Ruthenium Chloride Catalysed Oxidation of Tertiary Amines to Amine Oxides with Molecular Oxygen

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Tertiary amines are catalytically oxidized with molecular oxygen in homogeneous solutions containing $RuCl_3{\cdot}xH_2O$ to afford as a major product the corresponding *N*-oxide, the first example of such an oxidation.

We have discovered that $RuCl_3{\cdot}xH_2O$ will catalyse the molecular oxygen oxidation of tertiary amines to yield a variety of products. Of significance is the discovery that a major product is the corresponding *N*-oxide, making this reaction the first example of a catalytic molecular oxygen oxidation of a tertiary amine yielding its *N*-oxide.

Table 1

Substrate[a]	Solvent	Time/h	Conversion (%)	Products (mmol)
Dimethyldodecylamine	*o*-Dichlorobenzene	16	50	Dodecanoic acid (1.2), dodecanal (trace), dodecene (2.0), methyldodecylamine (trace), dimethylamine (trace), *N,N*-dimethyldodecamide (trace), *N*-methyl-*N*-dodecylformamide (trace), 2-methyl-5-decylisoxazolidine (1.8), formic acid (2.2), other minor products.
Dimethyldodecylamine	Acetone–H_2O	16	50	Dimethyldodecylamine oxide (1.8), formic acid (2.2), dodecanoic acid (1.2), plus other trace components.
NMe_3[b]	H_2O	16	80	Trimethylamine oxide (3.4), formic acid (4.0)[c], dimethylformamide (0.5), Me_2NOH (trace), dimethylamine (1.8), other minor products in trace levels including acetic acid.
NMe_3	H_2O	6	38	Trimethylamine oxide (1.4), formic acid (2.0), dimethylformamide (0.3), Me_2NH, traces of $MeNH_2$, and Me_2NOH.
Quinuclidine	Acetone–H_2O 9:1	16	No reaction	
Pyridine	H_2O	16	No reaction	

[a] 10 mmol. [b] Initial pH = 10.7, final pH = 7.8. [c] Primarily present as dimethylammonium formate.

In non-hydroxylic solvents (acetone and *o*-dichlorobenzene)† tertiary amines are oxidized catalytically with $RuCl_3{\cdot}xH_2O$,‡[1] but a complex mixture is obtained. Two major components found in the dimethyldodecylamine product mixture were dodecene and 2-methyl-5-decylisoxazolidine. These materials result from the Cope elimination products of dimethyldodecylamine oxide in a sealed system,[2] and their presence indicates that *N*-oxides are formed but are unstable under the reaction conditions. To stabilize the *N*-oxide product, the reaction was carried out in aqueous acetone, and in this the case *N*-oxide is indeed observed (Table 1). Using trimethylamine as a substrate gave systems that were easier to analyse (*i.e.* it is symmetrical and its *N*-oxide cannot undergo Cope elimination). Since NMe_3 is miscible in water, the reactions were also run in H_2O. When H_2O is used as solvent, the conversion rates and types of products are similar to those obtained with other solvents. A major product of the NMe_3 oxidation is trimethylamine oxide, but the yields never exceed 50%, an upper limit observed for all of these reactions.

All of the reaction mixtures contain low levels of *N,N*-dialkylamides and traces of hydroxylamines. Also, α-oxidation products such as acids (aldehydes) and secondary amines are major constituents of these reaction mixtures, and formation of these products parallels the rate of formation of *N*-oxide. The scope of this reaction is limited to aliphatic tertiary amines, since no reaction occurs with pyridine or substituted anilines. Bridgehead tertiary amines such as quinuclidine also do not react. For these catalytic oxidations the consumption of amine is first-order in both total Ru added and O_2 pressure (up to 250 lb in^{-2}). When *o*-dichlorobenzene solutions containing NR_3 (in 10-fold excess of $RuCl_3{\cdot}xH_2O$) are heated at 100 °C for several hours under argon,‡ little or no oxidation of amine occurs. These facts indicate that the 3+ oxidation state of ruthenium is *not* likely to be involved in this redox chemistry.

