Reduction of Pyridine *N*-Oxides by Titanium(III) [1]

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The reactions between $\mathrm{Ti^{III}}$ and a number of substituted pyridine *N*-oxides have been studied in a number of acids and have been found to exhibit the stoicheiometry, $2\mathrm{Ti^{III}} + \text{X-pyo} + \mathrm{H_2O} \longrightarrow 2[\mathrm{TiO}]^{2+} + \text{X-Hpy}^+ + \mathrm{H}^+$ and to obey the rate law (i). The reactions are suggested to proceed by the stepwise reduction of the pyridine *N*-oxide by

$$\frac{-d[\mathrm{Ti^{III}}]}{2dt} = \frac{k[\mathrm{Ti^{III}}][\text{X-pyo}]}{[\mathrm{H^+}]} \qquad \text{(i)}$$

$[\mathrm{Ti(OH)}]^{2+}$ *via* a free-radical path. The rate constants, which range from 5.6×10^{-4} to 0.75 $\mathrm{s^{-1}}$, are influenced more by the steric and complexation effects of the ring substituents (Br, Cl, Me, OMe, CN, or $\mathrm{CO_2H}$) than by their electron-donating or -withdrawing properties.

THE use of the titanium(III) ion as a reducing agent in the analysis of both inorganic [2] and organic [3,4] species is well known, as is its application to organic syntheses.[5-7] Although many of the inorganic systems have been subjected to mechanistic investigations,[8-16] similar studies of the reduction of organic species are comparatively rare. Because titanium(III) reductions frequently show differences in rates as well as in rate laws when compared with other reducing agents, and because $\mathrm{Ti^{III}}$ is known to reduce heterocyclic amine *N*-oxides,[17] an investigation of the kinetics and mechanism of these reactions seemed of interest. It was felt that the results of such a study might be helpful not only in furthering our understanding of the behaviour of $\mathrm{Ti^{III}}$ as a reductant but also in adding to our knowledge about heterocyclic amine *N*-oxides, which have long been of interest in this laboratory.[18]

EXPERIMENTAL

Complete details of the experimental methods can be found in ref. 19.

Materials.—The various *N*-oxides were prepared and/or purified as described previously.[20] Stock solutions of known concentrations were prepared by dissolving known weights of the *N*-oxides in acids of the appropriate concentrations. These solutions were deoxygenated with $\mathrm{N_2}$ which had been purified by passage through a solution of $\mathrm{V^{2+}}$,[21] stored under $\mathrm{N_2}$, and deoxygenated again immediately prior to use. The oxidizing ability of these solutions toward $\mathrm{Ti^{III}}$ was constant, even over extended periods of time.

Stock solutions of $\mathrm{Ti^{III}}$ in HCl were prepared by dissolving a known weight of $\mathrm{TiCl_3}$ (Alfa Inorganics) in a measured volume of standard HCl. Solutions of $\mathrm{Ti^{III}}$ in the other acids investigated (HBr, HI, and $\mathrm{H_2SO_4}$) were prepared by heating $\mathrm{TiH_2}$ (Alfa) under reflux with the appropriate acid for several hours under nitrogen.

The solutions of $\mathrm{TiCl_3}$ and $\mathrm{Ti_2[SO_4]_3}$ were standardized with $\mathrm{K_2[Cr_2O_7]}$,[22] while the concentration of $\mathrm{Ti^{III}}$ in the solution of $\mathrm{TiBr_3}$ was determined by titration with an $\mathrm{FeCl_3}$ solution using $[\mathrm{NH_4}][\mathrm{SCN}]$ as indicator,[23] as was the concentration of $\mathrm{Ti^{III}}$ in the $\mathrm{TiI_3}$ solution after the iodide ion had been replaced with chloride by ion exchange. Solutions were standardized daily since the concentration of $\mathrm{Ti^{III}}$ decreased gradually with time, even when stored under nitrogen. The $[\mathrm{H^+}]$ in these solutions was determined by means of ion exchange. Specifically, the eluant from an ion-exchange column (Dowex 50W-X8, $\mathrm{H^+}$ form) to which a known volume of the titanium(III) solution had been added was titrated with standard Na[OH]. The total amount of $\mathrm{H^+}$ found was corrected for the amount of $\mathrm{H^+}$

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replaced on the resin by Ti^{III} and Ti^{IV}. The concentrations of the latter species were determined as described previously (for Ti^{III}), and as the difference between the concentration of Ti^{III} and the total titanium, which was determined spectrophotometrically as the titanium(IV) peroxide complex.[24]

