Cooperative activating effects of metal ion and Brønsted acid on a metal oxo species†

Gui Chen, Li Ma, Po-Kam Lo, Chi-Keung Mak, Kai-Chung Lau and Tai-Chu Lau

Metal oxo (M=O) complexes are common oxidants in chemical and biological systems. The use of Lewis acids to activate metal oxo species has attracted great interest in recent years, especially after the discovery of the CaMn4O5 cluster in the oxygen-evolving centre of photosystem II. Strong Lewis acids such as Sc3+ and BF3, as well as strong Brønsted acids such as H2SO4 and CF3SO3H, are commonly used to activate metal oxo species. In this work, we demonstrate that relatively weak Lewis acids such as Ca2+ and other group 2 metal ions, as well as weak Brønsted acids such as CH3CO2H, can readily activate the stable RuO4− complex towards the oxidation of alkanes. Notably, the use of Ca2+ and CH3CO2H together produces a remarkable cooperative effect on RuO4−, resulting in a much more efficient oxidant. DFT calculations show that Ca2+ and CH3CO2H can bind to two oxo ligands to form a chelate ring. This results in substantial lowering of the barrier for hydrogen atom abstraction from cyclohexane.

Introduction

High-valent metal oxo (M=O) complexes are common oxidants in the chemical laboratory and in biological systems. Brønsted acids have long been used to increase the oxidizing power of M=O via protonation of the oxo ligand (M=O + HX → M−OH+ + X−). However, in recent years, the use of Lewis acids (LA) such as metal ions and boranes to activate M=O has received tremendous attention (M=O + LA → M=O-LA).1-3 In particular, the interest in understanding the interaction of Lewis acids with metal oxos is stimulated by the discovery that the oxygen-evolving center (OEC) of photosystem II (PSII) is composed of a CaMn4O4 cubane and a dangling Mn linked via two µ-oxos.4-10 A possible role of Ca2+ is to function as a Lewis acid to modulate the redox reactivity of the manganese oxo complexes.

Strong Lewis acids such as BF3 and Sc3+ are usually used to activate metal oxo species. For example, we have reported that Ca2+ and other group II ions, as well as by weak Lewis acids such as alkanoic acid to modulate the redox reactivity of the manganese oxo complexes.

Metal oxo complexes are common oxidants in chemical and biological systems. The use of Lewis acids to activate metal oxo species has attracted great interest in recent years, especially after the discovery of the CaMn4O5 cluster in the oxygen-evolving centre of photosystem II. Strong Lewis acids such as Sc3+ and BF3, as well as strong Brønsted acids such as H2SO4 and CF3SO3H, are commonly used to activate metal oxo species. In this work, we demonstrate that relatively weak Lewis acids such as Ca2+ and other group 2 metal ions, as well as weak Brønsted acids such as CH3CO2H, can readily activate the stable RuO4− complex towards the oxidation of alkanes. Notably, the use of Ca2+ and CH3CO2H together produces a remarkable cooperative effect on RuO4−, resulting in a much more efficient oxidant. DFT calculations show that Ca2+ and CH3CO2H can bind to two oxo ligands to form a chelate ring. This results in substantial lowering of the barrier for hydrogen atom abstraction from cyclohexane.

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+VII, RuO$_4^-$ is a mild oxidant that readily oxidizes alcohols but is inactive towards alkanes. However, in the presence of a few equiv. of group 2 metal ions or acetic acid, it readily oxidizes cyclohexane at ambient conditions. Notably, the use of Ca$^{2+}$ and CH$_3$CO$_2$H together produces a remarkable cooperative effect on RuO$_4^{-}$, resulting in a much more efficient oxidant than the use of a strong Lewis acid in the presence or absence of a Bronsted acid.

