Aromatic Hydroxylation. Part 6.[1] Oxidation of Naphthalene by Dioxygen in the Presence of Iron(II) Salts

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The major products from the oxidation of naphthalene with dioxygen in the presence of an iron(II) salt and an organic reducing agent are *cis*- and *trans*-1,2-dihydroxy-1,2-dihydronaphthalene, 2,3-epoxy-3,4-dihydro-*cis*- and -*trans*-4-hydroxynaphthalen-1(2*H*)-one, *cis*-2-formylcinnamaldehyde, and 1- and 2-naphthol. A series of labelling experiments using $^{18}O_2$ and deuterionaphthalenes reveal the origin of the oxygen in the dihydrodiols and quinone epoxides and the absence of a large value of the NIH shift for formation of 1- or 2-naphthol. The suggested mechanism involves a free radical co-oxidation of naphthalene and the organic reducing agent by dioxygen with iron–oxygen complexes, behaving as oxy-radicals, as the active oxidising species.

In the last ten years very significant progress has been made in unravelling the mechanisms used by biological systems for the direct incorporation of oxygen from dioxygen into aromatic molecules,[2] and in particular much detailed information is now available about the action of the mono-oxygenases.[2b] By contrast little is known of the mechanism of aromatic oxygenation by the chemical ' model ' system which utilise dioxygen.[2b,d-f,3] Although similar in a number of respects, both the chemical and biological systems require a redox system (autoxidisable metal ion and/or an organic reducing agent) and are capable of oxidising aromatic compounds under mild conditions; the chemical systems seem to involve mechanisms different from the biological analogues. Ironically rather than mechanistic studies of the ' model ' systems helping in the understanding of the mono-oxygenases the reverse is now more correct.

Of the ' model ' systems that generate oxidants by the reduction of dioxygen, Udenfriend's system [aqueous Fe^{II} ion, ascorbic acid, ethylenediamine tetra-acetic acid (EDTA), and dioxygen] [4] has been the most extensively investigated. These studies have included modifications of the system such as the removal of ascorbic acid [5] or its replacement with other organic reducing agents [6] or exchanging Fe^{II} ion for other autoxidisable metal ions.[2f,3a,6c,7] More recently a related system involving Fe^{II} ion, 2-mercaptobenzoic acid, and dioxygen with aqueous acetone as solvent was reported by Ullrich.[8] In all the investigations the major criteria that have been used to assess the chemical hydroxylating systems as models for mono-oxygenases have included substrate specificity, product distribution, and the magnitude of the NIH shift.

Several oxidising species have been suggested, namely,

[1] Part V, R. Higgins, K. M. Kitson, and J. R. Lindsay Smith, *J. Chem. Soc.* (*B*), 1971, 430.

[2] (*a*) O. Hayaishi, *Ann. Rev. Biochem.*, 1969, **38**, 21; (*b*) D. M. Jerina, J. W. Daly, and B. Witkop, in ' Biogenic Amines and Physiological Membranes in Drug Therapy, Part B,' eds. J. H. Biel and L. G. Abood, Marcel Dekker, New York, 1971, p. 413; (*c*) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 1972, **28**, 1129; (*d*) V. Ullrich, *Angew. Chem. Internat. Edn.*, 1972, **11**, 701; (*e*) G. A. Hamilton, in ' Molecular Mechanisms of Oxygen Activation,' ed. O. Hayaishi, Academic Press, New York, 1974, p. 405; (*f*) A. A. Akhrem, D. I. Metelitsa, and M. E. Skurdo, *Russ. Chem. Rev.*, 1975, **44**, 398.

[3] (*a*) M. B. Dearden, C. R. E. Jefcoate, and J. R. Lindsay Smith, *Adv. Chem. Ser.*, 1968, **77**, 260; (*b*) D. M. Jerina, *Chem. Tech.*, 1973, **4**, 120.

[4] (*a*) S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, *J. Biol. Chem.*, 1954, **206**, 731; (*b*) B. B. Brodie, J. Axelrod, P. A. Shore, and S. Udenfriend, *ibid.*, p. 741.

[5] C. Nofre, A. Cier, and A. Lefier, *Bull. Soc. chim. France*, 1961, 530.

[6] (*a*) G. A. Hamilton, R. J. Workman, and L. Woo, *J. Amer. Chem. Soc.*, 1964, **86**, 3390; (*b*) M. Viscontini, H. Leidner, G. Mattern, and T. Okada, *Helv. Chim. Acta*, 1966, **49**, 1911; (*c*) H. Staudinger, B. Kerekjarto, V. Ullrich, and Z. Zubrzycki, in ' Oxidases and Related Redox Systems,' eds. T. King, H. S. Mason, and M. Morrison, Wiley, New York, 1965, p. 815.

[7] (*a*) V. Ullrich, D. Hey, H. Staudinger, H. Buch, and W. Rummel, *Biochem. Pharmacol.*, 1967, **16**, 2237; (*b*) H. Mimoun and I. Seree de Rah, *Tetrahedron*, 1975, **31**, 777.

