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Catalytic oxygenative degradation of 4-chlorocatechol by a nonheme iron(III) complex—Mechanism and prevention of catechol ester formation

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Abstract

We examined the oxygenative degradation of 4-chlorocatechol and 4-*tert*-butylcatechol catalyzed by iron(III)-tris(pyridin-2-yl)amine complex from the standpoint of repressing the formation of 4-chlorocatechol esters of the oxygenated products that causes the incomplete degradation of 4-chlorocatechol. Analysis of the products revealed that 4-chlorocatechol esters are formed by the reaction of muconic anhydride, which is the monooxygenated product, with catechols. It was found that the use of MeOH as the solvent instead of MeCN completely suppressed the catechol ester formation through the methanolysis of muconic anhydride, which greatly improves the degradation efficiency of 4-chlorocatechol.

Keywords: Oxygenative degradation; Chlorocatechol; Nonheme

1. Introduction

Halogenated aromatic compounds comprise a major class of environmental pollutants such as PCBs, dioxins, and other halogenated pesticides [1,2]. Some bacteria can use these compounds as sole sources of carbon and energy. For example, Gram-positive bacterium *Rhodococcus opacus* degrades chlorobenzene taking the pathway shown in Scheme 1 [3–5], in which chlorobenzene is converted to 4-chlorocatechol (4-Cl-catH_2), and then oxygenated with the insertion of oxygen atoms between the two hydroxyl groups by nonheme iron(III)-dependent catechol dioxygenases. The resulting 3-chloromuconate is further converted to *cis*-dienelactone by chloromuconate cycloisomerase, and finally metabolized to TCA cycle intermediates.

In the model studies for catechol dioxygenases, we have first found that 3- and 4-chlorocatechols are catalytically oxygenated by iron(III) complexes with O_2 in MeCN in a similar fashion to chlorocatechol dioxygenases [6]. This model reaction is unique and beneficial in terms of green chemistry in the following points: (1) the cleavage of the aromatic ring proceeds under mild conditions; (2) the catalytic system requires only molecular oxygen instead of any strong oxidants such as hydrogen peroxide; (3) chlorocatechols can be directly converted to *cis*-dienelactone, eliminating the chlorine atom. In the stoichiometric conditions, [Fe^{III}(TPA)(4-Cl-cat)]BPh_4 (TPA = tris(pyridin-2-yl)amine) in MeCN transforms the chlorocatecholate ligand exclusively to *cis*-dienelactone upon exposure to O_2, which is considered as a result of sequential reactions of the oxygenative cleavage of the intradiol C–C bond of 4-Cl-cat, cyclization and dechlorination [6]. On the other hand, the catalytic oxygenation of 4-Cl-catH_2 by the iron(III)-TPA complex gives a mixture of 3-chloromuconate, *cis*-dienelactone and their chlorocatechol esters [6]. The chlorocatechol ester formation should be avoided from the viewpoints of conversion of chlorinated aromatic compounds to aliphatic products, since the chlorocatechol moiety incorporated in the ester is not cleaved by the iron(III)-TPA complex. With the aim of developing

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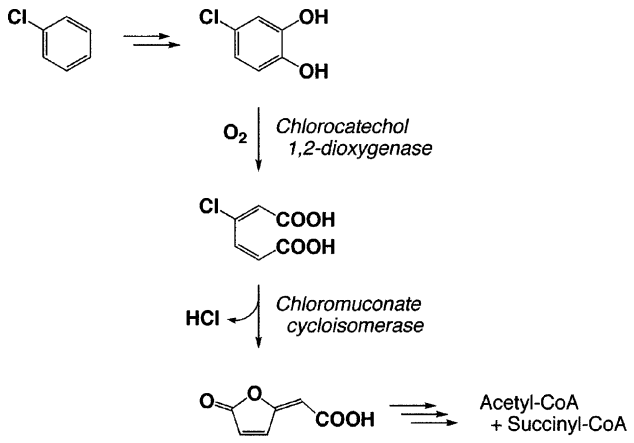


Scheme 1.

the conditions for highly catalytic degradation of chlorocatechols, we here studied the mechanisms of the catechol ester formation in the oxygenative degradation of 4-Cl-catH_2 (**1**) and 4-*tert*-butylcatechol (4-*t*Bu-catH_2, **2**) catalyzed by the iron(III)-TPA complex and found that the use of MeOH as the solvent instead of MeCN is a simple and useful way for the efficient degradation of **1**.

