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Ley–Griffith Oxidation Mechanism | *Very Important Paper* |

Hydrogen-Bonding Interactions in the Ley–Griffith Oxidation: Practical Considerations for the Synthetic Chemist

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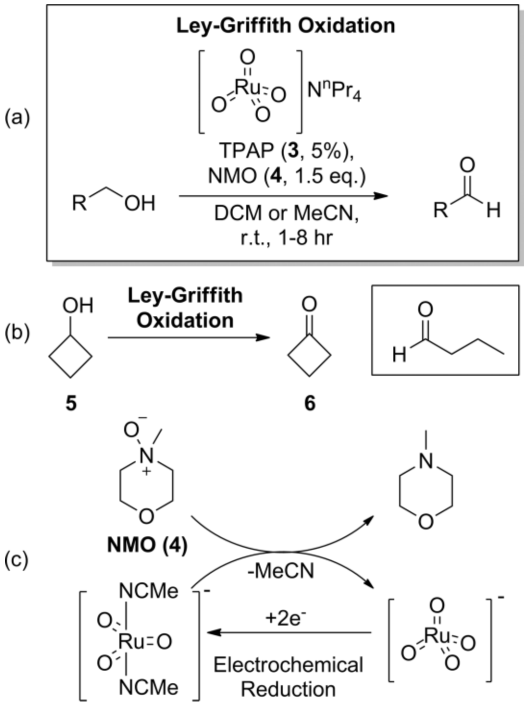
Abstract: The Ley–Griffith oxidation, which is catalyzed by tetra-*n*-propylammonium perruthenate (TPAP, *n*$Pr_4N[RuO_4]$), is a popular method for not only controlled oxidation of primary alcohols to aldehydes, but also a host of other synthetically useful transformations. While the fundamental reaction mechanism has recently been elucidated, several key hydrogen-bonding interactions between the reagents were implicated but not investigated. Herein the prevalence of H-bonding between the co-oxidant *N*-methylmorpholine *N*-oxide (NMO), the alcohol substrate, water and the perruthenate catalyst is established. These observations help to rationalize the importance of drying the reagents and lead to several practical suggestions.

Introduction

The synthesis of an aldehyde (**1**) via a controlled one-step oxidation of a primary alcohol (**2**) is a highly utilized chemical reaction deployed in academic and industrial settings.[1] Amongst the multitude of reagents and conditions available to perform this functional group transformation,[2,3] selectivity (avoiding over-oxidation), versatility (tolerance of other functional groups), and operational simplisticity are key criteria.[4] Legacy reagents such as pyridinium chlorochromate (PCC)[5] and pyridinium dichromate (PDC),[6] are held in high esteem, but the most commonly used conditions are the Swern,[7] DMP/IBX,[8–11] and Ley–Griffith oxidations.[12–17] The Ley–Griffith oxidation is catalyzed by tetra-*n*-propylammonium perruthenate {TPAP (**3**), *n*$Pr_4N[RuO_4]$} in combination with an excess of the co-oxidant *N*-methylmorpholine *N*-oxide (**4**, NMO), both of which are available commercially (Scheme 1a). Unlike other oxidation protocols mentioned above the Ley–Griffith oxidation is operationally simple and does not generate stoichiometric quantities of noxious byproducts. Like many reactions, modifications of the Ley–Griffith reaction have been reported through alterations to the catalyst,[18,19] co-oxidants,[20–27] and solvents.[28–30] However, the original conditions are most commonly utilized.



Scheme 1. a) Ley–Griffith oxidation. b) Oxidation of cyclobutanol to cyclobutanone. c) Regeneration of perruthenate from Ru^V.

Surprisingly, unlike other popular oxidation protocols, the mechanism of the TPAP oxidation remains poorly understood Until recently, only Lee et al.[31–33] had attempted to elucidate the mechanism. Lee et al. focused on the perruthenate catalyst alone (i.e. in the absence of the essential co-oxidant NMO), using an excess of alcohol (20 equiv.), and employed a single spectroscopic method (UV/Vis). Under these conditions (stoichiometric, not catalytic) $[RuO_4]^-$ irreversibly decomposed to a black, insoluble ruthenium dioxide ($RuO_2{\cdot}2H_2O$) which obscured the UV/Vis signals of the remaining perruthenate anion as well as the oxidized organic product. This work is quoted throughout the literature of the Ley–Griffith oxidation,[13–15] stating the mechanism is auto-catalytic and that TPAP is a three electron oxidant.[14] However, the oxidation of cyclobutanol (**5**) to cyclobutanone (**6**) in 95 % yield (Scheme 1b), demonstrated that perruthenate acts as a 2 electron oxidant, and is different