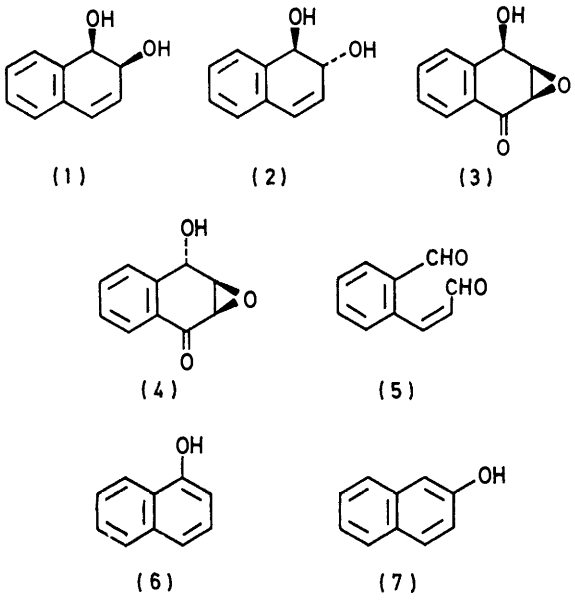
[8] V. Ullrich, *Z. Naturforsch.*, 1969, **24b**, 699.

the hydroxyl [5,6c,7a,9] and superoxide radicals,[6c,9b] and metal–oxygen complexes which behave either as oxy-radicals [3a,9c] or oxenoid intermediates [7b,8,10] (species that are capable of releasing either singlet or triplet oxygen atoms). However, the exact nature of the hydroxylating entities in these chemical systems remains unknown.

In this paper we report the results of our work on the hydroxylation of naphthalene by these chemical hydroxylating systems.

RESULTS AND DISCUSSION

Oxidation with Fe^{II} *Ion, 2-Mercaptobenzoic Acid and Dioxygen.*—When a solution of naphthalene in acetone containing Fe^{II} ion and 2-mercaptobenzoic acid was agitated in the presence of dioxygen oxidation products (1)–(7) were obtained. The formation of naphthols (6) and (7) of 3.2 was obtained. This value agrees well with that reported by Ullrich (4.0).[8]



quinones in this reaction was not investigated. In a previous study Ullrich detected compounds (2), (6), and (7) and suggested that this system provided a suitable model for the activation of dioxygen by cytochrome P-450.[8]

Although the absolute yields of these products were not determined the following amounts were isolated by preparative t.l.c. from a typical large scale reaction: (1) 27 mg, (2) 85 mg, (3) 28 mg, and (4) 62 mg. A reaction one-tenth the size of the above gave (5) 0.75 mg. The naphthols were not isolated; however, from a separate experiment using [*U*-^{14}C]naphthalene a ratio of 1,2-dihydroxy-1,2-dihydronaphthalenes (1) and (2) to naphthols (6) and (7) of 3.2 was obtained. This value agrees well with that reported by Ullrich (4.0).[8]

Table 1 records the deuterium content of products

TABLE 1

Amount of deuterium label retained (as % that in deuterionaphthalene) in products from oxidation of [1,4- and 2,6-$^2H_2$]naphthalene with iron(II) sulphate, 2-mercaptobenzoic acid, and dioxygen

	Deuterium retained (%) in products				
Substrate	(1)	(2)	(4)	(6)	(7)
[1,4-$^2H_2$]naphthalene	100	100	40—50	55.5	94.5
[2,6-$^2H_2$]naphthalene	100	100	100	100	47

(1), (2), (4), (6), and (7) when [1,4-$^2H_2$]- or [2,6-$^2H_2$]-naphthalene was used in place of naphthalene. These results indicate that there is no NIH shift for 2-hydroxylation [product (7)] and give a maximum value of 11% for 1-hydroxylation [product (6)]. These low values for the NIH shift agree well with previous results from the oxidation of benzenoid substrates with other chemical systems using dioxygen.[3a,11] As expected the *cis*- and *trans*-dihydrodiols (1) and (2) retain all the deuterium label whether the substrate is 1- or 2-deuteriated. The quinone epoxide (4) from [2,6-$^2H_2$]naphthalene shows complete retention of deuterium whilst 1.0—1.2 deuterium atoms are lost when [1,4-$^2H_2$]naphthalene is the substrate.

The oxidation of naphthalene was repeated with $^{18}O_2$ (98%) and with $^{18}O_2$ diluted with $^{16}O_2$ (56.3% $^{18}O_2$, 44.7% $^{16}O_2$) and the isotopic distribution of oxygen in the products (1)—(4) was measured (Table 2). For (1) or (2) the results show that not only are both the oxygen atoms derived from dioxygen but that each oxygen atom arises from a different dioxygen molecule. Previous studies [10c,12] using chemical hydroxylating systems with

TABLE 2

Percentages of each product with one, two, or three ^{18}O atoms from oxidation of naphthalene with iron(II) sulphate, 2-mercaptobenzoic acid, and labelled dioxygen

Product	$^{18}O_0$	$^{18}O_1$	$^{18}O_2$	$^{18}O_3$
(*a*) $^{18}O_2$ (>98%) *				
(1)	0	<1	100	
(2)	0	<1	100	
(3)	<1	4	79	16
(4)	<1	3	61	35
(*b*) $^{16}O_2$ (44.7%) with $^{18}O_2$ (55.3%) †				
(1) ‡	24	49	27	
(2) ‡	25	48	27	
(3)	22	51	27	<1
(4)	22	49	29	<1

* A hydrogen carbonate wash was used in the work-up of products. † A carbonate wash was used in the work-up of products. ‡ Percentages of ^{18}O in diols predicted if both oxygen atoms come from one molecule of dioxygen, $^{18}O_0$, 45; $^{18}O_1$, 0; and $^{18}O_2$, 55: if oxygen atoms come from different dioxygen molecules, $^{18}O_0$, 21; $^{18}O_1$, 51; and $^{18}O_2$, 28.

