Kinetic Deuterium Isotope Effect Profiles and Substituent Effects in the Oxidative N-Demethylation of *N*,*N*-Dimethylanilines Catalyzed by Tetrakis(pentafluorophenyl)porphyrin Iron(III) Chloride

Enrico Baciocchi,*,§ Osvaldo Lanzalunga,‡ Andrea Lapi,‡ and Laura Manduchi‡

Contribution from the Dipartimento di Chimica and Centro CNR di Studio sui Meccanismi di Reazione, Universita' La Sapienza, Piazzale A. Moro, 5 00185 Roma, Italy

Received January 16, 1998

Abstract: The mechanistic dichotomy (hydrogen atom transfer or electron-transfer mechanism) in the oxidative N-dealkylation of a series 4-X-*N*,*N*-dimethylanilines (X = MeO, Me, H, Br, CF_3, CN, NO_2) by PhIO, catalyzed by tetrakis(pentafluorophenyl)porphyrin iron(III) chloride (FeTPFPPCl), was investigated in CH_2Cl_2 by determining both the intra- and the intermolecular kinetic deuterium isotope effects and the effect of substituents on reactivity. The results were as follows: (a) The values of k_H/k_D(intra), obtained by the study of 4-X-*N*-methyl-*N*-trideuteriomethylanilines [2.0 (X=NO_2), 2.0 (X = CN), 2.6 (X = Br), 3.1 (X = H), 3.2 (X = Me), 3.3 (X = MeO)], regularly decreased on going from electron donating to electron withdrawing substituents, a trend exactly contrary to that found for the hydrogen atom transfer reactions of some of the same substrates with *tert*-butoxyl radicals. (b) The intermolecular kinetic deuterium isotope effects, k_H/k_D(inter), determined by competitive experiments with 4-X-substituted *N*,*N*-dimethyl- and *N*,*N*-bis(trideuteriomethyl)anilines [k_H/k_D(inter) for X = H, Br, and MeO, 1.6, 1.5 and 1.9, respectively], were significantly different from the corresponding k_H/k_D(intra) values. (c) The relative reactivities of 4-X-substituted *N*,*N*-dimethylanilines, determined by competitive kinetics, spanned a reactivity range of 25 (from X = NO_2 to X = MeO) and were nicely correlated by the substituent constants σ^+. A ρ value of −0.88 (r^2 = 0.98) was determined by this correlation. The relative reactivity can also be fitted to the Rehm−Weller equation for electron-transfer reactions. A value of 47 kcal mol $^{-1}$ for the reorganization energy was calculated. Altogether, the above results, and particularly points (a) and (b), allow us to dismiss the operation of a hydrogen atom transfer mechanism. A one electron transfer mechanism is instead consistent with these results and appears therefore the most likely pathway for the oxidative N-demethylation of *N*,*N*-dimethylanilines catalyzed by iron porphyrins. The intramolecular kinetic deuterium isotope effect profile is a useful tool for distinguishing electron transfer from hydrogen atom transfer mechanisms.

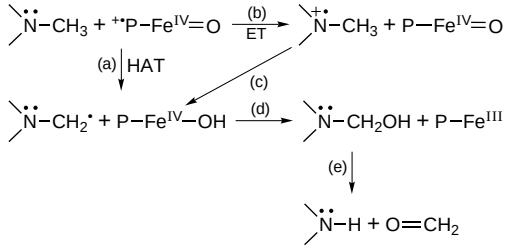
Introduction

It is generally believed that the N-dealkylation of tertiary alkylamines by cytochrome P450 is initiated by one-electron abstraction from the nitrogen atom by the enzyme active oxidant (an iron oxo complex, abbreviated as $P^{+\bullet}-Fe^{IV}=O$, where P is the protoporphyrin IX).[1] The nitrogen radical cation thus formed loses a proton from the a carbon atom to produce a carbon centered radical that is trapped by addition of the activated oxygen to the carbon (oxygen rebound). The resulting α-hydroxylated product subsequently decomposes to the dealkylation product (Scheme 1, path b−e).

