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Oxidation of tertiary benzamides by 5,10,15,20-tetraphenylporphyrinatoiron^{III} chloride–*tert*-butylhydroperoxide

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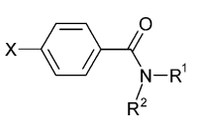
Tertiary benzamides are oxidized by the 5,10,15,20-tetraphenylporphyrinatoiron(III) chloride–Bu^{t}OOH system at the α-position of the *N*-alkyl groups. The major products are *N*-acylamides, although small amounts of secondary amides, the products of dealkylation, are also formed. Plots of initial rate *versus* initial substrate concentration for these reactions are curved, suggesting formation of an oxidant–substrate complex. The reaction rates are almost insensitive to the substituent in the benzamide moiety, but there is a kinetic deuterium isotope effect of 5.6 for the reaction of the *N,N*-$(CH_3)_2$ and *N,N*-$(CD_3)_2$ compounds. Comparison of the reaction products from *N*-alkyl-*N*-methylbenzamides reveals that, for all compounds studied except *N*-cyclopropyl-*N*-methylbenzamide, oxidation of the alkyl group is preferred, strongly so (by a factor of *ca.* 8) for *N*-allyl-*N*-methylbenzamide. In contrast to microsomal oxidation, there is no steric hindrance to oxidation of an isopropyl group. Thus, we propose that these reactions proceed *via* hydrogen atom abstraction to form an α-carbon-centred radical and we attribute the observed diminished reactivity of the *N*-cyclopropyl group to its known reluctance to form a cyclopropyl radical. Oxidation of *N*-methyl-*N*-(2,2,3,3-tetramethylcyclopropyl)methylbenzamide provides preliminary evidence for rearrangement of an intermediate radical. While it remains unclear how these reactions proceed directly to the *N*-acyl products, we have established that *N*-hydroxymethyl, *N*-alkoxymethyl and *N*-alkylperoxymethyl intermediates are not involved.

Introduction

Certain *N,N*-dialkylamides have important biological activity. For example *N,N*-diethyl-3-toluamide is the most effective insect repellent in world-wide use,[1] *N,N*-diethylnicotinamide is a respiratory stimulant[2] and *N,N*-dimethylformamide is an industrially important solvent that is toxic on occupational exposure.[3] All these compounds are known to undergo *in vivo* oxidative *N*-dealkylation in the liver. We have studied the mechanism of this biochemical *N*-dealkylation reaction using substituted *N,N*-dialkylbenzamides as model substrates and employing a combination of aryl substituent, kinetic deuterium isotope effects and *N*-alkyl structural effects on the kinetic constants together with product studies to probe which of the possible pathways is followed.[4,5,6] These studies were carried out using microsomes and, since the enzyme responsible, cytochrome P450, is membrane bound, access by the substrate to the active site often influences the kinetics of the reactions. For example, log V_{max}/K_M values for total dealkylation correlate with the log P value of the substrate.[7] Moreover, the large intrinsic isotope effect for the dealkylation reaction (≥ 6) is entirely suppressed,[5] which suggests that processes like membrane diffusion to the active site mask the rate at which the oxidative dealkylation proceeds. For this reason, we decided to study the oxidation of tertiary dialkylamides **1** by chemical model systems that avoid the physical constraints of the microsomal incubations. The two systems chosen were tetraphenylporphyrinatoiron(III) chloride **2**/*tert*-butyl hydroperoxide (TPPFe/Bu^{t}OOH) and tetraphenylporphyrinatoiron(III) chloride/iodosobenzene (TPPFe/PhIO), because they are known to be useful tools in the study of the mechanism of cytochrome P450 biooxidations.[8,9]



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	X	R^1	R^2
a	H	Me	Me
b	MeO	Me	Me
c	Cl	Me	Me
d	O_2N	Me	Me
e	H	CD_3	CD_3
f	H	Me	Et
g	H	Me	Bu
h	H	Me	Pr^i
i	H	Me	Allyl
j	H	Me	*cyclo*-C_3H_5
k	H	Me	*cyclo*-$(C_3H_5)CH_2$
l	H	Me	*cyclo*-$(2,2,3,3\text{-}Me_4C_3H)CH_2$
m	H	Et	Et

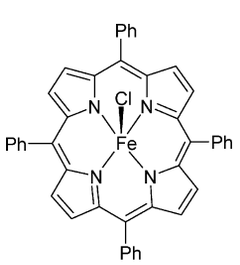

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Table 1 Values of V_{max}, V_{max}/K and K for the oxidation of *N,N*-dimethylbenzamides **1a–e** by TPPFe/Bu^{t}OOH in CH_2Cl_2 at 30 °C. [TPPFe] =10^{-3} mol dm^{-3}, [Bu^{t}OOH] = 0.2 mol dm^{-3}

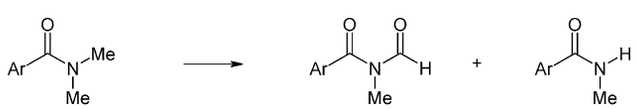
		Model system			Microsomes[b]
Substrate	IE[a]/eV	10^6 V_{max}/mol dm^{-3} s^{-1}	K/mol dm^{-3}	10^6 V_{max}/K/s^{-1}	V_{max}/K_M/h^{-1} (nmol P450)$^{-1}$
1a	9.04 (9.55)	1.22	0.47	2.61	1.33
1b	8.40 (9.26)	1.59	0.70	2.29	1.15
1c	9.16 (9.66)	1.43	0.59	2.45	1.6
1d	9.46 (10.0)	0.814	0.33	2.43	1.11
1e	(9.55)	0.223	0.47	0.465	0.97

[a] Values are the vertical IEs taken from ref.10. Values in parentheses are the corresponding IEs calculated by the AM1 semi-empirical method. [b] Data taken from ref. 5.