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to aqueous perruthenate oxidations which occur through a single electron oxidation mechanism.[33]

Our recent investigations unearthed a mechanism consistent with this observation whereby the alcohol is oxidized by $[Ru^{VII}O_4]^-$ in a 2-electron reaction. The products are a transient Ru^V species and the aldehyde/ketone. The role of the co-oxidant, NMO, is to re-oxidize $[Ru^VO_3(NCMe)_2]^-$ to $[Ru^{VII}O_4]^-$ which closes the catalytic cycle (Scheme 1c).[34] If Ru^V is not rapidly re-oxidised, or "rescued" by NMO, it disproportionates, forming ruthenate ($[Ru^{VI}O_4]^{2-}$) and solid ruthenium dioxide $Ru^{IV}O_2$. Synthetically, a large excess of NMO is employed so that re-oxidation of Ru^V is faster than disproportionation. However, even under these conditions, a small amount of $Ru^{IV}O_2$ is formed and this acts as a heterogeneous catalyst for the $[Ru^{VII}O_4]^-$-alcohol oxidation reaction.

It is interesting to note from Scheme 1 that each reagent in the Ley–Griffith reaction has the potential to form hydrogen bonds. An outer-sphere $[Ru^{VII}O]^-$:NMO•H_2O complex was implicated in previous EPR studies of the system and the actual perruthenate-alcohol oxidation reaction may also be facilitated by the formation of a hydrogen bonded, outer sphere complex (*vida infra*). X-ray crystal structures reveal that *N*-oxides are avid H-bond acceptors and an NMO:alcohol interaction is therefore also conceivable.

The typical protocol for conducting a Ley–Griffith oxidation includes the use of molecular sieves and dried solvents which also implies that hydrogen-bond interactions are important to the reaction. Here we investigate several of these possibilities via a combination of UV/Vis/GC–MS, NMR and theoretical (DFT) methods.

Results and Discussion

During the synthesis of the TPAP catalyst, crystals suitable for X-ray analysis were obtained and its structure was determined. $Pr_4N[RuO_4]$ is isostructural with $nPr_4N[ReO_4]$ and its Tc analogue, which was analyzed by powder X-ray diffraction.[35] In the present structure there was disorder in all four propyl arms of the cation, which contrasts with the well-ordered rhenium structure. The crystal structure analysis confirms that perruthenate is a slightly-distorted tetrahedral complex anion with O–Ru–O bond angles spanning the range 106.5(9)–114.1(9)° and Ru–O bonds in the range 1.67(2)–1.74(2) Å.

In order to explore the Ley–Griffith reaction in further depth the oxidation of a primary alcohol (1-octanol) by the TPAP catalyst ($nPr_4N[RuO_4]$) was initially followed using UV/Vis methods similar to Lee et al.;[31–33] however, NMO was added as a co-oxidant. A combination of two techniques (UV/Vis and GC–MS) were used to follow both the inorganic (UV/Vis) and organic (alcohol/aldehyde) components of the oxidation. Standard Ley–Griffith stoichiometry was employed (TPAP 0.05 equiv., NMO 1.5 equiv., 1-octanol 1 equiv.). The UV/Vis spectrum recorded at the beginning of the reaction matched the typical spectrum of the perruthenate anion previously reported[34,36] for commercial and our freshly synthesized crystalline TPAP (Figure 1a, time = 0 s). The reaction proceeded to completion over approximately 30 minutes (following the oxidation by GC–MS) during which time the UV/Vis spectrum of perruthenate became obscured by the featureless profile of suspended RuO_2. In the first experiment (Figure 1a) the NMO hydrate, which is the typical reagent for the Ley–Griffith oxidation, was dried be-