**Results and discussion**

**Effects of Lewis acids on oxidation of cyclohexane by Ru$^{VIII}$O$_4$ and Ru$^{VII}$O$_4$**

Tetraoxo complexes of ruthenium in oxidation states +VIII and +VII are known, with Ru$^{VIII}$O$_4$ being a much stronger oxidant than Ru$^{VII}$O$_4^-$.$^3$ As a comparison, we have initially chosen to study the effects of Brønsted and Lewis acids (metal ions and BF$_3$) on the oxidation of alkanes by RuO$_4$. RuO$_4$ is a strong oxidant that is known to oxidize alkanes slowly at room temperature.$^{26}$ In our hands, when RuO$_4$ (0.01 M) was treated with an excess of cyclohexane (1.0 M) in CH$_3$CN, 0.2 mol of cyclohexanone/mol of RuO$_4$ (20 mol%) was produced after 5 h at 23 °C, as analysed by GC and GC/MS (Fig. 1a and Table S1†). No cyclohexanol could be detected. Since we previously reported that the oxidation of alkanes by MnO$_4^-$ is greatly enhanced by just a few equiv. of BF$_3$, we attempted to do the same with RuO$_4$. However, when BF$_3$ was added to RuO$_4$, no enhancement in the rate of cyclohexane oxidation was observed; on the contrary, a lower yield of cyclohexanone (11 mol%) was obtained (Fig. 1a and Table S1†). We then examined if Ca$^{2+}$ can activate RuO$_4$, but virtually no effect on cyclohexane oxidation was observed when a few equiv. of Ca(OTf)$_2$ (OTf is CF$_3$SO$_3^-$) was added. We also tried to activate RuO$_4$ with Bronsted acids such as CF$_3$SO$_3$H and CH$_3$CO$_2$H (AcOH), but again there were no effects. These results indicate that the oxo ligands in the highly electrophilic RuO$_4$ have little or no affinity for CH$_3$CO$_2$H and various Lewis acids.

On the other hand, RuO$_4^-$ is a much weaker oxidant than RuO$_4$; it is known to oxidize alcohols but not alkanes.$^{27}$ When we treated $[^{15}$Pr$_3$N$]$$[RuO_4]$ with cyclohexane in CH$_3$CN, no product could be detected after 5 days at 23 °C. Electrospray ionization mass spectrometry (ESI/MS) of the solution after 5 days shows that RuO$_4^-$ and $[^{15}$Pr$_3$N$]$ are the only species present. The UV/Vis spectrum of the solution also remained unchanged after 5 days. However, upon adding 4 equiv. of BF$_3$ to $[^{15}$Pr$_3$N$]$ $[RuO_4]$ in CH$_3$CN, 10 mol% of cyclohexanone was produced within 3 h at 23 °C (Fig. 1b and Table S2†). Again, no cyclohexanol product could be detected. More significantly, Ca(OTf)$_2$ is also able to activate RuO$_4^-$, and a higher yield of 14 mol% of cyclohexanone was attained (Fig. 1b, S1 and Table S2†). As will be described below, the RuO$_4^-$/Ca$^{2+}$ system functions as one-electron oxidant, and since the oxidation of cyclohexane to cyclohexanone is a four-electron process, the actual yield is 56%. Other group II metal ions were also found to activate RuO$_4^-$, with cyclohexanone production ranging from 11 to 15 mol% (Fig. 2, Table S2†). The relatively strong Lewis acid Sc(OTf)$_3$ was also used and it gave the highest amount of 23 mol% of cyclohexanone. The rate and yield decrease in the order of Sc$^{3+}$ (pK$_a$ = 4.3) > Mg$^{2+}$ (11.2) > Ca$^{2+}$ (12.7) > Sr$^{2+}$ (13.2) >> Ba$^{2+}$ (13.4); this trend correlates with their pK$_a$ values in H$_2$O, which is a measure of their Lewis acidity.$^{28}$ These results indicate that the oxo ligands in RuO$_4^-$ are much more basic than those in RuO$_4$, so they readily bind to Lewis acids. Electron-withdrawing by the Lewis acids via the oxo ligand enhances the oxidizing power of RuO$_4^-$. The initial rate for cyclohexanone production by $[^{15}$Pr$_3$N$]$ $[RuO_4]$ increases with [Ca$^{2+}$] but eventually levels off at [Ca$^{2+}$] > 5 mM (Fig. 3a). A plot of 1/(initial rate) versus 1/[Ca(OTf)$_2$] is linear (Fig. 3b). In addition, when the concentration of RuO$_4^-$ was doubled, the initial rate was also doubled. Such a kinetic behavior can be represented by eqn (1) and (2). The reacting calcium species is proposed to be Ca(OTf)$_2^-$, as supported by results of DFT calculations described below. The reacting species is proposed to be Ca(OTf)$_2^-$, as supported by results of DFT calculations described below. The initial rate of the reaction is shown in eqn (3).

