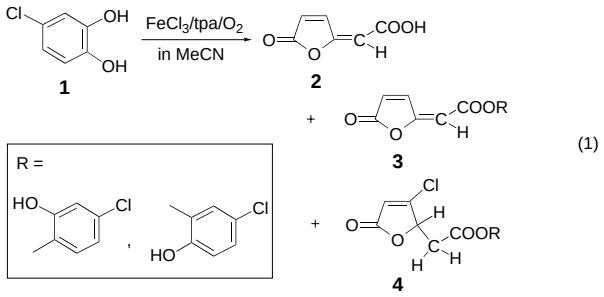
Oxygenative Cleavage of Chlorocatechols with Molecular Oxygen Catalyzed by Non-Heme Iron(III) Complexes and Its Relevance to Chlorocatechol Dioxygenases**

Takuzo Funabiki,* Tamio Yamazaki, Atsushi Fukui, Tsunehiro Tanaka, and Satohiro Yoshida

Numerous halogenated aromatic compounds are released that are difficult to degrade by chemical or biological oxidations into the environment. Recently, non-heme iron enzymes (chlorocatechol dioxygenases, CCD), which function in the degradation of mono- and polyhalocatechols, were purified.[1–5] This suggests the possibility of developing non-heme iron complexes which decompose halogenated arenes in a fashion similar to that of the chlorocatechol dioxygenases. We report here the first example of the oxidative cleavage of 3- and 4-chlorocatechols with molecular oxygen by a non-heme iron complex, which is accompanied with dehydrochlorination of the oxygenated products.

Recent remarkable progress in the enzymatic studies of oxygenases has clarified the native and substrate-bound species of some catechol dioxygenases;[6–9] however, very little is known about CCD, which contains a high-spin iron(III) ion in the active center.[1] Various types of functional models for catechol dioxygenases have been described[10–23] since the first model oxygenation by a bipyridine(pyridine)iron complex was reported.[10, 12] In these model studies 3,5-di-*tert*-butylcatechol (dtbc) was extensively used as a substrate, because the electron-donating substituents at the 3- and 5-positions facilitate the oxygenation of this catechol and prevent formation of polymer products.[24] Here we show that catechols with electron-withdrawing substituents can also be oxygenated catalytically by model iron complexes.

4-Chlorocatechol (4-Cl-catH_2, **1**) was oxygenated at 25 °C in acetonitrile under an O_2 atmosphere (1 atm). When an excess of **1** was oxygenated by the iron complex prepared in situ by mixing $FeCl_3$ and tris(2-pyridylmethyl)amine (tpa), the three oxidatively cleaved products **2**–**4** were obtained [Eq. (1)]. Compounds **3** and **4** are the 4-chlorocatechol esters



(1)

of **2** and chlorolactonic acid, respectively. No other product was detected. Both isomers of the 4-chlorocatechol esters, formed by modification of different hydroxyl groups, were observed for **3** and **4** by ^1H and ^{13}C NMR spectroscopy; however, they were not isolated separately.

Figure 1 A shows the time course of the oxygenation of **1**, which proceeded fairly slowly and catalytically to give the products in a ratio of (**2**+**3**):**4** ≈ 1:1.3. As shown in Figure 1 B, the presence of an excess of tpa was beneficial. The maximal yield was obtained for a tpa:Fe ratio of 10:1.

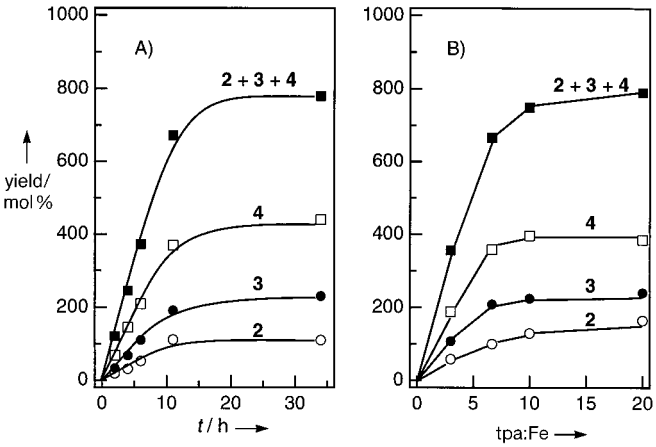


Figure 1. A) Time course of the oxygenation of **1** with O_2 catalyzed by the $FeCl_3$/tpa system. B) Effect of the tpa concentration. [$FeCl_3$] = 0.01 mmol, [tpa] = 0.1 mmol (A), [**1**] = 0.3 mmol in MeCN (5 mL). Yields [mol %] are based on the amount of Fe used.

