Iron-catalysed Oxidation of *N,N*-Dimethylaniline with Molecular Oxygen

Satoru Murata, Masahiro Miura,* and Masakatsu Nomura

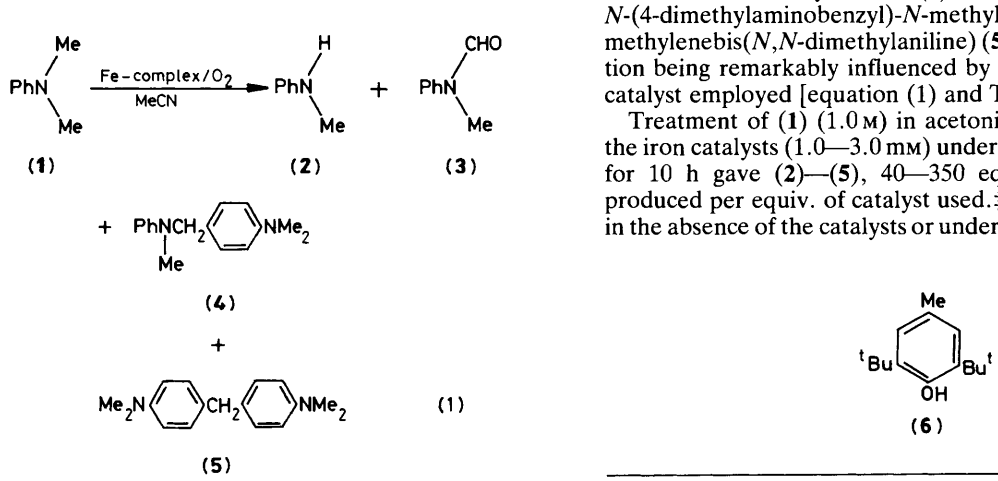
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

N,N-Dimethylaniline is oxidised by molecular oxygen in the presence of a number of iron complexes or salts in acetonitrile to give a mixture of *N*-methylformanilide and 4,4'-methylenebis(*N,N'*-dimethylaniline) together with *N*-methylaniline, the product composition being a marked function of the identity of the iron species employed.

Because of their relevance to enzymatic *N*-dealkylation and as models for cytochrome P-450 and the other iron-containing proteins, there have been numerous studies of tertiary amine oxidation with a number of model systems.[1—3] These model reactions are often performed with various alternative oxygen sources including iodosobenzene and hydroperoxides in the presence of appropriate iron species. For instance, it has been reported that the oxidation of *N,N*-dimethylbenzylamine with iodosobenzene catalysed by [Fe(tpp)]Cl† proceeds *via* initial one-electron oxidation, whereas with t-butylhydroperoxide hydrogen abstraction of the amine by the oxidant is the predominant reaction.[2d,f] On the other hand, oxidation using molecular oxygen directly has been little studied.[3,4]

In this communication, we report our findings that *N,N*-dimethylaniline (**1**) is efficiently oxidised in the presence of several iron complexes [Fe(salen)]OAc, $[Fe(salen)]_2O$, [Fe(tpp)]OAc, and $[Fe_3O(OAc)_6(H_2O)_3]Cl$ and simple iron salts $FeCl_3$ and $Fe(ClO_4)_3$ under molecular oxygen to give a mixture of *N*-methylaniline (**2**), *N*-methylformanilide (**3**), *N*-(4-dimethylaminobenzyl)-*N*-methylaniline (**4**), and 4,4'-methylenebis(*N,N*-dimethylaniline) (**5**), the product composition being remarkably influenced by the identity of the iron catalyst employed [equation (1) and Table 1].

Treatment of (**1**) (1.0 M) in acetonitrile in the presence of the iron catalysts (1.0—3.0 mM) under oxygen (1 atm) at 60 °C for 10 h gave (**2**)—(**5**), 40—350 equiv. of product being produced per equiv. of catalyst used.‡ It was confirmed that, in the absence of the catalysts or under nitrogen, no detectable



(**6**)

