Aromatic Hydroxylation by a New Iron(0)–Acetic Acid–Dioxygen System

Arthur François Duprat,* Patrice Capdevielle and Michel Maumy

Laboratoire de recherches organiques de l'ESPCI, associé au CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

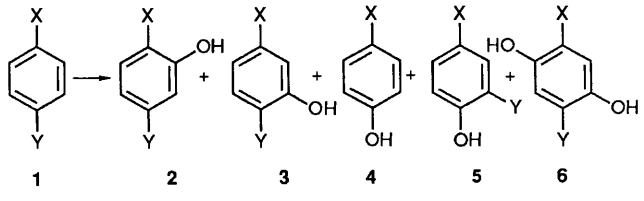
A new and simple system performs the hydroxylation of a number of aromatic compounds with moderate yields; a mechanism involving transitory formation of electrophilic Fe^{IV} oxo (ferryl) species is proposed and discussed.

Cytochrome P-450 enzymes represent an extraordinarily versatile class of biological iron-containing oxidation catalysts which are responsible for the metabolism of both endogenous and exogenous lipophilic substrates[1]. In recent years several models which mimic the activity of cytochrome P-450 have been explored to understand better this monooxygenases catalytic cycle as well as to develop new synthetic methods; high catalytic turnovers and remarkable regio- and stereoselectivity have recently been reported for alkene epoxidations and alkane hydroxylations.[2] On the other hand, the

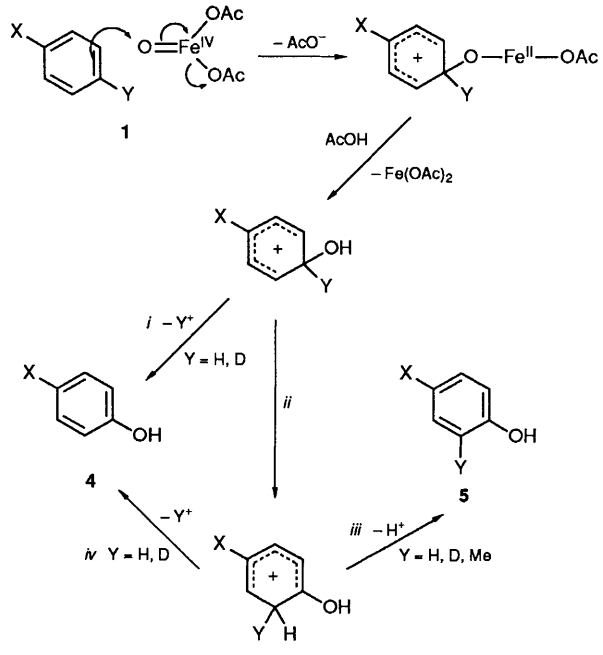
hydroxylation of aromatic substrates has not been the centre of interest in studies with P-450 model compounds. Thus, no major advance has been made since the results obtained with systems like Fenton's,[3] Udenfriend's,[4] Ullrich's[5] or Mimoun's.[6] The Gif system, discovered by Barton *et al.*,[7] which is very efficient with hydrocarbons as a model of alkane monooxygenase, provides only traces of phenol from benzene.[8] Some porphyrin systems are able to hydroxylate aromatic compounds, but the yields are moderate and no selectivity is observed.[9]

In this communication we describe a new and quite simple system where dioxygen is reductively activated by iron(II) generated by corrosion of Fe^0 in acetic acid, and in which several aromatic compounds are hydroxylated according to Scheme 1, with satisfactory yields. In a typical experiment, iron rods (43 mmol) and the substrate (10 mmol) were stirred in acetic acid (20 ml) under a dioxygen atmosphere at 90 °C, until the iron had been completely consumed. The brown precipitate of iron(III) acetate was discarded and the acidic mixture worked up for analysis. In the absence of dioxygen no products were detected; iron(III) acetate in acetic acid at 90 °C under O_2, in the absence of Fe^0, does not give any detectable oxidation.