2. Experimental

Reaction solutions were prepared by adding 10 eq. of catechol to the solution of $Fe(ClO_4)_3{\cdot}6H_2O$ (1.0 eq.), TPA (1.0 eq.) and diisopropylethylamine (2.0 eq.) in anhydrous MeCN or MeOH under N_2 in a glove box. The resulting deep-purple solutions were allowed to react with 1 atm O_2 at 25 °C for 3 days to ensure completeness of the reactions. In the case of 4-*t*Bu-CatH_2, the oxidation was also carried out by introducing 7.5 mL of O_2 into the anaerobic solution by using a syringe. A 2 mL of the oxygenated solution was taken and evaporated in vacuo. The residue was treated with 2 mL of 2 N HCl aq., and extracted with CH_2Cl_2 (3 × 2 mL). A 5 mM solution of anthracene in CH_2Cl_2 (1 mL) was added to the extracted solution and dried over Na_2SO_4. The product analyses were performed by ^{1}H and ^{13}C NMR and mass spectroscopies in addition to referring the reported ^{1}H NMR data: **1a** [6], **1a′** [6], **1b′** [6], **1b** [7], **2a** [8], **2b** [8], **2a″** [9], and **2b″** [9]. ^{1}H and ^{13}C NMR spectra were measured on a JEOL EX-400 spectrometer. Chemical shifts were related to TMS as an internal reference.

1a″—^{1}H NMR ($CDCl_3$): δ 8.38 (1H, d, J = 5.8 Hz), 6.47 (1H, d, J = 5.8 Hz), 5.94 (1H, s), 3.81 (3H, s) [10].

1c—^{1}H NMR ($CDCl_3$): δ 7.08 (1H, dd, J = 12.2 Hz, J = 2.0 Hz), 6.23 (1H, d, J = 2.0 Hz), 6.05 (1H, d, J = 12.2 Hz).

1c″—^{1}H NMR ($CDCl_3$): δ 7.02 (1H, dd, J = 12.2 Hz, J = 2.0 Hz), 6.25 (1H, d, J = 2.0 Hz), 6.05 (1H, d, J = 12.2 Hz), 3.76 (1H, s)

1d″—^{1}H NMR ($CDCl_3$): δ 8.53 (1H, d, J = 15.1 Hz), 6.62 (1H, d, J = 15.1 Hz), 6.37 (1H, s), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$): 167.0 (s), 165.8 (s), 147.2 (s), 135.7 (s), 128.8 (s), 123.0 (s), 52.2 (s).

2a′—^{1}H NMR ($CDCl_3$): (major isomer of esters) δ 7.57 (1H, d, J = 5.9 Hz), 6.96 (1H, s), 6.86 (1H, s), 6.15 (1H, d, J = 5.9 Hz), 3.28 (1H, d, J = 14.2 Hz), 3.11 (1H, d, J = 14.2 Hz), 1.25 (9H, s), 1.03 (9H, s); (minor isomer of esters) δ 7.58 (1H, d, J = 5.9 Hz), 7.07 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 6.94 (1H, d, J = 2.4 Hz), 6.83 (1H, d, J = 8.8 Hz), 6.15 (1H, d, J = 5.9 Hz), 3.29 (1H, d, J = 14.2 Hz), 3.11 (1H, d, J = 14.2 Hz), 1.24 (9H, s), 1.04 (9H, s); ^{13}C NMR ($CDCl_3$): (mixture of two esters) δ 172.7 (s), 172.6 (s), 167.6 (s), 167.5 (s), 156.8 (2s), 150.5 (s), 146.3 (s), 144.5 (s), 144.0 (s), 137.5 (s), 135.5 (s), 123.9 (s), 122.5 (2s), 121.4 (s), 119.2 (s), 117.6 (s), 117.1 (s), 114.8 (s), 92.8 (s), 37.9 (s), 37.8 (s), 34.5 (s), 34.2 (s), 31.4 (s), 31.3 (s), 25.4 (s); HRMS: calcd. for $C_{20}H_{26}O_5$ 346.1780, found 346.1778.