The 4-chlorocatecholatoiron complex [Fe(tpa)(4-Cl-cat)]BPh_4 (**5**) was isolated; it exhibits ligand-to-metal charge-transfer (LMCT) absorption bands at 479 and 786 nm. Although the complex did not crystallize in a form suitable for crystallography, a preliminary X-ray absorption spectroscopic study[25] suggested a structure similar to that of [Fe(tpa)(dtbc)]BPh_4, in which the catecholate ligand chelates the iron center.[19] Complex **5** decomposes upon contact to O_2 in acetonitrile with exclusive formation of the oxygenated product **2**. Interestingly, no other product, such as the ester or the lactonic acid **4** (R = H), was formed. Figure 2 shows

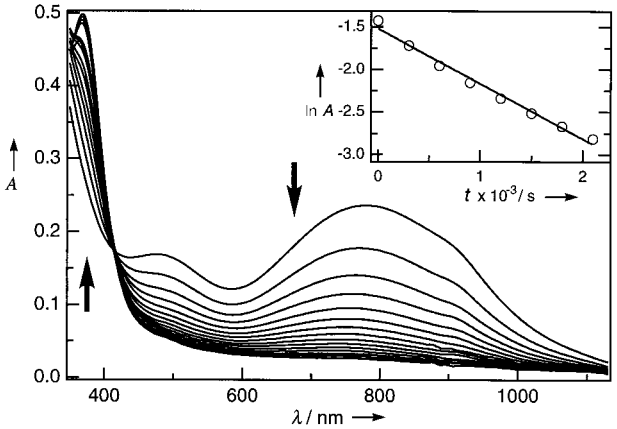


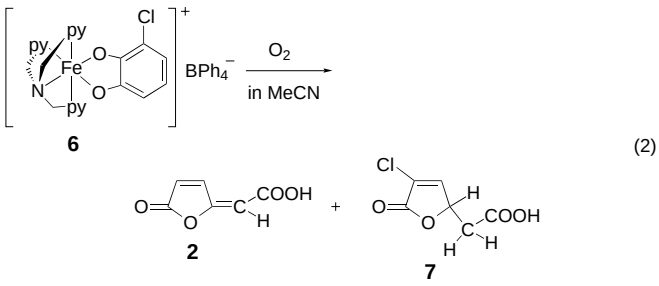
Figure 2. Oxygenation of **5** with O_2 monitored by electronic absorption spectroscopy in 5-min intervals at room temperature ([**5**] = 0.01 mmol in 5 mL MeCN under 1 atm of O_2). The arrows indicate the direction of the change in intensity of the absorption bands. Inset: plot of ln *A* vs. time *t*. *A* = absorption.

[*] Prof. T. Funabiki, T. Yamazaki, A. Fukui, T. Tanaka, S. Yoshida
Department of Molecular Engineering
Graduate School of Engineering,
Kyoto University
Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-5925
E-mail: funabiki@scl.kyoto-u-ac.jp

[**] We thank the Japenese Ministry of Education, Science, and Culture for grants (nos. 07455322, 07305062, 0215239, and 0216238), and M. Kodera, Doshisha University, for measuring the FAB mass spectra.

