nolte, R. J. M. *J. Mol. Catal.* **1984**, *26*, 333−335.
(26) Vandermade, A. W.; Smeets, J. W. H.; Nolte, R. J. M.; Drenth, W. *J. Chem. Soc., Chem. Commun.* **1983**, 1204−1206.
(27) Razenberg, J.; Nolte, R. J. M.; Drenth, W. *Tetrahedron Lett.* **1984**, *25*, 789−792.
(28) Kellen-Yuen, C. J. Shape-selective and enantioselective epoxidation catalyzed by manganese porphyrins: mimicking the selectivity of the cytochrome P-450 enzymes. Ph.D. Thesis, Stanford University, Stanford, CA, 1994.
(29) Lee, V. J. Enantioselective epoxidation of unfunctionalized olefins catalyzed by threitol-strapped metalloporphyrins. Ph.D. Thesis, Stanford University, Stanford, CA, 1992.
(30) Meunier, B.; Guilmet, E.; Decarvalho, M. E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668−6676.
(31) Collman, J. P.; Kodadek, T.; Raybuck, S. A.; Meunier, B. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 7039−7041.
(32) Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 1850−1859.
(33) Collman, J. P.; Chien, A. S.; Eberspacher, T. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1998**, *120*, 425−426.
(34) Nolte, R. J. M.; Razenberg, A. S. J.; Schuurman, R. *J. Am. Chem. Soc.* **1986**, *108*, 2751−2752.
(35) Razenberg, J.; Nolte, R. J. M.; Drenth, W. *J. Chem. Soc., Chem. Commun.* **1986**, 277−279.
(36) Razenberg, J.; Vandermade, A. W.; Smeets, J. W. H.; Nolte, R. J. M. *J. Mol. Catal.* **1985**, *31*, 271−287.

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sterically unhindered metalloporphyrins are even more susceptible to the formation of μ-oxo dimers[38−44] which are inactive in hydrocarbon oxidation. This dimerization is commonly prevented by increasing the steric bulk of the porphyrin ligand,[45−47] or by the addition of an exogenous ligand, often pyridine, imidazole, or various derivatives thereof, to the reaction mixture.[48−51]

A drawback to the added ligand strategy is the well-documented propensity of these metalloporphyrins to form 6-coordinate bis-ligated species in the presence of excess exogenous ligand.[52−55] Less well-documented is the susceptibility of these nitrogenous bases to oxidative degradation. Pyridines, in particular, have generally been regarded as reasonably robust.[28] Although pyridine is known to be oxidized by potassium monopersulfate ($KHSO_5$),[56−58] pyridines were reported to be stable toward oxidation in the Mn(por)/ClO^- catalytic system.[20,21,59] Low yields in metalloporphyrin-catalyzed hydrocarbon oxidations in the presence of pyridines or imidazoles were often attributed to the formation of the 6-coordinate bis-ligated catalyst complex.[12,41,60]

A later account of Mn(por)/ClO^- mediated epoxidation included an investigation into the fate of various nitrogenous ligands in the epoxidation of alkenes by manganese porphyrins:[32] *N*-hexylimidazole was oxidized to an unanalyzed mixture of products, but 4-*tert*-butylpyridine and 3-phenylpyridine were converted to their *N*-oxides, which were isolated in high yields. This competitive reaction became increasingly significant as less reactive olefins were employed, and as the olefin concentration neared zero. (A recent report presents the use of a Mn(por)/H_2O_2 catalytic system as a mild synthetic method for producing *N*-oxides from N-heterocycles.[61])

In the oxidation of alkanes, which are far less reactive than olefins, the undesirable side reaction of ligand oxidation is nontrivial. We report here our observation that the oxidation of pyridine is a significant competitive reaction pathway in iron porphyrin catalyzed alkane hydroxylations employing iodosylbenzene as the terminal oxidant. This finding has major consequences in the interpretation of kinetic and mechanistic studies carried out in the presence of pyridine.[33−36]

Covalently attached axial ligand "tails" are commonly employed in functional biomimetic modeling.[62−72] This approach has also been used for alkene epoxidation catalysts,[73−76] and in investigations of the effect of nitrogenous ligands on manganese-based epoxidation catalysts.[77] In alkane hydroxylations, the use of a covalently attached axial ligand avoids the problem of exogenous ligand oxidation competing with substrate oxidation. A pyridine-tailed analogue of Fe($TP_{F5}P$)Cl has been synthesized and evaluated as an alkane hydroxylation catalyst.