[9] (*a*) R. C. Krueger, *Fed. Proc.*, 1956, **15**, 294; (*b*) R. R. Grinstead, *J. Amer. Chem. Soc.*, 1960, **82**, 3472; (*c*) J. A. Blair and A. J. Pearson, *J.C.S. Perkin II*, 1975, 245.

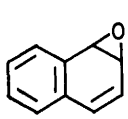
[10] (*a*) G. A. Hamilton, *J. Amer. Chem. Soc.*, 1964, **86**, 3391; (*b*) V. Ullrich, and H. Staudinger, in 'Biological and Chemical Aspects of Oxygenases' eds. K. Bloch and O. Hayaishi, Maruzen, Tokyo, 1966, p. 235; (*c*) V. Ullrich and H. Staudinger, *Z. Naturforsch.*, 1969, **24b**, 583; (*d*) L. I. Woolf, A. Jakubovic, and E. Chan-Henry, *Biochem. J.*, 1971, **125** 569.

[11] (*a*) D. Jerina, J. Daly, W. Landis, B. Witkop, and S. Udenfriend, *J. Amer. Chem. Soc.*, 1967, **89**, 3347; (*b*) J. R. Lindsay Smith, D. M. Jerina, S. Kaufman, and S. Milstein, *J.C.S. Chem. Comm.*, 1975, 881.

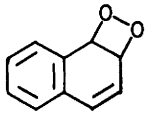
[12] H. S. Mason and I. Onoprienko, *Fed. Proc.*, 1956, **15**, 310.

$^{18}O_2$ which were limited to examining only phenolic products showed that the origin of the oxygen in these materials is dioxygen.

The oxygen isotopic content of the dihydrodiols and the presence of both *cis*- and *trans*-isomers eliminates both (8) and (9) as their likely precursors. Enzymic



(8)



(9)

hydration of the oxide (8) [2c] or its reaction with nucleophiles [13] is known to give only *trans*-1,2-dihydro-derivatives; further the oxygen in the 2-position in a product from such a reaction would have been derived from the solvent. Reduction of the dioxetan (9) would give only the *cis*-dihydrodiol (1) with both oxygen atoms derived from one molecule of dioxygen.[14]

The three oxygen atoms in the quinone epoxides (3) and (4) originate in dioxygen. Unfortunately the ready exchange of the carbonyl oxygen in the work-up procedure prevents an unambiguous assignment of its origin; however, the results show that the other two oxygen atoms are derived from different dioxygen molecules.

Attempts to oxidise compounds (1)—(3), (6), (7), 1,2-naphthoquinone, 1,4-naphthoquinone, or its 2,3-oxide in place of naphthalene with the Fe^{II} ion–2-mercaptobenzoic acid system either decomposed the substrate or gave recovered starting material. In no case did any of these compounds lead to other products observed in the oxidation of naphthalene.

Oxidation with Iron(II) *Sulphate, EDTA, Ascorbic Acid, and Dioxygen.*—A stirred suspension of naphthalene, [*U*-^{14}C]naphthalene, or [1,4,5,8-$^2H_4$]naphthalene, in aqueous iron(II) sulphate, EDTA, and ascorbic acid was oxidised by dioxygen to give products (1), (2), (5)—(7), and a trace of (8). The yields of oxidation products from this system are markedly lower than those from systems using 2-mercaptobenzoic acid in acetone. Boyland and his co-workers [15] in a previous study of the oxidation of naphthalene with this chemical hydroxylating system reported 1,2-dihydroxy-1,2-dihydronaphthalene of unspecified stereochemistry and the naphthols (6) and (7). The ^1H n.m.r. spectrum of the dihydrodiols isolated by preparative t.l.c. showed that the *trans*-isomer was the predominant product.[16] T.l.c. studies suggested (4) and 1,2-dihydroxynaphthalene were probable trace products although the amounts formed were too small for positive confirmation. The presence of naphthoquinones in the reaction was not investigated.

The relative yields of the naphthalene dihydrodiols (1) and (2) to naphthols (6) and (7) from a series of experiments using varying amounts of iron(II) sulphate and ascorbic acid are recorded in Table 3. The values

TABLE 3

Relative yields (%) of 1,2-dihydroxy-1,2-dihydrodiols and naphthols from the oxidation of [*U*-^{14}C]naphthalene with a selection of hydroxylating systems.