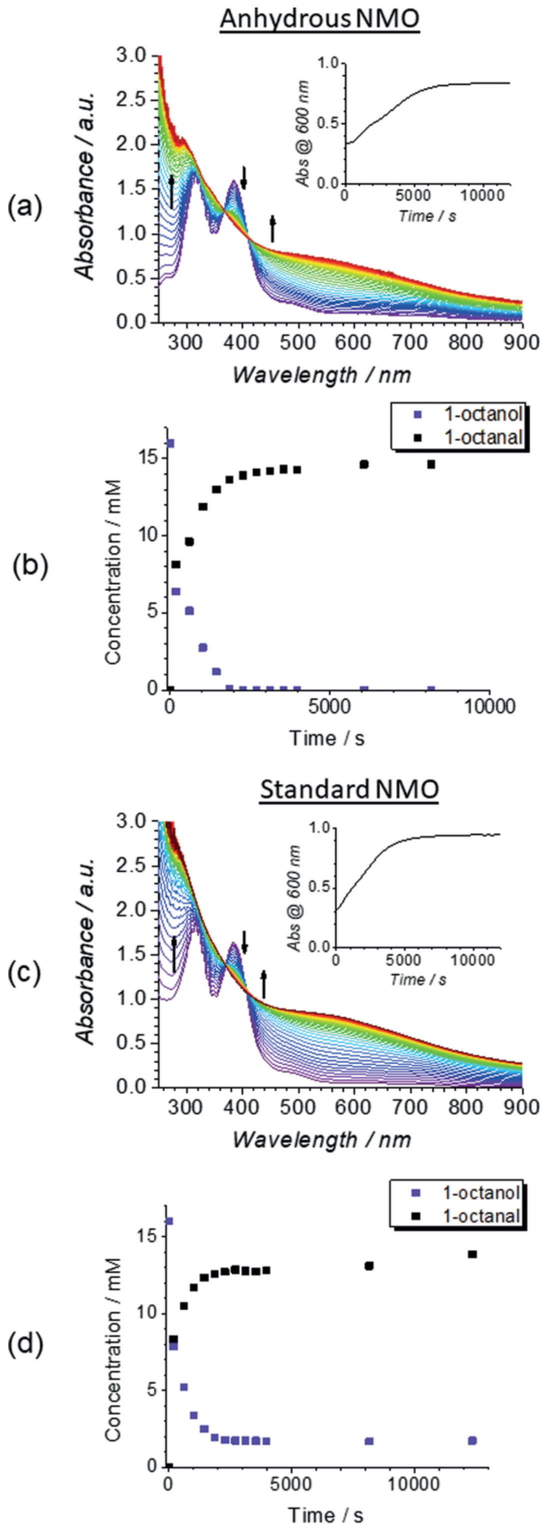
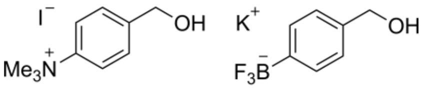


Figure 1. (a) Time-resolved UV/Vis and (b) GC–MS of 0.8 mM TPAP, 16.0 mM 1-octanol using anhydrous NMO. (c) Time-resolved UV/Vis and (d) GC–MS of 0.8 mM TPAP, 16.0 mM 1-octanol using NMO•H_2O.

fore use by dissolving it in acetonitrile over molecular sieves for 24 h. When the experiment was repeated using undried NMO-hydrate (Figure 2c/d) the oxidation reaction only proceeded to 80 % completion, at a slightly slower rate, and stalled; a similar shift in the UV/Vis to Figure 1a was observed.



7 **8**

Figure 2. 4-(hydroxymethyl)-*N*,*N*,*N*-trimethylbenzenaminium iodide (**7**) and potassium 4-(hydroxymethyl)phenyltrifluoroborate (**8**).

In the absence of NMO the reaction conditions and results were consistent with the work of Lee et al.[31–33] Of note was that these reactions were found to be sensitive to oxygen concentration, which is not the case when NMO is present. Following the reaction by ESI mass spectrometry and GC–MS simultaneously resulted in an identical GC–MS profile while the perruthenate anion and small amounts of the over-oxidation product, octanoate anion, were observed by ESI mass spectrometry. Following the reaction by ESI mass spectrometry showed no intermediate anions or cations involving a ruthenium isotope pattern in either positive or negative mode. Attempts to detect neutral charged intermediates was explored by following the oxidation of charged benzyl alcohols 4-(hydroxymethyl)-*N*,*N*,*N*-trimethylbenzenaminium iodide (**7**) and potassium 4-(hydroxymethyl)phenyltrifluoroborate (**8**).[37] No intermediates with a ruthenium isotope pattern were observed.