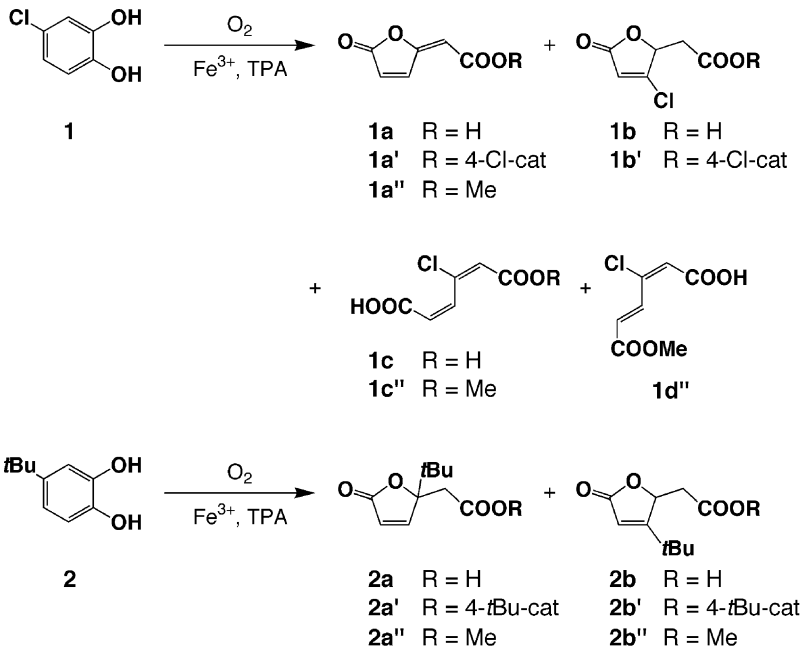
2b′—^{1}H NMR ($CDCl_3$): (major isomer of esters) δ 7.03 (1H, d, J = 2.4 Hz), 6.98 (1H, d, J = 8.8 Hz), 6.90 (1H, dd, J = 8.8 Hz, J = 2.4 Hz), 5.91 (1H, d, J = 2.0 Hz), 5.53–5.49 (1H, m), 3.36 (1H, dd, J = 16.1 Hz, J = 3.9 Hz), 3.36 (1H, dd, J = 16.1 Hz, J = 9.3 Hz), 1.27 (9H, s), 1.26 (9H, s); (minor isomer of esters) δ 7.13 (1H, dd, J = 8.3, 2.4 Hz), 7.05 (1H, d, J = 2.4 Hz), 6.92 (1H, d, J = 8.3 Hz), 5.91 (1H, d, J = 2.0 Hz), 5.53–5.49 (1H, m), 3.37 (1H, dd, J = 16.1 Hz, J = 3.9 Hz), 2.82 (1H, dd, J = 16.1 Hz, J = 9.3 Hz), 1.27 (9H, s), 1.26 (9H, s); ^{13}C NMR ($CDCl_3$): (mixture isomer of esters) δ 179.4 (s), 172.0 (2s), 167.3 (s), 167.2 (s), 150.7 (s), 146.5 (s), 144.6 (s), 143.9 (s), 137.4 (s), 135.3 (s), 124.1 (s), 121.6 (s), 119.3 (s), 117.5 (s), 117.0 (s), 116.0 (2s), 114.8 (s), 79.3 (2s), 38.7 (2s), 34.6 (s), 34.2 (s), 33.7 (s), 31.4 (s), 31.3 (s), 29.4 (s); HRMS: calcd. for $C_{20}H_{26}O_5$ 346.1780, found 346.1780.