  1433-7851/98/3704-0513 $ 17.50+.50/0

the changes in the electronic absorption spectrum upon exposure of **5** to O_2, which indicates decomposition of the complex. The complex of 3-chlorocatechol [Fe(tpa)(3-Cl-cat)]BPh_4 (**6**) was also isolated; it exhibits LMCT bands at 532 and 766 nm. The reaction of **6** with O_2 gives mostly **2** with a small amount of **7** [Eq. (2), py = 2-pyridyl]. The pseudo-first-order rate constants evaluated from the disappearance of the



lowest energy CT bands in acetonitrile (Figure 2) were 8.4×10^{-2} for **5** and $6.4 \times 10^{-2}\,M^{-1}s^{-1}$ for **6** ($[O_2] = 8.1$ mM in acetonitrile,[26] pressure 1 atm; $1000 - 1500 \times 10^{-2}\,M^{-1}s^{-1}$ is reported for the dtbc analogue in different solvents[19]). The result that **5** is a slightly more reactive than **6** is different from the situation with the enzymatic system, in which the oxygenation of 3-chlorocatechol is a little faster than that of 4-chlorocatechol.[1, 24]

Figure 3 shows the effect of 2,6-lutidine on the catalytic conversion of **1** by **5** and by the complex prepared in situ from $FeCl_3$ and tpa. In contrast to the case of the in situ system, the oxygenation of **1** by **5** proceeds catalytically even without

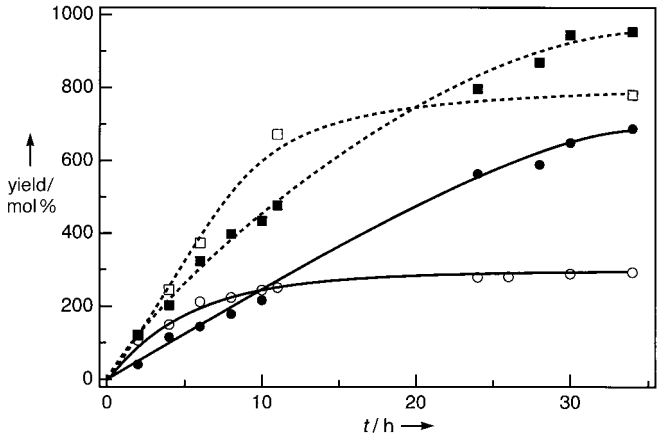
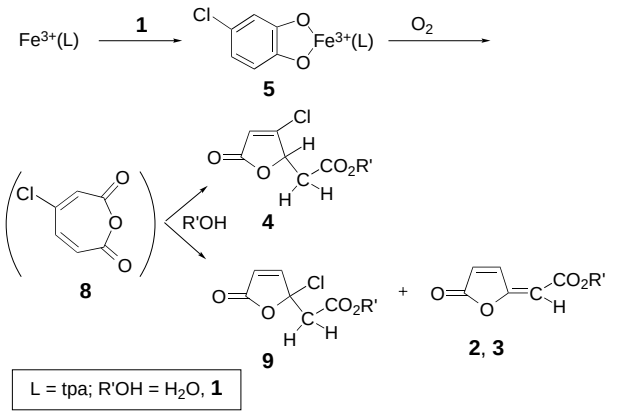


Figure 3. Effect of the addition of 2,6-lutidine on the yields of products in the oxygenation of **1** by **5** and by the complex prepared in situ from $FeCl_3$ and tpa. ○: **5**+**1** (1:29); ●: **5**+**1**+2,6-lutidine (1:29:333); □: $FeCl_3$+tpa+**1** (1:10:30); ■: $FeCl_3$+tpa+**1**+2,6-lutidine (1:10:30:333). $[FeCl_3] = [\mathbf{5}] =$ 0.2 mmol in MeCN (80 mL).

added tpa, and the reactivity is enhanced greatly by addition of 2,6-lutidine. A smaller effect was observed for the in situ system with an excess of tpa, except for the decrease in the initial rate. Since hydrogen chloride formed from $FeCl_3$ and by dehydrochlorination of the products binds to the tpa ligand, the addition of a base such as 2,6-lutidine or the presence of an excess of tpa are effective for maintaining the catalytic activity. However, the addition of these bases was not enough to prevent the termination of the reaction before complete conversion of **1**. This indicates that formation of HCl is not the sole cause of the deactivation. The stopping of the reaction even in the presence of **1** was accompanied by the disappearance of the LMCT band for the catecholate complexes. This suggests that the iron complexes are converted into inactive forms that are coordinated by product acids, as observed in the dtbc system.[19] Since the addition of base promoted the formation of esters rather than acid, it may be effective in retarding the formation of the inactive complexes coordinated by product acid.