It was clear that the stalling phenomenon of the octanol oxidation with wet NMO was due to the presence of water, however, how water was retarding the reaction was unclear. The use of 4 Å molecular sieves is essential to remove the water introduced from wet NMO•H_2O, and water generated during the reaction. For this reason, we suspected that water was sequestering the essential co-oxidant, NMO, and not necessarily degrading the perruthenate catalyst directly. *N*-Oxides are ubiquitous hydrogen-bond acceptors. In fact, NMO is used industrially in the Lyocell process to disrupt hydrogen-bonded networks between cellulose sheets through the strongly electron-donating *N*-oxide O-atom.[38–40] Crystal structures reveal that the O⁻-atom of NMO H-bonds to waters of hydration in the solid state (NMO•H_2O[41] and NMO•2.5H_2O[42]) as well as the hydroxyl protons of alcohols such as 1,2-cyclohexandiol in co-crystals.[43] The role of water as a hydrogen-bond donor was explored by ^1H NMR spectroscopy. The ^1H NMR spectra of NMO and 1-octanol in d_3-acetonitrile are presented in Figure 3. The hydroxyl peak of 1-octanol appeared as a triplet at δ = 2.44 ppm and the oxymethylene protons were clearly identified as a triplet of doublets at δ = 3.47 ppm. When a stoichiometric equivalent of NMO was added to 1-octanol, the hydroxyl proton shifted downfield to 4.78 ppm, where it appeared as a broad singlet. The oxymethylene peak shifted subtly and coupling was lost to the hydroxyl proton. The methyl singlet of NMO moved 0.05 ppm, while all other signals from both NMO and 1-octanol shifted only slightly (< 0.03 ppm). Together these observations indicated that the hydroxyl proton of 1-octanol was hydrogen-bonded to NMO in the manner shown (Figure 3).

Hydrogen bonding was further confirmed by diffusion-ordered NMR spectroscopy (DOSY) on the 1:1 NMO/1-octanol complex. In this experiment diffusion coefficients were generated according to the number of different molecules or spin systems present in the sample. Diffusion coefficients were determined to be $3.25(5) \times 10^{-5}$ $cm^2 s^{-1}$. When D_2O was added to the mixture and the measurement repeated, two separate systems were formed: one from the NMO signals with diffusion coefficients of $7.27(6) \times 10^{-5}$ $cm^2 s^{-1}$ and another from the 1-octanol signals with diffusion coefficients of $7.86(5) \times 10^{-5}$ $cm^2 s^{-1}$. Doubling of the diffusion coefficients of both 1-octanol and NMO upon addition of water strongly suggested that a hetero-dimeric structure was dissociating due to water being a competing H-bond partner; water being a product of the Ley–Griffith reaction (Scheme 2). Spectroscopic evidence for the bond between NMO and water supported the