Results and discussion

Products of reaction

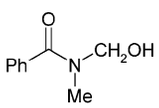
Oxidation of *N,N*-dimethylbenzamides **1a–d** by TPPFe/Bu^{t}OOH in CH_2Cl_2 gives rise to the corresponding *N*-formyl-*N*-methylbenzamides **3** (Scheme 1) as the major product, together with small quantities of the secondary amide **4**, the product of dealkylation. Yields were unaffected when the reactions were carried out under a nitrogen atmosphere. Oxidation by the TPPFe/PhIO system led to the same product distribution but in lower yields (4.1% *vs.* 7.4% after 72 h at 30 °C; for full reaction conditions see the Experimental). For this reason, and also because the oxidations in the presence of iodosobenzene are more difficult to analyse by HPLC, we decided to proceed using the TPPFe/Bu^{t}OOH system.



1 3 4

Scheme 1 Products from the reaction of *N,N*-dimethylbenzamides **1a–d** with TPPFeCl and Bu^{t}OOH.

Microsomal incubation of *N,N*-dimethylbenzamide yields *N*-hydroxymethyl-*N*-methylbenzamide that decomposes subsequently to *N*-methylbenzamide.[5] The pattern of products found in the reactions with TPPFe/Bu^{t}OOH would appear to suggest the intermediacy of the *N*-hydroxymethyl-*N*-methylbenzamide **5**. This compound could form the formyl derivative **3** by further oxidation of the hydroxymethyl group, and the secondary amide **4** by the loss of formaldehyde. However, even using the HPLC system that we have previously used to analyse for **5**,[5] we have been unable to detect such an intermediate in any of our reactions. Thus the chemical model system used in the present reactions appears not to mimic directly the microsomal system that we have used to investigate the oxidative dealkylation of *N,N*-dialkylbenzamides.



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Omitting either the porphyrin catalyst or the hydroperoxide from the incubation mixtures of the *N,N*-dialkylamides results in no reaction whatsoever. It seems reasonable, therefore, to suggest that TPPFe and Bu^{t}OOH react to form the active oxidant.

The rates at which the methyl groups were oxidised in the amide substrates **1a–d** were best determined by monitoring the reactions at timed intervals using HPLC, which is able to separate and quantify (using appropriate standards) the products and starting materials of the reactions. Given the very small quantities of *N*-methylbenzamides that are formed in these kinetic reactions, the most appropriate method of quantifying the total extent of reaction was to convert the *N*-formyl-*N*-methyl products to the corresponding *N*-methyl compounds. This was accomplished by treating samples of the reaction mixture with ethanolic sodium hydroxide and then measuring the total *N*-methylbenzamide present. Since the porphyrin and Bu^{t}OOH undergo unwanted side reactions that compete with *N*-alkyl oxidation, it proved necessary to use the initial rate method to determine reaction velocities. These were obtained by plotting product concentrations *versus* time over a 2 h period. At low extents of conversion these plots were found to be linear, the slopes giving the initial rate of reaction, v_i. However, plots of v_i determined using varying initial substrate concentrations but at fixed concentrations of TPPFe and Bu^{t}OOH are curved rather than linear (Fig. 1), implying that some kind of complex involving the substrate and the active oxidant is formed. Interpolation of the curves enables values of V_{max} (= k[oxidant], where k is the rate constant for the formation of the products from the catalysis complex) and V_{max}/K to be determined in a manner analogous to those obtained from the Michaelis–Menten kinetics in enzyme catalysed reactions. Values of V_{max}, V_{max}/K and K are given in Table 1, along with the microsomal V_{max}/K_m values[5] for comparison.

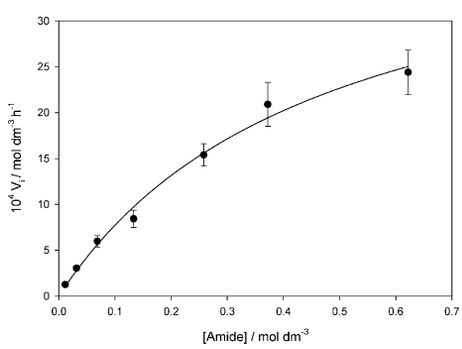


Fig. 1 Plot of initial rate, v_i *versus* substrate concentration for **1a**.

Effect of substituent in the aryl moiety

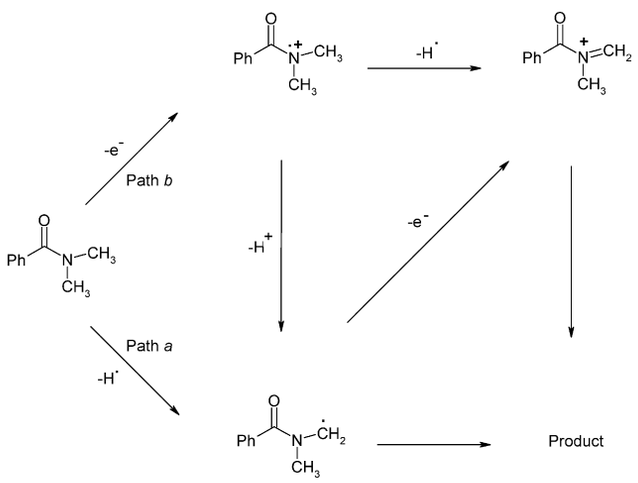
Inspection of the data in Table 1 for the aryl substituted compounds **1a–d** reveals that there is remarkably little variation in the magnitude of V_{max}, V_{max}/K and K with the aryl substituent, particularly so for the pseudo-first-order rate constant, V_{max}/K. What little variation there is appears not to follow any simple pattern with the electron withdrawing ability of the substituent, which contrasts with the experimental[10] and calculated (AM1 SFC MO) ionisation potentials for these compounds (Table 1).

