Metalloporphyrin-Catalyzed Oxidation of Saturated Hydrocarbons with Sodium Chlorite

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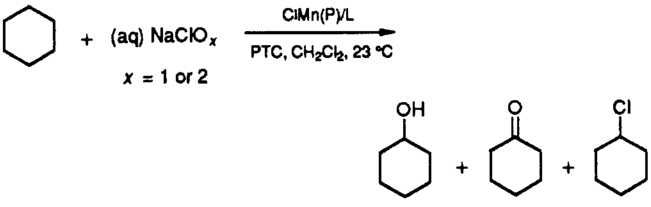
The oxygenation of unactivated hydrocarbons by cytochrome P-450 has stimulated interest in metalloporphyrin oxidation catalysis,[2] especially in "shunt" reagents as surrogate oxidants for the more elusive monooxygenase activation of dioxygen.[3] Despite success in "shunt"-based P-450 mimetic alkene epoxidation[2] and suicide deactivation,[4] catalysis of alkane hydroxylation is less well developed. We report herein the discovery of a new and efficient hydrocarbon oxidation catalyst when chlorite ($MClO_2$, M = Na) is employed as the oxidant rather than hypochlorite (MOCl, M = Li, Na) in the extensively studied[5] manganese porphyrin catalyst system.

The chlorite-based catalyst is remarkable. A metal-centered catalyst site results in parallel $2e^-$ and $4e^-$ oxygenation of alkanes to alcohols and ketones, in sharp contrast to the $2e^-$-oxidation capacity of metal–oxo sites usually associated with synthetic mimics of P-450,[6] and in particular those formed using hypochlorite.[5] Manganese porphyrin, ClMn(P),[7] catalyzed chlorite oxidation of cyclohexane demonstrates this unique reactivity (eq 1).[13] The chlorite-derived oxidant is both more robust—it produces 2 orders of magnitude more catalyst turnovers—and more reactive than the hypochlorite-based oxidant (Table I). As with the hypochlorite system, an axial ligand, L, is required for reactivity; pyridines have proven to be more stable than imidazoles.[14]



turnover number (moles of product/moles catalyst)				
	ClO^-	5	2	trace
	ClO_2^-	150	92	7

(1)

Upon treatment of the catalyst solution with sodium chlorite in the presence of axial base, a 60-nm blue shift is observed in the Soret band (λ = 480–420 nm).[15] This spectral change is not observed if the sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine is used, and neither is catalysis of hydrocarbon oxidation.[16] Chlorate (ClO_3^-) is completely inactive. Variation of the porphyrin meso substituent affects both the observed turnover numbers and the product distribution,[19] but for a given catalyst system, the ratio of alcohol/ketone/alkyl halide is constant through the course of a reaction, suggesting their parallel formation from a common intermediate. In addition, the oxidation of cyclohexane in the presence of 4-methylcyclohexanol yields only an insignificant amount of 4-methylcyclohexanone.[21] Thus, ketone products are not formed by sequential hydrocarbon hydroxylation and alcohol dehydrogenation. They manifest the four-electron-oxidation capacity of the oxidant derived from chlorite.

The chlorite-derived oxidant is 450 times as reactive with saturated hydrocarbons and not as selective in alkene epoxidation as the hypochlorite-derived oxidant. The yield and distribution of products are not affected by the presence of 100 equiv of 2,6-di-*tert*-butyl-4-methylphenol (DBMPH) in the chlorite hydroxylation; similar free-radical scavengers have been reported to inhibit hypochlorite hydroxylation.[5a]

The chlorite solutions employed in the above catalysis are basic (pH = 11.8) and are indefinitely stable,[22] as are solutions of hypochlorite and chlorate. Upon addition of a methylene chloride

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(2) (a) Hill, C. L. *Adv. Oxygenated Processes* **1988**, *1*, 1. (b) Bruice, T. C. *Aldrichimica Acta* **1989**, *21*, 87. (c) Jorgenson, K. A. *Chem. Rev.* **1989**, *89*, 431. (d) Mansuy, D.; Battioni, P. *Activation and Functionalization of Alkanes*; Hill, C. H., Ed.; Wiley-Interscience; New York, 1989; p 195.

