

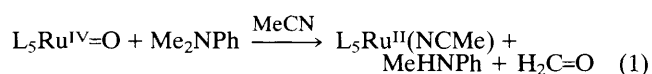
The Oxidative Demethylation of Tertiary Amines by Oxo(phosphine)ruthenium(IV) Complexes

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The oxidation of *para*-substituted *N,N*-dimethylanilines by oxo(phosphine)ruthenium(IV) complexes is shown to display cytochrome P-450-like reactivity, where tertiary amines are oxidatively dealkylated, yielding the corresponding *N*-methylaniline and formaldehyde.

Oxo(phosphine)ruthenium(IV) complexes¹ have proven to be very useful in the study of high valent metal-oxo chemistry, where the reactivity of these complexes with organic substrates has been found to mimic the reactivity of cytochrome P-450. For example, linear rate enhancements based on the hydrophobicity of the substrate were observed in the oxidation of primary alcohols in aqueous media.² In addition, oxygen atom transfer reactions from the metal complex to the substrate were observed in the oxidation of alkenes and sulphides.^{3,4} A reaction characteristic of cytochrome P-450 is the oxidative dealkylation of tertiary amines, a mechanism important in the natural detoxification of nitrogen-containing drugs.⁵ Typically, the oxidation of amines catalysed by transition metal complexes results in the formation of amine *N*-oxides.⁶ However, cytochrome P-450 selectively *N*-dealkylates tertiary amines rather than form the corresponding *N*-oxide compounds. While this reactivity has been studied a great deal using naturally occurring enzymes, including cytochrome P-450, horseradish peroxidase, and chloroperoxidase,⁷ relatively few studies have been conducted with simple model systems.⁸⁻¹⁰ We now wish to report the oxidative *N*-dealkylation of tertiary amines using an oxo(phosphine)ruthenium(IV) complex as the oxidant. This is the first example of the stoichiometric dealkylation of a tertiary amine by isolated (oxo)ruthenium(IV) complexes, as well as the first reported aerobic dealkylation of tertiary amines using a ruthenium catalyst.



The reaction of *N,N*-dimethylaniline with the oxo(phosphine)ruthenium(IV) complexes, $[Ru^{IV}(bpy)_2(O)(PPh_3)](ClO_4)_2$ and $[Ru^{IV}(bpy)_2(O)(PEt_3)](ClO_4)_2$, (*bpy* = 2,2'-bipyridine) proceeds as illustrated in equation 1. The kinetics of all of the reactions were determined spectrophotometrically, while under pseudo-first-order conditions, where the tertiary amine substrate was in excess. The kinetics of the oxidations were second-order, strictly first-order in both substrate and oxidant. Product distribution reactions were conducted under an inert atmosphere and analysed by gas chromatography. The formation of formaldehyde was determined using the method of Nash.¹¹ Values for the second-order rate constants for the oxidation of tertiary amines are listed in Table 1. For the reaction of $[Ru^{IV}(bpy)_2(O)(PR_3)]^{2+}$ (where $PR_3 = PPh_3$ or PEt_3) with *N,N*-dimethylaniline in acetonitrile, the final electronic spectrum of the metal complex, after the complete reaction, corresponded to the respective $[Ru^{II}(MeCN)(bpy)_2(PR_3)]^{2+}$ complex. The two-electron reduction of the ruthenium complex was consistent with an oxygen atom transfer from the (oxo)ruthenium(IV) moiety to the target substrate, with the oxygen atom incorporated into the formaldehyde byproduct. The stoichiometric oxidation of *N,N*-dimethylaniline, *N,N*-dimethyl-*p*-toluidine, and 4-chloro-*N,N*-dimethylaniline by $[Ru^{IV}(bpy)_2(O)-$

$(PPh_3)](ClO_4)_2$ in acetonitrile produced *N*-methylaniline, *N*-methyl-*p*-toluidine, and 4-chloro-*N*-methylaniline in 94%, 82%, and 75% yields, respectively. The oxidation of the same substrates by $[Ru^{IV}(bpy)_2(O)(PEt_3)](ClO_4)_2$ in acetonitrile produced the corresponding *N*-methylanilines in 75%, 98%, and 72% yields, respectively. No other amine products from the oxidations were detected in any case. Corresponding yields of formaldehyde were also observed for each of the respective reactions.