Stoicheiometry.—The quantity of Ti^{III} which reacts with a given pyridine *N*-oxide was established by combining a known quantity of the *N*-oxide with an excess of $TiCl_3$ and titrating the remaining Ti^{III} with standard ammonium iron(III) sulphate.[25] In all cases 2 mol of $TiCl_3$ were consumed per mol of *N*-oxide (X-pyo), suggesting that the production of the substituted pyridine is as shown in equation (1). Further support for this view was obtained when

$$2Ti^{3+} + \text{X-pyo} + H_2O \longrightarrow 2[TiO]^{2+} + \text{X-Hpy}^+ + H^+ \quad (1)$$

the product from the reduction of 2-carboxypyridine *N*-oxide with Ti^{III} was isolated and identified as pyridine-2-carboxylic acid.

Kinetics.—The progress of the reactions was followed by observing the disappearance of Ti^{III} at 500 nm on a Cary 14 spectrophotometer, using 10-cm cells as reaction vessels. The empty cells were flushed with nitrogen, the required volumes of titanium(III) solution and acid were added under a current of nitrogen, and the cell was sealed with a serum cap. The cell and a flask containing the *N*-oxide solution (also sealed with a serum cap) were placed in the thermostatted (±0.2 °C) cell compartment. After thermostatting, the required amount of the *N*-oxide solution was injected into the titanium(III) solution using a syringe which had been previously flushed with nitrogen.[25] Several reactions were carried out in a two-compartment flask in which the reactant solutions were thermostatted separately, then mixed, and forced into the cell with dry nitrogen. These two methods yielded equivalent results. Kinetic runs were made over a range of reactant concentrations and the data were treated by both instantaneous rate and pseudo-first-order methods to establish the order in the reactant concentrations and to compute the rate constants.

Free-radical Determinations.—When acrylonitrile was added to titanium(III)–pyridine *N*-oxide solutions under the same conditions as in the kinetic runs polymerization occurred in each case, quite rapidly in most. Because polymerization did not occur when acrylonitrile was added to the individual reactants, it is apparent that free radicals are produced during the course of the reaction,[26] as has also been found for the titanium(III) reduction of NH_2OH.[27,28]

RESULTS

Order in the Reactant Concentrations.—By combining the instantaneous rate of disappearance of Ti^{III} at several points during a given kinetic run with different values of x and y it was possible to calculate values for k in the equation. Rate $= k[Ti^{III}]^x[\text{X-pyo}]^y$. When k was constant throughout a run, the values of x and y were taken as the reaction orders in $[Ti^{III}]$ and [X-pyo], respectively. For an excess of Ti^{III}, k was constant to within ±5% for $x = y = 1$ indicating that the reaction is first order in the concentration of both reactants under these conditions, a view which is supported by the behaviour of pseudo-first-order plots which were linear for four or more half-lives and gave k values which agreed to ±5% with those calculated as described above.

The disappearance of Ti^{III} was also first order in the presence of excess of pyridine *N*-oxide, but with an apparent rate constant which was slightly larger than that in excess of Ti^{III}. This behaviour is suggestive of the presence of higher-order terms for pyridine *N*-oxide which become relatively more important when this reactant is in excess. Repeated attempts to quantify the contributions of any such higher-order terms with a more complicated rate equation were unsuccessful and all the subsequent studies were made under pseudo-first-order conditions, excess of Ti^{III}, where such contributions would be expected to be minimized and the reaction would be first order in both $[Ti^{III}]$ and [X-pyo].

An investigation of the relation between the reaction rate and the H^+ concentration revealed an inverse first-order dependence for this species. Some data which show the effect of H^+ and ionic strength on the rate of reduction of 4-methylpyridine *N*-oxide are given in Table 1. The ionic strength was adjusted by adding sodium chloride, and $TiCl_3$ was the reducing agent. As can be seen, changing the ionic strength had little effect. Also, the observation that the rate of reduction of a given *N*-oxide is the same, within experimental error, regardless of whether Cl^-, Br^-, I^-, or $[HSO_4]^-$ is present indicates that these reactions are not anion-dependent.