Isotope effect

Interestingly, the data for the *N,N*-di(trideuteriomethyl) substrate **1e** reveal that the rate differences observed for this compound as compared with **1a** are entirely due to the rate at which the complex breaks down to products. Thus, the

magnitude of the kinetic deuterium isotope effect (KDIE) obtained for both V_{max} and V_{max}/K is 5.6 whereas no isotope effect is obtained for K, as is to be expected if K is related to the formation of a substrate/active oxidant complex.

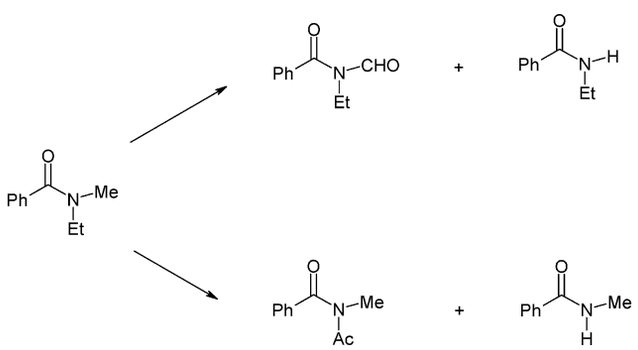
Such a large primary KDIE together with the absence of any correlation of the rates of reaction with aryl substituent tends to point to a mechanism that involves direct hydrogen atom abstraction from the substrate (Scheme 2, path *a*) rather than formation of an amide radical cation *via* electron transfer (Scheme 2, path *b*).



Scheme 2 Pathways for the oxidation of *N,N*-dimethylbenzamide.

Effect of the alkyl group

We extended our studies to the oxidation of several different substituted *N*-alkyl-*N*-methylbenzamides, **1f–i**, to examine the effect of the alkyl group. For these compounds, by determining the relative amounts of products formed we were able to quantify the relative rate of alkyl *versus* methyl oxidation. For example, for *N*-ethyl-*N*-methylbenzamide, **1f**, oxidation using the chemical model system gave rise to two major products, *N*-formyl-*N*-ethylbenzamide and *N*-acetyl-*N*-methylbenzamide, and two minor products, *N*-methylbenzamide and *N*-ethylbenzamide (Scheme 3).



Scheme 3 Products obtained from the oxidation of **1f** by TPPFe/Bu^{t}OOH.

After treatment of an aliquot of the reaction mixture with NaOH (to promote deacylation) the relative extent of *N*-methyl *versus* *N*-ethyl oxidation is determined by HPLC quantitation of the two secondary amides. For compound **1f**, the relative rate of ethyl *versus* methyl oxidation, after correction for the number of potential hydrogen atoms that can be removed, (two for Et, three for Me) is 1.11 (±0.20) (Table 2), which reveals a slight preference for the oxidation of the ethyl group. This ratio was found to be invariant with either time or substrate concentration.

In contrast, when **1f** was subjected to microsomal incubation it displayed either no preference for the oxidation of the alkyl group (V_{max}), or a preference for oxidation of the methyl group (V_{max}/K_M) (Table 2).[4] Similar results were obtained for microsomal incubation of the other amides **1g–1k**,[4,11] except for **1i** which showed a distinct preference for the oxidation of the alkyl group. The microsomal results showed that most probably the amide approaches the active site of the enzyme at a conformation that favours the metabolism of the smallest group, though in a substrate like **1i**, the stability of the allyl radical[7] could result in a higher rate constant for the metabolism of the allyl group.

Table 2 Relative rates of alkyl *versus* methyl oxidation, corrected for the number of oxidisible hydrogen atoms, for compounds **1a**,**f–l**, using TPPFe/Bu^{t}OOH at 30 °C in CH_2Cl_2

	Relative rate, *N*-R/*N*-Me		
		Microsomes	
Substrate	TPPFeCl/Bu^{t}OOH	V_{max} [a]	V_{max}/K_M [a]
1a	1.0		
1f	1.11 (± 0.20)	1.0	0.44
1g	1.40 (± 0.25)	0.9	0.82
1h	1.25 (± 0.34)	0.08	0.04
1i	7.89 (± 0.45)	5.1	1.75
1j	0.65 (± 0.11)	0	0
1k	1.61 (± 0.20)	0.76	0.13
1l	5.63 (± 0.98)	—	—

[a] Data taken from refs. 4 and 7.

Relative rate data for the TPPFe/Bu^{t}OOH model oxidations of the amides containing other *N*-alkyl groups are also contained in Table 2. These show that, in general, the larger the *N*-alkyl group (**1g**,**h**) the greater the preference for the oxidation of the alkyl group over the methyl group. This would be entirely consistent with the stabilisation of the carbon-centred radical afforded by the inductive effect of the larger alkyl group. Unfortunately, it is also consistent with the formation of an iminium ion (see Scheme 2), the larger alkyl group being able to preferentially form the more stable iminium ion due to greater inductive stabilization. Interestingly, the reaction of the isopropyl group in compound **1h** is clearly not subject to steric restraints. This is in contradistinction to the microsomal reaction where the oxidation of the Pr^i group was clearly disfavoured.[4]

As in the microsomal oxidations, a more marked effect was seen with *N*-allyl-*N*-methylbenzamide, **1i**. In this substrate the relative rate of allyl *versus* methyl oxidation after correction for the number of potential hydrogen atoms that can be removed is 7.89 (±0.45) (Table 2). This reveals a marked preference for the oxidation of an allyl group, consistent with the enhanced stability of the allyl carbon-centred radical.