It is reasonable to assume that the intradiol cleavage proceeds stepwise via the monooxygenated product **8**, similar to the case of dtbc.[12, 18, 19, 22, 23] The absence of **8** among the products must be due to the fact that it is more reactive with respect to water or chlorocatechols than the dtbc analogue. Esters are most probably formed directly from **8** by the reaction with chlorocatechols (Scheme 1) rather than by esterification of lactonic acids, since lactonic anhydrides react readily with water or alcohols.[27] This is reflected by the nearly constant ratio for **2**:**3**:**4** throughout the reaction (see Figure 1).



Scheme 1. Mechanism for the oxygenation of **1**.

Formation of oxygenated products from chlorocatecholatoiron complexes **5** and **6** suggests that these complexes are intermediates in the catalytic oxygenation. It is noticeable that the dehydrochlorinated product **2** is mainly formed from **5** and **6** in the absence of excess catechol. The selective formation of **2** is similar to the situation with the enzymatic system.[28] The dehydrochlorination occurs readily without extra catalysts in the model system, whereas manganese-containing chloromuconate cycloisomerases are known to catalyze the reaction in the enzymatic system.[29] In the model system other types of lactonic acids (e.g. **4**) are formed as catechol esters. The formation of esters is promoted by the presence of an excess of catechols and base such as 2,6-lutidine. It is likely that **8** is converted preferentially into **2** via **9** by reaction with water, but into both types of lactonic acid esters **4** and **9** by reaction with catechols.[27]

We have shown that the CCD model reaction is greatly dependent on the ligand. The ligand tpa is proved to be effective for the CCD model reaction, but it is not good

  1433-7851/98/3704-0514 $ 17.50+.50/0

enough for oxygenation of polychlorocatechols. However, the present result suggests that oxygenation of polyhalocatechols will be possible by the development of ligands in the future.

Experimental Section

The oxygenations were performed in a 20-mL cylindrical flask at 25 °C and under 1 atm of O_2. MeCN (5 mL) was added to $FeCl_3$ (0.01 mmol), **1** (0.30 mmol), and tpa (0.1 mmol), and the solution stirred. Aliquots of the reaction solution (0.5 mL) were diluted with CH_2Cl_2, washed with 2 N HCl to remove iron complexes, and quantitatively analyzed by ^{1}H NMR spectroscopy by monitoring specific ^{1}H NMR peaks (naphthalene as internal reference) and using the gravimetric method.[14] The products were separated by preparative HPLC and identified by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. Two types of esters were detected for **3** and **4**, whose ratios were estimated to be about 2:1 for **3** and 1.4:1 for **4** based on the relative intensities of characteristic ^{13}C NMR signals for the products.

The 3- and 4-chlorocatecholatoiron complexes [Fe(tpa)(Cl-cat)]BPh_4 (**5** and **6**) were prepared by a modification of the reported methods.[19, 22] **5**: Elemental analysis calcd for $FeC_{48}H_{41}N_4O_2BCl$: C 71.34, H 5.11, N 6.93, Cl 4.39; found: C 71.05, H 5.25, N 6.88, Cl 4.40; FAB-MS: *m*/*z*: 488 ($M^+ - BPh_4$). **6**: Elemental analysis calcd for $FeC_{48}H_{41}N_4O_2BCl$: C 71.34, H 5.11, N 6.93, Cl 4.39; found: C 70.58, H 5.03, N 6.99, Cl 4.42.

The reaction of **5** or **6** with O_2 was started by adding MeCN (80 mL) to **5** or **6** (0.2 mmol) at 25 °C and under 1 atm of O_2. The oxygenations were also performed in the presence of **1** (5.8 mmol) and 2,6-lutidine (66.7 mmol).