TABLE 1

Effect of $[H^+]$ and ionic strength on the rate of reaction of Ti^{3+} with a 4-methylpyridine *N*-oxide at 25 °C. $[Ti^{3+}] = 2.5 \times 10^{-2}$ mol dm^{-3}, [4Me-pyo] $= 1.67 \times 10^{-3}$ mol dm^{-3}

$\frac{[H^+]}{\text{mol dm}^{-3}}$	$\frac{I}{\text{mol dm}^{-3}}$	$\frac{k_{obs.}[Ti^{3+}]^{-1}}{\text{dm}^3\text{ mol}^{-1}\text{ s}^{-1}}$
0.25	0.65	0.22
0.25	0.26	0.25
0.50	0.65	0.13
0.50	1.15	0.14
0.50	1.15	0.07

TABLE 2

Parameters for Ti^{III}–XC_5H_4NO reactions in 0.5 mol mol dm^{-3} HCl at 25 °C

X	$\frac{10^2k}{\text{s}^{-1}}$	$\frac{\Delta H^\ddagger}{\text{kcal mol}^{-1}}$	$\frac{\Delta S^\ddagger}{\text{cal K}^{-1}\text{ mol}^{-1}}$
H	7.6	12.3 ± 0.5	−21 ± 4
3-Me	7.0	16.8	−6
4-Me	6.5	14.4	−14
3-Cl	8.9	17.8	−2
4-Cl	10.2	14.4	−14
4-Br	9.8	13.9	−15
4-OMe	10.0	13.9	−16
3-CO_2H	9.7	18.8	−1
2-Me	1.07	17.7	−5
2-CN	0.200		
3-CN	3.6	16.0	−10
4-CN	0.056	16.0	−14
4-CO_2H	0.75	18.2	−6
2-CO_2H	75		

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These results can be summarized in the rate law (2).

$$\frac{-\mathrm{d}[\mathrm{Ti^{III}}]}{2\mathrm{d}t} = \frac{k[\mathrm{Ti^{III}}][\text{X-pyo}]}{[\mathrm{H^+}]} \qquad (2)$$

Nature of the Pyridine N-*Oxide*.—In order to investigate the effect of different substituents on the reaction rate, a total of 14 different pyridine *N*-oxides were reduced with $\mathrm{Ti^{III}}$. The calculated rate constants for these reductions are given in Table 2 together with the activation parameters which were calculated by applying the Arrhenius equation to rate data obtained over a 30° temperature interval.

DISCUSSION

The fact that the rates of these reactions are inversely related to the $\mathrm{H^+}$ concentration can be understood if the active reducing species is $[\mathrm{Ti(OH)}]^{2+}$, which is produced by the hydrolysis of $\mathrm{Ti^{III}}$ in aqueous solution ($K_a = 1.6 \times 10^{-3}$ mol dm^{-3}),[29] as has been proposed for the titanium(III) reduction of iodine,[8] $\mathrm{Pu^{VI}}$,[9] $\mathrm{V^{V}}$,[13] and $\mathrm{U^{VI}}$,[14] as well as carboxylato-[15] and chloro-cobalt(III) complexes.[16] A second, although less likely, possibility is that the hydrogen ion decreases the concentration of the free *N*-oxide species by the reaction $\text{X-pyo} + \mathrm{H^+} \longrightarrow \text{X-Hpyo}^+$. This explanation seems inadequate, not only because the pyridine *N*-oxides are very weakly basic (*e.g.* pK_a for pyo is 0.79)[30] but also because the chromium(II) reductions of these same *N*-oxides are not $\mathrm{H^+}$-dependent,[31] and the existence of a protonation path involving *N*-oxide should be independent of the nature of the reducing agent.[32]

Two observations may be made from the data in Table 2. First, with the exception of the large value for the 2-carboxyl- and the small values for the 2- and 4-cyano-compounds, the range of k values for the reduction of the pyridine *N*-oxides is quite limited, varying by a factor of only 10. Secondly, the k values appear to bear little relation to the electronic properties of the *N*-oxides as reflected in their Hammett σ values, despite the wide variation in these values ($-0.60 < \sigma_{\text{pyo}} < 0.34$).[33] These two observations are closely related and contrast sharply with the polarographic reduction of these same *N*-oxides for which the $E_{\frac{1}{2}}$ values vary over a wide range and exhibit a linear correlation with σ.[34]

Although the comparison of kinetic and thermodynamic quantities (such as k and $E_{\frac{1}{2}}$) is risky, many mutual correlations of these parameters with Hammett σ coefficients are known,[35] and might also be expected in this instance. The absence of such a relation in the present data can be attributed to the difference in the respective reduction processes. That is, while reductions of the various *N*-oxides at the surface of a mercury drop are likely to be controlled by the ease with which electrons can be added to these species (*i.e.* by their σ values), their reduction by metal ions will depend on two factors. Not only will the ease of electron transfer be important as in the polarographic process, but also the co-ordinating ability of the *N*-oxides will have an influence.