$$\text{Ca(OTf)}^+ + \text{RuO}_4^- \underset{K}{\overset{k}{\rightleftharpoons}} \text{[Ca(OTf)]}^+ \cdot \text{RuO}_4^- \quad (1)$$

$$\text{[Ca(OTf)]}^+ \cdot \text{RuO}_4^- + \text{c} - \text{C}_6\text{H}_{12} \underset{k}{\rightarrow} \text{products} \quad (2)$$

**Kinetics of the oxidation of cyclohexane by RuO$_4^-$/Ca$^{2+}$**

Initial rate = \( \frac{kK}[\text{Ca(OTf)}_2^+] \frac{[\text{RuO}_4^-][\text{c} - \text{C}_6\text{H}_{12}]}{1 + K[\text{Ca(OTf)}_2^+]} \) (3)
From Fig. 3b, \( k = 1/\text{[intercept [RuO}_4^−] = (4.63 \pm 0.13) \times 10^{-5} \text{ M}^{-1} \text{s}^{-1} \) and \( K = \text{[intercept/slope] = (6.83 \pm 0.18) \times 10^{3} \text{ M}^{-1} \) at 23 °C. The observed equilibrium constant \( K \) indicates relatively strong binding of Ca(Otf) to RuO₄, in accordance with the observed rate saturation behaviour.

**Activation of RuO₄− by Bronsted acids**

The effects of Bronsted acids on cyclohexane oxidation by RuO₄ were also investigated. Addition of 1 equiv. of the strong acid CF₃SO₃H (pKₐ = 0.23 in H₂O) to [Pr₄N][RuO₄] (0.01 M) in CH₃CN containing excess cyclohexane led to the formation of 15 mol% of cyclohexanone after 3 h at 23 °C. However, addition of ≈4 equiv. of CF₃SO₃H to [Pr₄N][RuO₄] resulted to rapid formation of a black precipitate with only a trace amount of cyclohexanone. Such a phenomenon is due to disproportionation of RuO₄−, as represented by eqn (4):²⁹

\[
4\text{RuO}_4^- + 4\text{H}^+ \rightarrow 3\text{RuO}_4 + \text{RuO}_2 + 2\text{H}_2\text{O} \quad \text{E}^0 = 0.46 \text{ V} \quad (4)
\]

Interestingly, [Pr₄N][RuO₄] is also readily activated by the relatively weak acid CH₃CO₂H (pKₐ = 4.76) to oxidize cyclohexane to cyclohexanone, with no evidence of disproportionation even in the presence of high concentrations of AcOH (>1 M). Upon addition of 12–48 equiv. of AcOH to [Pr₄N][RuO₄] in CH₃CN containing excess cyclohexane, the brown solution gradually turned green, and 16 mol% of cyclohexanone was produced within 1–2 h at 23 °C. The oxidation state of the ruthenium product was determined to be +6 (see below, Fig. S3†), hence the actual yield is 64%. Although the yield is independent of [AcOH], the rate of oxidation increases with increasing [AcOH] (Fig. 4); a plot of the initial rate versus [AcOH] gives a straight line. The initial rate is also doubled when [RuO₂ ] is doubled. A proposed reaction scheme is shown in eqn (5)–(7). The first step involves protonation of an oxo ligand of RuO₄− by AcOH, this step is supported by DFT calculations described below. The resulting [Ru(O)₃(OH)] species is hydrogen-bonded to a second AcOH molecule to generate the active intermediate [AcOH-Ru(O)₃(OH)] that oxidizes cyclohexane. The rate law is shown in eqn (8); at \( K'[\text{CH}_3\text{CO}_2\text{H}] \ll 1 \), the rate law becomes that of eqn (9).

\[
\text{RuO}_4^- + \text{CH}_3\text{CO}_2\text{H} \rightarrow [\text{Ru(O)}_3(\text{OH})] + \text{CH}_3\text{CO}_2^- \quad (5)
\]

\[
[Ru(O)_3(OH)] + \text{CH}_3\text{CO}_2\text{H} \xrightarrow{K} [\text{CH}_3\text{CO}_2\text{H-Ru(O)}_3(\text{OH})] \quad (6)
\]

\[
[\text{CH}_3\text{CO}_2\text{H-Ru(O)}_3(\text{OH})] + c-\text{C}_6\text{H}_{12} \rightarrow \text{products} \quad (7)
\]

\[
\text{Initial rate} = \frac{k'K'[\text{CH}_3\text{CO}_2\text{H}]}{1 + K'[\text{CH}_3\text{CO}_2\text{H}]} [\text{RuO}_4^-][c-\text{C}_6\text{H}_{12}] \quad (8)
\]