This mechanism, however, was recently questioned by Dinnocenzo and Jones and their associates.[2] These authors determined the intramolecular deuterium kinetic isotope effect in the oxidation of a number of 4-substituted *N*,*N*-dimethylanilines by a variety of cytochrome P450 enzymes and found kinetic deuterium isotope effect values almost identical to those obtained when the same substrates were reacted with *tert*-butoxyl radicals.[3] Since there is general agreement that the latter species react with *N*,*N*-dimethylanilines by a hydrogen atom transfer (HAT) mechanism, it was concluded that this mechanism should also operate for the case of the enzymatic oxidation.

According to this mechanism (Scheme 1, path a), the carbon radical is formed from the reactants in a single step. Steps d

Scheme 1



§ Dipartimento di Chimica.

‡ Dipartimento di Chimica and Centro CNR di Studio sui Meccanismi di Reazione.

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S0002-7863(98)00187-5 CCC: $15.00
Published on Web 05/29/1998

and e then follow, as in the ET mechanism. Additional support to this conclusion came from the observation that the deprotonation of *N*,*N*-dimethylaniline radical cations (an essential step in the ET mechanism) exhibits a kinetic deuterium isotope effect profile significantly different from that actually found in the cytochrome P450 induced reactions. Moreover, subsequent work showed that the kinetic deuterium isotope effect profile as a mechanistic probe could also be applied as well to other cytochrome P450 induced hydroxylation reactions involving substrates different than *N*,*N*-dimethylanilines.[4]

Iron porphyrins are well recognized chemical models of cytochrome P450 capable of mimicking most reactivity aspects of this enzyme, including the N-dealkylation of tertiary amines.[1d,5] Indeed, the active oxidant, in the oxidations catalyzed by iron tetraarylporphyrins, is an iron oxo complex, formed by the reaction of an oxygen donor with the iron porphyrin (eq 1, where P now indicates the synthetic porphyrin and SO is an oxygen donor), structurally similar to the one involved in cytochrome P450 induced reactions.[1a,6] It would therefore seem reasonable, even though by no means certain, to expect that the two systems also share the main mechanistic features.

$$P-Fe^{III} + SO \rightarrow {}^{+\bullet}P-Fe^{IV}=O + S \qquad (1)$$

This, however, would not be the case if the conclusions by Dinnocenzo and Jones are correct. Accordingly, the available information on the reaction selectivity of the oxidation of *N*,*N*-dimethylanilines by tetraphenylporphyrin iron(III) chloride (FeTPPCl), using iodosylbenzene (PhIO) as the oxygen source,[5c,d] appears more in line with the ET mechanism reported in Scheme 1 than with the HAT mechanism proposed by Dinnocenzo and Jones for the N-dealkylations promoted by cytochrome P450.[2] Moreover, it should be noted that Lindsay Smith and co-workers proposed an ET mechanism for the N-dealkylation of *N*,*N*-dimethylbenzylamines induced by FeTPPCl and PhIO.[7] Since the oxidation potentials of *N*,*N*-dimethylanilines[8a] are significantly lower than those of *N*,*N*-dimethylbenzylamines,[8b] it would seem reasonable to expect that the ET mechanism also holds for the former substrates. Thus, if these conclusions are correct, we are faced with the following dilemma: either the biomimetic and enzymatic oxidative N-dealkylation of *N*,*N*-dimethylanilines react by different mechanisms or the kinetic deuterium isotope effect profile is not a reliable mechanistic probe to distinguish ET from HAT mechanisms.

In view of the great general interest toward the development of mechanistic probes to distinguish HAT and ET mechanisms, we felt it worthwhile to obtain further information on the mechanism of the oxidation of *N*,*N*-dimethylanilines induced by synthetic iron porphyrins by using a number of mechanistic criteria, including the intramolecular kinetic deuterium isotope effect profile. Our main aim was that of reaching definitive conclusions on the mechanism of these reactions, at the same time testing the actual validity of the isotope effect profile as a mechanistic probe.