Hydroxylating system	Yields (%) of Dihydrodiol	Naphthol
Fe^{II}–ascorbic acid–O_2	9	91
Fe^{II}–2-mercaptobenzoic acid–O_2	76	24
Fe^{II}–O_2	7	93
Cu^{I}–O_2	33	67
Ti^{III}–O_2	45	55
Fe^{II}–H_2O_2	1	99

obtained from oxidations in the absence of ascorbic acid using Fe^{II}, Cu^{I}, or Ti^{III} salts and from Fenton's reagent (Fe^{II} ion with hydrogen peroxide) are included for comparison. It is noteworthy that the relative yields vary with the hydroxylating conditions although with Fe^{II} ion–dioxygen systems this value is unaffected by the presence of ascorbic acid.

The naphthol isomer distribution (Table 4) varies with

TABLE 4

Relative yields (%) of 1- and 2-naphthols from the oxidation of naphthalene and [1,4,5,8-$^2H_4$]naphthalene with iron(II) sulphate, ascorbic acid, and dioxygen

[Iron(II) sulphate]/mM	[Ascorbic acid]/mM	[Substrate]/mM	Yields (%) of 1-naphthol	2-naphthol
4.6	33	$C_{10}H_8$	82	18
4.6	33	$C_{10}H_4D_4$	75	25
14.4	33	$C_{10}H_8$	70	30
14.4	33	$C_{10}H_4D_4$	61.5	38.5
18.0	33	$C_{10}H_8$	66	34
18.0	33	$C_{10}H_4D_4$	57.5	42.5
14.4	66	$C_{10}H_8$	58	42
14.4	66	$C_{10}H_4D_4$	52.5	47.5

the intial concentration of Fe^{II} ion and ascorbic acid in the hydroxylating system; similar effects have been observed for the oxidation of benzenoid derivatives.[3a] Interestingly when naphthalene was replaced by [1,4,5,8-$^2H_4$]naphthalene the yield of 1-naphthol relative to that of the 2-isomer was decreased; however, we were unable to distinguish between a decrease in the yield of 1-naphthol with concomitant increase in 2-naphthol and a simple decrease in the amount of 1-naphthol. This isotope effect is being investigated in more detail using deuteriated benzenoid derivatives.

When (2) or the dihydrodiol mixture obtained from the oxidation of [1,4,5,8-$^2H_4$]naphthalene was reacted in place of naphthalene the material recovered was predominantly unchanged substrate with a small amount of 1-naphthol. The dehydration of (1) and (2) in aqueous acid is known to give predominantly 1-naphthol with $<5\%$ of the 2-isomer.[14]

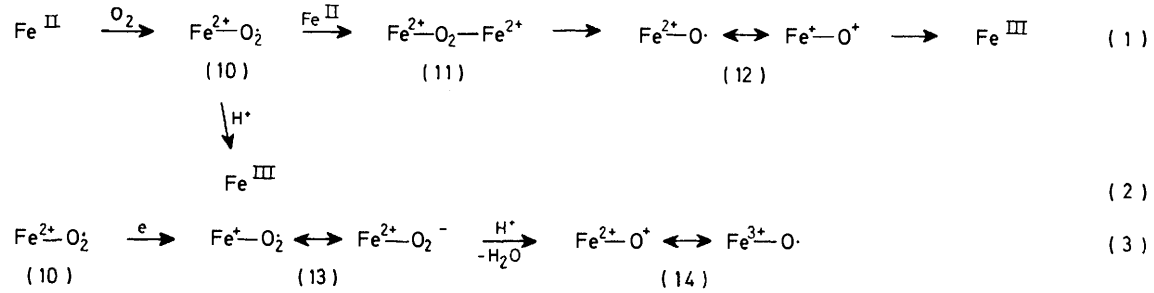
[13] A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. De Mannis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, *J. Amer. Chem. Soc.*, 1974, **96**, 6929.

[14] A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, T. R. Patel, J. F. Davey, and D. T. Gibson, *Biochem.*, 1975, **14**, 575.

[15] E. Boyland, M. Kimura and P. Sims, *Biochem. J.*, 1964, **92**, 631.

[16] D. M. Jerina, J. W. Daly, A. M. Jeffrey, and D. T. Gibson, *Arch. Biochem. Biophys.*, 1971, **142**, 394.

Mechanism.—Both the chemical hydroxylating systems give a similar range of oxidation products from naphthalene and in our opinion their mechanisms are also closely similar. The relative yields of the products from the two systems differ owing to the dependence of the individual steps on the reaction conditions. Hydroxylation by these systems is associated with small or negligible NIH shift values suggesting that the reactions are radical and not ionic processes. Chemical and biological hydroxylating systems that generate cationic intermediates directly or indirectly *via* the isomerism of arene oxides show significant values for the NIH shift [2b,c,11a] whereas hydroxylation by the hydroxyl radical is associated with small shift values.[11a,17]



The oxidation of alkenes with Udenfriend's system gives small amounts of alkene oxides;[18] however, the major products involve allylic oxidation and the mechanism is best rationalised as an alkene autoxidation [19] with the alkene oxides arising from the reaction of alkylperoxyl radicals with the alkenes.[19,20] We conclude that aromatic hydroxylation by these chemical hydroxylating systems does not involve oxene or an oxenoid oxidising species [10a] or arene oxides.