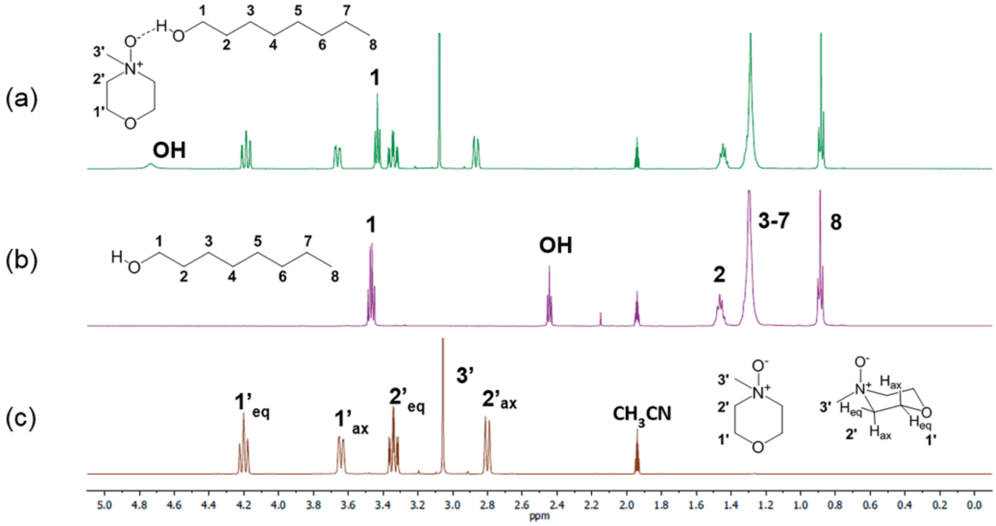
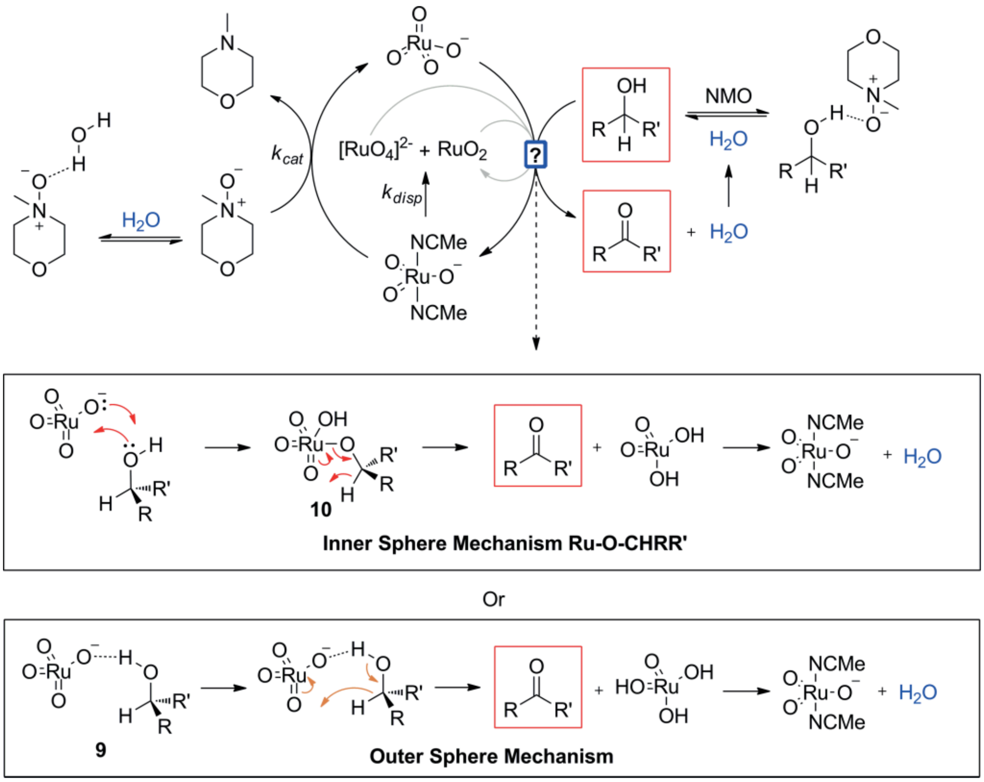


Figure 3. ^1H NMR spectra (500 MHz) of 1:1 NMO/1-octanol (a, green), 1-octanol (b, purple) and NMO (c, brown) in d_3-acetonitrile. Note: ax = axial, eq = equatorial.



Scheme 2. Mechanism of Ley–Griffith oxidation in acetonitrile.

assertion that water can prevent NMO from acting as a co-oxidant, resulting in the competitive disproportionation (and degradation) of Ru^{V}.

Therefore, in addition to the co-oxidant role, NMO also modulates the concentration of "free" alcohol, and hydrogen bonding to water. Under standard Ley–Griffith conditions an excess of NMO vs. alcohol is used, and the reaction conditions require an anhydrous environment, hence the hydrogen-bonded NMO-alcohol species will be favored initially. However, as the oxidation reaction proceeds, the concentration of NMO decreases and water is liberated. Together these lead to a higher concentration of non-H-bonded alcohol, which reacts with perruthenate. However, NMO concentration will decrease and the production of water creates NMO hydrate, thus further decreasing the efficiency of reoxidation of Ru^{V} by NMO.

The nature of the intermediate (or transition state) structure involving perruthenate and alcohol (in non-aqueous solvent) remains unknown, despite our extensive efforts. It is generally assumed that alcohols are oxidized by perruthenate through the formation of an alkoxide or organometallic transition state complex. The classic example highlighting this type of mechanism is the chromic acid oxidation of isopropyl alcohol for which the proposed isopropyl chromate intermediate was isolated.[44,45] However, no such complex has been observed with perruthenate (Scheme 2a).