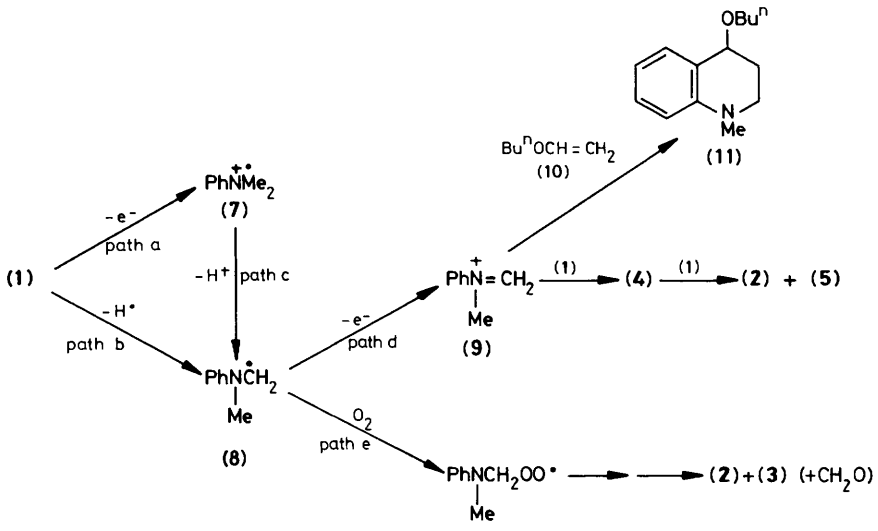
† *Abbreviations*: tpp = *meso*-tetraphenylporphyrinato, salen = *N,N'*-bis(salicylidene)ethylenediaminato.

‡ Products (**2**)—(**5**) were isolated by column chromatography on silica gel using hexane–ethyl acetate as eluant and were compared with authentic specimens.[8]

Table 1. Oxidation of *N*,*N*-dimethylaniline with molecular oxygen.[a]

Catalyst	Conc. of catalyst /mM	Products/mM[b] (2)	(3)	(4)	(5)	(11)	Conc. of (1) (mM) after reaction[b]	Catalyst turnover number
$FeCl_3$	3.0	43	—	10	65	—	760	39
$FeCl_3$[c]	3.0	27	—	3	61	—	760	30
$FeCl_3$[d]	3.0	10	—	—	—	105	855	38
$Fe(ClO_4)_3 \cdot 6H_2O$	3.0	48	—	4	81	—	763	44
[Fe(salen)]OAc	3.0	172	335	33	—	—	204	180
[Fe(salen)]OAc[c]	3.0	—	—	—	—	—	—	—[e]
[Fe(salen)]OAc[d]	3.0	69	52	2	3	90	713	72
$[Fe(salen)]_2O$	1.5	169	333	25	1	—	246	352
[Fe(tpp)]OAc	3.0	45	144	83	48	—	527	107
$[Fe_3O(OAc)_6(H_2O)_3]Cl \cdot 2H_2O$	1.0	66	64	100	17	—	588	247

[a] The reaction was carried out at 60 °C in acetonitrile under oxygen (1 atm) for 10 h. $[(1)]_0$ = 1.0 M. [b] Determined by g.l.c. analysis. [c] Reaction in the presence of 2,6-di-t-butyl-4-methylphenol (50 mM). [d] Reaction in the presence of n-butyl vinyl ether (2.0 M). [e] No product was detected.



Scheme 1

amount of the products was formed. In the reaction with either iron(III) chloride or perchlorate, the dimerised product (**5**) was obtained as the major product together with (**2**) and (**4**). In contrast, with [Fe(salen)]OAc or $[Fe(salen)]_2O$ the mono-oxygenated product (**3**) was the predominant product; the turnover number related to the catalyst used (mol product/mol catalyst) was considerably higher than that of the reaction using simple iron salts. In the reactions with the two model complexes [Fe(tpp)]OAc and $[Fe_3O(OAc)_6(H_2O)_3]Cl$,[5—7] the yield of (**3**) was comparable with that of the dimerised products (**4**) and (**5**).

Addition of 2,6-di-t-butyl-4-methylphenol (**6**) (50 mM) completely inhibited the oxidation of (**1**) using [Fe(salen)]OAc, whereas the reaction using $FeCl_3$ was little affected. The intramolecular kinetic isotope effect (k_H/k_D by g.c.–m.s. analysis) calculated from the product ratio of *N*-trideuteriomethylaniline to (**2**) in the reaction of *N*-methyl-*N*-trideuteriomethylaniline using $FeCl_3$ was found to be 1.6. In contrast, a relatively large isotope effect (k_H/k_D = 5.0) was observed in the reaction with [Fe(salen)]OAc. These results suggest that the oxidation of (**1**) using $FeCl_3$ proceeds *via* initial one-electron oxidation to give an aminium cation radical (**7**) (path a in Scheme 1), whereas with [Fe(salen)]OAc hydrogen abstraction at the α-position of the nitrogen to give α-amino radical (**8**) (path b) is the predominant reaction, although the active species in each case is unclear. In the reaction with $FeCl_3$, the radical (**8**) may also be formed by the proton loss from (**7**) (path c) followed by a further one-electron oxidation to give an iminium cation (**9**) (path d). The subsequent electrophilic dimerisation reaction affords (**4**) which is further transformed into (**5**).[8] This is supported by the fact that the rection of (**1**) using $FeCl_3$ in the presence of n-butyl vinyl ether (**10**) (2.0 M) gave 4-n-butoxy-1,2,3,4-tetrahydro-1-methylquinoline (**11**) selectively.[9]§ The one-elec-