In this paper we report on an investigation of the PhIO promoted oxidation of a number of 4-substituted *N*,*N*-dimethylanilines, catalyzed by tetrakis(pentafluorophenyl)porphyrin iron(III) chloride (FeTPFPPCl). FeTPFPPCl is a significantly more efficient catalyst than FeTPPCl,[9] which has allowed us to conveniently investigate a wide range of substituted *N*,*N*-dimethylanilines. On the other hand, its reduction potential is higher than that of FeTPPCl.[10] Therefore, if an ET mechanism is operating with FeTPPCl, *a fortiori* it should operate with FeTPFPPCl.

Results

The reactions of a number of 4-X substituted *N*,*N*-dimethylanilines (X = MeO, Me, Br, H, CF_3, CN, NO_2) with PhIO in the presence of FeTPFPPCl were studied in CH_2Cl_2. In most experiments 100 μmol of substrates were reacted with PhIO (50 μmol) and FeTPFPPCl (2 μmol) in CH_2Cl_2 (1 mL). In all cases, clean N-demethylation was observed with the formation of the corresponding *N*-methylaniline. Dimerization products, if present, were formed in negligible amounts.

Intramolecular kinetic deuterium isotope effects, $(k_H/k_D)_{intra}$, were determined by reacting 4-X-substituted *N*-trideuteriomethyl-*N*-methylanilines (*X* = MeO, Me, H, Br, CN, NO_2) with PhIO and FeTPFPPCl, under the same conditions as above. At the end of the reaction, the formed CH_2O and CD_2O were converted into the corresponding dimedone adducts and the ratio of the two adducts was measured by GC-MS. In some cases, $(k_H/k_D)_{intra}$ was also determined by measuring the molar ratio between the 4-X-*N*-trideuteriomethylaniline and the 4-X-*N*-methylaniline produced in the reaction, by GC-MS. Intermolecular kinetic deuterium isotope effects, $(k_H/k_D)_{inter}$, were obtained in competitive experiments by reacting an equimolecular mixture of 4-X-*N*,*N*-bis(trideuteriomethyl)aniline and the corresponding *N*,*N*-dimethylaniline with PhIO and the iron porphyrin. For these experiments, the concentration of the two substrates was always at least 10 times larger than that of the product *N*-methylanilines. In this case too, at the end of the reaction, CH_2O and CD_2O were reacted with dimedone and the ratio of the dimedone adducts measured by GC-MS. All values of k_H/k_D are reported in Table 1.

The relative reactivity of the 4-X-*N*,*N*-dimethylanilines was determined in competitive experiments, by reacting couples of substrates with FeTPFPPCl and PhIO. Since the two substrates were in excess with respect to the oxidant, the relative reactivity was determined by the molar ratio of the two formed *N*-methylanilines, which was measured by GC. The relative reactivity values for the various *N*,*N*-dimethylanilines, with respect to X = H (k_X/k_H), are reported in Table 2. When the $\log(k_X/k_H)$ values are plotted against the substituent constants σ^+, the good (r^2 = 0.98) correlation shown in Figure 1 is obtained, which allows us to calculate a ρ^+ value of − 0.88. The data of Table 2 were also fitted to the Rehm−Weller

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Table 1. Isotope Effect Profiles for Oxidative Dealkylation of 4-X-*N*,*N*-Dimethylanilines by FeTPFPPCl and PhIO and for Hydrogen Atom Abstraction by *t*BuO• [a]

	isotope effect (k_H/k_D)[b]		
X	FeTPFPPCl intra	FeTPFPPCl inter	$ArNMe_2$ + *t*BuO• [c]
NO_2	2.0(1)		3.9(1)
CN	2.0(1), 1.8(1)[d]		3.7(1)
Cl			2.9(2)
Br	2.6(3)	1.5(2)	
H	3.1(2), 3.0(2)[d]	1.6(1)	2.6(1)
CH_3	3.2(2)	1.9(2)	
CH_3O	3.3(2)		

[a] Measured by determining the CH_2O/CD_2O ratio (see text). [b] All isotope effects are an average of at least three independent determinations. The error (standard deviation) in the last significant digit is given in parentheses. [c] Reference 2b. [d] Measured by the *N*-trideuteriomethylaniline/*N*-methylaniline ratio.

