Oxygen atom transfer reactions by Ru(V) oxo complexes: Models by cytochrome P450 oxidase

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Ruthenium(V) oxo complexes of the composition LRuv=O {L=ethylenediaminetetraacetate (EDTA), propylenediaminetetraacetate (PDTA), N-hydroxyethylethylenediaminetriacetate (HEOTA)} and the ion [O = RuVCl₂(H₂O)₃]⁺ act as excellent catalysts in the oxygen atom transfer reactions to organic substrates. These nonporphyrinic complexes of Ru(V) oxo species are isolated and are much more stable than the Fe(V) oxo complexes of the porphyrins. They are good models for the Cytochrome P450 oxidase type of reactions.

Cytochrome P-450 dependent monoxygenases are widely distributed in nature and catalyze in general the transfer of an O atom from molecular O₂ to a substrate RH; the second oxygen atom is reduced to water by the involvement of two electrons and two protons in the reaction:

\[ \text{RH} + \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \xrightarrow{\text{P-450}} \text{ROH} + \text{H}_2\text{O} \]

The substrates RH include endogeneous compounds such as steriods, fatty acids, prostaglandins and leukotrienes and exogeneous compounds such as drugs and environmental products. The oxidized product ROH is finally eliminated from the kidney.

Iron porphyrins were successfully used as models for Cyt P-450 oxidase in the presence of oxidants such as iodosylbenzene, hydroperoxides, NaOCl and amine oxides. The studies were also extended to porphyrinic complexes of chromium and manganese. Recently, non-transition elements such as aluminium was also used to catalyse Cyt P-450 type of reaction.

In our laboratory we have been engaged in the oxidation of organic compounds by the Ru(III) complexes of aminopolycarboxylic acids (EDTA, PDTA) in the presence of molecular O₂. These complexes are particularly attractive since they are quite resistant to ligand oxidation by molecular O₂. In these processes the Ru(V) oxo complex LRuv=O (L=EDTA-H, PDTO-H, HEDTA) formed as an intermediate can readily transfer an O atom to the substrate. We have now isolated and characterized these oxo complexes. We have also been able to synthesize a simple Ru(V) oxo complex [O = RuVCl₂(H₂O)₃]⁺ by the electrochemical oxidation of the cation [RuIIICl₂(H₂O)₃]⁺ (ref. 18).

Materials and Methods

The complexes K[RuIII(L)Cl] (L = EDTA-H, PDTA-H, HEDTA) were synthesized by interacting K₂[RuCl₄] with an aminopolycarboxylic acid ligand (L) as described earlier and characterised. The complexes [RuIII(EDTA-H)]⁺ (1), [RuIII(PDTA-H)]⁺ (2) and [RuIII(HEDTA)]⁺ (3) rapidly get aquated to give the neutral species, [RuIII(EDTA-H)(H₂O)]⁻ (1a), [RuIII(PDTA-H)(H₂O)]⁻ (2a) and [RuIII(HEDTA)(H₂O)]⁻ (3a) respectively, at low pH (< 3.0). Iodosylbenzene was prepared by the literature method. All other chemicals used were of AR grade. Doubly distilled water and purified dioxane were used wherever necessary.

Synthesis of K[RuV(BEDTA)]·3H₂O (4), K[RuV(PDTO)]·3H₂O (5) and

\[ [\text{Ru}^V = \text{O}(\text{EDTA})] \]

To a solution (1 mmol in 5 ml) of the complex [LRuvCl₂]⁻ (1-3), was slowly added iodosylbenzene (1.2 mmol) dissolved in 10 ml of water-dioxane mixture (50%, v/v). The reaction mixture was allowed to stir in the dark for one hour at room temperature and the iodobenzene (PhI) so formed was extracted with ether. The solution was concentrated at room temperature and in vacuo to 2-3 ml. On addition of ethanol, a greenish yellow compound was precipitated in each case which was filtered, washed with...
ethanol-water (9:1) mixture and dried in vacuo (yield: 70% for 4 and 5, 72% for 6, yield calculated on the basis of complexes 1-3 taken). Complexes 4-6 (Fig. 1) can also be prepared by interacting complexes 1-3 with NaOCl. This procedure was adopted especially for preparing $^{18}$O oxo-complexes by interacting complexes 1-3 with Na$^{18}$OCl. Na$^{18}$OCl was prepared by following the usual procedure taking $H_2^{18}$O as solvent.