At \( K'[\text{CH}_3\text{CO}_2\text{H}] \ll 1 \)

\[
\text{Initial rate} = k'K'[\text{AcOH}][\text{RuO}_4^-][c-\text{C}_6\text{H}_{12}] = k_{\text{AcOH}}[\text{AcOH}][\text{RuO}_4^-][c-\text{C}_6\text{H}_{12}] \quad (9)
\]

From the slope of Fig. 4b and using [RuO₄−] = 0.01 M and [c-C₆H₁₂] = 1.0 M, \( k_{\text{AcOH}} \) is found to be (2.72 ± 0.13) \times 10⁻³ M⁻¹ s⁻¹ at 23 °C.

**Cooperative activating effects of metal ions and AcOH**

Remarkably, when the oxidation of cyclohexane by RuO₄− was carried out in the presence of Ca²⁺ and AcOH, both the rate and product yield were enhanced, as shown in Fig. 5. The amount of cyclohexanone produced by the RuO₄−/Ca²⁺/AcOH system is 38 mol%, compared with ca. 16 mol% by both RuO₄−/Ca²⁺ and RuO₄−/AcOH systems. In this case, the oxidation state of the ruthenium product was found to be +5 (see below, Fig. S3†), so this system functions as a two-electron oxidant and the actual yield is 76%, higher than the 64% using Ca²⁺ or AcOH alone.

![Fig. 3](image1.png)

**Fig. 3** Effects of [Ca(Otf)₂] on cyclohexane oxidation by RuO₄ in CH₃CN. Conditions: [Pr₄N][RuO₄] (0.01 M), cyclohexane (1.0 M) in CH₃CN at 23 °C. (a) Plot of initial rate vs. [Ca(Otf)₂]. (b) Plot of 1/initial rate vs. 1/[Ca(Otf)₂] (slope = (3.16 ± 0.15) × 10⁻⁶, y-intercept = (2.16 ± 0.06) × 10⁻⁶, r = 0.988).

![Fig. 4](image2.png)

**Fig. 4** (a) Effects of CH₃CO₂H on cyclohexane oxidation by RuO₄ in CH₃CN. Conditions: [Pr₄N][RuO₄] (0.01 M), cyclohexane (1.0 M) in CH₃CN at 23 °C. (b) Plot of initial rate versus [AcOH]. (slope = (2.72 ± 0.13) \times 10⁻³ M⁻¹ s⁻¹, r = 0.9908).

![Fig. 5](image3.png)

**Fig. 5** Time trace for cyclohexane oxidation by [Pr₄N][RuO₄] (0.01 M) in CH₃CN at 23 °C in the presence of (a) 1 equiv. Ca²⁺, (b) 12 mol equiv. of AcOH and (c) 1 mol equiv. Ca²⁺ + 12 mol equiv. AcOH.
The yield of cyclohexanone was increased to 92% when the amount of acetic acid was increased to 250 equiv. (CH₃CN/AcOH: 6:1, Table 1). Note that in the absence of Ca(OTf)₂, the yield of cyclohexanone did not increase with [AcOH], as illustrated in Fig. 4a. Similar cooperative effects of M²⁺ and AcOH were also found for other group 2 ions (Table 1), with a maximum yield of 99% observed for Sr²⁺/AcOH. However, no such cooperative effects were found for stronger Lewis acids such as BF₃ and Sc(OTf)₃, the yields remain the same in the absence or presence of AcOH. These results demonstrate the strong cooperative effects of relatively mild Brønsted and Lewis acid in activating a metal oxo species. Although the reaction rate is lower than that of BF₃ or Sc(OTf)₃, the Group 2 ion/AcOH combination is much more efficient in terms of product yield. Similar to the case of CF₃SO₃H discussed above, partial decomposition of RuO₄⁻ occurs in the presence of a strong Lewis acid, hence resulting in lower yields.