2: HR-MS: *m*/*z* (E/I): 140.0113 (M^+); ^{1}H NMR ($CDCl_3$): $\delta = 5.96$ (d), 6.52 (dd), 8.37 (d); ^{13}C NMR ($CDCl_3$): 101.5, 125.1, 141.8, 161.9, 167.3, 169.6.

3 (mixture of two esters): HR-MS: *m*/*z* (E/I): 265.9980 (M^+); ^{1}H NMR ($CDCl_3$): $\delta = 6.17$ (d), 6.57 (dd), 8.40 (d), 6.92 – 7.19 (4-Cl-catH); ^{13}C NMR ($CDCl_3$): 100.3 (s), 100.4 (s), 125.5 (2s), 141.7 (2s), 162.5(2s), 163.1(s), 167.1 (2s), 118.2 – 147.7 (4-Cl-catH).

4 (mixture of two esters): HR-MS: *m*/*z* (E/I): 301.9750 (M^+); ^{1}H NMR ($CDCl_3$): $\delta = 2.91 - 3.45$ (m), 5.45 (dd), 6.27 (s), 6.77 – 7.13 (4-Cl-catH); ^{13}C NMR ($CDCl_3$): 36.6 (s), 36.7 (s), 79.5 (s), 79.6 (s), 118.4 (s), 159.1 (2s), 166.3 (s), 166.5 (s), 169.0 (2s), 117.8-148.4 (4-Cl-catH).

7: MS *m*/*z* (E/I): 176; ^{1}H NMR ($CDCl_3$): $\delta = 2.75$ (dd), 2.98 (dd), 5.38 (ddd), 7.48 (d); ^{13}C NMR ($CDCl_3$): 37.3, 76.2, 128.8, 146.4, 166.8, 172.1.

Received: August 22, 1997 [Z 10845 IE]
German version: *Angew. Chem.* **1998**, *110*, 527 – 530

Keywords: chlorocatechols · dioxygenases · enzyme mimetics · iron · non-heme iron complexes · oxygenations