**Electrochemical synthesis of**

\[ [Ru^{III}(H_2O)_4Cl_2]^+ \] (7)

Complex 7 was obtained by the coulometric oxidation of $[Ru^{III}(H_2O)_4Cl_2]^+$ (ref. 18) at 0.95 V at pH 1.8. The coulometric experiments were performed using glassy-carbon electrodes to suppress the hydrogen production. The resultant solution was treated with an excess of Bu$_3$N$^-$PF$_6$ salt to precipitate the complex. The complex was recrystallised from $H_2$O-EtOH mixture. It is to be noted that under the specified experimental condition, water oxidation does not take place at a potential less than 1.25 V.

**Instrumentation**

Microanalyses were carried out using a Carlo Erba elemental analyser. Absorption spectra were recorded on a Shimadzu UV-vis 160 spectrophotometer coupled with a TCC-240A temperature controller. IR and far IR spectra were recorded on Beckman Acculab 10 (4000-600 cm$^{-1}$) and Perkin Elmer 621 (600-200 cm$^{-1}$) spectrometers, respectively. Magnetic susceptibility measurements were carried out at room temperature with a PAR vibrating sample magnetometer. The pH measurements were carried out with a Digison pH meter. The electrochemical studies were performed using a PAR (Princeton Applied Research) instrument (model 174 A). The polarographic experiments were carried out with a glassy carbon working electrode (and SCE as reference) in 0.1 M HClO$_4$ medium. EPR studies were performed on a Bruker ESP-300 X-band spectrometer with an attached ESP 1600 data system. Magnetic field was calibrated by ERO 35 M NMR gaussmeter with DPPH as a field marker.

**Kinetic studies**

The kinetics of oxygenation of complexes 1-3 to oxo-complexes 4-6 with iodosylbenzene were studied spectrophotometrically using stopped-flow technique. A HI-TECH stopped-flow (SF-51) coupled with an Apple IIe data analyser was used for this purpose. The time course of the reaction was followed by monitoring the development of oxo-peak at 390 nm. The stoichiometric oxygen atom transfer from oxo-complexes (4-6) to the organic substrates was studied spectrophotometrically by the conventional mixing techniques. The reaction was followed by monitoring the disappearance of the characteristic oxo-peak of the complexes at 390 nm. The pseudo-first order rate constants were calculated by the usual procedure from the absorbance versus time trace.

**Electrocatalysis**

Oxidation of organic substrates catalysed by complex 8 was carried out electrochemically at the anode (GCE) in 50% (v/v) water-dioxane mixture. The catalyst to substrate concentration ratio was kept at 1:100. Controlled potential electrolysis was carried out at 0.95 V. At chosen intervals of time an aliquot of the electrolysed solution was withdrawn and subjected to gas chromatographic analysis for determination of oxidation products.

**Product analysis**

Reaction products were identified by direct analysis of reaction mixture using gas chromatography. A Shimadzu gas chromatograph (GC-9A) equipped with a stainless steel column containing 10% cellophane 20 M on 90-100 mesh Anakrom working on TCD at 200°C (N$_2$ carrier gas) was used for this purpose. GC parameters were quantified with authentic samples of oxidation products of the organic substrates (under investigation) prior to the analysis of experimental products. For identification of oxidation products of cis-and trans-stilbene, the reaction
mixture was extracted with diethyl ether and after the solvent (ether) evaporation the residue was quantitatively transferred to NMR tube using CDCl₃ as solvent. IH NMR spectra of the reaction products were recorded on a JEOL FX-100 NMR spectrometer using TMS as internal standard.