The kinetics of cyclohexane oxidation by RuO₄⁻/Ca²⁺/AcOH were investigated. Saturation kinetics were also observed when [Ca²⁺] was increased (Fig. 6). Based on Fig. 6 and the mechanisms proposed above for RuO₄⁻/Ca²⁺ and RuO₄⁻/AcOH, the mechanism for this system can be represented by the following equations.

\[
\text{RuO}_4^- + \text{CH}_3\text{CO}_2\text{H} \rightarrow [\text{Ru} (\text{O})_3 (\text{OH})] + \text{CH}_3\text{CO}_2^- 
\]

\[
[\text{Ru} (\text{O})_3 (\text{OH})] + \text{Ca(OTf)}^+ + \text{CH}_3\text{CO}_2H \overset{K'}{\Rightarrow} [\text{Ca(OTf)}^+ \cdot \text{CH}_3\text{CO}_2H \cdot \text{Ru} (\text{O})_3(\text{OH})]
\]

\[
[\text{Ca(OTf)}^+ \cdot \text{CH}_3\text{CO}_2H \cdot \text{Ru} (\text{O})_3(\text{OH})] + c \rightarrow \text{CaH}_2 \overset{K''}{\rightarrow} \text{products}
\]

The rate-law is as shown in eqn (13):

\[
\text{Initial rate} = \frac{k' k'' [\text{Ca(OTf)}^+]_2}{1 + K'' [\text{Ca(OTf)}^+]_2} \cdot [\text{RuO}_4^-] \cdot [\text{AcOH}][c - \text{CaH}_2]
\]

Fig. 6 (a) Plot of initial rate vs. [Ca²⁺⁺] for the Ca(OTf)₂/AcOH activated oxidation of cyclohexane (0.10 M) by RuO₄⁻ (0.01 M) in CH₃CN at 23.0 °C. (b) The corresponding plot of 1/initial rate vs. 1/[Ca²⁺⁺]. Slope = (6.29 ± 0.64) × 10⁶, y-intercept = (1.29 ± 0.09) × 10⁵, r = 0.9504. Conditions: RuO₄⁻ (0.01 M); cyclohexane (1.0 M); AcOH (0.12 M); Ca(OTf)₂ (0.002 M – 0.40 M).

From eqn (11) and Fig. 6b, K’’ and K’ are found to be (2.05 ± 0.31) × 10⁻⁵ M⁻¹ and (6.49 ± 0.45) × 10⁻⁴ M⁻¹ s⁻¹, respectively.

A similar cooperative effect was also found for Mg²⁺/AcOH (Fig. S4†). However, no increase in rate and yield were found for Sc³⁺/AcOH (Fig. S5†).

**Ruthenium intermediates and products**

Electrospray ionization mass spectrometry (ESI/MS) was employed to detect any intermediate formed between RuO₄⁻ and Ca²⁺. The mass spectrum of [Pr₄N][RuO₄] in CH₃CN exhibits a single peak at m/z 166.1 due to RuO₄⁻ (Fig. S6†). Upon addition of 0.25 equiv. of Ca(OTf)₂, a new peak at m/z 653.9 appeared, which is assigned to [RuO₄⁻·Ca(CF₃SO₃)₂]. CF₃SO₃H⁻ (Fig. S7†). MS/MS of this ion (m/z 653.9) gives fragment peaks due to CF₃SO₃⁻ (m/z 148.9) and RuO₄⁻ (m/z = 165.9) (Fig. S8†). This result provides evidence for the binding of Ca²⁺ to RuO₄⁻.

The brown color of the solution of [Pr₄N][RuO₄]/Ca(OTf)₂ gradually lightened during cyclohexane oxidation, eventually a dark brown precipitate was observed and the solution became colorless. The dark precipitate, which is probably a Ca²⁺-bridged polymeric species, was dissolved in 0.1 M HNO₃ and the solution was titrated spectrophotometrically with the strong oxidant (NH₄)₂Ce(NO₃)₆ (Ce(IV)). Upon addition of Ce(IV) to the solution was titrated spectrophotometrically with the strong oxidant (NH₄)₂Ce(NO₃)₆ (Ce(IV)). Upon addition of Ce(IV) to the solution, two peaks were observed, which is assigned to [RuO₄⁻·Ca(CF₃SO₃)₂]. CF₃SO₃H⁻. The peaks were shi
d to 2.3 ± 0.3 equiv. of Ce(IV) was consumed (Fig. S2†). This result indicates that the oxidation state of Ru in the dark brown product is +6 and hence the Ca²⁺/RuO₄⁻ system acts as one-electron oxidant in the reaction with cyclohexane.

