Extradiol Oxygenation of 3,5-Di-*tert*-butylcatechol with O₂ by Iron Chlorides in Tetrahydrofuran–Water as a Model Reaction for Catechol-2,3-dioxygenases

Takuzo Funabiki,* Izumi Yoneda, Michiya Ishikawa, Mikio Ujiie, Yasutaka Nagai and Satohiro Yoshida

Division of Molecular Engineering, Kyoto University, Kyoto, Japan

Selective extradiol oxygenation of 3,5-di-*tert*-butylcatechol 1 with O_2 catalysed by Fe^{2+} is achieved in THF in the presence of water; the different selectivity obtained by $FeCl_2$ and $FeCl_3$ in THF–H₂O and THF–pyridine supports the explanation of the intra- and extra-diol oxygenations by Fe^{3+} and Fe^{2+} , respectively, as proposed in the enzymatic systems.

Catecholdioxygenases are the central objects in the studies of dioxygenases since discovery of insertion of molecular oxygen into pyrocatechol to form muconic acid. Great efforts have been made for clarifying the mechanism from enzymatic and model chemistry aspects, but many problems are left unclear in the reaction steps in the cleavage of the carbon-carbon bonds with insertion of oxygen and in the mechanism of the selectivity control. Since the discovery of the intradiol oxygenation of 1 with cleavage observed between C(1) and C(2) by a bipyridine(pyridine)iron complex in THF,² the mechanism of the intradiol oxygenation by iron(III) oxygenases such as pyrocatechase has been discussed on the basis of results obtained for iron(III) complexes as function models.³ However, extradiol oxygenation, with cleavage between the C(1) and C(6) or C(2) and C(3) carbons atoms, has received little study in terms of model systems. This is because Fe²⁺ is liable to be oxidized to Fe³⁺ and catechol is little activated upon coordination to a Fe²⁺ centre.

Previously we have found that both intra- and extra-diol oxygenations are catalysed by a bipyridine(pyridine)iron complex.⁴ We here report that the oxygenations to form 2-5 in eqn. (1) are catalysed by FeCl₂ or FeCl₃ in the presence of a small amount of water (without addition of further ligands) and that the extradiol oxygenation proceeds in preference to





Oxygenations were performed in a 20 cm³ cylindrical flask at 25 °C and 1 atm O₂. In a typical case, the reaction was initiated by addition of H₂O (0.18 cm³) and THF (9.82 cm³) to FeCl₂ (25 mg, 0.20 mmol) or FeCl₃ (32 mg, 0.20 mmol) and 1 (133 mg, 0.60 mmol) in the flask. The solution was stirred magnetically and products extracted with CH₂Cl₂ were quantitatively analysed by ¹H NMR. This was performed by the gravimetric method, *i.e.*, weights of pieces of paper in the shapes of specific ¹H NMR peaks⁴ of products cut from their expanded copies were compared with that of the methyl peak of toluene. The usual integration method on the NMR recorder is not useful because a mixture of products exhibited



Fig. 1 Effect of the water concentration on the intra- and extra-diol oxygenations of 1 by FeCl₂ and FeCl₃ in THF-H₂O. (*a*) FeCl₂ or (*b*) FeCl₃ (0.20 mmol), 1 (0.60 mmol), THF + H₂O (10 cm³), 1 atm O₂, 25 °C. Yields formed after 100 min, based on [Fe]. (\bigcirc) Intradiol 2, (\Box) extradiol 4, (\blacksquare) extradiol 5, (\triangle) 4 + 5

Fable 1 Oxygenation of DTBC	catalysed by iron chlorides in	THF-H ₂ O and THF-py ^a
------------------------------------	--------------------------------	--

	Iron chloride	Additive ^b (Yields of products/mol % ^d		
			Conv. ^c	$\frac{\text{Intra- and extra-diol}}{2-5(2:3:4:5)}$	Others	
					6-8(6:7:8)	9
	FeCl ₂	H ₂ O	97	46.8 (16:0:84:0)	12.6 (14:66:0)	128
	FeCl ₃	H_2O	75	46.8 (31:0:66:3)	27.3 (9:87:4)	132
	FeCl ₂	py	92	$42.1(45:17:5:33^{e})$	24.5 (7:79:14)	155
	FeCl ₃	ру	91	$40.6(35:39:0:26^{e})$	19.6 (0:90:10)	182

^{*a*} FcCl₂ or FcCl₃ (0.20 mmol), 1 (0.60 mmol), THF + H₂O (or py) (10 cm³), 1 atm O₂, 25 °C. ^{*b*} H₂O or py (10 mmol). ^{*c*} Conversion of 1. ^{*d*} Yields formed after 100 min, based on [Fe]. ^{*e*} 5 was partly converted to 3,5-di-*tert*-butyl-5-formylfuran-2-one.

many peaks in the similar region. Reactions were also performed in the presence of pyridine in place of H_2O . Table 1 shows the results after 100 min. Identified products other than the intradiol oxygenation (2 and 3) or extradiol oxygenation products (4 and 5) were 6–9 in which quinone 9 was formed in the highest yield. Yields of the oxygenated products were slightly greater in THF-H₂O than in THF-py. In THF-H₂O, the extradiol oxygenation products (4 + 5) were much more abundant than the intradiol (2), especially in the case of FeCl₂. It is characteristic that the dioxygenated product, 3, is not formed in THF-H₂O. In THF-py (2 + 3) was greater than (4 + 5) both with FeCl₂ and FeCl₃, but extradiol oxygenation (4 + 5) was promoted by FeCl₂ than FeCl₃.