Experimental Section

Materials. Iron[5,10,15,20-tetra(pentafluorophenyl)porphyrin] chloride (Fe($TP_{F5}P$)Cl) was synthesized and metalated in a method analogous to that found in the literature.[78] Iodosylbenzene (PhIO) was prepared from iodosylbenzene diacetate.[79] Pyridine was dried over KOH, then distilled from BaO, and stored in amber glass. Pyridine *N*-oxide and cyclohexane were purified by standard procedures;[80] after removal of olefin contaminants, cyclohexane was dried, fractionally distilled, and stored over 4 Å molecular sieves under argon. Methylene chloride was dried and distilled from P_4O_{10} under N_2 and then stored over 4 Å molecular sieves under argon. Other materials were purchased in the highest possible purity and used as received, after confirming purity by GC and/or GC−MS.

(37) Collman, J. P.; Zhang, X. M.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404−1411.
(38) Ellis, P. E.; Lyons, J. E. *Coord. Chem. Rev.* **1990**, *105*, 181−193.
(39) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243−6248.
(40) Groves, J. T. *J. Chem. Educ.* **1985**, *62*, 928−931.
(41) Iamamoto, Y.; Assis, M. D.; Ciuffi, K. J.; Sacco, H. C.; Iwamoto, L.; Melo, A. J. B.; Nascimento, O. R.; Prado, C. M. *J. Mol. Catal. A* **1996**, *109*, 189−200.
(42) The two following references concern the synthesis of μ-oxo dimers.
(43) Fleischer, E. B.; Srivastava, T. S. *J. Am. Chem. Soc.* **1969**, *92*, 2403−2405.
(44) Kobayashi, H.; Higuchi, T.; Kaizu, Y.; Osada, H.; Aoki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3137−3141.
(45) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884−2886.
(46) Traylor, P. S.; Dolphin, D.; Traylor, T. G. *J. Chem. Soc., Chem. Commun.* **1984**, 279−280.
(47) Bag, N.; Chern, S. S.; Peng, S. M.; Chang, C. K. *Tetrahedron Lett.* **1995**, *36*, 6409−6412.
(48) Zhang, X. Synthetic analogues of cytochrome P-450 and dioxygen-binding hemoproteins. Ph.D. Thesis, Stanford University, Stanford, CA, 1992.
(49) The newer polyhalogenated porphyrin ligands which contain halogens on the β-pyrrolic positions as well as on the *meso*-aryl groups are not susceptible to dimerization because the porphyrin macrocycle is ruffled or saddle-shaped, rather than planar.
(50) Dolphin, D.; Traylor, T. G.; Xie, L. Y. *Acc. Chem. Res.* **1997**, *30*, 251−259.
(51) Senge, M. O.; Medforth, C. J.; Forsyth, T. P.; Lee, D. A.; Olmstead, M. M.; Jentzen, W.; Pandey, R. K.; Shelnutt, J. A.; Smith, K. M. *Inorg. Chem.* **1997**, *36*, 1149−1163.
(52) Walker, F. A.; Lo, M. W.; Ree, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 5552−5560.
(53) Satterlee, J. D.; Lamar, G. N.; Frye, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 7275−7282.
(54) Satterlee, J. D.; Lamar, G. N.; Bold, T. J. *J. Am. Chem. Soc.* **1977**, *99*, 1088−1093.
(55) Coyle, C. L.; Rafson, P. A.; Abbott, E. H. *Inorg. Chem.* **1973**, *12*, 2007−2010.
(56) Robert, A.; Meunier, B. *New J. Chem.* **1988**, *12*, 885−896.
(57) Kennedy, R. J.; Stock, A. M. *J. Org. Chem.* **1960**, *25*, 1901−1906.
(58) Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532−537.
(59) Collman, J. P.; Brauman, J. I.; Hampton, P. D.; Tanaka, H.; Bohle, D. S.; Hembre, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 7980−7984.
(60) Nappa, M. J.; Tolman, C. A. *Inorg. Chem.* **1985**, *24*, 4711−4719.
(61) Thellend, A.; Battioni, P.; Sanderson, W.; Mansuy, D. *Synthesis* **1997**, 1387−1388.
(62) Collman, J. P.; Schwenninger, R.; Rapta, M.; Broring, M.; Fu, L. *Chem. Commun.* **1999**, 137−138.
(63) D'Souza, F.; Hsieh, Y. Y.; Deviprasad, G. R. *Inorg. Chem.* **1996**, *35*, 5747−5749.
(64) Morgan, B.; Dolphin, D.; Jones, R. H.; Jones, T.; Einstein, F. W. B. *J. Org. Chem.* **1987**, *52*, 4628−4631.
(65) Saxton, R. J.; Wilson, L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 359−361.
(66) Momenteau, M.; Lavalette, D.; Mispelter, J.; Lhoste, J. M. *Inorg. Chim. Acta* **1983**, *79*, 100−101.
(67) Collman, J. P.; Groh, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 1391−1403.
(68) Traylor, T. G.; Mincey, T. C.; Berzinis, A. P. *J. Am. Chem. Soc.* **1981**, *103*, 7084−7089.
(69) Traylor, T. G. *Acc. Chem. Res.* **1981**, *14*, 102−109.
(70) Scheidt, W. R.; Reed, C. A. *Chem. Rev.* **1981**, *81*, 543−555.
(71) Mashiko, T.; Reed, C. A.; Haller, K. J.; Kastner, M. E.; Scheidt, W. R. *J. Am. Chem. Soc.* **1981**, *103*, 5758−5767.
(72) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; Lamar, G. N.; Delgaudio, J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182−4192.
(73) Banfi, S.; Montanari, F.; Quici, S. *Gazz. Chim. Ital.* **1990**, *120*, 435−441.
(74) Montanari, F.; Banfi, S.; Quici, S. *Pure Appl. Chem.* **1989**, *61*, 1631−1636.
(75) Montanari, F.; Penso, M.; Quici, S.; Vigano, P. *J. Org. Chem.* **1985**, *50*, 4888−4893.
(76) Bortolini, O.; Momenteau, M.; Meunier, B. *Tetrahedron Lett.* **1984**, *25*, 5773−5776.
(77) Meunier, B.; Decarvalho, M. E.; Bortolini, O.; Momenteau, M. *Inorg. Chem.* **1988**, *27*, 161−164.
(78) Collman, J. P.; Tyvoll, D. A.; Chng, L. L.; Fish, H. T. *J. Org. Chem.* **1995**, *60*, 1926−1931.
(79) Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1963**, *43*, 60−61.
(80) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, England, 1980.