Yields of the products were determined by ^{1}H NMR spectroscopy using anthracene as an internal standard. 4-*t*Bu-cat esters were isolated as a mixture of isomers through a reverse-

Table 1
Yields (%) of the oxygenated products of catechols

Cat	Solvent	Cat[a]	**a**	**b**	**c**	**a′**	**b′**	**a″**	**b″**	**c″**	**d″**
1	MeCN	26	10	6	0	10	15				
	MeOH	6	0	0	10	0	0	5	0	37	6
2	MeCN	0	6	87	0	0	0				
	MeCN[b]	0	2	27	0	13	17				
	MeOH	0	0	0	0	0	0	27	34		

[a] Unreacted catechol.
[b] Reacted with 6 eq. of O_2.



Scheme 2.

phase HPLC column (STR ODS-II). The obtained products are illustrated in Scheme 2 and their yields are listed in Table 1.

3. Results and discussion

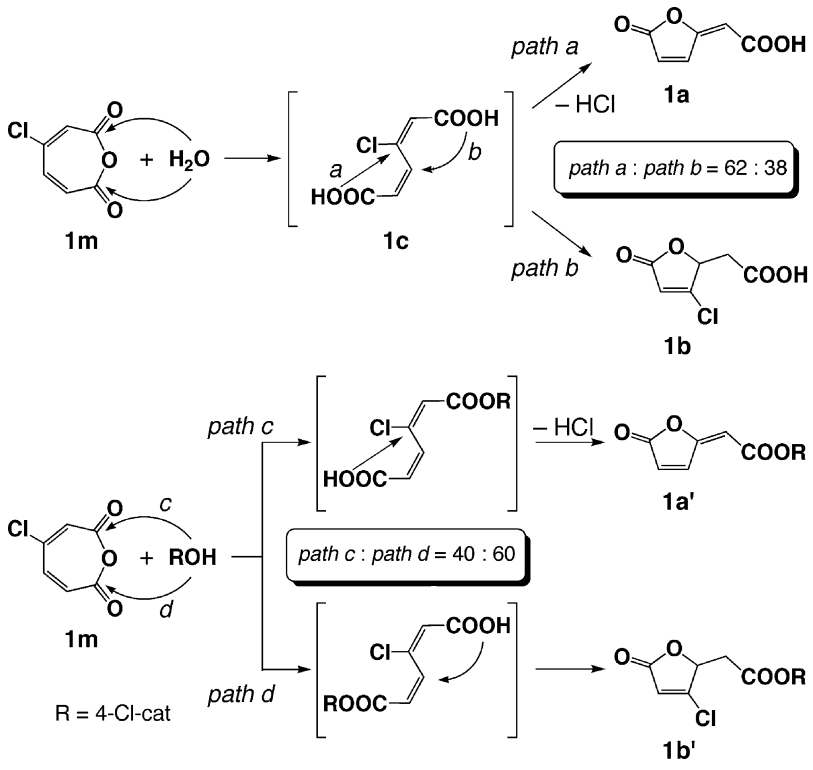
3.1. Oxygenation of 4-Cl-catH_2 in MeCN

The oxygenation of 4-Cl-catH_2 (**1**) in MeCN afforded a mixture of *cis*-dienelactone (**1a**) and 3-chloromuconolactone (**1b**) in 10% and 6% yields, respectively, their 4-Cl-cat esters (**1a**′: 10%, **1b**′: 15%), and **1** (26%). The recovery of **1** is due to the deactivation of the catecholatoiron(III) complex by HCl produced during the catalytic cycle [6]. It has been revealed that the oxygenation reaction of 3,5-di-*tert*-butylcatechol promoted by nonheme iron(III) complexes proceeds stepwise via 2,4-di-*tert*-butylmuconic anhydride, which is a monooxygenated product [11–15]. Similarly, the oxygenation reaction of 4-Cl-catH_2 would afford 3-chloromuconononic anhydride **1m** as a monooxygenated product, and its hydrolysis gives only **1c** through the attack of water to either of the carbonyl carbon atoms of **1m** as shown in Scheme 3. Cyclization of **1c** competitively affords two types of lactonic acids **1a** and **1b** by *paths a* and *b*, respectively. The ratio of *paths a* and *b* is estimated at 62:38, which indicates that the carboxylate group favorably attacks the carbon atom attached to the electron-withdrawing chloride substituent via *path a*.