The hydroxylation of various substrates is reported in Table 1. Moderate yields and selectivities are obtained with benzenic hydrocarbons **1a–d**. Higher conversions, yields and selectivities are observed for substrates bearing π-electron donating substituents (**1e,f** and 1,3,5-trimethoxybenzene). Anisole **1e** and acetanilide **1f** give mainly *ortho*- and *para*-phenols in equal amounts (after correction due to the statistical factor); the corresponding *meta*-isomers are more oxidisable in the reaction medium than the *ortho*- and *para*-phenols, but this greater oxidisability cannot alone account for the low proportion or the absence of the *meta*-substituted phenols (as shown by preliminary stability studies). With strong π-electron-acceptor substituents (nitrobenzene and acetophenone, **1g, h**), the oxygenation is more difficult to achieve and conversion is lowered, meta-phenols being chiefly obtained. Phenols arising from hydroxylation are more reactive than the starting substrates, so in most cases dihydroxy compounds (mainly as hydroquinones) are isolated, especially from benzene and toluene. Interestingly, with [4-$^2H_1$]toluene **1c**, an NIH shift of deuterium, typical of aromatic hydroxylation by P-450 monooxygenases,[10] is observed (Scheme 2, path *ii* + *iii*). Analysis of *p*-cresol indicates a retention of 26% of the initial deuterium in the *meta*-position, *i.e.* a ratio of **4c** to **5c** of 2.8 (26% = 22/85 and 2.8 = 74/26, where 85% is the deuterium content of starting toluene). A much less common methyl NIH shift[11] is also observed from *p*-xylene **1d**; 0.3% of **5d** could be determined besides 5.3% of the 'normal' hydroxylation product, **2d**, *i.e.* 5% of methyl migration. Finally, oxidation of a 1:1 mixture of normal and perdeuteriated toluene was carried out. No significant nuclear isotope effect (k_H/k_D = 1.02 ± 0.02) was associated with the *ortho*-, *meta*- and *para*-hydroxylations of toluene. A similar result was pointed out by Jerina *et al.*[12] during formation of phenols by hepatic monooxygenases.



Scheme 1 *Conditions*: Fe^0–O_2–AcOH, 90 °C



Scheme 2 Proposed *para*-hydroxylation mechanism by ferryl species

Table 1 Hydroxylation of aromatic compounds with Fe^0–O_2–AcOH

	Substrate[f] 1	X	Y	Conversion (%)[a]	Total yield of hydroxylation (%)[a]	Yield (%)[a] 2	3	4	5	6
a	Benzene	H	H	[d]	7.9 —	4.0				3.8
b	Toluene[b]	Me	H	[d]	8.9 —	3.5	1.6	1.7		2.0
						52	*23*	*25*		
c	[4-$^2H_1$]Toluene (85% D)	Me	D	[e]	[e]	[e]	[e]	*78*	*22*	[e]
d	*p*-Xylene[b]	Me	Me	60	7.2 (12)	5.3	—	—	0.3	1.6
e	Anisole[c]	OMe	H	52	15.6 (30)	9.6	—	6.0		
						62		*38*		
f	Acetanilide	NHAc	H	52	18.8 (36)	12.6	0.3	5.9		
						67	*2*	*31*		
g	Nitrobenzene	NO_2	H	20	1.5 (8)	—	1.4	<0.1		
							95	*5*		
h	Acetophenone	COMe	H	20	2.6 (13)	0.3	1.6	0.3		0.4
						14	*72*	*14*		

[a] Conversion and yields (based on starting materials) are determined by GLC; value in brackets is yield based on substrate reacted. Isomer distributions for monophenols are in italics. [b] With methyl substituents benzylic oxidation was observed, yielding 3.4 and 11.2% of additional products for **1b** and **1f** respectively. [c] In addition, 5.2% of the *O*-demethylation phenol was observed; this important reaction is developed elsewhere. [d] No starting material was recovered after workup. [e] Not determined. [f] 1,3,5-Trimethoxybenzene afforded 27% (46%) of 2,4,6-trimethoxyphenol with 59% conversion.

These preliminary results suggest that a powerful electrophilic oxidizing species is responsible for hydroxylation of benzenic compounds *via* a cationic intermediate. This species is unlikely to be of Fenton's type (HO· radical intermediate) since: (*i*) in contrast with our data (no detectable trace of *p*-cresol), in the classical Fenton's system *p*-xylene mainly affords *p*-cresol (75%) by an *ipso*-substitution reaction,[13] without any methyl shift; (*ii*) nitrobenzene is found to give mainly the *meta*-isomer when the *ortho*- and *para*-positions are attacked under Fenton's conditions;[14] (*iii*) the rate of oxidation of anisole is not affected by addition of significant amounts of dioxane in the system whereas HO· readily reacts with dioxane.[15]

In all cases, the isomer ratios give support to the hypothesis of a strong electrophilic oxidant.[16]

Formation of an electrophilic intermediate, Fe^{IV}=O (ferryl), first proposed by Bray and Gorin[17] in 1932, requires the initial production of iron(II) acetate by corrosion of Fe^0 in hot acetic acid. We postulate then, according to Hammond and Wu,[18] the homolytic cleavage of an early formed μ-peroxo-diiron(III) intermediate to afford a reactive oxo-iron(IV) species (ferryl) [eqn. (1)].