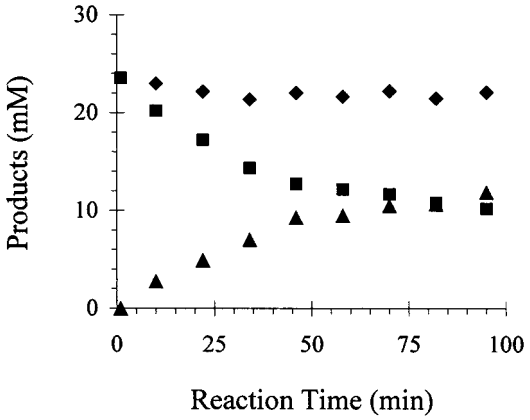


Figure 1. Plot of pyridine oxidation to pyridine *N*-oxide: ◆, pyridine + pyridine *N*-oxide; ■, pyridine; ▲, pyridine *N*-oxide. Reaction conditions: 0.5 mM Fe($TP_{F5}P$)Cl, 25 mM pyridine, 50 μmol of PhIO (would be 50 mM, if completely dissolved), 5 mM PhCl (internal GC standard), 1 mL total volume in CH_2Cl_2, 0 °C, Ar.

Product Analysis. Reaction products were detected and quantified using a Hewlett-Packard 5890A gas chromatograph fitted with a (5% phenyl)-methyl siloxane capillary column (DB-5, J&W Scientific, 0.32 mm ID x 30 m) and flame-ionization detector. All peaks were identified by co-injection with the known compounds. Oxidation products were quantified by comparison with an internal standard (chlorobenzene): calibration plots for detector response were prepared for iodobenzene, cyclohexanol, cyclohexanone, pyridine, pyridine *N*-oxide, and pentafluoropyridine versus the internal standard, using known stock solutions which approximated experimental concentrations.

Samples were sent to the University of California, San Francisco Mass Spectrometry Facility, for MS analyses.

