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# Isotope effect profiles in the *N*-demethylation of *N*,*N*-dimethylanilines: a key to determine the p$K_a$ of nonheme Fe(III)–OH complexes†

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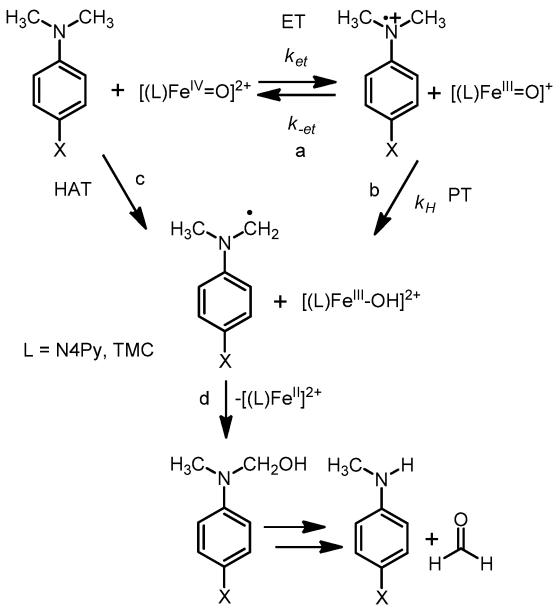
***N*-demethylation of *N*,*N*-dimethylanilines promoted by $[(N4Py)Fe^{IV}{=}O]^{2+}$ occurs by an electron transfer–proton transfer (ET–PT) mechanism with a rate determining PT step. From the bell-shaped curve of the KDIE profile it has been estimated that the p$K_a$ of $[(N4Py)Fe^{III}{-}OH]^{2+}$ is 9.7.**

Oxidative *N*-dealkylation of *N*,*N*-dialkylanilines promoted by high-valent iron oxo species in heme[1,2] and nonheme[3] iron enzymes is a process of great biological importance and has been the subject of intense investigation by several research groups in the last three decades. The interest in the *N*-dealkylation process has been extended to the catalytic systems composed of synthetic heme[4] and nonheme[5–8] models and several mechanistic studies were undertaken in order to investigate the possible mechanistic dichotomy: electron transfer–proton transfer (ET–PT) *vs.* hydrogen atom transfer (HAT) mechanism.

The mechanism of *N*-dealkylation of *N*,*N*-dialkylanilines promoted by nonheme iron(IV)–oxo model compounds $[(N4Py)Fe^{IV}{=}O]^{2+}$ and $[(TMC)Fe^{IV}{=}O]^{2+}$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) has been analysed in detail by Nam and coworkers.[5] The application of several mechanistic criteria based on a linear free-energy correlation, inter- and intramolecular kinetic isotope effects and product analysis of probe substrate oxidation[1–2,4] strongly supported the occurrence of the ET–PT mechanism shown in Scheme 1 for the *N*-demethylation of *N*,*N*-dimethylanilines. In the first step (a) an electron transfer from the *N*,*N*-dimethylaniline to the nonheme iron(IV)–oxo complex leads to the formation of the *N*,*N*-dimethylaniline radical cation and the reduced iron–oxo complex, $[(L)Fe^{III}{=}O]^{+}$. The latter species then acts as a base deprotonating the radical cation to give an α-aminomethyl radical and an iron(III)–hydroxo complex, $[(L)Fe^{III}{-}OH]^{2+}$ (path b). After a rebound process (path d) a carbinolamine and the resting state of the nonheme iron(II) complex are formed. Finally decomposition of the carbinolamine leads to the main reaction products *N*-methylaniline and formaldehyde.




Scheme 1 HAT *vs.* ET-PT mechanism in the *N*-demethylation of *N*,*N*-dialkylanilines promoted by the nonheme oxoiron(IV) complex.

The analysis of the kinetic deuterium isotope effect (KDIE) profile has been applied as an additional tool to distinguish the HAT and ET–PT pathway in the *N*-demethylation of *N*,*N*-dimethylanilines,[2,9] moreover when the ET–PT mechanism operates it provides useful information about the rate determining step of the whole process.[2a,10]

Along this line we considered it worthwhile to investigate the KDIE profile in the *N*-demethylation of *N*,*N*-dimethylanilines promoted by a mononuclear nonheme oxoiron(IV) complex, namely $[(N4Py)Fe^{IV}{=}O]^{2+}$ (N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-piridyl)methylamine) (Fig. 1).