On the other hand, catechol esters **1a**′ and **1b**′ are formed by the direct attack of 4-Cl-catH_2 to **1m**. Similarly to the hydrolysis, the ratio of the two catechol esters **1a**′ and **1b**′ reflects the competitive attack of 4-Cl-catH_2 to either of carbonyl carbon atoms of **1m**. Therefore, the ratio of 40:60 indicates that 4-Cl-catH_2 slightly favors the attack on the carbonyl group at 6-position of **1m** over that at 1-position, i.e., *path d* over *path c* in Scheme 3. This is slightly surprising because the electron-withdrawing chlorine atom at 3-position of **1m** would make path *c* feasible. At this moment, the reason is unclear, but it is probable that significant amounts of HCl that is produced during the reaction might affect the steps of the catechol ester formation.

3.2. Oxygenation of 4-tBu-catH_2 in MeCN

In the catalytic oxygenation of 4-*t*Bu-catH_2 (**2**) in MeCN, 3-*tert*-butylmuconic anhydride **2m** was observed after 1 h, but after 72 h only two isomers of muconolactone **2a** and **2b** were obtained in 6% and 87% yields, respectively, and neither **2m** nor any catechol esters (**2a**′, **2b**′) were obtained. It is probable that the water molecules derived from hydrated iron(III) salts or produced during the catalytic oxygenation reaction attack the carbonyl groups of **2m** to yield 4- or 3-*tert*-butylmuconolactone (**2a** or **2b**) via 3-*tert*-butylmuconic acid as a common intermediate as shown in Scheme 4. Therefore, the ratio of **2a** and **2b** reflects the competition of two cyclization paths of 3-*tert*-butylmuconic acid; i.e., *paths e* and *f* in Scheme 4. It seems reasonable that *path f* is much favored over *path e* because the latter includes the attack of the carboxylate group to the carbon attached with the electron-donating *tert*-butyl group. It has been reported that the reaction of 4-*tert*-butylcatecholatoiron(III) complexes with O_2 affords 3-*tert*-butylmuconolactone **2b** but not **2a** [6]. Thus, the oxidation conditions affect the competitive steps



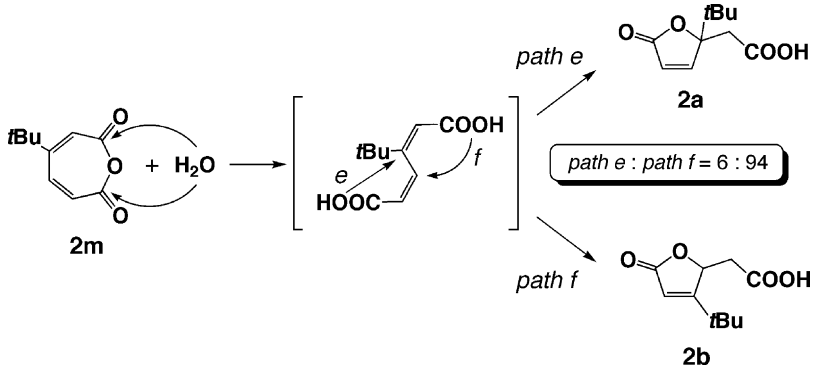
Scheme 3.

of *paths e* and *f*, probably through the interaction between muconic acid and the iron(III) complex in the coordination sphere.

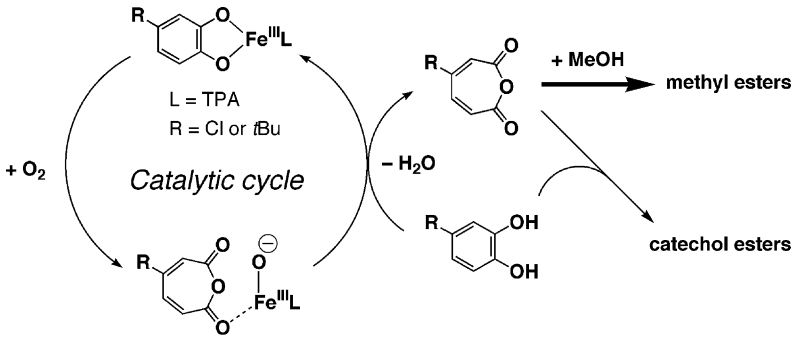
3.3. Formation of 4-tBu-cat esters in MeCN