Although the hydroxyl radical, and the superoxide radical or its anion have been invoked as reactive intermediates in chemical hydroxylating systems that require metal ions and dioxygen,[5,6c,7a,9a] there is evidence that these systems do not generate significant amounts of hydrogen peroxide [6a,7b,9b,c,21] and do not involve these radicals.[3] Metal ion-oxygen complexes which offer attractive alternative oxidising species [2f,3a,10a,22] were suggested from the dependence of the phenolic isomer distribution, from the oxidation of benzenoid compounds, on the metal ion used.[3a,22] More recently Julia and his co-workers,[23] who examined the hydroxylation of phenyl glycinate, 1-methoxy-2-phenoxyethane, and 1-dimethylamino-2-phenoxyethane with Udenfriend's system, concluded from the strong preference for 2-hydroxylation of the aromatic ring that intramolecular hydroxylation had occurred by a hydroxylating species attached *via* a metal ion to the heteroatom in the side chain. Further evidence for metal ion–oxygen complexes being the oxidants in these systems comes from recent studies by Blair and Pearson [9c] and by Metelitsa and his co-workers.[2f,24]

Although the detailed mechanisms of the steps involved in the autoxidation of Fe^{II} ions are not known they can be represented by the general equations (1) and (2).[25] Evidence for these steps comes from kinetic studies,[25a] from the preparations of Fe^{II} complexes (10) capable of reversible oxygenation,[25b,26] and the recent preparation of a binuclear complex (11) beteeen Fe^{II} and dioxygen.[27]

The mechanism by which cytochrome P-450 activates dioxygen in biological systems for aromatic hydroxylation is thought to involve the formation of an Fe^{II}–dioxygen complex (10) followed by one-electron reduction to give (13). The active oxidant is either (13) [2d] or is derived from (13) by loss of water.[28]

We propose that the active species in the chemical hydroxylating systems studied here are metal ion–oxygen complexes acting as radical oxidants. Possible complexes include those of dioxygen, (10) and (13) (Fe^{II} and Fe^{III} derivatives of superoxide or peroxide), and those of mono-oxygen, (12) and (14) (iron derivatives of the hydroxyl radical). It is noteworthy that iron–oxygen complexes can in principle act as ionic or radical

[17] (*a*) C. R. E. Jefcoate, J. R. Lindsay Smith, and R. O. C. Norman, *J. Chem. Soc.* (*B*), 1969, 1013; (*b*) B. A. J. Shaw, D.Phil. Thesis, 1971, University of York.

[18] J. R. Lindsay Smith, B. A. J. Shaw, and D. M. Foulkes, unpublished work.

[19] (*a*) F. R. Mayo, *Acc. Chem. Res.*, 1968, **1**, 193; (*b*) R. A. Sheldon and J. K. Kochi, *Oxidation Combustion Rev.*, 1973, **5**, 135.

[20] (*a*) G. H. Twigg, *Chem. and Ind.*, 1962, 4; (*b*) S. J. Moss and H. Steiner, *J. Chem. Soc.*, 1965, 2372.

[21] R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.*, 1962, 138.

[22] R. O. C. Norman and J. R. Lindsay Smith, in 'Oxidases and Related Redox Systems,' eds. T. King, H. S. Mason, and M. Morrison, Wiley, New York, 1965, p. 131.

[23] (*a*) P.-E. Bost, F. Ricalens, and M. Julia, *Compt. rend.*, 1972, **275c**, 577; (*b*) M. Julia and P.-E. Bost, *ibid.*, 1973, **276c**, 1195.

[24] A. A. Akhrem, M. E. Skurbo, D. I. Metelitsa, and S. M. Bel'ski, *Kinetika i Kataliz*, 1975, **16**, 366.