[1] J. B. Broderick, T. V. O'Halloran, *Biochemistry* **1991**, *30*, 7349 – 7358.
[2] C. Hinteregger, M. Loidi, F. Streichsbier, *FEMS Microbiol. Lett.* **1992**, *97*, 261 – 266.
[3] C. B. Miguez, C. W. Greer, J. M. Ingram, *Can. J. Microbiol.* **1993**, *39*, 1 – 5.
[4] M. A. Bhat, T. Ishida, K. Horiike, C. S. Vaidyanathan, *Arch. Biochem. Biophys.* **1993**, *300*, 738 – 746.
[5] O. V. Maltseva, I. P. Solyanikova, L. A. Golovleva, *Eur. J. Biochem.* **1994**, *226*, 1053 – 1061.
[6] D. H. Ohlendorf, A. M. Orville, J. D. Lipscomb, *J. Mol. Biol.* **1994**, *244*, 586 – 608.
[7] A. M. Orville, N. Elango, D. H. Ohlendorf, J. D. Lipscomb, *J. Inorg. Biochem.* **1995**, *59*, 367.
[8] S. Han, L. D. Eltis, K. J. Timmis, S. W. Muchmore, J. T. Bolin, *Science* **1995**, *270*, 976 – 980.
[9] T. Senda, K. Sugiyama, H. Narita, T. Yamamoto, K. Kimbara, M. Fukuda, M. Sato, K. Yano, Y. Mitsui, *J. Mol. Biol.* **1996**, *255*, 735 – 752.
[10] T. Funabiki, H. Sakamoto, S. Yoshida, K. Tarama, *J. Chem. Soc. Chem. Commun.* **1979**, 754 – 755.
[11] T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Yoshida, *Chem. Lett.* **1983**, 917 – 920.
[12] T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Tada, M. Tsuji, H. Sakamoto, S. Yoshida, *J. Am. Chem. Soc.* **1986**, *108*, 2921 – 2932.
[13] T. Funabiki, T. Konishi, S. Kobayashi, A. Mizoguchi, M. Takano, S. Yoshida, *Chem. Lett.* **1987**, 719 – 722.
[14] T. Funabiki, I. Yoneda, M. Ishikawa, M. Ujiie, Y. Nagai, S. Yoshida, *J. Chem. Soc. Chem. Commun.* **1994**, 1453 – 1454.
[15] M. G. Weller, U. Weser, *J. Am. Chem. Soc.* **1982**, *104*, 3752 – 3754.
[16] M. G. Weller, U. Weser, *Inorg. Chim. Acta* **1985**, *107*, 243 – 245.
[17] D. D. Cox, S. J. Benkovic, L. M. Bloom, F. C. Bradley, P. J. Nelson, L. Que, Jr., D. E. Wallick, *J. Am. Chem. Soc.* **1988**, *110*, 2026 – 2032.
[18] D. D. Cox, L. Que, Jr., *J. Am. Chem. Soc.* **1988**, *110*, 8085 – 8092.
[19] H. G. Jang, D. D. Cox, L. Que, Jr., *J. Am. Chem. Soc.* **1991**, *113*, 9200 – 9204.
[20] A. Dei, D. Gatteschi, L. Pardi, *Inorg. Chem.* **1993**, *32*, 1389 – 1395.
[21] C. Sheu, A. Sobkowiak, S. Jeon, D. T. Sawyer, *J. Am. Chem. Soc.* **1990**, *112*, 879 – 881.
[22] W. O. Koch, H.-J. Krüger, *Angew. Chem.* **1995**, *107*, 2928 – 2981; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2671 – 2674.
[23] M. Duda, M. Pascaly, B. Krebs, *Chem. Commun.* **1997**, 835 – 836.
[24] "Oxygenases and Model Systems": T. Funabiki in *Catalysis by Metal Complexes*, *Vol. 19* (Eds.: R. Ugo, B. R. James), Kluwer, Dordrecht, **1997**, pp. 1 – 393 .
[25] T. Funabiki, T. Yamazaki, A. Fukui, T. Tanaka, S. Yoshida, unpublished results.
[26] D. T. Sawyer, *Oxygen Chemistry*, Oxford University Press, New York, **1991**, p. 21.
[27] T. R. Demmin, M. M. Rogic, *J. Org. Chem.* **1980**, *45*, 1153 – 1156.
[28] D. Ghosal, I.-S. You, D. K. Chatterjee, A. M. Chakrabarty, *Science* **1985**, *228*, 135 – 142.
[29] R. Blasco, R.-M. Wittich, M. Mallavarapu, K. N. Timmis, D. H. Pieper, *J. Biol. Chem.* **1995**, *270*, 29229 – 29235.

The Asymmetric Horner – Wadsworth – Emmons Reaction Mediated by An External Chiral Ligand**

Masashi Mizuno, Kunihiko Fujii, and Kiyoshi Tomioka*

The past decade has witnessed considerable activity in the area of asymmetric Horner – Wadsworth – Emmons (HWE) reactions of prochiral ketones for the synthesis of olefins with a chiral axis.[1] Asymmetric HWE reactions of anions derived from chiral phosphoranes,[2] phosphane oxides,[3] phosphonamides,[4] phosphonamidates,[5] and phosphonates[6] to produce chiral olefins have been well documented. Carboxylic acid derivatives with chiral alcohol[7] or amine[8] moieties also lead to chiral carbonyl olefination products. In spite of impressive progress with asymmetric reactions based on internal chiral auxiliaries, comparatively little effort has been

[*] Prof. Dr. K. Tomioka, M. Mizuno, K. Fujii
Graduate School of Pharmaceutical Sciences
Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-01 (Japan)
Fax: (+81) 75-753-4604
E-mail: tomioka@pharm.kyoto-u.ac.jp

[**] We gratefully acknowledge financial support from the Japan Society for Promotion of Science (JSPS; RFTF-96P00302), the Japanese Ministry of Education, Science, Sports and Culture, and the Japanese Science and Technology Agency.

  1433-7851/98/3704-0515 $ 17.50+.50/0