Table 2. Yields and Relative Reactivities for Competitive Oxidative Dealkylation by FeTPFPPCl and PhIO of 4-X-*N*,*N*-Dimethylanilines[a]

	potential (V)	yields (%)[b]		
X	vs SCE[c]	PhNHMe	$4\text{-}XC_6H_4NHMe$	k_X/k_H[d]
NO_2	1.14	20.0	3.0	0.15(1)
CN	1.05	19.5	3.9	0.20(2)
CF_3	0.94	19.0	7.6	0.40(3)
Br	0.82	18.2	14.0	0.77(1)
CH_3	0.61	10.5	20.0	1.9(3)
CH_3O[e]	0.45	10.6	40.1	3.8(3)

[a] Substrates (100 μmol), PhIO (50 μmol), and FeTPFPPCl (2 μmol) in CH_2Cl_2 (1 mL). [b] Yields are referred to PhIO. [c] Data in MeCN, ref 8a. [d] All ratios are an average of at least three independent determinations. The error (standard deviation) in the last significant digit is given in parentheses. [e] Substrates (100 μmol), PhIO (10 μmol), and FeTPFPPCl (2 μmol) in CH_2Cl_2 (1 mL).

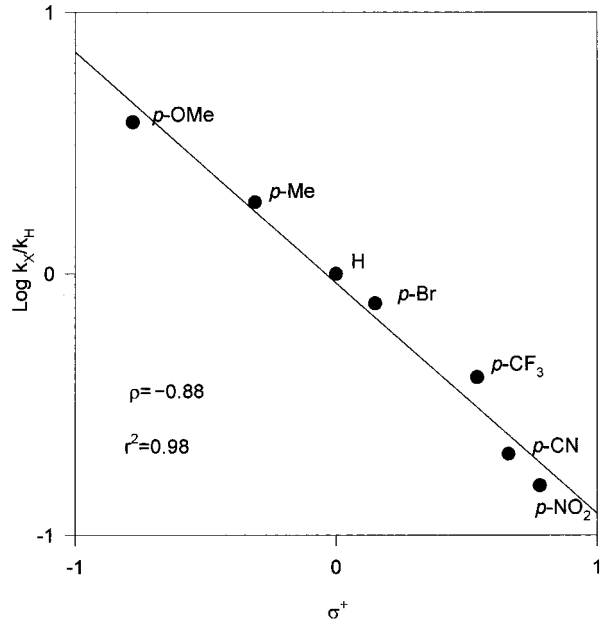

Figure 1. Linear free energy correlation diagram for the oxidation of 4-substituted *N*,*N*-dimethylanilines by PhIO and FeTPFPPCl.

equation for electron-transfer reactions (eq 2),[11] where $\Delta G^{\ddagger}$ is the activation free energy for the electron-transfer step, $\Delta G^{\circ\prime}$ is the standard free energy for the same step corrected for the electrostatic interaction arising from the charge variation in the reactants upon electron transfer and λ the reorganization energy, that is the energy required for the adjustment in nuclear geometry and solvation shell which make the electron-transfer possible.

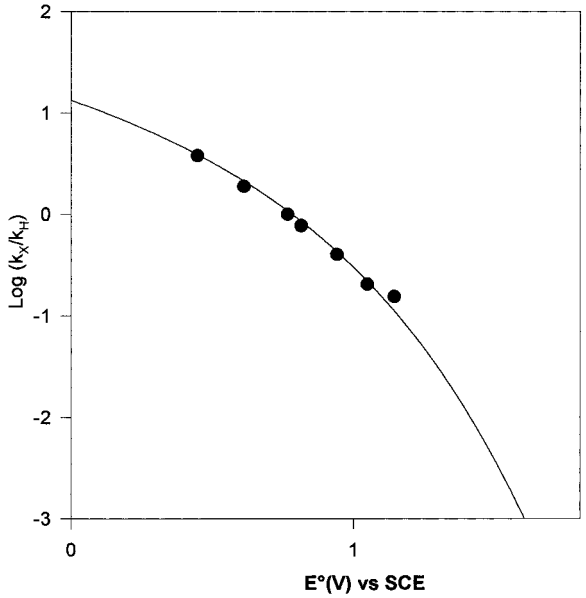

Figure 2. Diagram of $\log(k_X/k_H)$ vs E° for the reactions of dimethylanilines with FeTPFPPCl and PhIO. The solid circles correspond to the experimental values; the curve is calculated by a nonlinear least-squares fit to the Rehm−Weller equation.