It is important to clarify the reasons why 4-*tert*-butylcatechol esters are not formed under the catalytic conditions. We notice the remarkable difference in the reaction rate between 4-*t*Bu-catH_2 and 4-Cl-catH_2; that is, 4-*tert*-butylcatecholatoiron(III) complex $[Fe(TPA)(4\text{-}t\text{Bu-cat})]^+$ reacts more rapidly with O_2 ($k_{ox} = 21\ M^{-1}\ s^{-1}$) than 4-chlorocatecholatoiron(III) complex $[Fe(TPA)(4\text{-Cl-cat})]^+$ ($k_{ox} = 0.16\ M^{-1}\ s^{-1}$) [16]. Due to this high reactivity of $[Fe(TPA)(4\text{-}t\text{Bu-cat})]^+$ species, 4-*t*Bu-catH_2 **2** should be rapidly converted to muconic anhydride **2m** under 1 atom O_2, in agreement with formation of **2m** in the initial stage of the catalytic oxidation of **2**. This could account for no formation of 4-*t*Bu-cat esters, because muconic anhydride **2m** would be attacked by water molecules rather than by 4-*t*Bu-catH_2 **2** due to low concentrations of 4-*t*Bu-catH_2 **2**.

To examine whether the 4-*t*Bu-catH_2 esters are formed if there is enough amount of **2**, the reaction was performed under the limited amount of O_2 that should result in incomplete consumption of 4-*t*Bu-catH_2 **2**. Thus, the oxygenation of **2** (10 eq.) by the complex prepared in situ with $Fe(ClO_4)_3{\cdot}6H_2O$ (1.0 eq.), TPA ligand (1.0 eq.), and diisopropylethylamine (2.0 eq.) in MeCN were performed in the



Scheme 4.



Scheme 5.

presence of only 6 eq. of O_2. The reaction gave two isomers of catechol esters (**2a**′: 13%, **2b**′: 17%) as expected besides two isomers of muconolactones (**2a**: 2%, **2b**: 27%). This result indicates that the ready formation of 4-Cl-cat esters is due to the low reactivity of 4-chlorocatecholatoiron(III) complex $[Fe(TPA)(4\text{-Cl-cat})]^+$ with O_2 since there is enough amount of **1** to react with **1m** even in the presence of excess amount of O_2.

In order to prevent the formation of 4-Cl-cat esters, **1m** should be converted rapidly to other products that do not react with **1**. For this purpose, we here examined the possibility of methanolysis of **1m** to prevent the catechol ester formation as shown in Scheme 5, by referring to the formation of methyl esters of muconate or muconolactone in the oxygenation reaction of the catecholatoiron(III) complexes in MeOH [17,18].

3.4. Oxygenation of 4-tBu-catH$_2$ in MeOH

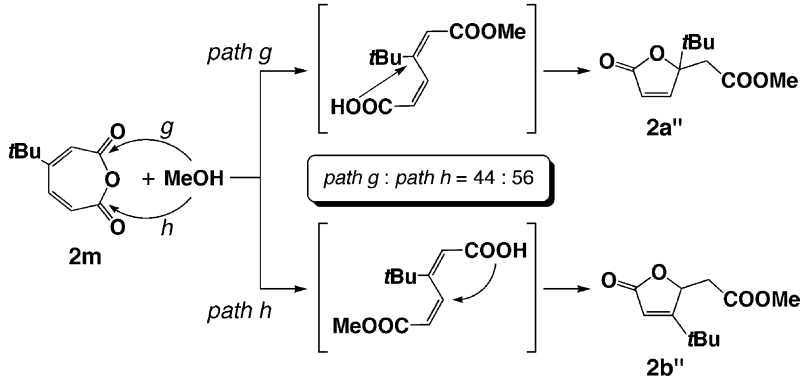
The catalytic oxygenation of **2** was performed in MeOH in the same conditions as in MeCN. As expected, only methyl esters of muconolactone, **2a**″ and **2b**″, were obtained in 27% and 34% yields, respectively. The product ratio of **2a**″ and **2b**″ indicates that the nucleophilic attack of MeOH slightly favor the carbonyl carbon atom at 6-position (*path h*) over that at 1-position (*path g*). This may reflect the position of the electron-donating *tert*-butyl group on **2m** (Scheme 6).