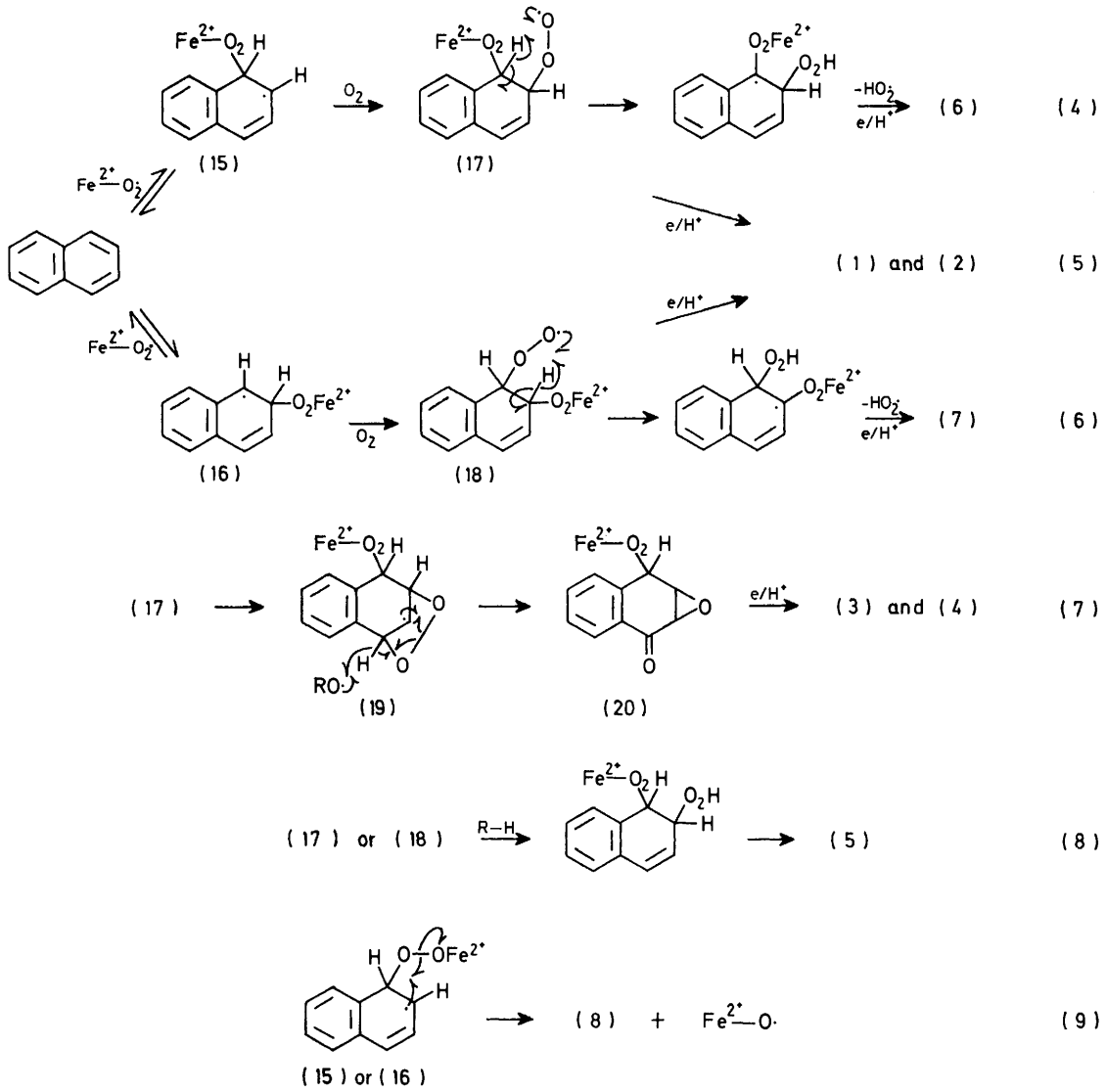
[25] (*a*) G. S. Hammond and C.-H. S. Wu, *Adv. Chem. Ser.*, 1968, **77**, 186; (*b*) W. S. Brinigar, C. K. Chang, J. Geibel, and T. G. Traylor, *J. Amer. Chem. Soc.*, 1974, **96**, 5597.

[26] (*a*) J. P. Collman, R. R. Gagné, R. T. Habert, J.-C. Marchon, and C. A. Reed, *J. Amer. Chem. Soc.*, 1973, **95**, 7868; (*b*) J. P. Collman, R. R. Gagné, and C. A. Reed, *ibid.*, 1974, **96**, 2629; (*c*) W. S. Brinigar and C. K. Chang, *ibid.*, p. 5595; (*d*) J. Almog, J. E. Baldwin, and J. Huff, *ibid.*, 1975, **97**, 227; (*e*) O. Leal, D. L. Anderson, R. C. Bowman, F. Basolo, and R. L. Burwell, *ibid.*, p. 5125.

[27] V. McKee, S. M. Nelson, and J. Nelson, *J.C.S. Chem. Comm.*, 1976, 225.

[28] (*a*) J. H. Dawson, R. H. Holm, J. R. Trudell, G. Barth, R. E. Linder, E. Bunnenberg, C. Djerassi, and S. C. Tang, *J. Amer. Chem. Soc.*, 1976, **98**, 3707; (*b*) F. Lichtenberger, W. Nastainczyk, and V. Ullrich, *Biochem. Biophys., Res. Comm.* 1976, **70**, 939.

oxidants [29] and both diamagnetic and paramagnetic dioxygen complexes of iron(II) have been prepared.[26b] Since, however, there is insufficient evidence to decide which of the iron oxygen complexes is (are) the oxidising species in these chemical systems the Fe^{II}–dioxygen complex (10) will be assumed to be the oxidant. The mechanism we propose for the oxidation of naphthalene [equations (4)—(9)] is illustrated using (10) but with only slight modification (10) can be replaced by another iron–oxygen species. The primary role of the ascorbic and 2-mercaptobenzoic acids in these hydroxylating systems is to reduce Fe^{III} to Fe^{II} ion. This regeneration of Fe^{II} ion should be seen as a step in the metal ion-catalysed free radical autoxidation of the organic acid [30]



and the overall process as a co-oxidation of naphthalene and organic reducing agent.

The initial addition of the oxidant to naphthalene is probably a reversible free-radical aromatic oxygenation [31] and the predominant fate of the adducts (15) and (16) is a rapid trapping by dioxygen. The latter process is comparable with the oxidation of cyclohexadienyl [32] or benzocyclohexadienyl [33] radicals by dioxygen. The closely related very fast reaction of alkyl radicals with

[29] V. Ullrich and H. Staudinger, in 'Microsomes and Drug Oxidation,' eds. J. R. Gillette, A. Conney, G. Cosmides, R. Estabrook, J. Fouts, and G. Mannering, Academic Press, New York, 1969, p. 199.