(3) Progress has been made in the area of biomimetic dioxygen activation relevant to the function of monooxygenase enzymes. (a) Tabushi, I. *Coord. Chem. Rev.* **1988**, *86*, 1. (b) Leduc, P.; Battioni, P.; Bartoli, J. F.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 205. (c) Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1989**, *111*, 2900. (d) Sakurai, H.; Mori, Y.; Shibuya, M. *Inorg. Chim. Acta* **1989**, *162*, 23. (e) Okamoto, T.; Sasaki, K.; Oka, S. *J. Am. Chem. Soc.* **1988**, *110*, 1187. (f) Khenkin, A. M.; Shilov, A. E. In *The Role of Oxygen in Chemistry and Biochemistry*; Ando, W., Mora-oka, Y., Eds.; Elsevier Science: Amsterdam, 1988; p 563. (g) Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *Isr. J. Chem.* **1987/88**, *28*, 29.

(4) Collman, J. P.; Brauman, J. I.; Hampton, P. D. *J. Am. Chem. Soc.*, in press.

(5) The oxidation of hydrocarbons by hypochlorite catalyzed by manganese porphyrins was first reported by Tabushi and has since been examined by several research groups. (a) Tabushi, I.; Koga, N. *Tetrahedron Lett.* **1979**, 3681. (b) Guilmet, E.; Meunier, B. *Tetrahedron Lett.* **1980**, *21*, 4449. (c) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000. (d) Lee, R. W.; Nakagaki, P. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 1368. (e) van der Made, A. W.; Groot, P. M.; Nolte, R. J.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 73.

(6) Hydrogen peroxide,[8] organic peroxides and peracids,[9] iodosyl aromatics,[10] potassium hydrogen persulfate,[11] hypochlorite,[5] and hypobromite[12] have previously been used as "shunt" oxidants with manganese porphyrin catalysts.

(7) The following abbreviations are used: P = 5,10,15,20-tetraphenylporphyrin dianion (TPP), 5,10,15,20-tetrakis(2,4,6-trimethylphenyl)porphyrin dianion (TMP), 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin dianion (TF_5PP), and 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin dianion (TDCPP).

(8) (a) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462. (b) Nishihara, H.; Pressprich, K.; Murray, R. W.; Collman, J. P. *Inorg. Chem.* **1990**, *29*, 1000.

(9) (a) Yuan, L.-C.; Bruice, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 1643. (b) Cook, B. R.; Reinert, T. J.; Suslick, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7281.

(10) (a) Fish, R. H.; Price, R. T. *Organometallics* **1989**, *8*, 225. (b) Castellino, A. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 158. (c) Smegal, J. A.; Hill, C. L.; Schardt, B. C. *J. Am. Chem. Soc.* **1983**, *105*, 3510. (d) Battioni, P.; Lallier, J.-P.; Barloy, L.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1149. (e) Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1989**, *111*, 7443. (f) Tolman, C. A.; Druliner, J. D.; Nappa, M. I.; Herron, N. In *Activation and Functionalization of Alkanes*; Hill, C. H., Ed.; Wiley-Interscience: New York, 1989; p 361.

(11) Robert, A.; Meunier, B. *Nouv. J. Chem.* **1988**, *12*, 885.

(12) Poorter, B. D.; Ricci, M.; Bortolini, O.; Muenier, B. *J. Mol. Catal.* **1985**, *31*, 221.

(13) Standard reaction procedure: Onto MnCl(TMP) (0.46 μmol) and 4-*tert*-butylpyridine (0.2 mmol), benzyldimethyltetradecylammonium chloride (0.1 mmol, PTC), and substrate (3.7 mmol) dissolved in 10 mL of methylene chloride was layered the aqueous phase, 20 mL of 0.5 M (aq) $NaClO_2$, at room temperature for 3 h. Reaction was initiated by stirring and progress monitored by gas–liquid chromatography. Maximum turnovers are observed with a semicontinuous removal of the (aq) $NaClO_2$ solution and addition of "fresh" oxidant. With ClMn(TDCPP) as the catalyst and this semicontinuous addition of oxidant, the products cyclohexanol, cyclohexanone, and cyclohexyl chloride were formed in 950, 780, and 330 turnovers, respectively.

(14) Meunier, B.; Guilmet, E.; De Carvalho, M. E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668.

(15) Such absorptions have been assigned to Mn(IV) or Mn(V) species.[5d]

(16) Thermodynamically, hypochlorite is a slightly stronger oxidizing agent than chlorite. Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401.

(17) It is interesting to note the similar formation of alkyl chlorides reported for the hypochlorite system.[5b,12] Enzymatic halogenations have also been reported upon metabolism of chlorite.[18]

(18) Chiang, R.; Rand-Meir, T.; Makino, R.; Hager, L. P. *J. Biochem.* **1976**, *251*, 6340.

(19) We have also found that ClMn(TDCPP) is by far the most stable oxidation catalyst.[8a,20] Cyclohexane oxidation[13] using ClMn(P) with P = TDCPP, TF_5PP, TMP, and TPP yielded 552, 323, 265, and 12 turnovers, respectively. Nearly complete catalyst bleaching and destruction was observed in each case.