$$\Delta G^{\ddagger} = \frac{\Delta G^{\circ\prime}}{2} + \left[\left(\frac{\Delta G^{\circ\prime}}{2}\right)^2 + \left(\frac{\lambda}{4}\right)^2\right]^{1/2} \qquad (2)$$

Since $\Delta G^{\ddagger}/RT = 2.303(\log Z - \log k)$ and $k = k_{rel}k_H$, k_{rel} can be directly related to the activation free energy (eq 3), where $Z = 6 \times 10$.[11]

$$\log k_{rel} = 11.778 - \log k_H - \frac{\Delta G^{\ddagger}}{2.303RT} \qquad (3)$$

$\Delta G^{\circ\prime}$ values were calculated from the potential data reported in Table 2, taking the internuclear distance as 5 Å[11b] and estimating the E° value of the iron oxo complex of FeTPFPP as 1.6 V vs SCE.[12] An excellent correlation (Figure 2), using λ and k_H as adjustable parameters, was obtained that allowed us to calculate a λ value of 47 kcal mol $^{-1}$.

Discussion

The data in Table 1 clearly show that the $(k_H/k_D)_{intra}$ values for the N-dealkylations catalyzed by FeTPFPPCl are significantly influenced by the nature of the X substituent, in particular a steady rise of these values on going from electron withdrawing to electron releasing substituents is observed. When these values are compared with the corresponding ones for the hydrogen abstraction reaction of some 4-X-*N*,*N*-dimethylanilines with *tert*-butoxyl radicals[2b,3] (also displayed in Table 1), it can be immediately noted that the two sets of data exhibit an opposite trend with respect to the effect of the nature of X. Accordingly,

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(12) (a) The E° value, vs SCE, for the iron−oxo complex of Fe^{III}TPFPPCl was estimated by summing the difference between the E° value of Fe^{III}-TPFPPCl (1.50 V vs AgCl/Ag in CH_2Cl_2, ref 10) and that of Fe^{III}TMPCl (1.15 V vs Hg/HgO in CH_2Cl_2)[12b] to the E° value measured for the iron-oxo complex of Fe^{III}TMPCl (1.35 V vs Hg/HgO in CH_2Cl_2).[12b] (b) Groves, J. T.; Gilbert, J. A. *Inorg. Chem.* **1986**, *25*, 123−125.

$(k_H/k_D)_{intra}$ for the reactions promoted by *tert*-butoxyl radicals increases as we move from electron releasing to electron withdrawing substituents. This sharply different intramolecular isotope effect profile leads us to conclude that the N-dealkylation of *N*,*N*-dimethylanilines promoted by FeTPFPPCl *does not occur* by a HAT mechanism and that the ET mechanism is probably operating.

While the exclusion of an HAT mechanism appears sound, it is, however, important to examine whether the observed profile is consistent with an ET mechanism. Dinnocenzo and Jones[2b] found that the deprotonation of 4-substituted *N*,*N*-dimethylaniline radical cations by pyridine exhibits a maximum value of $(k_H/k_D)_{intra}$ for the radical cation whose pK_a is comparable with that of the proton abstracting base. Clearly, no such maximum is observed in our case, but we should consider that a different base, probably P−Fe^{IV}=O, the reduced form of the iron oxo complex, is operating in the reactions catalyzed by FeTPFPPCl. Even though no information is available on the basicity of this species, it seems reasonable to suppose that it should be a much stronger base than pyridine.[13] Thus, it is possible that the pK_a of the radical cation (ranging from 3 to 12)[8a] never comes near to that of P−Fe^{IV}=O. On the other hand, the observed increase in $(k_H/k_D)_{intra}$ as we go from electron withdrawing to electron donating substituents can be justified since the pK_a of the radical cation also increases and in this way we should move toward the maximum value of the kinetic deuterium isotope effect.