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† Electronic supplementary information (ESI) available: Details of oxidation procedures and calculations of p$K_a$ of 4-X-*N*,*N*-dimethylaniline radical cations in $CH_3CN$. See DOI: 10.1039/c5cc00411j



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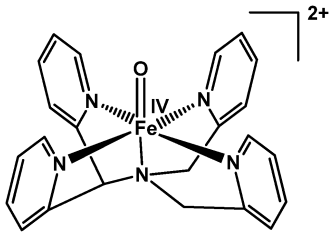


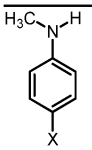
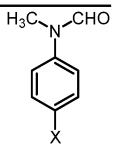

Fig. 1 $[(N4Py)Fe^{IV}{=}O]^{2+}$.

The iron(IV)–oxo complex $[(N4Py)Fe^{IV}{=}O]^{2+}$ was prepared by oxidation of the corresponding iron(II) complex, $[(N4Py)Fe^{II}(OTf)_2]$, with PhIO in $CH_3CN$ as reported in previous studies.[11] After 50 min from the addition of 20 equiv. of 4-X-*N*,*N*-dimethylanilines (X = $OCH_3$, $CH_3$, Br, $CF_3$, CN, $NO_2$) to the solution of $[(N4Py)Fe^{IV}{=}O]^{2+}$ in $CH_3CN$ at 25 °C, product analysis revealed that 4-X-*N*-methylanilines and $CH_2O$, identified as dimedone adduct, were produced as major reaction products (Table 1). Minor amounts of *N*-methylformanilides (4-X-$C_6H_4N(CH_3)CHO$) were also observed in addition to the *N*-demethylated products. These products might be formed by further oxidation of the α-hydroxylamine intermediate by the nonheme iron(IV)–oxo complex[8a] or by the iron-catalyzed oxidation of *N*,*N*-dimethylanilines in the presence of oxygen.[12] The latter hypothesis is supported by the observation that the yields of *N*-methylformanilides are significantly reduced when the oxidation of *N*,*N*-dimethylanilines has been carried out in a degassed (freeze-thaw) reaction mixture.

Intramolecular KDIEs, $(k_H/k_D)_{intra}$, were determined, by GC-MS analysis, from the molar ratio of $CH_2O$ and $CD_2O$ (as dimedone adducts) produced in the reactions of *N*-methyl-*N*-trideuteriomethylanilines with $[(N4Py)Fe^{IV}{=}O]^{2+}$.[2c,d,4a,10]

Intermolecular KDIEs, $(k_H/k_D)_{inter}$, were obtained in a similar way using the ratio of the dimedone adducts of $CH_2O$ and $CD_2O$ produced in competitive experiments by reacting an equimolecular mixture of *N*,*N*-dimethylaniline and *N*,*N*-bis(trideuteriomethyl)-aniline with $[(N4Py)Fe^{IV}{=}O]^{2+}$.

Table 1 Products and yields in the oxidation of 4-X-*N*,*N*-dimethylanilines by $[(N4Py)Fe^{IV}{=}O]^{2+}$ in $CH_3CN$ at 25 °C[a]

| | Yields[b] | |
|---|---|---|
| X |  |  |
| $NO_2$ | 6.9 | 1.0 |
| | 7.7[c] | — |
| CN | 9.4 | 2.2 |
| $CF_3$ | 9.5 | 2.5 |
| Br | 8.7 | 2.1 |
| $CH_3$ | 8.8 | 2.7 |
| | 9.7[c] | — |
| $OCH_3$ | 6.0 | 2.8 |

[a] Iodosylbenzene (12.5 μmol), $[(N4Py)Fe^{II}(OTf)_2]$ (2.5 μmol) and 4-X-*N*,*N*-dimethylanilines (50 μmol) in $CH_3CN$ (500 μL). [b] Yields (mol%) refer to the amount of substrates. [c] In the absence of oxygen (freeze-thaw cycles).