General Oxidation Procedure. A stock solution containing the catalyst and GC internal standard (PhCl) in CH_2Cl_2 was prepared under inert atmosphere conditions, such that 100 μL of the stock solution contained 0.5 μmol of catalyst and 5 μmol of PhCl. PhIO (50 μmol, 11.05 mg) and a stir bar were placed in a 10 mL round-bottomed flask, which was sealed with a SubaSeal septum. The flask was placed in an ice bath, and the atmosphere in the flask was replaced with Ar. Subsequently, the appropriate amounts of substrate(s) and solvent, totaling 900 μL, were syringed into the flask.

To initiate the reaction, 100 μL of the catalyst stock solution was injected. At appropriate intervals, 5 μL aliquots were removed, diluted with 15 μL of CH_2Cl_2, and filtered through a microfiber glass plug. Samples were analyzed immediately by GC.

Stability of Exogenous Ligands. Various concentrations of ligand (pyridine *N*-oxide or pentafluoropyridine) were added to the reaction flask containing oxidant and solvent. Controls were carried out both in the presence and in the absence of 0.5 M cyclohexane. The catalyst was added and reactions were monitored as above.

3-(3′-Pyridyl)propionyl Chloride Hydrochloride. 3-(3′-Pyridyl)-propionic acid (0.1 mmol) was dissolved in 2 mL of freshly distilled $SOCl_2$ and stirred at room temperature for 4 h; the excess $SOCl_2$ was then removed and the residue was dried in vacuo. The residue was dissolved in dry DMF and used for the acylation reaction without further purification.[63,81,82]

***meso*-5-(2′-Amino-4′-*tert*-butyl-6′-nitrophenyl)-10,15,20-tris(pentafluorophenyl)porphyrin (1)**. To a solution of 0.5 mmol of *meso*-5-(4′-*tert*-butyl-2′,6′-dinitrophenyl)-10,15,20-tris(pentafluorophenyl)-porphyrin[83] in 1000 mL of N_2-sparged CH_2Cl_2 was added 20 mmol of concentrated HCl in one portion at 0 °C under N_2 in the dark, immediately followed by 3 mmol of $SnCl_2 \cdot 2H_2O$. The reaction mixture was stirred at 0 °C and monitored by TLC. After several hours, when the starting material was no longer observed by TLC, the reaction was neutralized by bubbling with NH_3(g). The mixture was washed successively with saturated aqueous $NaHCO_3$, water, and brine and then dried with Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel with 1:1 CH_2Cl_2:hexanes (v/v) as the eluent, to give the corresponding amino porphyrin.

Yield: 60%. UV−vis (λ_{max}, CH_2Cl_2): 414, 510 nm. ^{1}H NMR ($CDCl_3$): δ 8.93 (d, J = 4.4 Hz, 2H), 8.86 (s, 4H), 8.78(d, J = 4.4 Hz, 2H), 7.88 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 3.56 (s, 2H), 1.59 (s, 9H), −2.83 (s, 2H) ppm. LSIMS: calcd for $C_{48}H_{24}F_{15}N_6O_2$ (M^+ + H) 1001.2, found 1001.1.

***meso*-5-(4′-*tert*-Butyl-2′-nitro-6′-(3″-(3‴-pyridyl)propionamidophenyl))-10,15,20-tris(pentafluorophenyl)porphyrin (H_2(PyT-TP_{F5}P)) (2).** To a solution of 0.05 mmol of **1** in 5 mL of dry DMF was added 1 mmol of dry *N*,*N*-diethylaniline, followed by the dropwise addition of a solution of 3-(3′-pyridyl)propionyl chloride hydrochloride in dry DMF under N_2. The resulting mixture was stirred at room temperature for 3 h, after which time the reaction was quenched by the addition of methanol. The solvent was removed in vacuo, and the residue was redissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water, and brine, and then dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative TLC on a silica gel plate with 1:1 CH_2Cl_2:hexanes (v/v) as the eluent.

Yield: 68%. UV−vis (λ_{max}, CH_2Cl_2): 412, 510 nm. ^{1}H NMR ($CDCl_3$): δ 9.03 (d, J = 1.7 Hz, 1H), 8.88 (s, 4H), 8.78 (d, J = 4.7 Hz, 2H), 8.74 (d, J = 4.7 Hz, 2H), 8.22 (d, J = 1.8 Hz, 1H), 7.80 (d, J = 4.3 Hz, 1H), 7.54 (s, 1H), 6.52 (d, J = 7.6 Hz, 1H), 6.51 (s, 1H), 6.44 (dd, J = 7.6, 4.4 Hz, 1H), 2.14 (t, J = 7.7 Hz, 2H), 1.66 (s, 9H),