Rate constants and activation parameters [from the plot of $\ln(k/T)$ versus $1/T$] were determined for the reaction between *para*-substituted *N,N*-dimethylanilines ($X = H, Me, Cl$) and the (oxo)ruthenium(IV) complexes. The results obtained are given in Table 1. The uniform nature of the activation parameters suggests that a similar mechanism is occurring in the initial oxidation of the tertiary amines by the different oxo complexes. The plots of $\log(k_X/k_H)$ versus the Hammett parameters, σ_X ,¹² for the *para* substituents give ρ values as the slope, where the magnitude and sign of the resulting ρ values are indicative of the sensitivity of the reaction to the presence of electron donating or withdrawing substituents on a reagent. With $[Ru^{IV}(bpy)_2(O)(PPh_3)](ClO_4)_2$ as the oxidant of the *para* substituted *N,N*-dimethylanilines, $\rho = -2.1 \pm 2.7$ ($r^2 = 0.99$), while for $[Ru^{IV}(bpy)_2(O)(PEt_3)](ClO_4)_2$ as the oxidant, $\rho = -1.4 \pm 4.4$ ($r^2 = 0.94$).[†] These ρ values are reminiscent in magnitude and sign of the ρ value of -2.4 , reported by Rindone, for the oxidation of *N,N*-dimethylaniline by lead tetra-acetate in 1:1 (v/v) acetic anhydride-chloroform solution.¹³ A nitrogen-centred, radical cation transition state has been described by Rindone for this reaction, which is similar to the transition state described for cytochrome, P-450 catalysed oxidations,^{14,15} where a ρ value of -0.61 was reported for the oxidation of *para* substituted *N,N*-dimethylanilines.¹⁶

Finally, in addition to the stoichiometric oxidation using isolated oxo(phosphine)ruthenium(IV) complexes, the aquo(phosphine)ruthenium(II) complex, $[Ru^{II}(OH_2)(bpy)_2(PPh_3)](ClO_4)_2$, catalyses the aerobic oxidative dealkylation of *N,N*-dimethylaniline when in the nonco-ordinating solvent α, α, α -trifluorotoluene. The catalysis occurs at room temperature and pressure, without the need for a coreductant. The only products found were *N*-methylaniline and formaldehyde, where the rate of product formation was first order in both substrate and catalyst. Similarly, the stoichiometric oxidation of *N,N*-dimethylaniline by $[Ru^{IV}(bpy)_2(O)(PPh_3)](ClO_4)_2$ in α, α, α -trifluorotoluene yielded *N*-methylaniline and formaldehyde exclusively, in 75% yield. This identical result suggests that the oxidant in the catalytic process may be $[Ru^{IV}(bpy)_2(O)(PPh_3)](ClO_4)_2$, which is formed in the reaction between $[Ru^{II}(OH_2)(bpy)_2(PPh_3)](ClO_4)_2$ and dioxygen.⁴ For the catalytic reaction, 47 turnovers occurred over 24 h when 0.4 mM

[†] The error limits listed for the ρ values were large because the Hammett plots contained only 3 data points; however, we felt that it was useful to report the relative sign and magnitude of these values in this communication.

Table 1. Second-order rate constants and activation parameters for the oxidation of *N,N*-dimethylanilines by oxo(phosphine)ruthenium(IV) complexes in acetonitrile.

Oxidant	Substrate	$k/\text{mol}^{-1}\text{dm}^3\text{s}^{-1}$ ^a	$\Delta H^\ddagger/\text{kcal mol}^{-1}$ ^b	$\Delta S^\ddagger/\text{e.u.}$ ^{b,c}
[Ru ^{IV} (bpy) ₂ (O)(PPh ₃)](ClO ₄) ₂	DMA ^d	9.0	9.0 ± 0.8	-23.4 ± 2.9
	DMT ^e	24.6	5.3 ± 0.7	-34.0 ± 3.7
	CDMA ^f	3.5	7.3 ± 0.5	-31.1 ± 3.0
[Ru ^{IV} (bpy) ₂ (O)(PEt ₃)](ClO ₄) ₂	DMA	3.2	8.8 ± 0.7	-26.4 ± 2.4
	DMT	7.4	7.2 ± 0.9	-29.9 ± 3.2
	CDMA	2.0	10.6 ± 0.3	-20.9 ± 1.2

^a $T = 21^\circ\text{C}$. ^b Uncertainty at 95% confidence limits. ^c e.u. (entropy units) = $\text{cal K}^{-1}\text{mol}^{-1}$; $\text{cal} = 4.184\text{ J}$. ^d DMA = *N,N*-dimethylaniline. ^e DMT = *N,N*-dimethyl-*p*-toluidine. ^f CDMA = 4-chloro-*N,N*-dimethylaniline.

catalyst was reacted with 0.4 M substrate under 1 atm of O₂(g) for 24 h.

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