Model Systems for Cytochrome P450-dependent Mono-oxygenases. Part 5.[1] Amine Oxidation. Part 17.[2] Oxidative *N*-Dealkylation of Tertiary Amines by Metalloporphyrin-catalysed Model Systems for Cytochrome P450 Mono-oxygenases

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NN-Dimethylbenzylamine has been oxidatively demethylated to *N*-methylbenzylamine and debenzylated to benzaldehyde by iodosylbenzene and by t-butyl hydroperoxide catalysed by tetraphenylporphyrinato-iron(III) or -manganese(III) chloride. The influence of substituents on the aromatic ring and of deuteriation of the benzylic hydrogens on the relative reactivity of the substrates and on the product distribution has been studied. The results suggest that the initial step in the metalloporphyrin-catalysed iodosylbenzene oxidations is an electron-transfer from the amine to a high valent oxometal species, whereas, with t-butyl hydroperoxide the mechanism is one of hydrogen abstraction from the amine by the t-butoxyl radical. The mechanisms of the subsequent steps are discussed.

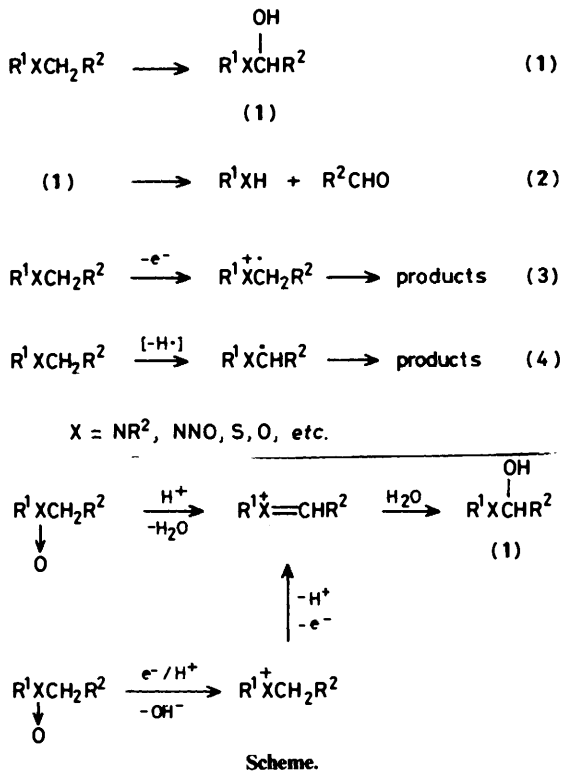
The cytochrome P450-dependent mono-oxygenases catalyse the oxidative dealkylation of a wide variety of heteroatom-substituted organic compounds.[3] It is now generally accepted that these reactions involve an initial α-oxygenation [reaction (1)] followed by heterolysis of the hydroxylated intermediate (**1**) [reaction (2)].[3] In all cases studied the origin of the oxygen in the α-hydroxylated intermediate (**1**) and in the carbonyl product has been shown to be dioxygen and not water.[4]

On the basis of studies on cytochrome P450-catalysed oxidations of saturated C–H bonds in hydrocarbons,[5] reaction (**1**) is unlikely to be a one-step 'oxene' insertion into the α-C–H bond of the substrate.[6] There are two reasonable alternative mechanisms for the initiation of the α-hydroxylation that are consistent with the source of oxygen in (**1**); either an electron- or a hydrogen atom-transfer from the amine to the active oxidant [reactions (3) and (4) respectively]. Pathways involving heteroatom oxygenation followed by rearrangement to (**1**) either by an elimination–addition process (*cf.* Polonovski reaction[7]) or by a redox mechanism (Scheme)[8] are incompatible with the origin of the oxygen in (**1**).

For a particular substrate whether the cytochrome P450-catalysed oxidation proceeds *via* reaction (3) or (4) will probably depend on the substrate's oxidation potential.[3g,9] For tertiary amines, which have relatively low oxidation potentials, it is generally accepted that oxidations occur by an initial electron-transfer [reaction (3)][10] whereas with substrates having higher oxidation potentials, such as ethers and nitrosamines, the preferred route is *via* hydrogen atom-abstraction [reaction (4)].[3f,h,11]

To obtain more information about the mechanisms of these reactions we have looked at the oxidation of some tertiary amines by chemical models for the cytochrome P450 mono-oxygenases. We report here our investigations into the oxidations brought about by iodosylbenzene and by t-butyl hydroperoxide in the presence of tetraphenylporphyrinato-iron(III) and -manganese(III) chloride.†

† Abbreviations: Fe^{III}TPPCl for tetraphenylporphyrinatoiron(III) chloride and Mn^{III}TPPCl for tetraphenylporphyrinatomanganese(III) chloride.



Scheme.