(20) Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338.

(21) When 85 μmol of 4-methylcyclohexanol was added to the standard cyclohexane reaction,[13] only 6 μmol of 4-methylcyclohexanone was formed whereas 87 μmol of cyclohexanol and 51 μmol of cyclohexanone were produced.

(22) Chlorous acid (HOClO, pK_a ~ 2) is unstable and decomposes to a mixture of chloride, chlorate, and chlorine dioxide, but in mildly alkaline solutions, chlorite is reported to be stable for periods up to a year. (a) Gordon, G.; Kieffer, R. G.; Rosenblatt, D. H. *Prog. Inorg. Chem.* **1972**, *15*, 201. (b) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon: Oxford, 1984; p 1007.

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Table I. Observed Rates of Hydroxylation[a] and Epoxidation with Oxychloride Anions Catalyzed by Mn(TMP)Cl/4-*tert*-Butylpyridine

	initial turnover freq, min^{-1}		
substrate	LiOCl	$NaClO_2$	$NaClO_3$
cyclohexane	0.04	18	none
cycloalkene	230[b]	49[c]	none[c]

[a] Reference 13. [b] Reference 5c; using cyclooctene and an imidazole ligand. [c] Cyclohexene.

solution of ClMn(P) and phase-transfer catalyst (PTC) to each of these, in the absence of hydrocarbon substrate, only the chlorite solution decomposes. It disproportionates irreversibly to chloride and chlorate (eq 2).[23] The catalyzed decomposition of chlorite

$$3ClO_2^- \xrightarrow[\text{PTC, CH}_2\text{Cl}_2\text{, 23 °C}]{\text{ClMn(P)/L}} Cl^- + 2ClO_3^- \tag{2}$$

in the presence of 1 equiv of chlorate reveals that the latter inhibits both the chlorite disproportionation and hydrocarbon hydroxylation.[25] Inner-sphere atom transfer between the oxychloride anions, even with very favorable thermodynamics, is known to be extremely slow in basic solution.[26] Transition-metal catalysis of such oxygen atom transfers has not previously been observed.

In aqueous solution, chlorine dioxide (ClO_2) should exist in equilibrium with a mixture of chlorite and chlorate, but the uncatalyzed rate of equilibration is very slow (eq 3).[27] We have

$$ClO_2^- + ClO_3^- + H_2O \rightleftharpoons 2ClO_2 + 2OH^- \tag{3}$$

observed that a solution of ClO_2 in CCl_4[28] shows a very low activity for heptane hydroxylation and instead rapidly bleaches the manganese porphyrin catalyst. As ClO_2 reacts rapidly with DBMPH, an excess of the latter can act as a stabilizer against porphyrin bleaching by ClO_2. DBMPH has no effect on the rate or distribution of products in the hydrocarbon hydoxylation by chlorite; it is clear that ClO_2 is not the active oxidant under these conditions.

The regioselectivity of heptane oxidation does not distinguish chlorite from other manganese-based oxidants.[31,8a] Both favor $\omega - 1$ functionalization when hindered porphyrins (TMP or TDCPP) are used, as is also observed in P-450.[32] Likewise, the oxidations of adamantane and 2-methylpentane yield product distributions with a similar regioselectivity[34] to that observed with manganese porphyrins and a series of alternative "shunt" oxidants.[7] Active-site steric constraints appear to control the regioselectivity.

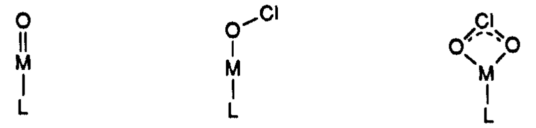
A: metal oxo B: metal hypochlorite C: metal chlorite

Figure 1. Possible structures present in metalloporphyrin-catalyzed "shunt" reagent oxidations.

In conclusion, we report herein the discovery of both chlorite disproportionation and hydrocarbon oxidation catalyzed by manganese(III) porphyrins in the presence of an axial base (4-*tert*-butylpyridine). The observed oxidations are metal centered and yield, via parallel pathways, products of both two-electron (alcohol) and four-electron (ketone) oxidation. As evidenced by its relative reactivity for epoxidation and hydroxylation, its longevity (yields $>10^3$ based on metalloporphyrin), its insensitivity to free-radical scavengers that inhibit hypochlorite, and its parallel formation of two- and four-electron-oxidation products, the identity of the chlorite oxidant is fundamentally different from that formed by hypochlorite and other shunt reagents in combination with manganese porphyrins. A metal–oxo species or a hypochlorite complex (A and B, Figure 1) is implicated as the active oxidant in the latter cases. Unique reactivity may, therefore, be proposed for a chlorite complex (C, Figure 1), including the ability to deliver the four-electron-oxidation capacity of chlorite to appropriate substrates. Note that such a process would not require a formal redox change at the metal.