In cyclohexane oxidation by [Pr₄N][RuO₄]/AcOH, the brown solution gradually turned dark green but no precipitate was observed. ESI/MS of the dark green solution shows the appearance of a peak at m/z 209 (Fig. S9†), which can be assigned to [RuO₄⁻·AcO]⁻. When CH₃CO₂H was replaced by CD₃CO₂D, the m/z 209 peak was shifted to m/z 212, indicating that the m/z 209 peak consists of 1 AcO⁻ ion. The assignment of +6 oxidation state to the ruthenium product is also supported by Ce(IV) titration, which consumes two equiv. of Ce(IV) to generate RuO₄⁻. Hence the RuO₄⁻/AcOH system also functions as one-electron oxidant.

**Table 1 Oxidation of cyclohexane by [Pr₄N][RuO₄]/Lewis acid in CH₃CN/AcOH (6:1, v/v)²**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield of cyclohexanone (°)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ca(OTf)₂</td>
<td>92</td>
<td>5 h</td>
</tr>
<tr>
<td>2</td>
<td>Ca(OTf)₂</td>
<td>92</td>
<td>5 h</td>
</tr>
<tr>
<td>3</td>
<td>Ca(OTf)₂</td>
<td>91</td>
<td>5 h</td>
</tr>
<tr>
<td>4</td>
<td>Sr(OTf)₂</td>
<td>99</td>
<td>5 h</td>
</tr>
<tr>
<td>5</td>
<td>Mg(OTf)₂</td>
<td>86</td>
<td>5 h</td>
</tr>
<tr>
<td>6</td>
<td>Ba(OTf)₂</td>
<td>86</td>
<td>5 h</td>
</tr>
<tr>
<td>7</td>
<td>BF₃</td>
<td>42</td>
<td>3 min</td>
</tr>
<tr>
<td>8</td>
<td>Sc(OTf)₃</td>
<td>46</td>
<td>3 min</td>
</tr>
</tbody>
</table>

² Conditions: [Pr₄N][RuO₄], 0.01 M; Lewis acid, 0.04 M; cyclohexane, 1.0 M; solvent, CH₃CN/HOAc (6:1, v/v); at 23 °C. Under argon. In the presence of 10 equiv. of BrCCl₃, only a trace amount of bromocyclohexane was detected.的设计为: 

**Table 1 Oxidation of cyclohexane by [Pr₄N][RuO₄]/Lewis acid in CH₃CN/AcOH (6:1, v/v)²**

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² Conditions: [Pr₄N][RuO₄], 0.01 M; Lewis acid, 0.04 M; cyclohexane, 1.0 M; solvent, CH₃CN/HOAc (6:1, v/v); at 23 °C. Under argon. In the presence of 10 equiv. of BrCCl₃, only a trace amount of bromocyclohexane was detected. Yield = [mol of cyclohexanone]/[mol of [Pr₄N][RuO₄]] × 2 × 100%, no cyclohexanol was detected.
On the other hand, spectrophotometric titration of the product solution of Ca²⁺/AcOH/RuO₄⁻ after cyclohexane oxidation shows that it consumes 3.1 ± 0.2 equiv. of Ce(IV), hence in this case the oxidation state of the Ru product is +5 and the system is a two-electron oxidant towards cyclohexane (Fig. S3†).

**Mechanistic studies**

The same results were obtained for cyclohexane oxidation carried out under argon or air (Tables 1 and S2†). Also, the addition of BrCCL₃, a radical scavenger, had little effects on the oxidation of cyclohexane, and only a trace amount of bromocyclohexane was detected (Tables 1 and S2†). These results indicate that no freely diffusing alkyl radicals are formed in the oxidation of cyclohexane by RuO₄⁻ in the presence of Ca²⁺ and/or AcOH.

The kinetic isotope effects (KIE) for cyclohexane oxidation by RuO₄⁻ under various conditions were determined by competitive oxidation of an equimolar mixture of c-C₆H₁₂ and c-C₆D₁₂. The KIE for RuO₄⁻/Ca²⁺, RuO₄⁻/AcOH and RuO₄⁻/Ca²⁺/AcOH were found to be 6.4 ± 0.2, 13.9 ± 0.4 and 6.5 ± 0.2, respectively. Such large KIEs are indicative of C–H bond cleavage in the rate-limiting step.