[30] (*a*) T. J. Wallace, A. Schriesheim, and W. Bartok, *J. Org. Chem.*, 1963, **28**, 1311; (*b*) M. M. Taqui Khan and A. E. Martell, *J. Amer. Chem. Soc.*, 1967, **89**, 4176; (*c*) Y. Ogata, Y. Kosugi, and T. Morimoto, *Tetrahedron*, 1968, **24**, 4057.

[31] (*a*) O. Volkert and D. Schulte-Frohlinde, *Tetrahedron Letters*, 1968, 2151; (*b*) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, 1968, **90**, 1818; (*c*) C. Walling and R. A. Johnson, *ibid.*, 1975, **97**, 363.

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[33] (*a*) I. Balakrishnan and M. P. Reddy, *J. Phys. Chem.*, 1968, **72**, 4609; (*b*) A. M. Jeffrey and D. M. Jerina, *J. Amer. Chem. Soc.*, 1972, **94**, 4048.

dioxygen is a well known process in the autoxidation of aliphatic compounds.[19] Spectroscopic evidence for the oxygen adduct of the hydroxycyclohexadienyl radical has been obtained from pulse radiolysis studies on aqueous benzene.[34] Loss of the superoxide radical from (17) and (18), probably by an internal abstraction, followed by reduction leads to the naphthols (6) and (7) respectively. Studies on the oxidation of cyclohexadienyl[32b] and hydroxycyclohexadienyl[34] radicals by dioxygen have shown that at low concentration the resulting cyclohexadienylperoxyl radicals are aromatised by a unimolecular elimination of superoxide radical. Intramolecular hydrogen abstraction, a typical reaction of oxy-radicals, would lead to the naphthols and would give a low value for the NIH shift.

Adducts (17) and (18) should be a mixture of *cis*- and *trans*-isomers although steric repulsions between the peroxy-groups should lead to a preponderance of the latter. This stereochemical preference is reflected in the relative proportions of (1) and (2), which probably arise by reductive cleavage of these adducts, for with both the chemical hydroxylating systems the *trans*-dihydrodiol (2) is the major product. The proposed route to (1) and (2) is in agreement with the $^{18}O_2$ labelling experiments.

The formation of the quinone epoxides (3) and (4) from adduct (17) involves a cyclisation to give the cyclic peroxyl radical (19) which is analogous to the mechanism for the isomerism of allylic peroxyl radicals.[35] The radical (19) is then oxidised with concomitant homolytic cleavage of the peroxide bond to give (20), as a mixture of *cis*- and *trans*-isomers, which reacts further to give (3) and (4).

The dialdehyde (5) probably arises from (17) or (18) by a modification of the mechanism for the formation of mucondialdehyde from benzene and hydroxyl radicals in the presence of dioxygen[32a,36] [equation (8)]. We favour this mechanism over an alternative *via* the cyclic peroxide (9) since there is no evidence for the formation of (9).

The trace of naphthalene 1,2-oxide (8) formed in the oxidation of naphthalene with Udenfriend's system probably arises from adducts (15) or (16) as shown in equation (9). Although other routes to the epoxides are possible we believe that this reaction which is equivalent to the epoxidation of alkenes by peroxyl radicals[20] is the most likely. Certainly epoxidation of naphthalene by the model systems studied in this work is not a major oxidation pathway.

EXPERIMENTAL

Materials.—Iron(II) sulphate, naphthalene, and acetone were AnalaR or research grade materials. Commerical ethylenediamine tetra-acetic acid disodium salt, 2-mercaptobenzoic acid, L-ascorbic acid, and 1- and 2-naphthol were used without further purification. [*U*-^{14}C]Naphthalene (diluted to 37.7 μCi mmol^{-1}) and $^{18}O_2$ (>98 atom %) were obtained from the Radiochemical Centre, Amersham and Isomet Corporation, respectively. The following compounds were prepared: (±)-*cis*-[37] and (±)-*trans*-1,2-dihydroxy-1,2-dihydronaphthalene,[38] [1,4-$^2H_2$]naphthalene[14] (10% $^2H_1$, 90% $^2H_2$), [2,6-$^2H_2$]naphthalene[14] (3% $^2H_0$, 21% $^2H_1$, 76% $^2H_2$), [1,4,5,8-$^2H_4$]naphthalene[39] (1.3% $^2H_1$, 18.4% $^2H_2$, 30.6% $^2H_3$, 47.5% $^2H_4$, 2.2% $^2H_5$), 2,3-epoxy-3,4-dihydro-*cis*- and -*trans*-4-hydroxynaphthalen-1(2*H*)-one,[40] and *cis*-2-formylcinnamaldehyde.[14]

Methods.—T.l.c. was performed on silica gel with fluorescent indicator using either Eastman chromatogram sheets (13181) or Analtech glass plates or plates prepared from silica GF_{254} (E. Merck). Glass columns were used in a Pye series 104 gas chromatograph with a flame ionisation detector for g.l.c. analyses.