Results

Analytical Method.—In our initial investigations into the oxidation of *NN*-dimethylbenzylamines by the metalloporphyrin-catalysed model systems the product work-up and analysis used methods similar to those we have reported before.[12] This involves separating the basic and non-basic materials and analysing each separately by g.c. To obtain good repeatability by this procedure requires using relatively large amounts of the reactants. However, the precise analysis of small scale reactions can be achieved directly by g.c. without prior

Table 1. Yields of products from the oxidation of substituted *NN*-dimethylbenzylamines by the Fe^{III}TPPCl–PhIO system in benzene

Substrate $XC_6H_4CH_2NMe_2$	Product yield (%)[a] XC_6H_4CHO	$XC_6H_4CH_2NHMe$	Ratio XC_6H_4CHO:$XC_6H_4CH_2NHMe$
X = 4-MeO	51	27	1.9
4-Me	47	25	1.9
H	49	25	2.0
4-Cl	50	24	2.1
4-Br	51	24	2.1
3-CN	46	24	1.9
4-CN	51	19	2.7

[a] Yields ±5%, based on PhIO.

Table 2. Yields of products from the oxidation of substituted *NN*-dimethylbenzylamines by the Mn^{III}TPPCl–PhIO system in benzene

Substrate $XC_6H_4CH_2NMe_2$	Product yield (%)[a] XC_6H_4CHO	$XC_6H_4CH_2NHMe$	Ratio XC_6H_4CHO:$XC_6H_4CH_2NHMe$
X = 4-MeO	49	32	1.5
4-Me	47	30	1.6
H	50	30	1.7
4-Cl	55	33	1.7
4-Br	49	33	1.5
4-CN	47	32	1.5

[a] Yields ±5%, based on PhIO.

Table 3. Effect of Fe^{III}TPPCl concentration on oxidation of *NN*-dimethylbenzylamine by iodosylbenzene in benzene[a]

[Fe^{III}TPPCl]/μmol cm^{-3}	Product yield (%)[b] PhCHO	$PhCH_2NHMe$	Total yield (%)	Ratio PhCHO:$PhCH_2NHMe$
8.3	37	18	55	2.0
1.7	49	25	74	2.0
0.17	61	30	91	2.0

[a] $PhCH_2NMe_2$ (0.17 mmol cm^{-3}) and PhIO (15 μmol cm^{-3}). [b] Yield based on PhIO.

work-up. An acidic polyester column, which selectively adsorbs the amines, was used to analyse the non-basic materials. Then, following the addition of 1,2-diaminoethane to the reaction mixture, after the analysis of non-basic materials, the amines were analysed on a second column using a polyether or mixed polyether–Apiezon L phase. The role of the diamine was to react preferentially with the formaldehyde thus preventing reaction with the product secondary amines leading to peak distortion on the gas chromatograph.[12] The 1,2-diaminoethane also reacted with other aldehydic products and simplified the chromatography of the amines.

Product Yields and Distributions.—Solutions of ring-substituted *NN*-dimethylbenzylamines in benzene are oxidised in high yield by iodosylbenzene catalysed by Fe^{III}TPPCl or by Mn^{III}TPPCl (Tables 1 and 2), and these yields are unaffected by carrying out the reactions under nitrogen. The oxidant unaccounted for by these products, as has been noted by others, is largely consumed in competitive side reactions such as the destruction of the catalyst. Thus in the absence of the substrate iodosylbenzene oxidises the metalloporphyrin with a concomitant complete loss of the Soret band in the visible spectrum. However, in the presence of the tertiary amine substrate, which competes for the active oxidant, the catalyst is protected and the intensity of the Soret band is only partially reduced. Lowering the concentration of the catalyst, while maintaining the concentration of the other reactants, results in an increased yield of products (Table 3). These results are in agreement with the view that the catalyst destruction is an intermolecular rather than an intramolecular process.[13]

Blank experiments show that little oxidant is lost in further oxidation of the products from *NN*-dimethylbenzylamine and that negligible oxidation (<0.1%) occurs in the absence of oxidant or catalyst.

Changing the substituent on the aromatic substrate has no measurable influence on the ratio of debenzylation to demethylation, with the exception of the 4-cyano group which leads to an increase in the proportion of debenzylation when oxidised by the Fe^{III}TPPCl–PhIO system. Both catalysts give more debenzylation than demethylation. Allowing for the statistical preference for demethylation, the benzyl C–H bonds are approximately six times more reactive than the methyl ones with Fe^{III}TPPCl–PhIO and the corresponding figure for the Mn^{III}TPPCl–PhIO system is 4.8.