Because co-ordination and electron transfer oppose one another, a levelling of rates might be expected. That is, the electron-withdrawing substituents which would favour transfer of an electron from the metal ion would not favour co-ordination, and the electron-donor substituents which would enhance co-ordination would deter the transfer of an electron. Thus, the fact that the σ values enhance processes which oppose one another makes it unlikely that a linear correlation between σ and the overall reduction process would exist.

Despite the limited range of k values and the absence of a linear relation between them and σ, it is possible to distinguish three categories of behaviour. In the first group, with k values between 0.065 and 0.102 s^{-1}, are *N*-oxides with substituents which are incapable of interacting with $[\mathrm{Ti(OH)}]^{2+}$ themselves and for which the redox reactions will be subject to the conflicting factors mentioned above. The second category comprises *N*-oxides which react more slowly (5.6 and $10^{-4} < k < 0.036$ s^{-1}). The members of this group are of two types: those with substituents in the *ortho* position which would be expected to inhibit co-ordination between the *N*-oxide and $[\mathrm{Ti(OH)}]^{2+}$ due to steric factors, and those with strongly electron-withdrawing groups in positions where resonance interactions with the *N*-oxide moiety are possible (2-CN, 4-CN, and 4-$\mathrm{CO_2H}$). It is unclear at this point whether the retardation of the reaction by these groups is due to the interaction of $[\mathrm{Ti(OH)}]^{2+}$ with them in preference to the *N*-oxide or simply to the weak complexation of $[\mathrm{Ti(OH)}]^{2+}$ by the *N*-oxide group by these extremely poor donors. However, the fact that k for 3-carboxypyridine *N*-oxide is appreciably larger than the values discussed above, even though the $\mathrm{CO_2H}$ group would be expected to co-ordinate as well in the *meta* position as in the *para*, would seem to emphasize the importance of the resonance interaction between the *N*-oxide and these electron-withdrawing groups and thus the second explanation offered above.

In contrast to the other electron-withdrawing substituents, the *o*-carboxyl group actually increases the rate of reduction ($k = 0.75$ s^{-1}). Since chelates with a number of metal ions have been reported for this *N*-oxide,[36,37] it is likely that the increased rate may be due to the carboxyl group fixing the $[\mathrm{Ti(OH)}]^{2+}$ ion in close proximity to the *N*-oxide where the electron can be transferred readily.

The activation parameters were determined (from Arrhenius plots over a 30° range) to be 12.3—18.8 kcal mol^{-1} ($\Delta H^{\ddagger}$) and -1 to -21 cal K^{-1} mol^{-1} ($\Delta S^{\ddagger}$) at 25 °C.*

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Little speculation can be made about the reaction mechanism based on these results.[38]

In conclusion, a valid mechanism for the reduction of pyridine N-oxides by $\mathrm{Ti^{III}}$ must fit the following observations: (*a*) a first-order dependence on $[\mathrm{Ti^{III}}]$ and [X-pyo]; (*b*) an inverse first-order dependence on $[\mathrm{H^+}]$; (*c*) the presence of free-radical species in the reaction mixture; and (*d*) the seeming importance of co-ordination between $\mathrm{Ti^{III}}$ and the N-oxides as indicated by the relative rates of reduction. A possible mechanism which satisfies these conditions is one in which $\mathrm{Ti^{III}}$ is hydrolyzed to $[\mathrm{Ti(OH)}]^{2+}$ with an equilibrium constant, K_a. The $[\mathrm{Ti(OH)}]^{2+}$ then transfers an electron to a pyridine N-oxide molecule (in what is probably the rate-limiting step) generating a free radical which subsequently oxidizes a second $[\mathrm{Ti(OH)}]^{2+}$. The rate law for the rate-determining step will be $-\mathrm{d}[\mathrm{Ti^{III}}]/\mathrm{d}t = k[\mathrm{Ti(OH)^{2+}}][\text{X-pyo}]$ and because $[\mathrm{Ti(OH)^{2+}}] = K_a[\mathrm{Ti^{III}}]/[\mathrm{H^+}]$, the rate law becomes (3) in accordance with experiment [equation (2)].

$$\frac{-\mathrm{d}[\mathrm{Ti^{III}}]}{\mathrm{d}t} = \frac{kK_a[\mathrm{Ti^{III}}][\text{X-pyo}]}{[\mathrm{H^+}]} \qquad (3)$$

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