Mechanistic probes

Included in Table 2 are compounds **1j**, **1k** and **1l** that were synthesised as possible probes for the reaction mechanism. Compound **1j** is *N*-cyclopropyl-*N*-methylbenzamide. In a mechanism where electron abstraction to form an amide radical cation is the first step, it might be expected that the radical cation from **1j** would rearrange (Scheme 4) thereby giving products originating from the opening of the cyclopropyl ring. This strategy has been adopted to intercept radical cations in the oxidative dealkylation of tertiary amines by cytochrome P-450.[12,13] However, no ring opening products could be detected in the chemical model oxidation of **1j**. Moreover, formation of a carbon-centred radical at the α-carbon of the cyclopropyl ring is unlikely given that the difficulty of abstracting a hydrogen atom in a cyclopropane ring is well known, as illustrated by the relative rate of 0.2 for the reactivities of C–H bonds in cyclopropane and neopentane towards the Bu^{t}OO$^\bullet$ radical.[14] Thus, for a mechanism that proceeds *via* hydrogen-

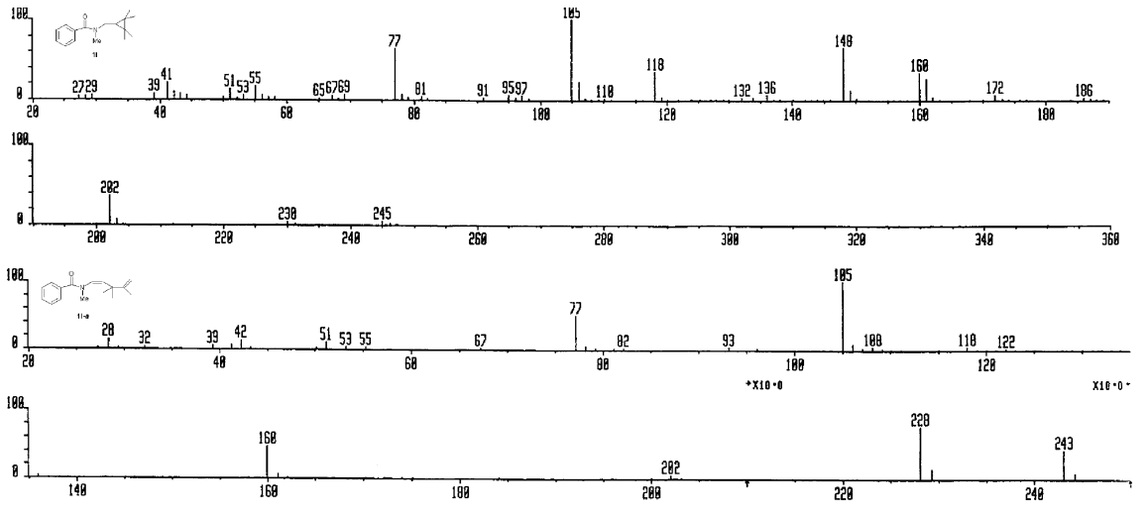
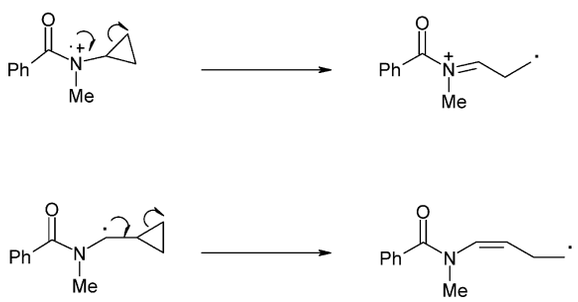


Fig. 2 Mass spectra of **1l** and **1l-*a***.

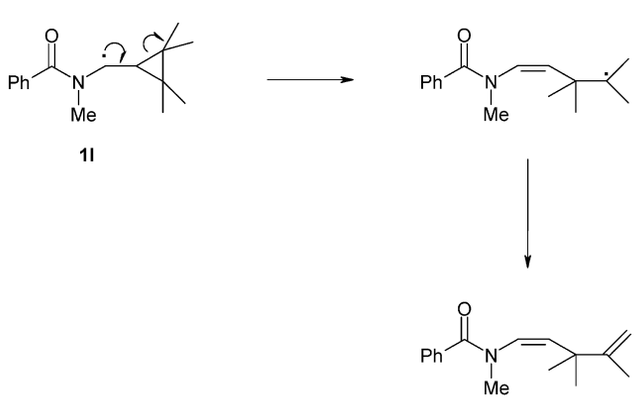


Scheme 4 Mechanistic probes for amide dealkylation.

atom abstraction to form a carbon-centred radical, it is to be expected that the cyclopropyl group would be more difficult to oxidise than the methyl group. Our results are consistent with this; the relative rate of cyclopropyl *versus* methyl *N*-dealkylation, after correction for the number of potential hydrogen atoms that can be removed, is 0.65 (±0.11) (Table 2). While steric arguments could be invoked to explain the lower reactivity of the cyclopropyl group, the isopropyl group in **1h** is more susceptible to oxidation than a methyl group and twice as likely to undergo reaction than the cyclopropyl group (Table 2).

Compounds **1k** and **1l** were studied because a cyclopropyl ring adjacent to a methylene group can potentially intercept a radical located in the methylene group, *via* opening of the cyclopropyl ring and diversion of the reaction to other products (Scheme 4). Methylcyclopropanes have been successfully used to probe a carbon-centred radical mechanism in the cytochrome P450-catalysed hydroxylation of alkanes and to measure the rate of oxygen rebound in this oxidation.[15] Bowry *et al.* calibrated a series of α-alkyl-substituted cyclopropylcarbinyl radicals by measuring the rate constants for ring opening of methylcyclopropyl radicals.[16] These authors also measured rate constants for hydrogen-atom abstraction by the *tert*-butoxyl radical from various positions in twelve substituted cyclopropanes. The reactivity of the methylene groups adjacent to the cyclopropyl ring is well illustrated by the relative rates of 1.63 to 0.053 for H atom abstraction from methylene *versus* methyl group in the ethyl group of ethylcyclopropane (cyclopropane C–H bonds have a relative rate lower than 0.02).

