Oxidative *N*-Dealkylation of *N,N*-Dimethylbenzylamines by Metalloporphyrin-catalysed Model Systems for Cytochrome P450 Mono-oxygenases

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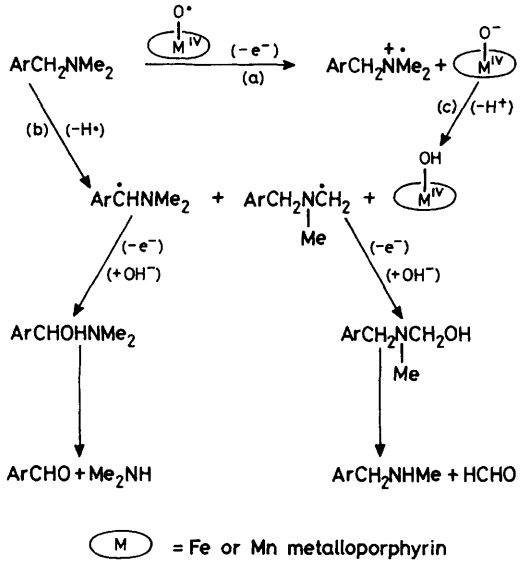
Iodosylbenzene, catalysed by tetraphenylporphyrinato-iron(III) or -manganese(III) chloride, oxidises tertiary amines by an initial one-electron transfer process whereas with t-butyl hydroperoxide with these catalysts the oxidation is initiated by hydrogen atom abstraction.

Recent research suggests that the oxidative dealkylation of tertiary amines by cytochrome P450-dependent mono-oxygenases is initiated by a one-electron transfer from the amine to the active oxidant [Scheme 1, path (a)].[1] Subsequent steps of proton loss and hydroxylation lead to the unstable intermediate α-hydroxyalkylamine[2] and subsequently to secondary amine and aldehyde (Scheme 1). Our interest in the mechanisms of chemical and biological oxidative dealkylations[3] has led us to examine *N*-dealkylation with some metalloporphyrin-catalysed model systems for cytochrome P450-dependent mono-oxygenases. We report here how a combination of inter- and intra-molecular kinetic isotope effect measurements and substituent effect studies shows a clear distinction between oxidations initiated by electron transfer and by hydrogen atom abstraction.

The metalloporphyrins, tetraphenylporphyrinato-iron(III) and -manganese(III) chloride (Fe^{III}TPPCl and Mn^{III}TPPCl) are efficient catalysts for the oxidation of *N,N*-dimethylbenzylamine by iodosylbenzene or by t-butyl hydroperoxide (yield >80%, based on oxidant) to give both benzaldehyde (debenzylation) and *N*-methylbenzylamine (demethylation). These reactions do not produce detectable quantities of *N*-oxides, and *N,N*-dimethylbenzylamine *N*-oxide, unlike *N,N*-dimethylaniline *N*-oxide,[4] is stable under the reaction conditions.

Competitive oxidations with 3- and 4-substituted *N,N*-dimethylbenzylamines yield relative rate data that give good linear correlations against Hammett σ constants (Table 1). The small negative ρ values for both iodosylbenzene systems, -0.41 ± 0.02 (Fe^{III}TPPCl) and -0.22 ± 0.01 (Mn^{III}TPPCl) are consistent with a rate-determining electron transfer [Scheme 1, path (a)].[5] The smaller ρ value with Mn^{III}TPPCl catalysis suggests that, for this process, the transition state occurs earlier on the reaction profile and involves a smaller build-up of positive charge than that of the Fe^{III}TPPCl system. By contrast, the absence of substituent effects on the rates of the t-butyl hydroperoxide oxidations ($\rho = 0.0 \pm 0.05$) suggests that these dealkylations may be brought about by an initial hydrogen atom abstraction [Scheme 1, path (b)].