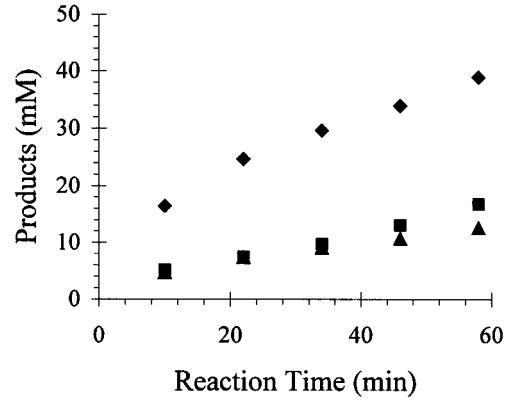


Figure 2. Competitive oxidation of cyclohexane and pyridine: ◆, iodobenzene (PhI); ■, pyridine *N*-oxide; ▲, cyclohexanol. PhI is a reaction byproduct which is used as a measure of PhIO consumption. Reaction conditions: 0.5 mM Fe(TP_{F5}P)Cl, 500 mM cyclohexane, 25 mM pyridine, 50 μmol of PhIO (would be 50 mM, if completely dissolved), 5 mM PhCl (internal GC standard), 1 mL total volume in CH_2Cl_2, 0 °C, Ar.

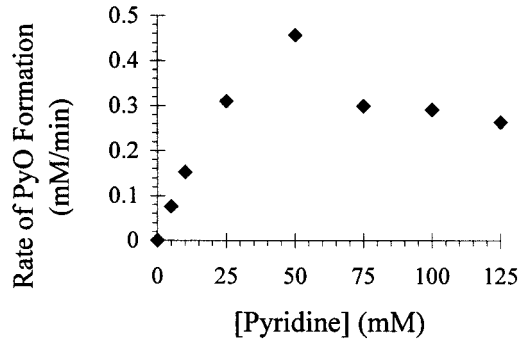


Figure 3. Rate dependence of pyridine oxidation on pyridine concentration. Reaction conditions: 0.5 mM Fe(TP_{F5}P)Cl, 5−150 mM pyridine, 50 μmol of PhIO (would be 50 mM, if completely dissolved), 5 mM PhCl (internal GC standard), 1 mL total volume in CH_2Cl_2, 0 °C, Ar.

(81) Collman, J. P.; Broring, M.; Fu, L.; Rapta, M.; Schwenninger, R.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 8082−8083.
(82) Bracher, F.; Papke, T. *Monatsh. Chem.* **1996**, *127*, 91−95.
(83) Rose, E.; Soleilhavoup, M.; ChristTommasino, L.; Moreau, G.; Collman, J. P.; Quelquejeu, M.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 2042−2044.