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(23) The sum of hypochlorite, chlorite, and chlorate was determined by iodometric titration of the bromine formed upon treatment of acidified samples with bromide.[24] The sum of hypochlorite and chlorite, in the presence of chlorate, was assayed by simple iodometric titration without bromide treatment. Under standard reaction conditions,[13] the initial rate of disproportionation is about 180 min^{-1}, over 10 times the rate of hydroxylation, thus requiring a significant excess of oxidant for hydrocarbon oxidation by chlorite.

(24) Bassett, J.; Denney, R. C.; Jeffrey, G. H.; Mendham, J. *Vogel's Textbook of Quantitative Inorganic Analysis*, 4th ed.; Longman Group: London, 1978; p 381.

(25) It is thus advantageous[13] to remove semicontinuously and add a new aqueous chlorite layer during the course of a hydroxylation to avoid developing a high concentration of chlorate in the aqueous layer. The origin of this inhibition may be a phase-transfer effect.

(26) Taube, H. *Mechanistic Aspects of Inorganic Reactions*; ACS Symposium Series 198; American Chemical Society: Washington, DC, 1982; p 151.

(27) Taube, H.; Dodgen, H. *J. Am. Chem. Soc.* **1949**, *71*, 3330.

(28) Chlorine dioxide was prepared via the method of Taube[29] and analyzed via its characteristic UV absorption at ca. 360 nm (ϵ = 1250 M cm^{-1}).[30]

(29) Taube, H.; Dodgen, H. *J. Am. Chem. Soc.* **1949**, *71*, 2501.

(30) Kieffer, R. G.; Gordon, G. *Inorg. Chem.* **1968**, *7*, 235.

(31) In chlorite hydroxylation of heptane catalyzed by the hindered porphyrins ClMn(P), P = TDCPP and TMP, the relative reactivities per hydrogen at carbons 1:2:3:4 were 3:54:24:19; in contrast, for the flat porphyrins P = TF_5PP and TPP, this ratio was 1:37:32:30.[13] These may be compared to ratios observed in cytochrome P-450 hydroxylation[32] and free-radical chlorination[33] of heptane 9:74:11:6 and 11:31:29;29, respectively.

(32) (a) Frommer, U.; Ullrich, V.; Staudinger, H.; Orrenius, S. *Biochim. Biophys. Acta* **1972**, *280*, 487. (b) Ullrich, V. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 701.

(33) Hendry, D. G.; Mill, T.; Piszkiewicz, L.; Howard, J. A.; Eigenmann, H. K. *J. Phys. Chem. Ref. Data* **1974**, *3*, 937.

(34) Adamantane shows a relative reactivity per tertiary:secondary hydrogen of 88:12 while the relative reactivity per tertiary:secondary:primary hydrogen for oxidation of 2-methylpentane is 114:28:1. The regioselectivity of P-450 for 2-methylpentane is 150:25;1.[32b]

[3 + 2 + 2] Cycloaddition Reactions between Formaldehyde *O*-Oxide and Keto Aldehydes: A New Method for the Synthesis of Polycyclic Peroxides

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[3 + 2] cycloaddition reactions between carbonyl oxides, generated in situ by ozonolysis of olefins, and carbonyl compounds to give ozonides (1,2,4-trioxolanes) are well established.[1] Recently, it has been found that carbonyl oxides readily undergo cycloaddition reactions with alkenes,[2] imines,[3] and nitrones[4] af-

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(1) (a) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978, Vol. 1; 1982, Vol. 2. (b) Griesbaum, K.; Volpp, W.; Greinert, R.; Greunig, H.; Schmid, J.; Henke, H. *J. Org. Chem.* **1989**, *54*, 383. (c) Bunnelle, W. H.; Meyer, L. A.; Schlemper, E. O. *J. Am. Chem. Soc.* **1989**, *111*, 7612. (d) Bunnelle, W. H. *Ibid.* **1989**, *111*, 7613.

(2) (a) Wojciechowski, B. J.; Pearson, W. H.; Kuczkowski, R. L. *J. Org. Chem.* **1989**, *54*, 115. (b) Graziano, M. L.; Iesce, M. R.; Cermola, F.; Giordano, F.; Scarparti, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1608.

0002-7863/90/1512-3690$02.50/0