Benzene solutions of the ring-substituted *NN*-dimethylbenzylamines are also readily oxidised by t-butyl hydroperoxide under nitrogen (yields 70—85%) in the presence of Fe^{III}TPPCl or Mn^{III}TPPCl (Table 4). With this oxidant, unlike iodosylbenzene, both catalysts give the same product distributions. The selectivity for oxidation of benzyl over methyl C–H bonds is 2—3.

In none of the oxidations above were any *N*-oxides detected amongst the products and when a solution of *NN*-dimethylbenzylamine *N*-oxide was stirred with either metalloporphyrin catalyst, neither *NN*-dimethylbenzylamine nor its oxidation products were detected.

Table 4. Yields of products from the oxidation of substituted *NN*-dimethylbenzylamines by the Mn^{III}TPPCl–Bu^tO_2H system in benzene under nitrogen[a]

Substrate $XC_6H_4CH_2NMe_2$	Product yield (%)[b] XC_6H_4CHO	Product yield (%)[b] $XC_6H_4CH_2NHMe$	Ratio XC_6H_4CHO:$XC_6H_4CH_2NHMe$
X = 4-MeO	34	46	0.73
4-Me	30	44	0.68
H	33	42	0.78
4-Cl	36.5	43	0.85
4-Br	38	46.5	0.81
3-CN	33	46	0.71
4-CN	39	40	0.97

[a] Both Fe^{III}TPPCl and Mn^{III}TPPCl give the same results. [b] Yield ±5%, based on Bu^tO_2H.

Table 5. Yields and relative reactivities from Fe^{III}TPPCl–PhIO oxidations of substituted *NN*-dimethylbenzylamines in competition with *NN*-dimethylbenzylamine[a]

Competitive substrate $XC_6H_4CH_2NMe_2$	Products from $XC_6H_4CH_2NMe_2$ (%)[b]	Products from $PhCH_2NMe_2$ (%)[b]	k_X/k_H
X = 4-MeO	37	50	1.35
4-Me	38	46	1.20
4-Cl	43	36	0.85
4-Br	46	37	0.80
3-CN	45	29	0.65
4-CN	47	26	0.55

[a] Substrate (0.5—1.0 mmol), PhIO (45 μmol), and Fe^{III}TPPCl (4.3 μmol) in benzene (3 cm^3). [b] Yield based on PhIO.

Table 6. Yields and relative reactivities from Mn^{III}TPPCl–PhIO oxidations of substituted *NN*-dimethylbenzylamines in competition with *NN*-dimethylbenzylamine[a]

Competitive substrate $XC_6H_4CH_2NMe_2$	Products from $PhCH_2NMe_2$ (%)[b]	Products from $XC_6H_4CH_2NMe_2$ (%)[b]	k_X/k_H
X = 4-MeO	43	49	1.15
4-Me	46	49	1.05
4-Cl	41	36	0.9
4-Br	45	40	0.9
4-CN	49	35	0.7

[a] Substrate (0.5—1.0 mmol), PhIO (45 μmol), and Mn^{III}TPPCl (4.3 μmol) in benzene (3 cm^{-3}). [b] Yield based on PhIO.

Competitive Oxidations.—The product yields from competitive oxidations give information on the relative reactivities of the substrates towards the active oxidants. For the iodosylbenzene-promoted reactions there is a small but significant increase in the rate of oxidation with increasing electron donation by the substituent (Tables 5 and 6). However, the rate of the t-butyl hydroperoxide oxidations is unaffected by the substituent on the *NN*-dimethylbenzylamine.

Intermolecular Kinetic Isotope Effects.—The relative reactivities of *NN*-dimethylbenzylamine and its [α,α-$^2H_2$] analogue were measured by direct competition of the substrates for the oxidants and, indirectly, by competing each substrate separately against 4-chloro-*NN*-dimethylbenzylamine. For the former experiments, kinetic isotope effects were determined from the relative yields of the products benzaldehyde and [α-^{2}H]benzaldehyde by g.c.–m.s. analysis. Table 7 shows that the isotope effects for the oxidations with iodosylbenzene are significantly smaller than those from the t-butyl hydroperoxide systems.

Table 7. Intermolecular kinetic isotope effects from the competitive oxidations of *NN*-dimethylbenzylamine and *NN*-dimethyl[α,α-$^2H_2$]-benzylamine catalysed by Fe^{III}TPPCl or Mn^{III}TPPCl in benzene

Oxidising system	Kinetic isotope effect
Fe^{III}TPPCl–PhIO	1.3 ± 0.1[a]
Mn^{III}TPPCl–PhIO	1.3 ± 0.1[a]
Fe^{III}TPPCl–Bu^tO_2H	2.8 ± 0.2[b]
Mn^{III}TPPCl–Bu^tO_2H	2.8 ± 0.2[b]

[a] k_H/k_D from g.c.–m.s. analysis of PhCHO:PhCDO. [b] k_H/k_D from external competition of each substrate with 4-chloro-*NN*-dimethylbenzylamine.