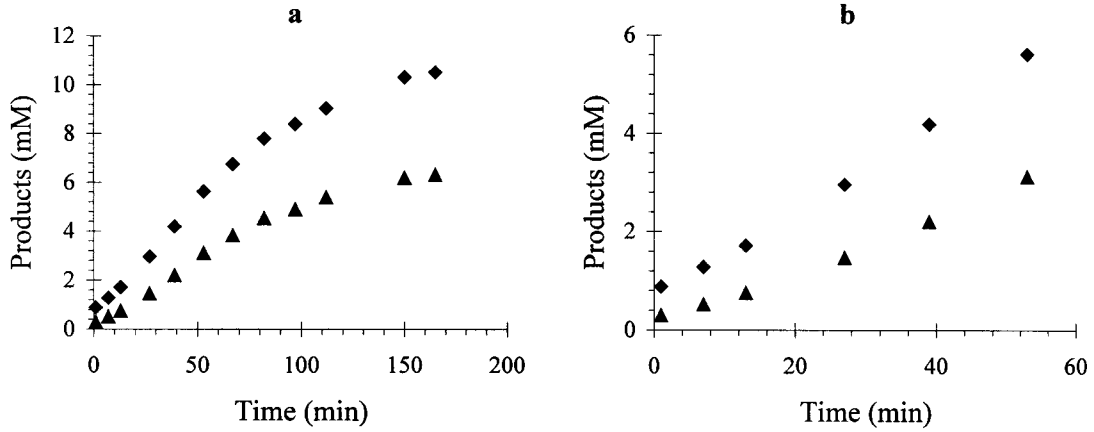
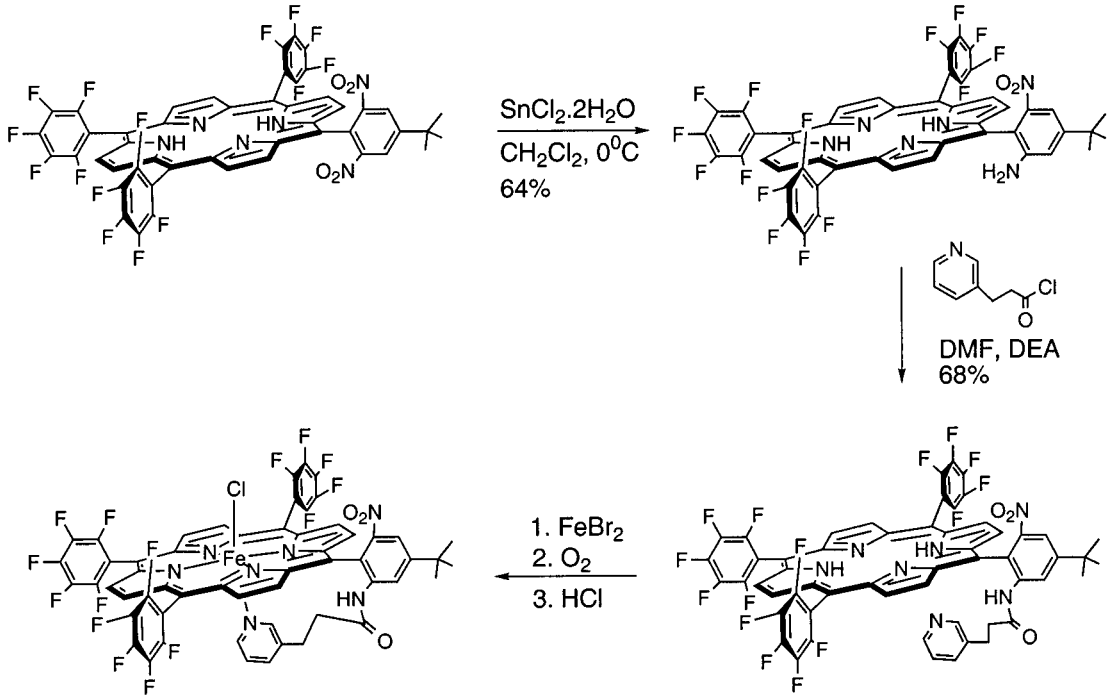


Figure 4. (a) Cyclohexane oxidation by Fe(PyT-$TP_{F5}P$)Cl and (b) enlargement of the plot in Figure 4a, showing initial stages of the reaction: ◆, iodobenzene (PhI); ▲, cyclohexanol. Reaction conditions: 0.1 mM Fe(PyT-$TP_{F5}P$)Cl, 500 mM cyclohexane, 50 μmol of PhIO (would be 50 mM, if completely dissolved), 5 mM PhCl (internal GC standard), 1 mL total volume in CH_2Cl_2, 0 °C, Ar.

Scheme 1. Synthesis of Pyridine-Tailed Catalyst, Fe(PyT-$TP_{F5}P$)Cl



1.46 (t, J = 7.7 Hz, 2H), −2.90 (s, 2H) ppm. LSIMS: calcd for $C_{56}H_{31}F_{15}N_7O_3$ (M^+ + H) 1134.2, found 1134.1.

Iron [*meso*-5-(4′-*tert*-Butyl-2′-nitro-6′-(3″-(3‴-pyridyl)propionamidophenyl))-10,15,20-tris(pentafluorophenyl)porphyrinato] Chloride (Fe(PyT-$TP_{F5}P$)Cl). The free-base porphyrin **2** was metalated by a procedure analogous to that reported for $H_2TP_{F5}P$.[78] Yield: 82%. UV−vis (λ_{max}, CH_2Cl_2): 412 (Soret), 345 nm. LSIMS: calcd for $C_{56}H_{28}F_{15}N_7O_3Fe$ (M^+ − Cl) 1187.1, found 1186.9.