The suggestion of an ET mechanism based on the intramolecular kinetic deuterium isotope effect profile is fully supported by the values of the intermolecular deuterium kinetic isotope effects (Table 1) determined for X = Br, H, Me. Accordingly, these values (1.5, 1.6, 1.9, respectively) are significantly different from and smaller than the corresponding values (2.6, 3.1, 3.2) of $(k_H/k_D)_{intra}$. Clearly, this observation excludes a single-step reaction, involving the cleavage of the C−H bond, since in this case the same values of inter- and intramolecular kinetic isotope effects are expected. Thus, the HAT mechanism can be definitely dismissed. Different values for $(k_H/k_D)_{intra}$ and $(k_H/k_D)_{inter}$ are instead fully consistent with an ET mechanism, if, as is probable for an exoergonic reaction, the electron-transfer step is rate determining.[15] In the latter case, the $(k_H/k_D)_{inter}$ per deuterium atom should be a secondary kinetic isotope effect reflecting the different effect of CH_3 and CD_3 on the rate of formation of the aminium radical cation. This is probably the situation in our reaction, as the $(k_H/k_D)_{inter}$ per deuterium atom is 1.1, a value typical of several oxidations of tertiary amines to aminium radical cations[7b] and in agreement with an effect that should be hyperconjugative in nature.[16]

In line with the electron-transfer mechanism is also the observation that the relative reactivity data exhibit a good correlation with the substituent constants σ^+ and nicely fit the Rehm−Weller equation for electron-transfer reactions (Figures 1 and 2, respectively). It should be noted that *all* substituents fit the Hammet plot, which indicates that no change of mechanism occurs along the series.

The ρ^+ value (−0.88) is larger than that (−0.4) found in the oxidation of *N*,*N*-dimethylbenzylamines catalyzed by FeTPPCl.[7b] Perhaps one would have expected a larger increase in selectivity on going from *N*,*N*-dimethylbenzylamines to *N*,*N*-dimethylanilines, since in the latter substrates the nitrogen atom is directly bonded to the aromatic ring. However, it should be considered that different iron oxo complexes are involved in the two systems and particularly that the one acting in the reactions with *N*,*N*-dimethylbenzylamines is less reactive and therefore probably more selective than that involved in the reactions of *N*,*N*-dimethylanilines.[17] Moreover, there are two additional factors that may justify the small difference in selectivity between the reactions of *N*,*N*-dimethylanilines and *N*,*N*-dimethylbenzylamines. First, in *N*,*N*-dimethylaniline radical cations, the positive charge is located on the ring to a very small extent, most of it residing on the nitrogen atom.[18] Thus, ring substituents may probably exert only a relatively small effect on the aminium radical cation stability. Second, as suggested by Lindsay Smith,[7b] it may be that the reaction is characterized by an early transition state with very little buildup of positive charge on the nitrogen atom.

From the Rehm−Weller fit a value of 47 kcal mol^{-1} is calculated for the reorganization energy λ associated with the transfer of one electron from the *N*,*N*-dimethylaniline to the iron oxo complex. This value seems reasonable since an extensive reorganization is expected on going from *N*,*N*-dimethylaniline to its radical cation, which is practically a distonic species, as already mentioned, with the positive charge on the nitrogen atom and the unpaired electron on the ring.[18] Thus, the nitrogen hybridization changes from sp^3 to sp^2, and there is a shortening of the N−C_{aryl} bond and significant changes in the C−C ring lengths.[19] Changes in the C−H lengths for *N*-methyl groups are also expected since, as already noted, these groups stabilize the positive charge on nitrogen by hyperconjugative effect.[20] Substantial reorganization energy is also expected for the iron oxo complex. Accordingly, there is tight coupling between iron(IV) and the porphyrin radical cation[6a] and the energy of the iron−oxygen bond undergoes a large increase on going from $P^{+\bullet}$−Fe^{IV}=O to P−Fe^{IV}=O.[22] It must be recognized that a lower λ value was predicted on the basis of the low reorganization energies measured[23] or calculated[24] for the self-exchange reactions of anilines. However, apart from the fact that more recent calculations have produced higher values,[19] it has to be mentioned that very often reorganization energies from self-exchange reactions lead to low estimates for the overall λ value of electron-transfer processes.[25,26]