Table 2 Redox potential of 4-X-*N*,*N*-dimethylanilines, $pK_a$ values of 4-X-*N*,*N*-dimethylaniline radical cations and isotope effect profiles for the *N*-demethylation of 4-X-*N*,*N*-dimethylanilines promoted by $[(N4Py)Fe^{IV}{=}O]^{2+}$ [a]

| | | | Isotope effects[d] | |
|---|---|---|---|---|
| X | Potential(v) *vs.* SCE[b] | $pK_a$ radical cation[c] | $(k_H/k_D)_{intra}$ | $(k_H/k_D)_{inter}$ |
| $NO_2$ | 1.23 | 5.8 | 3.9(1) | 4.2(7) |
| CN | 1.15 | 7.2 | 4.2(2) | 4.2(2) |
| $CF_3$ | 1.11 | 7.9 | 4.6(3) | 4.9(5) |
| Br | 0.92 | 11.1 | 4.5(3) | 4.4(1) |
| $CH_3$ | 0.72 | 14.5 | 3.5(1) | 3.4(1) |
| $OCH_3$ | 0.55 | 17.3 | 2.3(1) | 2.3(1) |

[a] Measured by determining the $CH_2O/CD_2O$ ratio (see the text). [b] Data obtained in $CH_3CN$, see ref. 15 and 16. [c] In $CH_3CN$, calculated by applying a thermochemical cycle, see ref. 10 and 15. [d] Average of at least three independent determinations. The error (standard deviation) in the last significant digit is given in parentheses.

The intra and intermolecular KDIE values are reported in Table 2 together with the one-electron oxidation potentials ($E^\circ$) of the *N*,*N*-dimethylanilines.

Data in Table 2 clearly show that the $(k_H/k_D)_{intra}$ values are significantly influenced by the nature of the aryl substituents, in particular a rise in these values followed by a decrease on going from electron withdrawing to electron releasing substituents is observed. This trend is different from that observed in the hydrogen abstraction from 4-X-*N*,*N*-dimethylanilines by the *tert*-butoxyl radical[2c] where a steady decrease of the $(k_H/k_D)_{intra}$ values was observed upon decreasing the electron withdrawing properties of the substituents. The observation of a maximum value in the profile is instead in accordance with that observed in the deprotonation of 4-substituted-*N*,*N*-dimethylaniline radical cations by pyridine, the maximum value of $(k_H/k_D)_{intra}$ being observed for the radical cation whose $pK_a$ is comparable with that of the proton abstracting base.[2c] Thus the KDIE profile further support the occurrence of an ET–PT mechanism in the *N*-demethylation of *N*,*N*-dimethylanilines promoted by $[(N4Py)Fe^{IV}{=}O]^{2+}$.‡

The observation that the inter- and intramolecular KDIE values are greater than 1 implies that the first ET process is coupled with the ensuing PT process. As previously found in the *N*-demethylation catalysed by the heme model system iron tetramesitylporphyrin,[2a] the observation of high KDIE values in the ET–PT mechanism was interpreted on the basis of a competition between back electron transfer from the reduced iron–oxo complex to the nitrogen radical cation (*i.e.*, $k_{-et}$ in Scheme 1) and proton transfer from the nitrogen radical cation to the reduced iron–oxo complex (*i.e.*, the PT step in Scheme 1). Using the steady-state assumption, the [*N*,*N*-dimethylaniline radical cation/reduced iron–oxo complex] pair is constant, it is possible to derive an expression that relates $(k_H/k_D)_{inter}$ and $(k_H/k_D)_{intra}$ (eqn (1)).[2a]

$$(k_H/k_D)_{inter} = (k_H/k_D)_{intra}\{(k_D/k_H)_{intra} + (k_{-et}/k_H)\}/\{1 + (k_{-et}/k_H)\} \quad (1)$$

when the ET is the rate-determining step ($k_{-et}/k_H \ll 1$), eqn (1) reduces to $(k_H/k_D)_{inter} = 1$. On the other hand, when $k_{-et}/k_H \gg 1$ it becomes $(k_H/k_D)_{inter} = (k_H/k_D)_{intra}$ as observed in our case.§