Based on the experimental results, the oxidation of alkane by RuO₄⁻ in the presence of Lewis acid (LA) appears to be consistent with a mechanism that involves the initial binding of LA to RuO₄⁻ to generate a precursor complex, which then reacts with alkane via a H-atom abstraction/O-rebound mechanism to generate the corresponding alcohol. Such a mechanism is commonly accepted for C–H bond activation by cytochrome P₄₅₀ and various metal oxo species. However, since only ketones are detected in the present case, this suggests that the initially formed alcohol is rapidly oxidized to give the ketone. This is supported by a competitive experiment involving the oxidation of a mixture of cyclohexane and cyclopentanol (10:1) by RuO₄⁻/Ca²⁺, which resulted in the rapid and exclusive formation of cyclopentanone (Fig. S10†). No alkene or products derived from its oxidation were observed in the oxidation of alkane by RuO₄⁻/Ca²⁺, which rules out a dehydrogenation mechanism that has been shown to occur in alkane oxidation by non-heme iron(n) oxo species. The binding of a Lewis acid to RuO₄⁻ enhances its oxidizing power, as observed in non-heme iron(n) oxo complexes and manganese oxo clusters.

**Theoretical calculations**

In order to obtain further insights into the activating effects of Ca(n) and AcOH on RuO₄⁻, the reaction mechanisms for the oxidation of cyclohexane catalysed by RuO₄⁻ in the presence of Ca(OTf)₂ and/or AcOH have been theoretically studied by density functional theory (DFT). As a comparison similar studies with RuO₄ have also been carried out.

In the oxidation of cyclohexane by [RuO₄⁻]⁻ in CH₃CN (Fig. 7), cyclohexane and [RuO₄⁻]⁻ first form an intermediate, INT1(RuO₄⁻), in which the two species are weakly attracted together ([RuO₄⁻·C₆H₁₂]). HAT then occurs from C₆H₁₂ to Ru=O via a transition state TS1(RuO₄⁻) to form a second intermediate, INT2(RuO₄⁻). The reaction barrier (ΔG²₉₈⁻) for the HAT is 26.8 kcal mol⁻¹ in CH₃CN. Such a large ΔG²₉₈⁻ agrees with the experimental observation that RuO₄⁻ hardly reacts with cyclohexane at room temperature. The C1 of the cyclohexyl radical in INT2(RuO₄⁻) bears ~0.93 electrons, consistent with a HAT process. The cyclohexyl radical then binds to another oxo ligand to generate an alkoxo intermediate [RuO₂(OH)(OC₆H₁₁)]⁻ via TS2(RuO₄⁻). It should be noted that the step after H-abstraction is not characterized as a rebound step, in contrast to cytochrome P₄₅₀ and other mono-oxo species. Rather, another oxo group which is not used for H-atom abstraction combines with the carbon atom with a low barrier. Because of this reactivity pattern, a ruthenium-bound alkoxide instead of alcohol is formed as an intermediate. Then in the next step, proton transfer from Ru=OH to the alkoxide occurs via TS3(RuO₄⁻) to generate the cyclohexanol product. Similar reaction pathways are observed for cyclohexane oxidation by RuO₄, except in this case no radical intermediate (INT2) is formed (Fig. S11†). The reaction barrier (ΔG²₉₈⁻) is 17.8 kcal mol⁻¹, consistent with the experimental observation that RuO₄ reacts readily with cyclohexane at room temperature.

In the oxidation of cyclohexane by RuO₄⁻ in the presence of [Ca(OTf)₂], the reaction mechanism is similar. [Ca(OTf)₂]⁻ forms an intermediate, INT1(CaOTf), with RuO₄⁻; the Ca is bound to two oxo ligands. Due to the electron withdrawing effects of Ca(n) centre, the Ru–O bond lengths are changed from 1.740 (in RuO₄⁻, Table S3†) to 1.775 (oxo bond to Ca) and 1.709 Å (free oxo) in INT1(CaOTf). HAT from C₆H₁₂ then occurs via the shorter and more electrophilic Ru=O bond. In this case there is no cyclohexyl radical intermediate, INT2(RuO₄⁻); HAT and binding of cyclohexyl radical to a second oxo occur in a single step. The ΔG²₉₈⁻ for the oxidation of cyclohexane by [RuO₄⁻·CaOTf] (Fig. 7 and Table S3† entry 3), via TS1(CaOTf), is 18.5 kcal mol⁻¹. Such a lowering of 8.3 kcal mol⁻¹ is in agreement with the observed accelerating effect of Ca(n). We have also found the ΔG²₉₈⁻ for the oxidation of cyclohexane by [RuO₄⁻·Ca(OAc)] (Table S3† entry 5) is higher than that by [RuO₄⁻·CaOTf], so [RuO₄⁻·CaO]⁺ should not be the active species in the oxidation of cyclohexane.