If a carbon-centred radical is formed in the model amide oxidations then we might expect oxidation to occur faster in the methylene part of the cyclopropylmethyl group than in the *N*-methyl group. Besides, if the ring opening of the radical occurs at a rate faster than the rate of oxygen rebound to the carbon-centred radical then ring-opening products would also be expected. When substrate **1k** was subjected to the TPPFe/Bu^{t}OOH oxidation no products originating from ring opening were detected. When **1l** was subjected to the same oxidation system, a product that had an M_r of two mass units lower was identified by GC-MS of the reaction mixture (Fig. 2), which we tentatively assign to the ring opened diene **1l-*a*** (Scheme 5). In both substrates **1k** and **1l**, reaction in the cyclopropylmethyl group was clearly favoured over the methyl group, the reactivity ratios being 1.61 (±0.20) for **1k** and 5.63 (±0.98) for **1l**, respectively, which is consistent with a carbon-centred radical mechanism. However, it is not clear why the ratio for **1l** is so much larger than that for **1k**, which is similar to those for other *N*-alkyl-*N*-methylamides (Table 2). AM1 SCF MO calculations are unable to reveal a reason for this difference (Table 3). Thus, the $\Delta\Delta H_f$ between the heats of formation of the amides **1a**, **1f**, **1k**, and **1l** and their corresponding radicals show that (i) radical formation from the Me group is essentially equi-energetic for all four compounds (ii) radical formation from the alkyl groups is favoured over radical formation from the Me group, and (iii) radical formation from the alkyl group in **1l** is the most favoured, but not enough compared to the other amides to account for the higher relative ratio for **1l** in Table 2.



Scheme 5 Possible pathway for formation of product **1l-*a*** in the chemical model oxidation of **1l**.

Possible intermediates

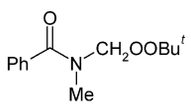
The data point to the involvement of a carbon-centred radical intermediate in the oxidation of *N,N*-dialkylbenzamides by TPPFe/Bu^{t}OOH. However, in contrast to the microsomal reaction, which follows a similar mechanism,[5,6] the products identified in the model reactions were either the *N*-acyl-*N*-alkylbenzamides or the corresponding *N*-alkylbenzamides rather than the *N*-hydroxyalkyl-*N*-alkylbenzamide (such as **5**). The latter compound is an attractive intermediate in these reactions because such hydroxylated compounds are the products of many reactions catalysed by similar oxidation

systems.[17] Further reaction of the *N*-hydroxyalkylbenzamides could be expected to follow one of two routes: oxidation to the corresponding *N*-acyl-*N*-alkylbenzamide or decomposition to the *N*-alkylbenzamide.

We investigated several compounds, including compound **5**, that could be possible intermediates in these model amide oxidations (Table 4). The rather unstable *N*-hydroxymethyl-*N*-methylbenzamide, **5**, the product of microsomal oxidation of *N,N*-dimethylbenzamide, formed only the corresponding *N*-methylbenzamide **4**. In the absence of either TPPFe or Bu^{t}OOH, compound **5** also decomposed to *N*-methylbenzamide but at rates that were five-fold lower. Thus, the *N*-hydroxymethyl compound may be an intermediate for the production of the minor reaction product, *N*-methylbenzamide, but it is not an intermediate in the formation of the *N*-formyl compound **3**.

The *N*-*tert*-butylperoxy ether **6** is another possible intermediate in the formation of **3**; this compound can be envisaged to be formed by hydrogen atom abstraction from *N,N*-dimethylbenzamide and subsequent combination of the carbon-centred radical with a Bu^{t}OO$^\bullet$ radical. Indeed, we were able to identify (HPLC retention time, mass spectrum and diode array UV spectrum) traces of this compound in the TPPFe/Bu^{t}OOH catalysed oxidation of *N,N*-dimethylbenzamide. Incubation of compound **6** with TPPFe/Bu^{t}OOH led to the formation of *N*-methylbenzamide as the main product; only small amounts of *N*-formyl-*N*-methylbenzamide were formed. The ratio of *N*-methylbenzamide/*N*-formyl-*N*-methylbenzamide was found to be 49 : 1, thus eliminating the *N*-*tert*-butylperoxy ether as an intermediate in the formation of *N*-formyl-*N*-methylbenzamide, but not as an intermediate in the small amounts of *N*-methylbenzamide that are formed concomitantly.

N-*tert*-Butoxymethyl-*N*-methylbenzamide (**7**, R = Bu^t) is a further possible intermediate in these amide oxidation reactions that could be formed by reaction of a carbon-centred radical with Bu^{t}OOH or, less likely, Bu^{t}O$^\bullet$. Unfortunately, all attempts to synthesise **7**, (R = Bu^t) failed. Consequently, we synthesised the corresponding methyl ether **7** (R = Me) and reaction of this led exclusively to the formation of *N*-methylbenzamide but not *N*-formyl-*N*-methylbenzamide. This eliminates the *N*-alkoxymethyl-*N*-methylamide as an intermediate for the formation of *N*-formyl-*N*-methylbenzamide.