These conclusions are confirmed by kinetic isotope effect measurements (Table 2). In the competitive oxidation of *N,N*-dimethylbenzylamine and its [α,α-$^2H_2$] analogue the iodosylbenzene systems show the small (secondary) effects that would be expected of a rate-determining electron transfer (typical values for the formation of an aminium radical are 1.3—15% per deuterium atom[5d,6]), whilst with t-butyl



Scheme 1

Table 1. Relative rates of oxidation of some 3- and 4-substituted *N,N*-dimethylbenzylamines ($XC_6H_4CH_2NMe_2$) by iodosylbenzene with a metallotetraphenylporphyrin catalyst.[a]

Substituent (X)	Relative rates of oxidation[b] Fe^{III}TPPCl	Mn^{III}TPPCl
4-OMe	1.35	1.15
4-Me	1.20	1.05
H	1.00	1.00
4-Cl	0.85	0.90
4-Br	0.80	0.90
3-CN	0.65	—
4-CN	0.55	0.70

[a] Each substrate was competed against $PhCH_2NMe_2$: substrates (0.5 mmol of each), PhIO (45 μmol), and M^{III}TPPCl (5 μmol) in PhH (3 cm^3). Relative rates of oxidation were obtained by comparing product yields from substituted and unsubstituted *N,N*-dimethylbenzylamines. [b] All values ± 5%.

Table 2. Kinetic isotope effects from the competitive oxidation of *N,N*-dimethylbenzylamine and [α,α-$^2H_2$]*N,N*-dimethylbenzylamine and from the oxidation of [α,α-$^2H_2$]*N,N*-dibenzylmethylamine.

Oxidising system[a]	Kinetic isotope effect (k_H/k_D) $PhCH_2NMe_2$, $PhCD_2NMe_2$	$PhCH_2NMeCD_2Ph$[b]
Fe^{III}TPPCl/PhIO	1.3 ± 0.1[c]	2.9 ± 0.1
Mn^{III}TPPCl/PhIO	1.3 ± 0.1[c]	2.0 ± 0.1
Fe^{III}TPPCl/Bu^tO_2H	2.8 ± 0.2[d]	3.1 ± 0.2
Mn^{III}TPPCl/Bu^tO_2H	2.8 ± 0.2[d]	3.1 ± 0.2

[a] Substrate (0.5 mmol), oxidant (45 μmol), catalyst (5 μmol) in PhH (3 cm^3). [b] k_H/k_D from g.c.–m.s. analysis of PhCHO : PhCDO. [c] k_H/k_D from g.c.–m.s. analyses of PhCHO : PhCDO and of $PhCD_2NHMe$ and $PhCH_2NHMe$. [d] k_H/k_D from external competition with 4-chloro-*N,N*-dimethylbenzylamine.

hydroperoxide the isotope effect is larger and comparable with the values found for hydrogen atom abstraction from α-C–H bonds in amines.[7] Isotope effects from internal competition experiments with [α,α-$^2H_2$]dibenzylmethylamine arise from the product-determining step which with the iodosylbenzene systems is loss of a proton from the aminium radical [Scheme 1, step (c)]. These isotope effects (Table 2) are within the range of values from analogous one-electron amine oxidations.[5c,d,6b,c,f] Recently similar but somewhat lower values have been reported from the oxidative demethylation of *N*-[$^2H_3$]methyl-*N*-methylaniline by reconstituted cytochrome P450 systems (k_H/k_D = 1.61—1.78).[1c] The difference between the isotope effects for the iron(III) and manganese(III) porphyrin-catalysed systems implicates the metal oxy anion (M^{IV}–O^-) as the base in step (c).

For the t-butyl hydroperoxide systems, since hydrogen atom abstraction is both rate- and product-determining, the same isotope effect is obtained whether it is measured by external or internal competition.

This work on amine oxidation is in agreement with the view that in the model systems that utilise t-butyl hydroperoxide there is a common active oxidant, the t-butoxyl radical,[8] and that in the iodosylbenzene systems the oxidant is a metalloporphyrin oxyl radical.[8,9] Our current studies of these mechanisms include the use of other mono-oxygen donors and metalloporphyrins, and obtaining suitable conditions to carry out detailed kinetic investigations.

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