Results and Discussion

The absorption spectra of oxo-complexes 4-6 contain several characteristic bands. The LMCT bands \([\pi^*(O) \rightarrow t_2g(\text{Ru}^V)]\) expected in the region 250-290 nm for Ru(V)-oxo complexes are masked by the CT bands of the aminopolycarboxylic acid (L) ligands which also show the characteristic absorption in the same region (250-290 nm). A close resemblance of the ligational absorption spectra of the precursor complex \([\text{Ru}^\text{III}(\text{N}_4\text{O})(\text{H}_2\text{O})]^2+\) and oxo-complex \([\text{Ru}^\text{V}(\text{N}_4\text{O})(\text{O})]^2+\) was also observed by Chi-Ming Che²⁵ where the spectra are dominated by intraligand \(\pi \rightarrow \pi^*\) transition of \(\text{N}_4\text{O}\) moiety [where \(\text{N}_4\text{OH} = \text{bis}(2\text{-pyridyl})\text{ethyl}(2\text{-hydroxy}-2\text{-pyridyl})\text{ethyl} \text{amine}\)]. However, complex 7, \([\text{Ru}^\text{V} = \text{O}(\text{H}_2\text{O})_3\text{Cl}_2]^+\), exhibited a distinct LMCT band \([\pi^*(O) \rightarrow t_2g(\text{Ru}^V)]\) at 293 nm \((\varepsilon_{\text{max}} = 3500)\). The bands exhibited at 391(8,000), 393(7500) and 393(8200) are assigned to MLCT[\(\text{Ru}^\text{V}(t_2g) \rightarrow \text{O}(\pi^*)\)] transitions of complexes 4, 5 and 6, respectively. For complex 7, this band was observed at 410 nm(1600). The low intensity band at 550(450) is assigned to the weak ligand field transition in complex 7, as observed for other ruthenium-oxo complexes²⁶. However, no such weak ligand field transition bands were observed for complexes 4-6 and also for \([\text{Ru}(\text{N}_4\text{O})(\text{O})]^2+\). IR spectra of complexes 4, 5 and 6 show peaks characteristic of \(\nu\text{Ru} = \text{O}\) at 890, 895 and 892 cm\(^{-1}\) respectively. The peak positions were found to be shifted to the region 872-880 cm\(^{-1}\) for \(^{18}\text{O}\) substituted oxo-complexes (LRu\(^V\) = \(^{18}\text{O}\)). A representative IR spectrum of the oxo-complex 7 is shown in Fig. 2 in which it is apparent that \(\nu\text{Ru} = \text{O}\) is shifted from 820 cm\(^{-1}\) to 800 cm\(^{-1}\) on \(^{18}\text{O}\) substitution. The presence of aminopolycarboxylate ligands in complexes 4-6 thus seems to strengthen the \(\text{Ru}^\text{V} = \text{O}\) bond as compared to \(\text{H}_2\text{O}\) and \(\text{Cl}^-\) in complex 7. The positions of \(\nu\text{Ru} = \text{O}\) in complexes 4-6 agree well with that reported²⁷ for \([\text{Ru}^\text{V} = \text{O}(\text{O}_2\text{COCE}_2)_2]^+\) at 900 cm\(^{-1}\).

The magnetic moment values reported are slightly higher than that required for one unpaired spin \((S = 1/2)\); this increase is attributed to orbital contribution to the magnetic moment. A \(\mu_{\text{eff}}\) of 2.2 B.M. was observed by Chi-Ming Che et al.²⁵ also for the \([\text{Ru}^\text{V} = \text{O}(\text{N}_4\text{O})]^2+\) complex.