§ The quinoline (**11**) was isolated as an oil by column chromatography on silica gel using hexane–ethyl acetate as eluant; m.s., *m/z* 219 (M^+); ^1H n.m.r. (400 MHz in $CDCl_3$), δ_H 0.91 (3H, t, *J* 7.6 Hz), 1.29—1.43 (2H, m), 1.52—1.62 (2H, m), 1.87—1.95 (1H, m) 2.08—2.14 (1H, m), 2.91 (3H, s), 3.11 (1H, dt, *J* 11.2, 4.4 Hz), 3.39 (1H, dt, *J* 3.4, 11.5 Hz), 3.36—3.65 (2H, m), 4.31 (1H, t, *J* 3.7 Hz), 6.61—6.65 (2H, m) 7.14—7.26 (2H, m).

tron oxidation of (**8**) to (**9**) in the reaction with [Fe(salen)]-OAc would be so slow as to compete with the reaction of (**8**) with molecular oxygen to give (**2**) and (**3**) (path e). The reaction of (**1**) using this complex in the presence of (**10**) afforded a mixture of (**3**) and (**11**).

Received, 25th August 1988; Com. 8/03460E

References

1 R. P. Hanzlik and R. H. Tullman, *J. Am. Chem. Soc.*, 1982, **104**, 2048; T. L. Macdonald, K. Zirvi, L. T. Burka, P. Peyman, and F. P. Guengerich, *ibid.*, 1982, **104**, 2050; G. T. Miwa, J. S. Walsh, G. L. Kedderis, and P. F. Hollenberg, *J. Biol. Chem.*, 1983, **258**, 14445; D. C. Heimbrook, R. I. Murray, K. D. Egeberg, S. G. Sligar, M. W. Nee, and T. C. Bruice, *J. Am. Chem. Soc.*, 1984, **106**, 1514; G. L. Kedderis and P. F. Hollenberg, *J. Biol. Chem.*, 1984, **259**, 3663; N. Murugesan and S. M. Hecht, *J. Am. Chem. Soc.*, 1985, **107**, 493.

2 (a) P. Shannon and T. C. Bruice, *J. Am. Chem. Soc.*, 1981, **103**, 4580; (b) N. Miyata, H. Kiuchi, and M. Hirobe, *Chem. Pharm. Bull.*, 1981, **29**, 1489; (c) T. Takata and W. Ando, *Tetrahedron Lett.*, 1983, **24**, 3631; (d) J. R. Lindsay Smith and D. N. Mortimer, *J. Chem. Soc., Chem. Commun.*, 1985, 64; (e) C. M. Dicken, Fu-Lung Lu, M. W. Nee, and T. C. Bruice, *J. Am. Chem. Soc.*, 1985, **107**, 5776; (f) J. R. Lindsay Smith and D. N. Mortimer, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1743; (g) K. Fujimori, S. Fujiwara, T. Takata, and S. Oae, *Tetrahedron Lett.*, 1986, **27**, 581; (h) K. Fujimori, T. Takata, S. Fujiwara, O. Kikuchi, and S. Oae, *Tetrahedron Lett.*, 1986, **27**, 1617; (i) F. Pautet, R. Barret, and M. Daudon, *Pharmazie*, 1986, **41**, 286; (j) D. T. Sawyer, L. Spencer, and H. Sugimoto, *Isr. J. Chem.*, 1987, **28**, 3.

3 T. Santa, N. Miyata, and M. Hirobe, *Chem. Pharm. Bull.*, 1984, **32**, 1252; E. I. Karasevich, A. M. Khenkin, and A. E. Shilov, *J. Chem. Soc., Chem. Commun.*, 1987, 731.

4 F. Benedini, G. Galliani, M. Nali, B. Rindone, and S. Tollari, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1963.

5 S. Ito, K. Inoue, and M. Matsumoto, *J. Am. Chem. Soc.*, 1982, **104**, 6450.

6 D. H. R. Barton, J. Boivin, M. Gastiger, J. Morzycki, R. S. Hay-Motherwell, W. B. Motherwell, and K. M. Schwartzentruber, *J. Chem. Soc., Perkin Trans. 1*, 1986, 947.

7 S. Murata, M. Miura, and M. Nomura, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1259.

8 J. M. Fayadh, D. W. Jessop, and G. A. Swan, *J. Chem. Soc.* (*C*), 1966, 1605; J. R. Lindsay Smith, R. O. C. Norman, and W. M. Walker, *J. Chem. Soc.* (*B*), 1968, 269; M. Grodowski and T. Latowski, *Tetrahedron*, 1974, **30**, 767.

9 R. B. Roy and G. A. Swan, *J. Chem. Soc.* (*C*), 1969, 1886.