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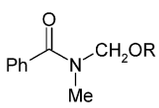

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Table 3 AM1SCF MO calculated heats of formation of the amides **1a**, **1f**, **1k** and **1l** and the corresponding $\Delta\Delta H_f$ values for formation of the corresponding carbon-centred radicals

Amide	ΔH_f/kJ mol^{-1}	$\Delta\Delta H_f$/kJ mol^{-1} Me-*H* loss	$\Delta\Delta H_f$/kJ mol^{-1} Alkyl-*H* loss
1a	−21.7	(*Z*)[b] 103 (*E*)[b] 98.2	—
1f	(*E*)[a] −47.1	103	82.1 (*transoid*)[c] 96.4 (*cisoid*)[c]
	(*Z*)[a] −46.9	98.1	86.1 (*transoid*)[c] 91.8 (*cisoid*)[c]
1k	(*E*)[a] 74.4	105	81.8 (*transoid*)[c] 95.7 (*cisoid*)[c]
	(*Z*)[a] 74.1	98.6	86.0 (*transoid*)[c] 94.7 (*cisoid*)[c]
1l	(*E*)[a] −6.4	104	80.1 (*transoid*)[c] 94.9 (*cisoid*)[c]
	(*Z*)[a] −5.5	98.2	82.8 (*transoid*)[c] 93.1 (*cisoid*)[c]

[a] Conformation of the amide. [b] Stereochemical relationship of the radical centre to the carbonyl oxygen atom. [c] Stereochemical relationship between the groups on the carbon-centred radical and those on the amide nitrogen atom.

Nature of the oxidant

The results obtained with our substrates are consistent with a hydrogen atom abstraction mechanism that leads to the formation of a carbon-centred radical. Using TPPFe/Bu^{t}OOH this carbon-centred radical could be formed either by direct hydrogen atom abstraction by the *tert*-butoxyl radical, as proposed by Mansuy for alkane hydroxylation,[18] or alternatively by an iron-oxo complex of the type Fe^{V}=O or Fe^{IV}–O$^\bullet$ formally equivalent to compound I of peroxidase (an oxene), as proposed by Mansuy for the same reactions in which iodosobenzene is used as oxygen source.[19]

It is accepted that an oxene is the active species in biomimetic systems employing porphyrins and iodosobenzene or peracids.[18] However, there is still some controversy as to whether high-valent iron-oxo complexes of the type Fe^{V}=O can be formed in model oxidations employing porphyrins and hydroperoxides as oxygen source. An oxene is considered to be the active species in the epoxidation of alkenes in the presence of TPPFe, hydroperoxides and imidazole.[18] Here imidazole acts as an electron-donating ligand to the iron of the porphyrin nucleus and catalyses the heterolytic scission of hydroperoxide O–O bond that is crucial for the formation of the oxene. Traylor has proposed that an oxene of the type Fe^{V}=O is formed even in the absence of imidazole, and that the reaction could be accelerated by the presence of water, alcohols or imidazole.[20,21] Amides are known to act as donor molecules in metallic complexes and have been shown to coordinate to Fe^{3+} *via* the oxygen atom.[22] DMF, like imidazole, can stabilise Fe^{IV}=O and possibly Fe^{V}=O iron-oxo complexes of porphyrins by coordinating axially with the iron.[23] Spectophotometric titrations of TPPFe solutions in the presence of imidazole demonstrated that the formation of a complex between imidazole and porphyrin led to a type II reverse spectrum.[24,25] Results obtained by us show that the addition of *N,N*-dimethylbenzamide to a solution of TPPFe has a similar effect on the spectrum of TPPFe (Fig. 3). *N,N*-Dialkylamides could thus act in a manner similar to imidazole facilitating the formation of

Table 4 Formation of *N*-formyl-*N*-methylbenzamide **3** and *N*-methylbenzamide **4** in the oxidation of *N,N*-dimethylbenzamide **1a** and of the possible intermediates **5**–**7**. [Substrate] = 0.5 × 10^{-3} M.

Substrate	X	R^1	R^2	Relative yield (%) *N*-formylbenzamide **3**	Relative yield (%) *N*-methylbenzamide **4**
1a	H	Me	Me	95	5
5	H	Me	CH_2OH	nd	100
6	H	Me	CH_2OOBu^t	2	98
7	H	Me	CH_2OMe	nd	100

nd = not detected.

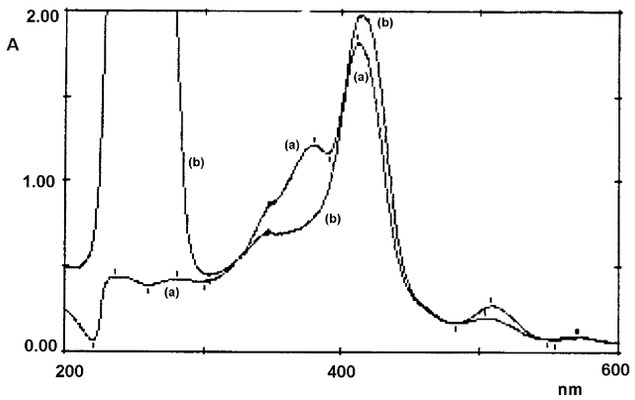
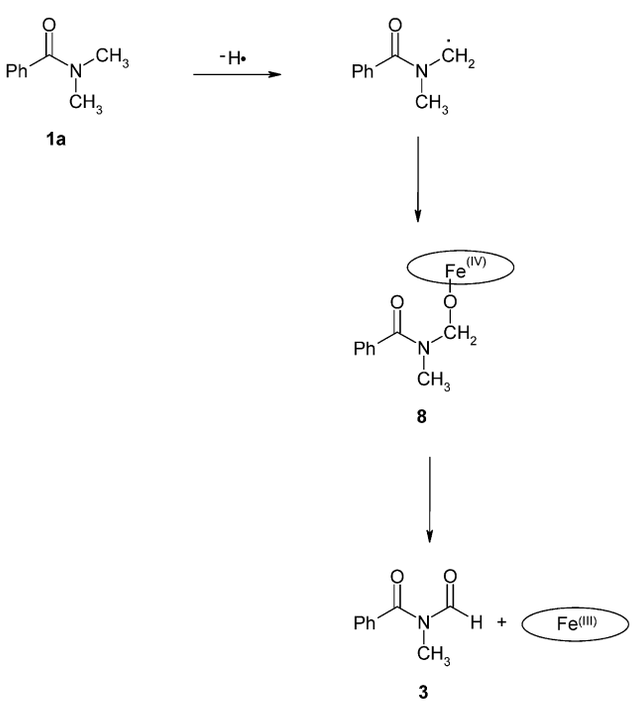