The EPR spectra of complexes 4, 5 and 6 as powder samples at 298 K show a single broad line centered at \(g = 2.218, 2.205\) and 2.105, respectively. The EPR spectrum of complex 7 at 77 K, however, is characteristic of a rhombic \(g\) tensor with the components \(g_1 = 2.102(1), g_2 = 2.0813(5)\) and \(g_3 = 2.0615(5)\) as shown in Fig. 3. The EPR spectrum of a solid sample of complex 7 is similar to that obtained for its solution. The EPR results are in accord with the EPR of, Ru(V)-oxo complexes with \(\mu_{\text{eff}} = 1.7\) B.M.) reported by Griffith et al.²⁸. The cyclic voltammograms of oxo-complexes 4-6 in 0.1 M HClO₄ at pH 1.0 exhibited two irreversible peaks; one at 0.99 V for 4, 0.98 V for 5 and 0.86 V for 6 and another 0.1 V for 4, 0.2 V for 5 and 0.1 V for 6. Reversible waves were observed at \(-0.17 V\) for 4, \(-0.24 V\) for 5 and \(0.22 V\) for 6 which are assigned to \(\text{Ru}^3+/\text{Ru}^2+\) redox couple. The cyclic voltammogram of complex 8 is represented in Fig. 4 in which two quasi-reversible peaks are seen. The \(E_{1/2}\)
values (vs SCE) calculated from cyclic voltamogram for Ru$^{5+}$/Ru$^{4+}$ and Ru$^{4+}$/Ru$^{3+}$ couples for complex 7 are 0.93 and 0.44 V respectively.

Our model studies with ruthenium(V) oxo complexes comprise the "shunt part" of the cytochrome P$_{450}$ cycle, namely the oxidation of the Ru(III) complexes LRu$^{III}$($H_2O$) ($L=EDTA$, PDTA, HEDTA), to the Ru(V) oxo species LRu$^V=O$ (complexes 4-6) or by electrochemical oxidation of the Ru(III) aquo complex, [(H$_2$O)$_5$Cl$_2$Ru$^{III}$]$^+$ (8) to the Ru(V) oxo species [(H$_2$O)$_5$Cl$_2$Ru$^V=O$]$^+$ (7). Complexes 4-6 were used for the stoichiometric transfer of an O atom to the substrate to form the corresponding [LRu$^{III}(H_2O)$] complexes and the oxidized substrate. In the case of complex 7 catalytic electrooxidation of the substrates was conducted at the anode.

**Kinetics of the oxidation of LRu$^{III}(H_2O)$ to LRu$^V=O$**

The kinetics of the formation of the oxo complexes 4-6 were studied spectrophotometrically by monitoring the appearance of the characteristic oxo peak at 391 nm. Under the pseudo-first order condition of excess of PhIO (iodosylbenzene) the reaction rate was found to be first order with respect to LRu$^{III}(H_2O)$ concentration. The value of the pseudo-first order rate constant increases linearly with an increase in the iodosylbenzene concentration. Based on the above kinetic results the oxygenation of the complexes [LRu$^{III}(H_2O)$] to the oxo-species 4-6 may be expressed as:

\[
LR^{III}(H_2O) + \text{PhIO} \rightarrow LR^{III}(OIPh) + H_2O
\]

**Table 1—Kinetic and activation parameters for the reaction,**

<table>
<thead>
<tr>
<th>System</th>
<th>Temp. (°C)</th>
<th>(k) (M$^{-1}$s$^{-1}$)</th>
<th>(\Delta H^\circ) (kcal/mol)</th>
<th>(\Delta S^\circ) (cal/deg mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. [Ru$^{III}$(EDTA)(H$_2$O)]$^-$</td>
<td>30</td>
<td>70.1</td>
<td>9 ± 1</td>
<td>~21 ± 1</td>
</tr>
<tr>
<td>2. [Ru$^{III}$(PDTA)(H$_2$O)]$^-$</td>
<td>30</td>
<td>75.8</td>
<td>8 ± 1</td>
<td>~23 ± 1</td>
</tr>
<tr>
<td>3. [Ru$^{III}$(HEDTA)(H$_2$O)]</td>
<td>30</td>
<td>8.0</td>
<td>9 ± 1</td>
<td>~19 ± 1</td>
</tr>
</tbody>
</table>