Oxidation Products of Iron [*meso*-5-(4′-*tert*-Butyl-2′-nitro-6′-(3″-(3‴-pyridyl)propionamidophenyl))-10,15,20-tris(pentafluorophenyl)-porphyrinato] Chloride, as Observed by LSIMS. Singly oxidized: calcd for $C_{56}H_{28}F_{15}N_7O_4FeCl$ (MO^+) 1238.1, found 1237.8. Doubly oxidized: calcd for $C_{56}H_{28}F_{15}N_7O_5FeCl$ (MO_2^+) 1254.1, found 1253.9. Triply oxidized: calcd for $C_{56}H_{28}F_{15}N_7O_6FeCl$ (MO_3^+) 1270.1, found 1270.7. Quadruply oxidized: calcd for $C_{56}H_{28}F_{15}N_7O_7FeCl$ (MO_4^+) 1286.1, found 1285.9. No attempt was made to identify the structures of the higher oxidation products recovered from the reaction mixture.

Results and Discussion

Oxidation of Pyridine. The iron chloride derivative of tetra(pentafluorophenyl)porphyrin (Fe($TP_{F5}P$)Cl) with iodosylbenzene (PhIO) as the oxygen donor is capable of oxidizing certain pyridines to their *N*-oxides. Typical data for the oxidation of pyridine is shown in Figure 1. As pyridine is consumed, pyridine *N*-oxide is formed at the same rate. The reaction is virtually quantitative. The total concentration of pyridine plus pyridine *N*-oxide remains constant throughout the reaction, demonstrating that pyridine is converted cleanly to the *N*-oxide, and that the product is stable under the reaction conditions. In contrast, the electron-deficient 2,3,4,5,6-pentafluoropyridine is not oxidized.[84]

The μ-oxo dimer of the catalyst, $[(TP_{F5}P)Fe]_2O$, is a stable compound which has been synthesized and isolated.[38−41] Under the oxidizing conditions of catalytic hydrocarbon oxidations, the presence of an axial ligand was intended to prevent the formation of these dimers. The use of nitrogenous ligands to

(84) The concentration of pentafluoropyridine remains constant when mixed in solution with the catalyst and iodosylbenzene, under reaction conditions analogous to both those used for the oxidation of pyridine and those used for the competitive oxidation of pyridine and hydrocarbon substrate.

block dimer formation in saturated hydrocarbon oxidation, however, is problematic at best.

The competitive oxidation of the axial ligand does not affect alkene epoxidations as strongly as alkane hydroxylations, since epoxidation is a much more facile reaction. Epoxidation is still favored over N-oxidation, at equimolar concentrations of olefin and pyridine.[32] Hydroxylations, on the other hand, are dominated by the oxidation of the axial ligand. Figure 2 plots the course of a reaction in which cyclohexane and pyridine are both present and act as competitive substrates. N-Oxidation is clearly significant, even at a 20:1 ratio of alkane to pyridine.

A study of pyridine oxidation rates in the absence of hydrocarbon substrate reveals a nonlinear dependence on pyridine concentration (Figure 3). The reaction rate increases rapidly from 5 to 50 mM pyridine and then falls off at higher pyridine concentrations. This result is consistent with the formation of a mono-ligated species at low pyridine concentrations, and the bis-ligated species at higher concentrations.[32] The mono-pyridine adduct is a more potent oxidation catalyst than Fe($TP_{F5}P$)Cl alone, which in turn, is a more effective catalyst than the bis-ligated form.

Competitive reversible binding of the substrate, the added ligand, and the ligand oxidation products greatly complicates the mechanistic model by requiring the addition of numerous equilibrium terms for the various ligation states of the catalyst. (These equilibrium terms are further complicated by the dynamic nature of the concentrations of these species.) Thus, the use of an unreactive axial ligand would greatly simplify these reactions.

To this end, pyridine *N*-oxide (PyO) and 2,3,4,5,6-pentafluoropyridine (F_5Py) have proven to be stable under our reaction conditions. In accordance with a previous report,[32] an equimolar amount of PyO results in enhanced reaction rates. Formation of the bis-ligated catalyst seems to occur for the *N*-oxides as well as for the pyridines: cyclohexane oxidation rates are lower in the presence of excess PyO than with no added axial ligand. This effect suggests that the formation of the $(PyO)_2$Fe($TP_{F5}P$) complex is more detrimental to the reaction rate than the formation of μ-oxo dimers under our conditions. In fact, when the catalyst concentration is lowered 10-fold to 0.05 mM and run without additional axial ligand, no evidence of μ-oxo dimer formation is detected during the initial stages of the reaction: yields of alcohol and ketone (<1%) are quantitative, and UV−vis analysis shows no sign of dimer formation.