3.5. Oxygenation of 4-Cl-catH$_2$ in MeOH

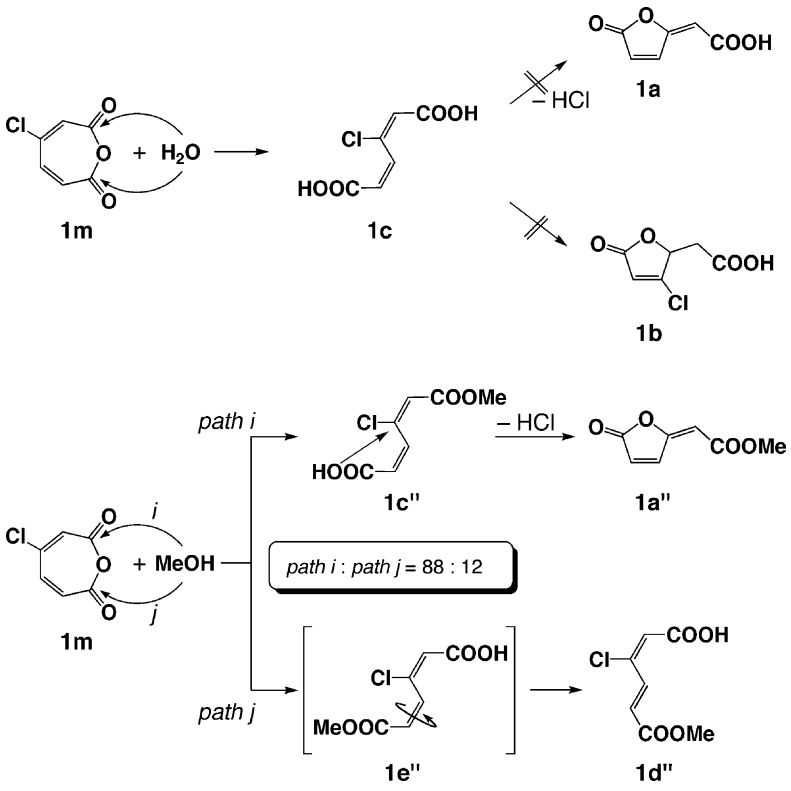
The catalytic oxygenation of **1** was performed in MeOH in the same conditions as in MeCN. Oxygenated products were 3-chloromuconic acid **1c** (10%), methyl ester of *cis*-dienelactone **1a**″ (5%), and monomethyl esters of choloromuconate (**1c**″: 37%, **1d**″: 6%). Thus, 4-Cl-cat esters were not formed under these conditions. Interestingly, **1c** was not cyclized to neither **1a** nor **1b**, which is in sharp contrast to the result in MeCN; **1c** was completely converted to **1a** and **1b**. Similarly, only ca. 12% of **1c**″ was converted to **1a**″ by cyclization accompanied with chlorine elimination. Another isomer of monomethyl esters of choloromuconate, **1e**″, was not obtained, but converted to **1d**″ via *cis*,*trans*-isomerization.

The ratio of *paths i* and *j* in Scheme 7 can be estimated to be 88:12 based on the product ratio of (**1c**″ + **1a**): **1d**″, which indicates that the MeOH molecule selectively attacks the carbonyl group at 1-position of **1m** (*path i*) rather than that at 6-position (*path j*). The electron-withdrawing chlorine substituent may promote the methanolysis at 1-position rather than that at 6-position.

Most importantly, the formation of catechol esters such as **1a**′ and **1b**′ was completely prevented by the effective



Scheme 6.



Scheme 7.

methanolysis of **1m** prior to the nucleophilic attack of 4-Cl-catH_2 to **1m**. This greatly improved the degradation efficiency of 4-Cl-catH_2 as shown by the decrease in the amount of recovered 4-Cl-catH_2 from 51% in MeCN to 6% in MeOH.