$$2(AcO)_2Fe^{II} + O_2 \rightarrow [(AcO)_2Fe^{III}\text{–O–O-}Fe^{III}(OAc)_2] \rightarrow 2[(AcO)_2Fe^{IV}{=}O \longleftrightarrow (AcO)_2Fe^{III}\text{–O}\cdot] \quad (1)$$

This short-lived intermediate could be responsible for the oxidation of the organic substrates according to Scheme 2 (written for the *para*-hydroxylation) which is a simplification of the numerous potential chemical mechanisms for cytochrome P-450 catalysed aromatic hydroxylations.[1a,19] The addition of $(AcO)_2Fe^{IV}$=O to the aromatic moiety is in competition with its reduction by iron(II) to afford iron(III) acetate, a problem which is general for biomimetic oxidations in the presence of a reducing agent.[20] It can explain the moderate efficiency of the system, since only a small fraction of iron (≤10%) is effective for hydroxylation.

Further interest in this system lies in its encouraging yields of phenols, and its mechanistic value as a model for mimicking the hydroxylation of aromatic compounds by monooxygenases, since such a simple model has not so far been studied.

Received, 8th October 1990; Com. 0/04528D

References

1 (*a*) P. R. Ortiz de Montellano, ed., *Cytochrome P-450*, Plenum, New York, 1986; (*b*) F. P. Guengerich and T. L. MacDonald, *Acc. Chem. Res.*, 1984, **17**, 9.

2 J. T. Groves, *J. Chem. Educ.*, 1985, **62**, 928; J. P. Collman, T. Kodadek and J. I. Brauman, *J. Am. Chem. Soc.*, 1986, **108**, 2588; B. Meunier, *Bull. Soc. Chim. Fr.*, 1986, 578; D. Mansuy, *Eur. J. Biochem.*, 1989, **184**, 267; D. H. R. Barton, F. Halley, N. Ozbalik, E. Young, G. Balavoine, A. Gref and J. Boivin, *New J. Chem.*, 1989, **13**, 177, and references cited therein.

3 H. J. H. Fenton, *J. Chem. Soc.*, 1894, **65**, 899; M. Martinon, *Bull. Soc. Chim. Fr.*, 1885, **43[2]**, 155; C. Walling, *Acc. Chem. Res.*, 1975, **8**, 125, and references cited therein.

4 B. B. Brodie, J. Axelrod, P. A. Shore and S. Udenfriend, *J. Biol. Chem.*, 1954, **208**, 741.

5 V. Ullrich, E. Amadori and H. Staudinger, *Z. Naturforsch., Teil B*, 1967, **22**, 226; V. Ullrich, D. Hey, H. Staudinger, H. Büch and W. Rummel, *Biochem. Pharm.*, 1967, **16**, 2237.

6 H. Mimoun and I. Seree de Roch, *Tetrahedron*, 1975, **31**, 777.

7 D. H. R. Barton, M. J. Gastiger and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1983, 41.

8 D. H. R. Barton, F. Halley, N. Ozbalik and W. Mehl, *Tetrahedron Lett.*, 1989, **30**, 6615.

9 C. K. Chang and F. Ebina, *J. Chem. Soc., Chem. Commun.*, 1981, 778; J. R. Lindsay Smith and P. R. Sleath, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1009; I. Tabushi and M. Morimitsu, *Tetrahedron Lett.*, 1986, **27**, 51.

10 G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop and S. Udenfriend, *Science*, 1967, **157**, 1524.

11 J. Daly, *Biochem, Pharm.*, 1970, **19**, 2979; W. Dünges, *Nature New Biology*, 1973, **243**, 60.

12 J. E. Tomaszewski, D. M. Jerina and J. W. Daly, *Biochemistry*, 1975, **14**, 2024.

13 J. O. Apatu, D. C. Chapman and H. Heaney, *J. Chem. Soc., Chem. Commun.*, 1981, 1079.

14 H. Loebls, G. Stein and J. Weiss, *J. Chem. Soc.*, 1949, 2074; R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.*, 1962, 138.

15 K. U. Ingold, in *Free Radicals*, ed. J. K. Kochi, Wiley, New York, 1973, p. 37.

16 F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 3rd edn., Plenum Press, 1990, Part A, p. 539.

17 W. C. Bray and M. H. Gorin, *J. Am. Chem. Soc.*, 1932, **54**, 2124.

18 G. S. Hammond and C-H. S. Wu, *Adv. Chem. Ser.*, 1968, **77**, 187.

19 R. P. Hanzlik, K. Hogberg and C. M. Judson, *Biochemistry*, 1984, **23**, 3048.

20 P. Battioni, J-F. Bartoli, P. Leduc, M. Fontecave and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 1987, 791.