Fig. 2 Electronic spectra of complexes formed by the reaction of FeCl₃ with 1 in THF-H₂O and THF-py.FeCl₃ (0.20 mmol), 1 (0.60 mmol), THF + H₂O (or py) (10 cm³), in Ar. (a) H₂O (20 mmol), (b) py (1 mmol), (c) py (10 mmol)



Scheme 1

J. CHEM. SOC., CHEM. COMMUN., 1994

Fig. 1 shows the effect of the concentration of water in THF-H₂O. The reaction did not proceed in the absence of water and was promoted by increasing concentration of water. Differently from the intradiol oxygenation, extradiol oxygenation was inhibited by high concentrations of water, remarkably so in the case of FeCl₃. Electronic spectra indicated the coordination of 1 to iron in argon (Fig. 2). For $FeCl_3$ the spectrum in THF-H₂O is similar to that in THF-py though the. peak intensity of the former is much smaller. Since the spectra were not observed in the absence of water or pyridine it is clear that these solvents are required to deprotonate (and thus coordinate 1 to Fe^{3+}), as well as stabilizing the complex by ligation. In THF-py, increasing the concentration of pyridine causes a red shift of the peak, indicating the formation of an octahedral complex with more coordinated pyridine molecules.5 The shoulder observed in THF-H₂O may correspond to a similar type of complex, but the intensity of the shoulder does not increase with increasing concentration of water. For FeCl₂, the same spectra were observed but only after introduction of oxygen. The solutions exhibiting the spectra as shown in Fig. 2 also show in their ESR spectra a characteristic single line peak at g = 2.01 corresponding to a 3,5-di-tertbutylbenzosemiquinonate– Fe^{2+} species (10), which is coordinated by chloride ligands and has a vacant site for coordination (five-fold coordination, probably pentagonal bipyramidal).5,6 At high concentrations of pyridine, formation of an octahedral catecholatoiron complex is shown by peaks at g = 4.20 and 8.99.

Scheme 1 rationalises the intra- and extra-diol oxygenations catalysed by Fe³⁺ and Fe²⁺ species, respectively, similarly to the enzymatic systems. For FeCl₃, an iron(11) species is formed in the oxidation of 1 to quinone 9. On the other hand, for $FeCl_2$, an iron(III) species is formed by oxidation of Fe^{2+} with O_2 . Reaction of 1 with Fe³⁺ leads to a fairly stable complex. 10, which is in equilibrium with 11. 10 gives only the intradiol oxygenation products by insertion of O_2 , probably via 12. For the extradiol oxygenation, there is no direct evidence for coordination of 1 to Fe²⁺, but it may occur prior to that of O_2 .⁷ As suggested by a molecular orbital calculation study,⁸ the coordinated oxygen $(-O_2^{-1})$ in 14 binds to C(1) to form 15, while the free oxygen may attack C(2) probably to form 13. The enhanced stability of 10 contributes to promote the intradiol oxygenation even in the FeCl₂ system as seen in THF-py; on the contrary, the extradiol oxygenation is promoted when 10 is unstable as seen in THF-H₂O

We thank the Ministry of Education, Science, and Culture for Grants.

Received, 22nd March 1994; Com. 4/01719F

References

- 1 O. Hayaishi, M. Katagiri and S. Rothberg, J. Am. Chem. Soc., 1955, 77, 5450.
- 2 T. Funabiki, H. Sakamoto, S. Yoshida and K. Tarama, J. Chem. Soc., Chem. Commun., 1979, 754.
- 3 D. D. Cox, S. J. Benkavic, L. M. Bloom, F. C. Bradley, M. J. Nelson and L. Que, Jr., *J. Am. Chem. Soc.*, 1988, **110**, 2026; D. D. Cox and L. Que, Jr., *J. Am. Chem. Soc.*, 1988, **110**, 8085.
- 4 T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Tada, M. Tsuji, H. Sakamoto and S. Yoshida, J. Am. Chem. Soc., 1986, 108, 2921.
- 5 T. Funabiki, H. Kojima, M. Kaneko, T. Inoue, T. Yoshioka, T. Tanaka and S. Yoshida, *Chem. Lett.*, 1991, 2143.
- 6 T. Funabiki, Y. Nagai, H. Kojima, T. Inoue, T. Tanaka, and S. Yoshida, to be published.
- 7 P. A. Mabrouk, A. M. Orville, J. D. Lipscomb and E. I. Solomon, J. Am. Chem. Soc., 1991, 113, 4053.
- 8 T. Funabiki, T. Inoue, H. Kojima, T. Konishi, T. Tanaka and S. Yoshida, J. Mol. Catal., 1990, 59, 367.