A study of cyclohexane oxidation rates in the presence of varying concentrations of exogenous F_5Py[42] yields a plot of rate vs F_5Py concentration which is similar in shape to but different in scale from that of Figure 3: as with Py, the rate of cyclohexane oxidation initially increases with increasing concentrations of F_5Py. The maximum rate, which is nearly double that of the F_5Py-free reaction, occurs at 1 M F_5Py; at higher F_5Py concentrations, the reaction rate declines. The high F_5Py concentrations which are required to observe the oxidation rate dependence on [F_5Py] are consistent with the reduced donor ability of F_5Py in comparison to that of Py.[85]

Pyridine-Tailed Catalyst. In order to reap the benefits of a donor ligand without the drawback of the competitive oxidation of excess ligand, we have synthesized a "pyridine-tailed" (PyT) version of Fe($TP_{F5}P$)Cl, in which a pyridine is covalently linked to the porphyrin by means of an amide bond to a *meso*-aryl substituent (Fe(PyT-$TP_{F5}P$)Cl) (Scheme 1). It has been demonstrated previously that the structure of this particular "tail" does allow the pyridine to coordinate to the metal.[81,86]

The yield, based on oxidant consumed, of cyclohexanol with Fe($TP_{F5}P$)Cl and 25 mM pyridine was 31%; this value increased to 51% when the parallel reaction was run using Fe(PyT-$TP_{F5}P$)Cl as the catalyst, without added exogenous ligand. However, the rate of cyclohexanol production in the Fe(PyT-$TP_{F5}P$)Cl case was only half the rate with Fe($TP_{F5}P$)Cl as the catalyst. Also, the oxidation rate with Fe(PyT-$TP_{F5}P$)Cl began slowing at only 20% of oxidant consumption, suggesting the existence of significant pathway(s) for catalyst decomposition or inactivation (vide infra).

There is reason to believe that for the balance of a typical alkane hydroxylation reaction, the active catalyst is in fact coordinated by the *N*-oxide form of the intramolecular ligand, which is produced from the original covalently linked pyridine during the initial turnovers of the reaction. Figure 4 shows the oxidation of cyclohexane using iodosylbenzene as the terminal oxidant. The plots of cyclohexanol and PhI production are sigmoidal, with a distinct rate change in the first few minutes. In agreement with the previous study,[32] which found that the *N*-oxide ligands gave slightly faster turnovers than their non-oxidized counterparts, the second rate in Figure 4 is greater than the initial rate.

"Preoxidation" of the covalently linked pyridine by first stirring Fe(PyT-$TP_{F5}P$)Cl with PhIO in CH_2Cl_2 before the addition of substrate eliminated the initial slow rate. Recovery and analysis of catalyst recovered from the mixture revealed the presence of a compound with a mass which is consistent with a single oxygen addition. Unfortunately, significant further oxidations and catalyst degradation were also indicated.

These findings are in accord with the suggestion[22−24] that pyridine *N*-oxide, with its formally negatively charged oxygen, should make a better electron donor than pyridine,[42,87] thus further lengthening and activating the M−O bond. In situ oxidation to the pyridine *N*-oxide tail is a simple, convenient method by which to generate a more active catalyst. This situation is reminiscent of the autoxidation of a chiral epoxidation catalyst which resulted in improved enantiomeric selectivities.[88]

Conclusion

Nitrogenous bases are known to be useful ligands in metalloporphyrin chemistry. However, many of these compounds are also highly susceptible to oxidation and should be chosen carefully: the oxidation of the axial ligand can become a major consumer of terminal oxidant, which is problematic especially when oxidizing less reactive substrates, employing a valuable oxygen source, developing oxidation systems for practical use, or studying the kinetics of a reaction. When exogenous ligands are required, polyhalogenated pyridines are more oxidation-resistant, although the protective halogens also reduce the donor ability of the ligand. The amount of exogenous ligand employed should be carefully optimized due to the concentration dependence of the interactions between the catalyst and ligands.

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(85) It should be noted that at 1 M, pentafluoropyridine comprises about 10% of the total reaction volume. Thus, a solvent effect may be an alternate explanation for the change in reaction rates.

(86) Collman, J. P.; Rapta, M.; Broring, M.; Raptova, L.; Schwenninger, R.; Boitrel, B.; Fu, L.; M, L. H. *J. Am. Chem. Soc.* **1999**, *121*, 1387−1388.

(87) Gilmartin, C.; Smith, J. R. L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 243−251.

(88) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460−461.