Table 8. Intramolecular kinetic isotope effects from the oxidation of *N*-[α,α-$^2H_2$]benzyl-*N*-methylbenzylamine and from the separate oxidations of *NN*-dimethylbenzylamine and *NN*-dimethyl[α,α-$^2H_2$]-benzylamine

Oxidising system	Kinetic isotope effects (k_H/k_D) $PhCH_2NMeCD_2Ph$[a]	Kinetic isotope effects (k_H/k_D) $PhCH_2NMe_2$ and $PhCD_2NMe_2$[b]
Fe^{III}TPPCl–PhIO	2.9 ± 0.1	2.5 ± 0.2
Mn^{III}TPPCl–PhIO	2.0 ± 0.1	2.0 ± 0.2
Fe^{III}TPPCl–Bu^tO_2H	3.1 ± 0.2	2.6 ± 0.2
Mn^{III}TPPCl–Bu^tO_2H	3.1 ± 0.2	2.6 ± 0.2

[a] k_H/k_D from g.c.–m.s. analysis of PhCHO:PhCDO. [b] Calculated from the ratio of debenzylation to demethylation in the separate oxidation of $PhCH_2NMe_2$ and $PhCD_2NMe_2$

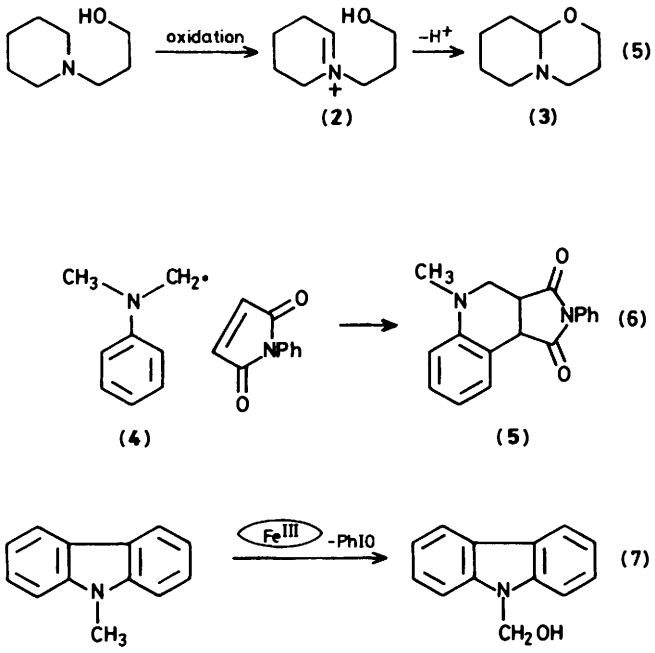
Intramolecular Kinetic Isotope Effects.—The relative yields of benzaldehyde and [α-^{2}H]benzaldehyde from the oxidations of *N*-[α,α-$^2H_2$]benzyl-*N*-methylbenzylamine were measured by g.c.–m.s. analysis and used to calculate intramolecular kinetic isotope effects. For some of the model systems less accurate values were also obtained from the ratio of debenzylation to demethylation from separate oxidations of *NN*-dimethylbenzylamine and its [α,α-$^2H_2$]analogue. In the calculation of the intramolecular isotope effects from the latter data it was assumed that the deuterium would only influence the rate of debenzylation, thus the rate of demethylation becomes an internal standard common to the oxidation of both substrates. All the model systems show medium-sized intramolecular kinetic isotope effects (Table 8).

Trapping and Attempted Trapping Experiments.—(a) *Iminium ions.* G.c. and g.c.–m.s. analysis of the products from the oxidation of 3-(*N*-piperidino)propan-1-ol by the Fe^{III}TPPCl–

Table 9. Secondary (intermolecular) kinetic isotope effects and Hammett ρ values for the one-electron oxidations of tertiary amines

Oxidising system	Deuteriated substrate	k_H/k_D % per deuterium	Hammett ρ value[a]	Ref.
Aq. $Fe(CN)_6^{3-}$	CD_3NBu_2	1.3	−0.989 ± 0.085	17
Aq. ClO_2	$N(CD_3)_3$	3.3	−0.924 ± 0.078	18
Aq. MnO_4^-	$N(CD_3)_3$	9		19
Aq. Autoxidation	$PrN[CD_2CH_2]_2$	12.5		20
N-Chlorobenzotriazole–PhH	$PhCD_2NMe_2$	15	−0.71 ± 0.03	12
Fe^{III}TPPCl–PhIO–PhH	$PhCD_2NMe_2$	15	−0.41 ± 0.02	This study
Mn^{III}TPPCl–PhIO–PhH	$PhCD_2NMe_2$	15	−0.22 ± 0.01	This study