The rate and activation parameters for the oxygenation of LRu$^{III}(H_2O)$ complexes with PhIO are given in Table 1. The low values of \(\Delta H^\circ\) and high negative values of \(\Delta S^\circ\) are consistent with the proposed mechanism (Eq. 1).

**Kinetics of epoxidation by olefins by oxo-complexes 4-6**

The absorption maxima of oxo-complexes in water-dioxane medium decreased upon addition of an olefin because of the formation of the epoxide which was identified by GC analysis. Under pseudo-first order conditions of excess olefin concentration, the reaction rate is first order with respect to oxo-complex concentration. The value of pseudo-first order rate constant \(k_{obs}\) increased with the increase in olefin concentration and at high olefin concentra-
Table 2 — Rates and activation for the oxidation of substrates (S) by LRu⁺⁻O complexes at 30°

<table>
<thead>
<tr>
<th>Substrate (S)</th>
<th>O = Ru⁺⁻(EDTA)</th>
<th>O = Ru⁺⁻(PDTA)</th>
<th>O = Ru⁺⁻(HEDTA)</th>
<th>SO (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k × 10⁴ (sec⁻¹)</td>
<td>ΔH' (kcal/mol)</td>
<td>ΔS' (e.u.)</td>
<td>k × 10⁴ (sec⁻¹)</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>1.25 ± 7.8</td>
<td>-50</td>
<td>1.33 ± 7.4</td>
<td>-51</td>
</tr>
<tr>
<td>Styrene</td>
<td>0.62 ± 8.8</td>
<td>-49</td>
<td>0.73 ± 8.4</td>
<td>-50</td>
</tr>
<tr>
<td>cis-Stilbene</td>
<td>0.48 ± 10</td>
<td>-45</td>
<td>0.60 ± 9.1</td>
<td>-48</td>
</tr>
<tr>
<td>trans-Stilbene</td>
<td>0.36 ± 12</td>
<td>-39</td>
<td>0.43 ± 11.0</td>
<td>-41</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>0.05 ± 8.0</td>
<td>-55</td>
<td>0.06 ± 8.0</td>
<td>-56</td>
</tr>
</tbody>
</table>

a = traces of cyclohexanone, cyclohexanol; b = traces of benzaldehyde, c = traces of trans-epoxide; d = traces of cis-epoxide

At high substrate concentration a zero order kinetics with respect to cyclohexane concentration was observed. On the basis of the above kinetic results the stoichiometric oxygen atom transfer from oxo-complexes to cyclohexane is supposed to proceed via the radical cage mechanism. The evidence for such a mechanism is the high k₄⁺⁴⁻ isotope effect observed in Cyt P₄₅₀ model reactions.

Electrooxidation of substrates mediated by complex 8

Controlled potential electrolysis was performed at 0.9 V, and on the basis of products formed a mechanism for oxygen atom transfer to the substrates mediated by the electrochemically formed complex 7 was proposed (Scheme 2). In the absence of the catalyst (complex 8) the reaction gave negligible amount of the oxidation products. Thus, an electrochemical ‘shuttle’ mechanism (Scheme 2) is believed to be operative in which Ru³⁺ gets reoxidised to Ru¹⁺ continuously at the anode followed by oxidation of...
organic substrates. The product yield, faradic efficiency and turn-over rate of this electrocatalytic system are summarised in Table 3.

References

15 Taqui Khan M M & Shukla R S, J molec Cat, 37 (1986) 269;