Fig. 3 UV-visible spectra of a solution of 2×10^{-5} M $TPPFe^{III}$ (a) and a solution of 2×10^{-5} M $TPPFe^{III}$ in the presence of 0.02 M *N,N*-dimethylbenzamide (b).

the oxene. Furthermore, we found the addition of water or imidazole increased the initial rate of formation of *N*-formyl-*N*-methylbenzamide from *N,N*-dimethylbenzamide (not shown), and when reactions were performed using iodosobenzene as the oxygen donor a similar product distribution was obtained suggesting a common oxene oxidant in these systems.

Mechanism for the formation of *N*-acyl-*N*-methylbenzamides

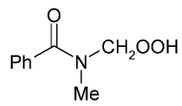
The carbon-centred radical must react to form the *N*-acyl-*N*-alkylbenzamides and the *N*-alkylbenzamides. However, the exact mechanism for this is still uncertain. Since none of the postulated intermediates **5**–**7** are responsible for the formation of the *N*-acylamide, we suspect an intermediate of the type of **8** (Scheme 6), similar to that implicated in the formation of alkylated porphyrins during the oxidation of alkenes,[26] to be involved.



Scheme 6 Possible mechanism for the formation of **3** from **1a**.

One can conceive of this intermediate being formed by reaction between a carbon-centred radical and the oxene Fe^{V}=O present in the medium. This intermediate could form the *N*-formylamide and regenerate $TPPFe^{III}$ to restart the cycle. Either the *tert*-butoxyl radical or a complex of the type Fe^{IV}–OH could abstract the hydrogen needed to form *N*-formyl-*N*-methylbenzamide and regenerate $TPPFe^{III}$.

Alternatively, the hydroperoxide **9** is an intermediate that could give rise to the acyl amides. A compound of this type was found to be formed in the dioxygen oxidation of *N*-methylpyrrolidone to *N*-methylsuccinimide.[27] However, we consider this unlikely since the *N*-acyl products are produced in identical yields when the reactions were carried out under an atmosphere of nitrogen. Unfortunately, all our attempts to make compound **9** failed.



9

The small amounts of *N*-alkylamides formed directly in the oxidation of *N,N*-dialkylamides can be explained by formation from the carbon-centred radical and subsequent reaction of this radical either with *tert*-ButOO•, *tert*-ButO• or HO•. All three possible products, *viz N-tert*-butylperoxymethyl-*N*-methylbenzamide, *N-tert*-butoxymethyl-*N*-methylbenzamide, and *N*-hydroxymethyl-*N*-methylbenzamide, lead to the formation of *N*-methylbenzamide when subjected to the conditions of the model oxidation. As *N-tert*-butylperoxymethyl-*N*-methylbenzamide can be identified in trace amounts in the oxidation of *N,N*-dimethylbenzamide we tentatively suggest this compound as an intermediate in the formation of the *N*-alkylbenzamides that appear as minor products in the reaction.

Experimental

Instrumentation

NMR spectra were recorded using JEOL FX90Q or JNM-EX400FT spectrometers. UV/vis and IR spectra were recorded using Shimadzu UV 160 and Nicolet 205 FTIR spectrophotometers, respectively. Mass spectra were recorded with a VG Mass Lab 25–250 spectrometer. GC-MS was performed using a Hewlett-Packard 5809-A gas chromatograph connected to the VG Mass Lab 25–250 spectrometer. HPLC was performed using a Varian 5000 instrument, a Cecil 2112 variable wavelength detector and a Spectra Physics Chrom Jet integrator. Diode array detection was performed using a Varian 9060 Polychrom detector. Elemental analyses were obtained from Medac Ltd, Brunel Science Centre, Cooper's Hill Lane, Englefield Green, Egham, TW20 0JZ, UK.

Reagents

Tetraphenylporphyrinatoiron(III) chloride was obtained from Aldrich. *N,N*-Dialkylamides **1a**–**h** and the product *N*-alkylamides were synthesised by the Shotten–Baumann[28] method from the appropriate amine and acid chloride. The dialkylamides were purified by column chromatography using ethyl acetate : hexane 5 : 2 as eluent and the *N*-alkylamides were recrystallised from ethanol. *N*-Alkyl-*N*-methylamides **1i**–**l** were synthesised from the appropriate monoalkylamine using *n*-butyllithium and iodomethane[4] and purified by column chromatography using ethyl acetate : hexane 5 : 2 as eluent. Iodosobenzene was synthesised by a published method.[29] *tert*-Butylhydroperoxide was obtained from Aldrich as a 70% aqueous solution, extracted with dichloromethane, dried (4 Å molecular sieves) and, after evaporation of the solvent, stored at −20 °C over 4 Å molecular sieves. Dichloromethane used for the model reactions was obtained from Merck (GLC grade) and was distilled before use.