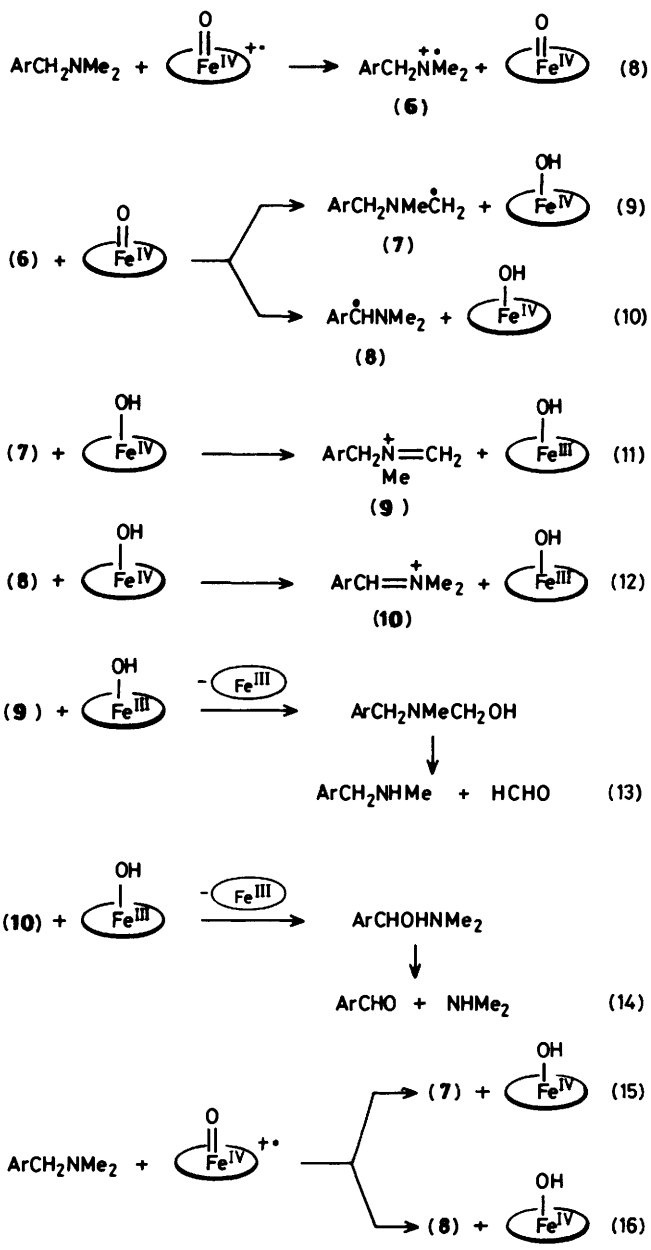
[a] ρ values obtained from oxidation of substituted *NN*-dimethylbenzylamines.



PhIO system revealed the presence of 5-oxa-1-azabicyclo-[4.4.0]decane (**3**) in 21% yield. This result is consistent with the oxidation of the aminoalcohol to iminium ion (**2**) which is then intramolecularly trapped to give the cyclised product (**3**) [reaction (5)].[14]

(b) *α-Amino-radicals.* An attempt to trap an α-amino-radical from the oxidation of *NN*-dimethylaniline in the presence of *N*-phenylmaleimide [reaction (6)][15] was unsuccessful. The only oxidation product detected by t.l.c. was *N*-methylaniline.

(c) *α-Carbinolamine.* In agreement with Miyata *et al.*,[16] who oxidised *N*-methylcarbazole with 2,6-dimethyliodosylbenzene and Fe^{III}TPPCl, we found that the main product with the Fe^{III}TPPCl–PhIO system is the carbinolamine *N*-hydroxymethylcarbazole [reaction (7)].



Discussion

Initial Oxidation Step in Iodosylbenzene Systems.—*NN*-Dimethylbenzylamines are good substrates for the metalloporphyrin-catalysed model systems: the yield of products (based on oxidant) is high (>70%).

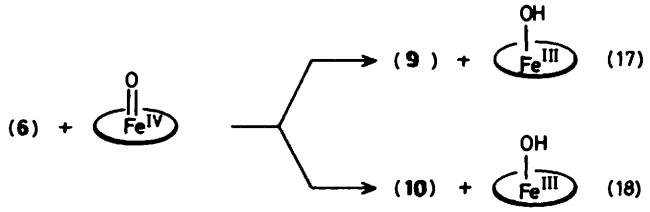
The results obtained from the oxidations with the iodosylbenzene systems are consistent with the initial step being electron transfer [reaction (8)] rather than hydrogen atom-abstraction [reaction (15) and (16)]. The small intermolecular kinetic isotope effects (Table 7) show that isotopic substitution of the α-hydrogens has only a small effect on the relative rate of oxidation. The values obtained with both metalloporphyrin catalysts are typical of secondary isotope effects for the oxidation of tertiary amines to an aminium radical [reaction (8)] (Table 9). In general, if the competitive reactions involve