In the presence of acetic acid, RuO₄⁻ is protonated to give INT1(AcOH), [RuO₂(OH)(AcO)·C₆H₁₂]. The AcO⁻ is held by two additional AcOH molecules through hydrogen bonding (structures given in Table S3†). The Ru–OH bond distance is 1.858 Å; protonation results in shortening of two of the Ru=O from 1.740 Å (in RuO₄⁻) to 1.709 Å. HAT by INT1(AcOH) occurs via one of the shorter and more electrophilic Ru=O; the resulting cyclohexyl radical then binds to Ru=OH·····OAc to generate Ru bound cyclohexanol in the same step, INT2(AcOH). The ΔG²₉₈⁻ for HAT from C₆H₁₂ to INT1(AcOH) via TS1(AcOH) is 15.2 kcal mol⁻¹, which is significantly lower than the ΔG²₉₈⁻ for RuO₄⁻ alone by 11.6 kcal mol⁻¹, in accordance with the experimentally observed accelerating effects of AcOH on RuO₄⁻.

In the presence of both [CaOTf]²⁻ and AcOH, the intermediate with RuO₄⁻, INT1(CaOTF + AcOH), consists of AcO⁻ and Ca forming a chelate ring with Ru=O and Ru=OH, as well as three H-bonded AcOH molecules (Fig. 7 and Table S3† entry 4). The free Ru=O bonds are further shortened to 1.692 Å. Accordingly
the $\Delta G_{298}^{\ddagger}$ for HAT from cyclohexane via TS1(CaOTf + AcOH) is lowered to 10.8 kcal mol$^{-1}$, which is smaller than the value of 18.5 kcal mol$^{-1}$ and 15.2 kcal mol$^{-1}$, respectively, with Ca(OTf)$^+$ or AcOH alone. This is in agreement with the observed cooperative activating effects of AcOH and Ca(II). HAT and binding of the resulting cyclohexyl radical to a Ca-bound oxo ligand occur in one step. Protonation by Ru–OH to the alkoxide then occurs to generate cyclohexanol. The potential energy surfaces (PES) for RuO$_4$/Ca(OTf)$^+$, RuO$_4$/AcOH and RuO$_4$/Ca(OTf)$^+$/AcOH are shown in Fig. S11.$^\dagger$ The $\Delta G_{298}^{\ddagger}$ for HAT by RuO$_4$ alone is 17.8 kcal mol$^{-1}$, consistent with the experimental observation that RuO$_4$ is able to oxidize cyclohexane at ambient conditions. There are little or no changes in the Ru=O distances of RuO$_4$ upon binding to Ca(OTf)$^+$ and/or AcOH, and there are only small changes in the reaction barriers, in agreement with experimental observations. This is in accordance with the Ru=O bonds being highly electrophilic and non-basic, hence there is little affinity for Lewis acids.

Conclusions

Our results demonstrate a remarkable cooperative effect of a weak Brønsted acid and a weak Lewis acid on the activation of a metal oxo species. RuO$_4^+$, although in high oxidation state of +VII, is a weak oxidant due to stabilization by the four oxo ligands. However, it can be readily activated by a mild Lewis acid such as Ca$^{2+}$ or other group II metal ions, as well as a weak Brønsted acid such as CH$_3$CO$_2$H. The addition of both Ca$^{2+}$ and CH$_3$CO$_2$H generates a highly efficient system that can oxidize unactivated C–H bonds with much higher yields than the use of strong Lewis acids such as Sc$^{3+}$ or BF$_3$, with or without CH$_3$CO$_2$H. Such an observation may provide insights into the design of active oxidants based on metal oxo species in combination with relatively weak Brønsted and Lewis acids, especially if the metal oxo or the substrate is sensitive to strong acids. Our studies may also be relevant to oxidation by metal oxo species in biological systems, where only mild Brønsted acids such as alkanoic or amino acids, and mild Lewis acids such as Zn$^{2+}$ or Ca$^{2+}$, are present in cells. So may be highly efficient oxidizing systems can be generated in biological systems using this strategy.

Conflicts of interest

There are no conflicts to declare.

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Notes and references