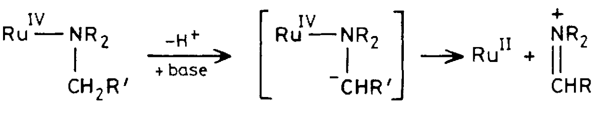
These oxidations are reminiscent of the $RuCl_3$-mediated oxygen oxidation of alcohols,[3] in which the two-electron oxidation[4] of a Ru^{II} complex (formed by disproportionation of an initial Ru^{III} complex[3,5]) by molecular oxygen yields peroxide and Ru^{IV}.[5] In the present case, a Ru^{II} amine complex formed by disproportionation of the initial Ru^{III} species‡[5] could react with oxygen to yield a peroxide and Ru^{IV}. The *N*-oxides would form by the well-known oxidation of a tertiary amine with peroxide [equations (1)—(3)].

$$2\ \text{‘}Ru^{III}(NR_3)_x\text{’} \rightarrow \text{‘}Ru^{II}(NR_3)_x\text{’} + \text{‘}Ru^{IV}(NR_3)_x\text{’} \quad (1)$$

$$\text{‘}Ru^{II}\text{’} + O_2 \rightarrow \text{‘}Ru^{IV}\text{’} + O_2^{2-} \quad (2)$$

$$NR_3 + HO_2^- \rightarrow O{\leftarrow}NR_3 + OH^- \quad (3)$$

For this to be catalytic, the Ru^{IV} product must be reduced. In the ruthenium(II)-mediated oxidation of alcohols using O_2, Ru^{IV} is reduced by the alcohol to yield Ru^{II} plus aldehyde or ketone.[3] For the tertiary amine oxidation the reductant must be the amine itself. A likely mechanism involves the Ru^{IV} oxidation of a co-ordinated amine to yield Ru^{II} and an iminium cation [equation (4)]. Any iminium species would rapidly hydrolyse giving the observed products, secondary amines, and aldehydes, with the latter oxidized rapidly under the reaction conditions to give acids.



$$\overset{IV}{Ru}-\underset{CH_2R'}{NR_2} \xrightarrow[+\,base]{-H^+} \left[\overset{IV}{Ru}-\underset{^-CHR'}{NR_2}\right] \longrightarrow Ru^{II} + \overset{+}{NR_2}{=}CHR' \quad (4)$$

This mechanism can also account for the formation of amide products, since it is known that HO_2^- is a very good nucleophile that will attack iminium cations to yield amides.[6] Hydroxylamines would form by peroxide attack on secondary

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† In a typical procedure the catalyst $RuCl_3{\cdot}xH_2O$[6] (0.02 M) and substrate (1.0 M) are dissolved in 10 ml of solvent (see Table 1 for details) to give a homogeneous solution which is transferred to a Griffen–Worden glass pressure reactor. The contents are then evacuated and pressurized with O_2 (50 lb in^{-2} gauge) and shaken in an oil bath at 100 °C. The reaction mixtures were analysed by g.c., t.l.c., analytical h.p.l.c. techniques, and by g.c.–mass spectroscopy in some cases. The *N*-oxide products were analysed by reverse phase h.p.l.c. and the product *N*-oxides were isolated and characterized by ^1H n.m.r. spectroscopy and elemental analyses.

‡ In these solvents soluble complexes of the type $RuCl_3(NR_3)_3$ form. With long chain amines such as dimethyldodecylamine these complexes are very soluble.

amines. This mechanism also correctly predicts the ratio of observed products. In the trimethylamine oxidation the amount of α-oxidation product, formic acid, should equal the total amount of products formed by reaction with peroxide: *N*-oxide plus amide (and hydroxylamine). This is observed for all the oxidations. The failure of a bridgehead amine to react is consistent with this mechanism, since the amine needs to function as the reductant of Ru^{IV} by forming an iminium cation and since the iminium cation needed to reduce Ru^{IV} would involve a very unfavourable, strained bridgehead nitrogen atom.[7]

In conclusion, we have shown that tertiary amines can indeed be catalytically oxidized with molecular oxygen to yield *N*-oxides. The overall mechanism, proposed on the basis of careful product distribution studies and other observations, suggests the possibility of carrying out useful hydrogen peroxide oxidations *via* a catalytic process utilizing molecular oxygen. Although the work described here is not practical since the amine substrate acts as a sacrificial two electron reductant of the oxidized catalytic metal, it does suggest that better catalyst systems can be designed utilizing discrete Ru^{II} complexes and better *in situ* reductants.

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