Table 10. Primary kinetic isotope effects for hydrogen atom-abstraction from amines

Oxidising system	Deuteriated substrate	k_H/k_D	Ref.
$Me_3CO^{\bullet}$	$N(CD_3)_3$	1.4 ± 0.7	21
Aq. ClO_2	$PhCD_2NHBu^t$	4.97 ± 0.5	18*b*
Aq. MnO_4^-	$PhCD_2NH_2$	7.0	22
Aq. ClO_2	$PhCD_2NH_2$	3.0 ± 0.3	18*b*
Fe^{III}TPPCl–Bu^tO_2H	$PhCD_2NMe_2$	2.8 ± 0.2	This study
Mn^{III}TPPCl–Bu^tO_2H	$PhCD_2NMe_2$	2.8 ± 0.2	This study

Table 11. Primary kinetic isotope effects for deprotonation of tertiary aminium radicals

Reaction system	Solvent	k_H/k_D	Ref.
Electrochemical oxidation	H_2O–MeOH	1.75	24
N-Chlorobenzotriazole	PhH	1.9	12
trans-Stilbene–*hν*	CH_3CN	2.2	28
$Fe(CN)_6^{3-}$	H_2O	3.6	17*b*
ClO_2	H_2O	4.8	18*b*
Fe^{III}TPPCl–PhIO	PhH	2.9	This study
Mn^{III}TPPCl–PhIO	PhH	2.0	This study

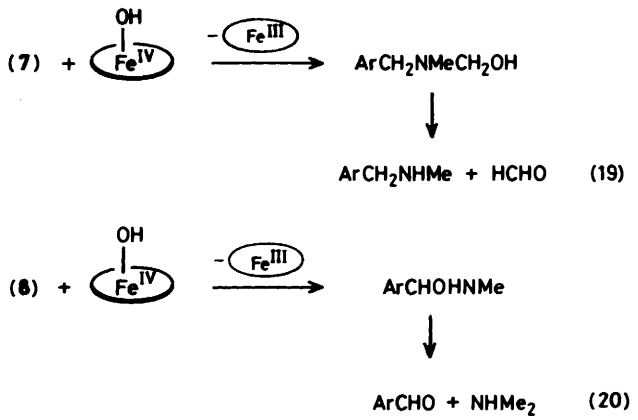


the abstraction of hydrogen atoms from the α-carbon of the amine [reactions (15) and (16)] the difference in reactivity would be larger, this being a primary kinetic isotope effect. Some kinetic isotope effects for hydrogen atom-abstraction from amines are collected in Table 10.

A plot of log (k_X/k_H), where k_X/k_H is the reactivity of the substituted *NN*-dimethylbenzylamine relative to the unsubstituted parent amine (Tables 5 and 6), against Hammett σ values gives good linear relationships, with ρ values of −0.41 ± 0.02 and −0.22 ± 0.01 for the Fe^{III}TPPCl- and Mn^{III}TPPCl-catalysed systems, respectively. These values are also consistent with the electron-transfer mechanism [reaction (8)]. However, they are lower than some ρ values from other well defined electron-transfer oxidations of *NN*-dimethylbenzylamines (Table 9) and this suggests that the transition state for electron-transfer in the metalloporphyrin–PhIO systems and particularly that catalysed by Mn^{III}TPPCl occurs early in the reaction profile and involves relatively little build-up of positive charge on the amine nitrogen.

Reactions following Initial Electron-transfer in the Iodosylbenzene Systems.—Following the initial electron-transfer two alternative product-determining steps can take place, either loss of an α-proton [reactions (9) and (10)] or hydrogen atom-abstraction [reactions (17) and (18)] from the aminium radical (**6**). The former is known to be a very fast reaction[23] and in electrochemical[24,25] and in many chemical amine oxidations[19b,26] it is followed by an electron-transfer to give an iminium ion [reactions (11) and (12)]. The latter path, which gives an iminium ion directly, has been proposed recently by Burka *et al.*[10d] for the oxidative dealkylation of amines by cytochrome P450 mono-oxygenases. Further reaction of the iminium ions with the tetraphenylporphyrinatoiron(III) hydroxide, possibly within a solvent cage, leads to the α-aminoalcohols. Intramolecular trapping of the iminium ion (**2**) in the oxidation of 3-(*N*-piperidino)propan-1-ol with Fe^{III}TPPCl–PhIO [reaction (5)] is in agreement with either mechanism but seems to rule out the alternative process (analogous to the 'oxygen rebound' oxidation of alkanes by this oxidising system[27]) where the hydroxyl group is transferred from the catalyst to the α-amino radical to give the α-aminoalcohol directly [reactions (19) and (20)].