^{1}H N.m.r. spectra were recorded at 100 and 60 MHz on Varian HA-100 and Perkin-Elmer R10 spectrometers, respectively. Mass spectra were measured with Hitachi RMU-7 and A.E.I. MS 12 and 9 spectrometers. An LKB combined gas chromatograph–mass spectrometer or a Pye chromatograph coupled to an A.E.I. MS 12 spectrometer was used to measure the deuterium content of the naphthols either as their trimethylsilyl ethers[41] or directly.

Oxidation using Iron(II) Ion, 2-Mercaptobenzoic Acid, and Dioxygen.—A solution of the substrate (0.1—0.5M), 2-mercaptobenzoic acid (0.1M), iron(II) sulphate (0.01M), and sodium hydroxide (0.005M) in aqueous 90% acetone (v/v) was vigorously shaken in air or dioxygen. The large scale reactions used 1 dm^3 of solvent whereas the isotopic labelling studies, the smallest experiments, employed 10 cm^3. When the initially blue solution had turned yellow, the white precipitate, 2,2′-dicarboxydiphenyl disulphide, was separated by centrifugation and the acetone removed by vacuum distillation. The residue was diluted with a little water, neutralised with saturated sodium carbonate, washed with 2-methylbutane, and extracted with ether. In some experiments an alternative procedure was used where the yellow reaction mixture was diluted with an equal volume of water, filtered, and the filtrate was extracted with ether. The ether solution of products was washed with sodium carbonate or hydrogen carbonate (5%) [this step was omitted in the analysis of products (5)—(7)], dried (Na_2SO_4 or $MgSO_4$), and analysed.

Products (1)—(5) were separated by preparative t.l.c. ($CHCl_3$) and the separated materials were eluted from the silica gel using methanol–ether (1 : 9). These products and the acetylated derivatives of (3) and (4) were identified by comparison of their n.m.r. and mass spectra with those of authentic compounds.

The relative yields of the dihydrodiols to naphthols were obtained using [*U*-^{14}C]naphthalene. The products were separated by t.l.c. [benzene–ethyl acetate–chloroform (1 : 1 : 1) with 5% triethylamine], eluted from the silica gel with methanol, and estimated by radioactive counting.

The isotopic contents of products (1)—(4) from experiments using deuterionaphthalene or ^{18}O-labelled dioxygen were determined by t.l.c. isolation followed mass spectrometry (an ionising voltage of 10—15 eV was used for these

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measurements). The deuterium content of the naphthols (6) and (7) was obtained by combined g.l.c.–mass spectrometry of their trimethylsilyl ethers.[41]

Oxidation using Iron(II) *Ion, EDTA, Ascorbic Acid, and Dioxygen.*—The substrate (7.5—19.0mM), EDTA (3.5—18mM), and ascorbic acid (14—140mM) were added to water or phosphate buffer (pH 7). Dioxygen was bubbled through this mixture while it was vigorously stirred and finally iron(II) sulphate (3.5—35mM) was added. After 2 h the mixture was extracted with ether. T.l.c. analyses showed spots corresponding to compounds (1), (2), (4)—(7), and 1,2-dihydroxynaphthalene, and acid treatment of the spots corresponding to (1) and (2) followed by rechromatography in the other direction showed that these materials had been converted into naphthols. The dihydrodiol product from eight oxidations was bulked, isolated by preparative t.l.c., and shown by n.m.r. to be predominantly the *trans*-isomer (2). The relative yields of the dihydrodiols to naphthols was obtained using [*U*-^{14}C]naphthalene as described above. Treatment of the ether solution of the oxidation products of naphthalene with hexamethyldisilazane followed by g.l.c. analysis of the naphthol trimethylsilyl ethers gave the ratio of yields of 1- to 2-naphthol.

A trace of naphthalene 1,2-oxide in the oxidation of [*U*-^{14}C]naphthalene was detected using the method of Jerina *et al.*[41]

Oxidations in the Absence of Organic Reducing Agent.—(a) *Iron*(II) *sulphate with dioxygen.* The method used here was the same as that described above with the ascorbic acid omitted.

(b) *Copper*(I) *chloride with dioxygen.* Copper(I) chloride (0.3 g) was dissolved in the minimum of 2M-hydrochloric acid and added to a vigorously stirred mixture of [*U*-^{14}C]-naphthalene (0.2 g) in phosphate buffer (pH 7; 400 cm^3) through which dioxygen was bubbled. After 2 h the mixture was extracted with ether and analysed as described above.

(c) *Titanium*(III) *chloride with dioxygen.* Dioxygen was bubbled through a vigorously stirred mixture of 15% titanium(III) chloride solution (1.5 cm^3), EDTA (0.5 g), and [*U*-^{14}C]naphthalene (0.2 g) in phosphate buffer (pH 7; 200 cm^3). After 1 h the products were extracted into ether and analysed.

(d) *Fenton's reagent.* A suspension of naphthalene or [*U*-^{14}C]naphthalene (0.8—4mM) in water or phosphate buffer (pH 7) containing iron(II) sulphate (1.5—8.0mM), and EDTA (0—7.8mM) was vigorously stirred and oxidised with hydrogen peroxide (17.6—30mM). The products were extracted into ether and analysed.

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