Thus, our results are consistent with the currently accepted ET–PT mechanism for the *N*-demethylation of *N*,*N*-dimethylanilines

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promoted by nonheme iron complexes[5–7] and suggest that *N*-demethylation by $[(N4Py)Fe^{IV}{=}O]^{2+}$ proceeds *via* a rate determining proton transfer step. In this respect it has to be noted that an ET followed by rate-limiting deprotonation of the radical cations and subsequent rapid ET from the deprotonated radicals has been proposed for the hydride transfer from NADH analogues to $[(N4Py)Fe^{IV}{=}O]^{2+}$ and other nonheme iron(IV)–oxo complexes.[19]

The analysis of the dependence of $(k_H/k_D)_{intra}$ on the p$K_a$ of the aniline radical cations provides useful information on the strength and nature of the deprotonating base.[10] The p$K_a$ values of the *N*,*N*-dimethylaniline radical cations in $CH_3CN$, estimated by applying a thermochemical cycle, are reported in Table 1 (the details of calculations are provided in the ESI†).[10,15] The plot of the $(k_H/k_D)_{intra}$ values as a function of the p$K_a$ of the *N*,*N*-dimethylaniline radical cations shows a bell-shaped profile with the $(k_H/k_D)_{intra}$ values that increase up to a maximum value and then decrease upon increasing the p$K_a$ (Fig. 2). The solid curve reported in Fig. 2 is obtained by fitting the experimental data to eqn (2) [where $\Delta pK_a = pK_a - pK_{a(max)}$] which is based on Marcus theory applied to acid-base reactions.[20]

$$\log(k_H/k_D) = [1 - (2.3RT\Delta pK_a)^2/\lambda_H\lambda_D]\log(k_H/k_D)_{(max)} \qquad (2)$$

From the quite satisfactory fit ($r^2$ = 0.995) it is possible to determine the values of $pK_{a(max)}$ (9.7) and $\lambda_H\lambda_D$ (44.9 kcal$^2$ mol$^{-2}$). By assuming that the reorganization energies associated with proton and deuteron abstraction are equal, the $\lambda$ value for this process is 6.7 kcal mol$^{-1}$. Interestingly, this value is very close to that (6.2 kcal mol$^{-1}$) determined when the same eqn (2) was applied to the $(k_H/k_D)_{intra}$ *vs.* p$K_a$ plot in the oxidation of *N*,*N*-dimethylanilines catalysed by the water soluble iron(III) tetrasulfonatophenylporphyrin.[10]

According to the theory, the maximum of the bell-shaped curve should be reached when the p$K_a$ of the *N*,*N*-dimethylaniline radical cation equals that of the protonated form of the abstracting base,[20,21] *i.e.* the nonheme iron(III) hydroxo complex $[(N4Py)Fe^{III}{-}OH]^{2+}$.

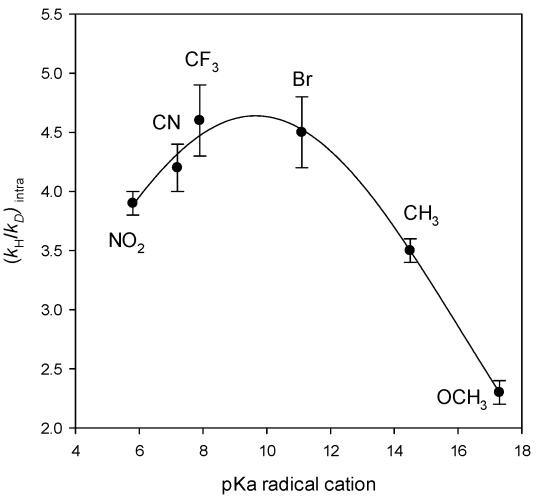


Fig. 2 Dependence of $(k_H/k_D)_{intra}$ for the oxidative *N*-demethylation of *N*-methyl-*N*-trideuteriomethylanilines promoted by $[(N4Py)Fe^{IV}{=}O]^{2+}$ on the p$K_a$ of 4-X-*N*,*N*-dimethylaniline radical cations in $CH_3CN$.