Since in both the proton loss [reactions (9) and (10)] and hydrogen atom-abstraction mechanisms [reactions (17) and (18)] the competition between the dealkylation pathways

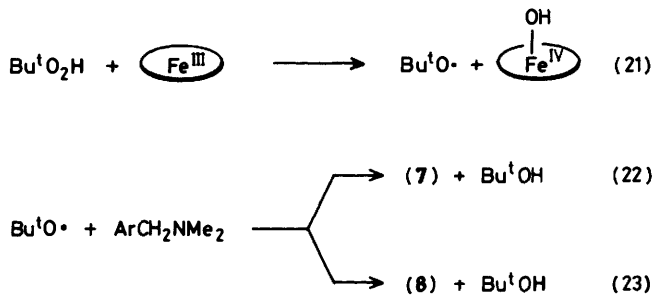


depends on the relative ease of alternative α-C–H bond cleavages, deuteriation of the benzylic C–H bonds should produce a kinetic isotope effect on the product distribution. The intramolecular kinetic isotope effects obtained in this way (Table 8) are in agreement with this conclusion. However, the data, although very comparable to the literature values for deprotonation of an aminium radical (Table 11), cannot be used to distinguish between the two mechanisms.

The negligible influence of substituents (except for 4-CN) on the product distribution (Table 1) is more consistent with a proton transfer than a hydrogen atom-abstraction, product-determining step. Several previous studies have noted the small effect of substituents on the alternative (methyl *versus* benzyl) proton losses from substituted *NN*-dimethylbenzylaminium radicals (**6**)[12,18a,24] and these have been discussed in terms of the substituent's ability to stabilise the forming α-amino radical.[12] Substituent radical-stabilising effects are generally small[29] and thus it is not surprising that they have little influence on this product-determining step. Perhaps most significantly the 4-CN group which is best able to stabilise the aminobenzyl radical (**8**) shows the greatest extent of debenzylation. The alternative hydrogen atom-abstraction mechanism [reactions (17) and (18)] might be expected to show more significant substituent effects. π-Donor (+*M*) substituents such as 4-OMe, which can stabilise the forming iminium ion (**10**) by direct conjugation should favour debenzylation and the opposite should be expected of electron-withdrawing groups like 4-CN. This is not observed in this study.

An attempt to trap an α-amino-radical intermediate from the oxidation of *NN*-dimethylaniline with Fe^{III}TPPCl–PhIO using the method described by Roy and Swan[15] was unsuccessful [reaction (6)] for although the substrate was demethylated none of the tetrahydroquinoline (**5**) was detected. Clearly, further work is needed to clarify whether or not α-amino-radicals are intermediates in these oxidations.

Mechanism of Oxidation by t-Butyl Hydroperoxide Systems.—As noted previously[30] for alkane and alkene oxid-



ations, we find that the mechanisms of the reactions brought about by the t-butyl hydroperoxide systems differ from those of models that use iodosylbenzene. Thus competitive oxidations with the former give a medium-sized intermolecular kinetic isotope (Table 7; 2.8 ± 0.2) and show the total absence of substituent effects in the reactions of the ring-substituted *NN*-dimethylbenzene (ρ 0.0 ± 0.05). Mansuy *et al.*[30] have proposed that the active oxidant is the t-butoxyl radical [reaction (21)] and our data are in agreement with such a species oxidising the tertiary amines by an initial hydrogen atom-abstraction [reactions (22) and (23)]. However, it is noteworthy that Griller *et al.*[21] using a competitive e.s.r. technique report a very low value for k_H/k_D (1.4 ± 0.7) for hydrogen atom-abstraction from $(CH_3)_3N$–$(CD_3)_3N$ by the t-butoxyl radical.

The initial hydrogen abstraction from the amine by the t-butoxyl radical [reactions (22) and (23)] is rate determining and also controls the direction of the dealkylation (product distribution). Consequently the intermolecular kinetic isotope effect (Table 7; k_H/k_D 2.8 ± 0.2) should, as is observed, be the same as, or very similar to, the intramolecular values (Table 8) (k_H/k_D 3.1 ± 0.2). These data compare well with reported kinetic isotope effects for hydrogen atom-abstraction from amines (Table 10).

Mansuy *et al.*[31] have also reported that when oxidations with metalloporphyrin–cumene hydroperoxide systems are carried out in the presence of the electron-donating ligand imidazole the alkoxyl radical is replaced by an oxometal active oxidant, similar to that in iodosylbenzene systems, which is formed by heterolysis of the hydroperoxide. However, the addition of imidazole to the Fe^{III}TPPCl–Bu^{t}O$_2$H amine oxidation in this study had no effect on the mechanism, as judged by the product distributions and kinetic isotope effects. It is possible that imidazole, in the presence of the large excess of substrate amine, is unable to compete successfully for the axial position of the metalloporphyrin. This may be particularly important for the iron(III) porphyrin catalyst where the influence of imidazole is less pronounced than for the manganese(III) system.