***N*-Methoxymethyl-*N*-methylbenzamide (7, R = Me).** *N*-Methylbenzamide (0.018 mol, 2.5 g) and paraformaldehyde (2.3 g) were added to chlorotrimethylsilane (30 cm^3) and refluxed. After 18 h chlorotrimethylsilane was evaporated and formation

of *N*-chloromethyl-*N*-methylbenzamide was confirmed by NMR spectroscopy (δ_H/ppm 3.10 (3H,s), 5.28 (2H,s), 7.45 (5H,m)). This (0.50 g, 0.00273 mol) was used without further purification and added to a solution of sodium methoxide (prepared by dissolving metallic sodium (0.25 g) in methanol (50 cm^3)). After 12 h, water 50 (cm^3) was added, the methanol evaporated and the residue extracted with dichloromethane (3 × 20 cm^3). The organic phase was washed with water, (2 × 10 cm^3), dried with $MgSO_4$ and purified by column chromatography using ethyl acetate : hexane 1 : 1 as eluent. The compound was obtained as an oil in 65% yield: ν_{max}/cm^{-1} 2934, 1647, 1446, 1436, 1180, 701; δ_H/ppm ($CDCl_3$) 3.07 (3H, s), 3.20 (3H, s), 4.59 (2H, s), 7.36 (5H, m); δ_{13C}/ppm ($CDCl_3$) 32.7, 55.1, 82.5, 127.3, 128.4, 128.5, 130.0, 125.6, 135.7, 172.5; *m*/*z* (%) 179 (9), 164 (39), 148 (13), 105 (100), 77 (42), 51 (13). $C_{10}H_{13}NO_2$ requires: C, 67.0; H, 7.31; N, 7.89%. Found: C, 67.1; H, 7.38; N, 7.54%.

***N*-*tert*-Butylperoxymethyl-*N*-methylbenzamide, 6.** *N*-Chloromethyl-*N*-methylbenzamide (0.50 g, 0.00273 mol), synthesised as described above and used without further purification, was dissolved in dry THF (20 cm^3). *tert*-Butyl hydroperoxide (0.49 g, 0.00546 mol) was added and the reaction left for 12 h. The solution was evaporated, the residue dissolved in dichloromethane, washed with water (3 × 10 cm^3), dried with $MgSO_4$, concentrated and purified by column chromatography using ethyl acetate as eluent. The compound was obtained as a solid in 63% yield: mp 42–45 °C; ν_{max}/cm^{-1} 2979, 2933, 1651, 1390, 1364, 1285, 1259, 925, 700; δ_H/ppm ($CDCl_3$) 1.15 (9H, s), 3.17 (3H, s), 5.00 (2H, s), 7.33–7.46 (5H m); δ_{13C}/ppm ($CDCl_3$) 23.2, 33.3, 80.7, 84.3, 126.9, 127.7, 128.0, 129.7, 131.0, 135.9, 172.9; *m*/*z* (%) 238 (6), 181 (2), 148, (92), 105 (100), 77 (36), 51 (14). $C_{13}H_{19}NO_3$ requires: C, 65.8; H, 8.07; N, 5.90%. Found: C, 65.4; H, 8.12; N, 5.86%.

Substrate oxidations

Amide oxidations were performed in CH_2Cl_2 using a solution that was 1 × 10^{-3} M in TPPFe and 0.2 M in *tert*-ButOOH. Usually, to 1 cm^3 of CH_2Cl_2 containing the required concentration of substrate, 0.5 cm^3 of a CH_2Cl_2 TPPFe solution (4 × 10^{-3} M) and 0.5 cm^3 of a CH_2Cl_2 Bu^{t}OOH solution (0.8 M) were added. Oxidation of amides **1a**–**e** was performed using initial substrate concentrations between 0.1 and 0.5 M. Oxidation of other amides was performed using a concentration of 0.5 M. Oxidations performed using iodosobenzene as oxidant were carried out by adding 4 × 10^{-4} mol of iodosobenzene to 2 cm^3 of a CH_2Cl_2 solution containing the substrate and TPPFe. Oxidation of **1a** in the presence of imidazole was performed using 10^{-2} M imidazole, 0.5 M **1a** and 1 × 10^{-3} M TPPFe. All reaction mixtures were incubated at 30 °C. At timed intervals aliquots (0.050 cm^3) were removed, diluted with ethanol 1 $cm^3$and injected into the HPLC (for amides **5**, **6** and **7**) or diluted with a solution of 0.1 × 10^{-3} M NaOH in ethanol, left for 10 min and then neutralised with HCl before injection into the HPLC.

HPLC analysis

Detection of the amides was performed using a 5 μm C-18 25 cm × 5 mm Jones chromatography column and an eluent consisting of 20% acetonitrile in water for **1a** and **1e**, 25% acetonitrile in water for **1b**, 27.5% acetonitrile in water for **1d**, 30% acetonitrile on water for **1c** and a gradient using 15% acetonitrile in 0.05 M pH 2.6 phosphate buffer at t = 0 to 42% acetonitrile in 0.05 M pH 2.6 phosphate buffer at t = 22 min for the other amides.

Mass spectral assay for reaction products

Substrates (usually 0.1 M) were subjected to oxidation as described above. The reactions were followed by HPLC and after 2 and 4 h one further portion of anhydrous Bu^{t}OOH was added. After 6 h an aliquot of the reaction mixture was diluted with ethanol and analysed in the GC-MS system using a 25 m × 0.5 mm BP-5 column 25 m, (start temperature 80 °C then 10 °C/ min up to 200 °C).

Molecular orbital calculations

Ionisation potentials for the dimethylbenzamides were calculated using the semi-empirical AM1 SCF MO program within the MOPAC 4.0 package.[30] All structures were geometry optimised using the Broyden–Fletcher–Golfarb–Shanno approach and performed on a VAX cluster.

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