Interestingly, the p$K_a$ value (9.7) obtained for $[(N4Py)Fe^{III}{-}OH]^{2+}$ is in excellent agreement with that ($pK_a \cong 10$) calculated for the same species by applying the thermochemical cycle defined by eqn (3).[22] In eqn (3), $BDE_{O-H}$ is the dissociation energy of the O–H bond in $[(N4Py)Fe^{III}{-}OH]^{2+}$ (78 ± 2 kcal mol$^{-1}$),[18b] $E^\circ$ is the reduction potential of $[(N4Py)Fe^{IV}{=}O]^{2+}$ (0.75 V, the value of 0.51 V *vs.* SCE in $CH_3CN$[17] was adjusted to the NHE scale by adding 0.24 V) and *C* is a constant that accounts for the redox potential of the couple ($H^+/H^\bullet$) and is dependent on solvent and the reference electrode used (47.2 kcal mol$^{-1}$ for $CH_3CN$ and NHE reference electrode).[15]

$$1.37pK_a = BDE_{O-H} - 23.06E^\circ - C \qquad (3)$$

It has to be noted that direct experimental determination of p$K_a$ values of nonheme iron(III)–hydroxo and manganese(III)–hydroxo complexes has been reported only for those systems where the ligand provides a sufficient stabilization of the active species.[23]

The analysis of the KDIE profile in the *N*-demethylation of *N*,*N*-dimethylanilines promoted by nonheme iron complexes might provide a useful tool for the determination of the p$K_a$ values for iron(III)–hydroxo complexes characterized by low stability. It is important to stress that the evaluation of these parameters in association with the redox potentials of iron–oxo complexes is of fundamental importance for the analysis of HAT processes promoted by these reactive species.

In summary, we have shown that the application of the kinetic isotope effect profile in the *N*-demethylation of *N*,*N*-dimethylanilines promoted by the nonheme iron–oxo complex $[(N4Py)Fe^{IV}{=}O]^{2+}$ provided a p$K_a$ value of 9.7 for $[(N4Py)Fe^{III}{-}OH]^{2+}$. Future analysis of isotope effect profiles in the *N*-demethylation of *N*,*N*-dimethylanilines will be extended to other nonheme high-valent iron–oxo and manganese–oxo complexes aimed at determining the p$K_a$ values for the protonated form of the reduced metal–oxo complexes.

## Notes and references

‡ The ET-PT mechanism has been confirmed by the analysis of the *N*-dealkylation products of the least oxidizable aniline 4-$NO_2$-$C_6H_4N(CH_3)$-$(CH_2CH_3)$ promoted by $[(N4Py)Fe^{IV}{=}O]^{2+}$. 4-$NO_2$-$C_6H_4NH(CH_2CH_3)$ was formed as the major product, as expected when an ET-PT mechanism is operating.[5,13] Accordingly, the deprotonation of the methyl group of the radical cation is favored with respect to the proton transfer from the ethyl group on the basis of the higher acidity of the methyl proton as compared to the ethyl one.[1g,h] On the other hand, formation of deethylated product would be preferred in HAT processes since bond dissociation energy (BDE) for the C–H bond in the methylene group is lower than that of the methyl C–H bond.[14]

§ With the exclusion of 4-$CH_3O$-$C_6H_4N(CH_3)_2$, relatively high $k_{-et}$ values are expected on the basis of the endergonic ET process. Accordingly the oxidation potentials of the *N*,*N*-dimethylanilines[4a,16] (see Table 2) are comparable (4-$CH_3O$-$C_6H_4N(CH_3)_2$) or higher than the reduction potential of $[(N4Py)Fe^{IV}{=}O]^{2+}$ (0.51 V *vs.* SCE).[17] Even though the latter value has to be taken with caution in view of the complexity of the electrochemical behaviour of the $Fe^{IV}/Fe^{III}$ couple in $CH_3CN$, the more reliable and significant higher value (0.9 V *vs.* $Fc^{+/0}$), determined by spectropotentiometric studies in $CH_3CN$ in the presence of 0.1 M $H_2O$, refers to the one-electron reduction of $[(N4Py)Fe^{IV}{=}O]^{2+}$ coupled with the transfer of a proton to give $[(N4Py)Fe^{III}{-}OH]^{2+}$.[18]

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