Conclusions.—Amine oxidation by the Fe^{III}TPPCl–PhIO and Mn^{III}TPPCl–PhIO systems proceeds by an initial electron-transfer to a high-valent oxometal species. This is probably very similar to the mechanism of tertiary amine oxidation by cytochrome P450 mono-oxygenases. With the model systems that utilise t-butyl hydroperoxide the active oxidant is the t-butoxyl radical and reaction occurs by hydrogen abstraction.

Experimental

Materials.—All the materials were of commercial reagent grade unless otherwise stated. *NN*-Dimethylbenzylamine (Aldrich) was purified by treatment with acetic anhydride followed by acidification and ether extraction to remove *N*-methylbenzylamine. The aqueous solution was then basified and the tertiary amine was recovered by ether extraction and purified by distillation. The substituted *NN*-dimethylbenzylamines were prepared by reaction of the corresponding benzaldehyde with dimethylformamide and formic acid, and the substituted *N*-methylbenzylamines were prepared from the corresponding benzyl bromide and methylamine following Eliel *et al.*[32] 3-Cyanobenzaldehyde was obtained from 3-bromobenzaldehyde and copper(I) cyanide in dimethylformamide by the method of Vogel.[33] The preparation of [α-^{2}H]benzaldehyde[34] (>98% D) and *NN*-dimethyl[α,α-$^2H_2$]benzylamine (>99% D)[12] have been reported. *N*-[α,α-$^2H_2$]Benzyl-*N*-methylbenzylamine (>96% D) was prepared by reduction of *N*-benzyl-*N*-methylbenzamide with lithium aluminium deuteride (Aldrich; >98% D).

Tetraphenylporphyrinato-iron(III) and -manganese(III) chlorides and iodosylbenzene were prepared as described previously.[35]

Methods.—G.l.c. analyses used a Pye series 104 or GCD chromatograph equipped with a flame ionisation detector and glass columns (1.6 m × 0.4 mm i.d.). The following packing materials were used: (10%, w/w) LAC-2R-446 (Phase Separations Ltd.) on acid-washed Celite (80—100 mesh) for aldehydes and iodobenzene; (10%, w/w) Carbowax 20M or (5%, w/w) of each of the phases Apiezon L and Carbowax 20M on Celite (80—100 mesh) which had been coated with (5%, w/w) KOH for amines.

For g.c.–m.s. a Pye series 104 chromatograph was coupled to an AEI MS 30 spectrometer.

H.p.l.c. analyses were carried out with an H.P.L.C. Technology pumping system, model RR/035, coupled to an Applied Chromatography System Ltd. single wavelength (254 nm) u.v. monitor, model 750-11. The column (25 cm) was packed with Techsil 5 C18 and analyses were performed isocratically with water–methanol mixtures as eluant.

N.m.r. spectroscopic methods have been described.[35]

Oxidation Procedures.—In the standard procedure used for single substrate oxidations, the iodosylbenzene (45 μmol) was added to a stirred solution of the catalyst (4.5 μmol) and amine (500 μmol) in benzene (3 cm^3) at room temperature. After 1 h the chromatography internal standard was added and the iodobenzene and aldehydic products were analysed by g.c. Following this analysis, diaminoethane (100 μml) was added to the mixture and after 15 min stirring, the amines were determined by g.c.

The reaction mixtures that used t-butyl hydroperoxide were thoroughly purged with oxygen-free nitrogen (British Oxygen white spot grade) before addition of the oxidant (45 μmol).

Competitive oxidations used the procedure described above with 500 μmol of each substrate.

Trapping Experiments.—The oxidation procedure described above, with 1 mmol of substrate, was used for the trapping experiments. The reactions of *NN*-dimethylaniline also included *N*-phenylmaleimide (1 mmol).

The products from the reaction of reactions of *NN*-dimethylaniline, in the presence of *N*-phenylmaleimide, were separated by t.l.c. on silica gel with light petroleum–benzene (7:3, v/v). *N*-Methylaniline was also analysed by g.c. The products from the reaction of *N*-methylcarbazole were separated by h.p.l.c. on ODS silica with water–methanol (1:9). The products from 3-(*N*-piperidino)propan-1-ol were analysed by g.c. on the base-treated Carbowax 20M phase.

Measurement of Kinetic Isotope Effects.—Kinetic isotope effects were determined by g.c.–m.s. from the relative yields of benzaldehyde and [α-^{2}H]benzaldehyde as described previously.[36]

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