Finally, it is worthwhile to note that dimerization products are not formed to a significant extent in the N-dealkylation of *N*,*N*-dimethylanilines promoted by FeTPFPPCl/PhIO. In sharp contrast, dimers are by far the main reaction products in the

(13) The possible role of the basicity of P−Fe^{IV}=O on the value of k_H/k_D has also been discussed for the reactions of *N*,*N*-dimethylaniline with cytochrome P450 and peroxidases.[1d,14]

(14) Okazaki, O.; Guengerich, F. P. *J. Biol. Chem.* **1993**, *268*, 1546−1552.

(15) In all cases the E° value (1.6 V) for the $P^{+\bullet}$−Fe^{IV}=O/P−Fe^{IV}=O couple[12] is always larger than that for the $(ArNMe_2)^{+\bullet}/ArNMe_2$ couple (Table 2).

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(20) The strong hyperconjugative effect of CH_3 groups has also been held responsible for the relatively high reorganization energy found for the $ArCH_3^{+\bullet}/ArCH_3$ system.[21]

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(24) Goez, M. *Z. Phys. Chem.* **1990**, *169*, 133−145.

(25) Eberson, L. *New J. Chem.* **1992**, *16*, 151−156.

(26) It should be noted that a value of λ = 22−25 kcal mol^{-1} has been reported for the reactions of *N*,*N*-dimethylanilines with cytochrome P450.[11b] However, the significance of this value is doubtful in light of the conclusions reported in ref 2.

oxidation of *N*,*N*-dimethylanilines by *bona fide* one-electron oxidants such as potassium 12-tungstocobalt(III)ate and tris-(1,10-phenanthroline)iron(III) hexafluorophosphate.[27] Clearly, this suggests an in-cage reaction for the deprotonation of the radical cation and the following oxygen rebound process, illustrated in Scheme 1, paths c and d (P = TPFPP).

Concluding Remarks

The results presented here clearly show the validity of the kinetic deuterium isotope effect profile criterion to distinguish ET from the HAT mechanism in the oxidative N-dealkylation of *N*,*N*-dimethylanilines induced by a chemical model of cytochrome P450. Accordingly, the application of this criterion led us to exclude the hydrogen atom transfer mechanism and to suggest an electron transfer mechanism. This conclusion was fully supported by the intermolecular kinetic deuterium isotope effect values and the relative reactivity data. Thus, if the above mechanistic probe works as well in enzymatic reactions, it would appear that the oxidative N-dealkylation of *N*,*N*-dimethylanilines by cytochrome P450 and by chemical models occurs by different mechanisms: a HAT mechanism in the former case and an ET mechanism in the latter.[28] Even though this conclusion is unexpected, we should not forget that on the whole the enzyme and the chemical model are very different reactants and that also the above-mentioned similarity in the active oxidant structure is far from being complete. Thus, in the active oxidant, the axial iron ligand is a cystein thiolate group in the enzyme but a chloride ion in the model. The importance of the thiolate group in determining the reactivity of cytochrome P450, also with respect to that of other hemoproteins, is well recognized.[29] Moreover, the environment in which the reaction actually occurs is profoundly different in the enzyme and in the chemical model. Among other things, the polarity of the medium is higher in the reaction of the synthetic iron porphyrin (CH_2Cl_2, $\epsilon = 9$) than in the reaction with cytochrome P450 (estimated $\epsilon = 3$),[11b] which might make the formation of radical ions easier in the former oxidation state than in the second. Finally, it should be considered that in the enzyme active site there may be some steric constraint which, in the radical cation, does not permit the SOMO on nitrogen to be collinear with the p orbital of the C−H bond to be cleaved (stereoelectronic effect). This might slow the deprotonation process, thus making reversible the formation of the radical cation and allowing the HAT mechanism to take over.[30]

Experimental Section

Methods. GLC analyses were performed on a Varian 3400 gas chromatograph (OV1 capillary column, 25 m × 0.2 mm). GC-MS analyses were performed on a HP5890 GC (OV1 capillary column, 12 m × 0.2 mm) coupled with a HP5970 MSD.