4. Conclusions

We found that the degradation efficiency of 4-Cl-catH_2 by the iron(III)-TPA complex is remarkably improved by changing the solvent from MeCN to MeOH. In MeCN, significant amounts of 4-Cl-catH_2 are transformed to 4-Cl-catH_2 esters of the oxygenated products and remain without degradation by the iron(III)-TPA complex. The catechol esters are also formed from 4-*t*Bu-catH_2 as a substrate in MeCN at the low concentration of dioxygen, indicating that catechol esters are formed by the reaction of muconic anhydride with free catechols. The use of MeOH as solvent effectively converts muconic anhydride to muconic acid and/or muconolactone derivatives by methanolysis before the reaction with free catechols, which results in complete suppression of the catechol ester formation. Thus, the efficient degradation of halogenated catechols by the iron(III)-TPA complex is required for rapid conversion of muconic anhydride to other products that do not react with catechols. This prerequisite seems to be perfectly satisfied during the enzymatic degradation of catechols; that is, catechol is oxygenated to muconic anhydride and then rapidly hydrolyzed to *cis,cis*-muconate in the active site. The present study encourages the development of new nonheme iron(III) complexes for efficient degradation of catechols by designing the catalyst that quantitatively converts muconic anhydride to muconic acid regardless of types of catechol substituents.

References

[1] D. Ghosal, I.-S. You, D.K. Chatterjee, A.M. Chakrabarty, Science 228 (1985) 135.
[2] M. Alexander, Science 211 (1981) 132.
[3] M. Ferraroni, J. Seifert, V.M. Travkin, M. Thiel, S. Kaschabek, A. Scozzafava, L. Golovleva, M. Schloman, F. Briganti, J. Biol. Chem. 280 (2005) 21144.
[4] M. Ferraroni, M.Y. Ruiz Tarifa, F. Briganti, A. Scozzafava, S. Mangani, I.P. Solyanikova, M.P. Kolomytseva, L. Golovleva, Acta Crystallogr. D Biol. Crystallogr. 58 (2002) 1074.
[5] M. Ferraroni, M.Y. Ruiz Tarifa, F. Briganti, A. Scozzafava, S. Mangani, I.P. Solyanikova, M.P. Kolomytseva, L. Golovleva, Acta Crystallogr. D Biol. Crystallogr. 58 (2002) 1074.
[6] T. Funabiki, T. Yamazaki, A. Fukui, T. Tanaka, S. Yoshida, Angew. Chem. Int. Ed. 37 (1998) 513.
[7] A.B. McKague, Synth. Commun. 29 (1999) 1463.
[8] T. Funabiki, D. Sugio, N. Inui, M. Maeda, Y. Hitomi, Chem. Commun. (2002) 412.
[9] M.M. Rogic, T.R. Demmin, W.B. Hammond, J. Am. Chem. Soc. 98 (1976) 7441.
[10] C.F. Ingham, R.A. Massy-Westropp, G.D. Reynolds, W.D. Thorpe, Aust. J. Chem. 28 (1975) 2499.
[11] D.D. Cox, L. Que, J. Am. Chem. Soc. 110 (1988) 8085.
[12] M. Duda, M. Pascaly, B. Krebs, Chem. Commun. (1997) 835.

[13] T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Tada, M. Tsuji, H. Sakamoto, S. Yoshida, J. Am. Chem. Soc. 108 (1986) 2921.
[14] H.G. Jang, D.D. Cox, L. Que Jr., J. Am. Chem. Soc. 113 (1991) 9200.
[15] W.O. Koch, H.J. Kruger, Angew. Chem. Int. Ed. Engl. 34 (1996) 2671.
[16] Y. Hitomi, M. Yoshida, M. Higuchi, H. Minami, T. Tanaka, T. Funabiki, J. Inorg. Biochem. 99 (2005) 755.
[17] G. Lin, G. Reid, T.D.H. Bugg, J. Am. Chem. Soc. 123 (2001) 5030.
[18] M. Pascaly, M. Duda, F. Schweppe, K. Zurlinden, F.K. Muller, B. Krebs, J. Chem. Soc. Dalton Trans. (2001) 828.