Materials. Dichloromethane was distilled from P_2O_5 under argon and degassed by argon bubbling (30 min) before use. Iodosylbenzene was prepared as described previously[32] and stored at −20 °C. Fe^{III}-TPFPPCl was purchased from Aldrich and used as received. 4-Methoxy-*N*,*N*-dimethylaniline was prepared from 4-methoxyaniline and trimethylorthophosphate;[33] 4-(trifluoromethyl)-*N*,*N*-dimethylaniline was prepared from 4-(trifluoromethyl)aniline and methyliodide.[2a] *N*-Methyl-*N*-(trideuteriomethyl)anilines and *N*,*N*-di(trideuteriomethyl)anilines were prepared by reaction of the corresponding *N*-methylanilines or anilines with CD_3I according to the conditions previously reported by Dinnocenzo et al.[2a] The other *N*,*N*-dimethylanilines were purchased from Aldrich and used as received. *N*-Methylanilines were prepared by the S.B. Kadin procedure, treating the corresponding anilines with succinimide and aqueous formaldehyde and reducing the obtained amminomethylsuccinimide with $NaBH_4$ in DMSO.[34]

Oxidation Procedures. All reactions were performed under argon atmosphere. Iodosylbenzene (50 μmol) was added to a stirred solution of the catalyst (2 mol) and aniline (100 μmol) in dichloromethane (1 mL) in a Schlenk tube sealed with a rubber septum. In the case of the intermolecular isotope effect, iodosylbenzene (25 μmol) was added to a stirred solution of the catalyst (2 μmol) and 100 μmol of each aniline in dichloromethane (1 mL). The mixture was stirred at room temperature for 15 min and then water (1 mL) was added with a syringe. The biphasic mixture was stirred for 15 min and then the aqueous layer was separated and incubated for 30 min with 1 mL of a 0.2 M dimedone solution in 0.2 M NaOH at room temperature. Then hydrochloric acid (4 M) was added dropwise until the mixture became acidic. The dimedone adduct was extracted with dichloromethane (3 × 4 mL), dried over anhydrous sodium sulfate, and analyzed by GC-MS. The deuterium isotope effect was determined as the ratio of the corrected signal intensities at *m*/*z* 294 and 292. The results were confirmed, in some cases (X = CN, H) by measuring the N-trideuteriomethylaniline/*N*-methylaniline ratio in the reaction mixture.

Competitive Oxidation. All reactions were performed under argon atmosphere. Iodosylbenzene (50 μmol, 10 μmol in the competitive oxidation with 4-CH_3O-*N*,*N*-dimethylaniline) was added to a stirred solution of the catalyst (2 μmol), 4-X-*N*,*N*-dimethylaniline and *N*,*N*-dimethylaniline (100 μmol of each substrate) in dichloromethane (1 mL) in a Schlenk tube sealed with a rubber septum. The mixture was stirred at room temperature for 30 min (5 min in the competitive oxidation with 4-CH_3O-*N*,*N*-dimethylaniline and 15 min in that with 4-CH_3-*N*,*N*-dimethylaniline) and then quenched by aqueous $Na_2S_2O_5$ (100 μL, 0.5 M). After 10 min NaOH (100 μL, 3 M) and the internal standard were added. The mixture was dried over anhydrous sodium sulfate and analyzed by GLC.

Acknowledgment. This work was carried out with the financial support of the Ministry of University and Technological Research (MURST) and the Italian National Council for Research (CNR).

JA980187I

(27) Unpublished results of this laboratory.

(28) Clearly, this conclusion rests on the validity of the deuterium kinetic isotope effect profile found by Dinnocenzo and Jones for the reactions with cytochrome P450. The trend in k_H/k_D values reported by these authors is very clear and convincing; however, it has to be noted that some doubts in this respect are presented in ref 1d.

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(30) This view seemed supported by some preliminary experiments concerning the oxidation of benzylaziridine by microsomal cytochrome P450 where we noted the opening of the aziridine ring and the formation of dimers.[31] Unfortunately, further study of this reaction showed that the formation of dimers probably was not due to the reaction of cytochrome P450.

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