The only experimental evidence suggesting a transition state of this type was reported by Lee et al., which involved comparing the oxidation rates of an alcohol to an ether by *n*Pr$_4$N[RuO$_4$].[32] Lee et al.[31–33] found that tetrahydrofuran (THF) was oxidized much more slowly than isopropyl alcohol. Westheimer et al.[44,45] found a straightforward explanation of this difference when investigating chromic acid oxidations. That is, the alcohol is oxidized by formation of an alkoxide intermediate, whereas this not possible for an ether. Accordingly, Lee et al. adopted this explanation. However, an alternative explanation was also offered by Westheimer et al. in their seminal paper. This alternate mechanism involved outer-sphere transfer of the α-hydrogen of the alcohol, as hydride, to one of the oxido ligands of the catalyst and subsequent loss of the hydroxyl proton (e.g. Scheme 2b). Further considerations showed this to be unlikely in the case of chromic acid. However, no such comparison has been made for *n*Pr$_4$N[RuO$_4$], which is deployed under very different conditions (no acid, non-aqueous solvent).

While the spectroscopic and spectrometric data presented above have supported perruthenate as the active oxidant, there are still questions as to the exact mechanism of the process. To address this, we implemented DFT methods to help elucidate the path of the reaction. To the best of our knowledge, the only computational investigation specifically of TPAP-mediated oxidations was reported by Rzepa (notably published online).[46] Using the ωB97XD/Def2-SVPP (SCRF = DCM) level of theory, anomalously high reaction barriers were calculated for the oxidation of methanol by ruthenium tetroxide ($[Ru^{VIII}O_4]$) which is capable of C–H oxidation ($\Delta G^{\ddagger}$ = 37.1 kcal/mol) though this was lowered when considering the triplet state of the metal ($\Delta G^{\ddagger}$ = 28.2 kcal/mol). The free energy barrier of reaction ($\Delta G^{\ddagger}$) for $[Ru^{VII}O_4]^-$ was calculated as 30.8 kcal/mol, which is also inconsistent with the reported outcome of the reaction. Importantly, only the inner sphere (or "ester") mechanism was considered. In preliminary computational studies we elected to use methods similar to those implemented by Rzepa [ωB97XD/6-31G(d),[47] LANL2DZ basis set on Ru, implicit acetonitrile solvation using the SMD method][48] with methanol as the alcohol component (R = R′ = H). The tetrabutylammonium cation was not explicitly modelled. The separated reactants were found to be lowest energy minima, with the hydrogen-bonded complex **9** and perruthenate ester **10** both higher in energy (ΔG = 2.3 and 12.8 kcal/mol respectively). This is congruent with the hydrogen-bonding ability of perruthenates and the lack of spectroscopic evidence for an ester intermediate. Furthermore, we were able to locate two transition states consistent with an inner sphere (TS-1) and outer sphere mechanism (TS-2, see supporting information), though at this level of theory the inner sphere mechanism was greatly preferred ($\Delta G^{\ddagger}$, TS-1 = 26.6 kcal/mol, TS-2 = 33.0 kcal/mol). However, as with Rzepa's results, the free energy barrier to reaction was larger than expected for a process that proceeds at or below room temperature. Due to the confounding factors (the larger errors associated with DFT modelling of transition metals compared to non-metals,[49] which would be compounded with the inclusion of the radical anion) there was limited confidence that the relative differences between the inner and outer sphere mechanisms could be determined. Computational studies in order to address these difficulties are ongoing.

Overall, however, it seems more likely that $n\mathrm{Pr_4N[RuO_4]}$ reacts with methanol via an outer sphere mechanism, because it is very difficult to perturb the coordination sphere of perruthenate; even highly concentrated, sterically unhindered ligands such as acetonitrile or water do not coordinate. This outer sphere mechanism is favored, with the anion and alcohol forming a hydrogen bonded adduct prior to the rate-determining step. Hydride transfer coupled to proton abstraction would then give the diprotonated reduced complex $[\mathrm{Ru^{V}O_2(OH)_2}]^{-}$ along with the carbonyl compound product (Scheme 2b). Rapid water elimination from $[\mathrm{Ru^{V}O_2(OH)_2}]^{-}$ and coordination by acetonitrile would form the unstable $[\mathrm{Ru^{V}(O)_3(NCMe)_2}]$ species (electrochemical reduction, Scheme 1), which we reported to be re-oxidized by NMO or disproportionate to give $[\mathrm{Ru^{VI}O_4(NCMe)}]^{2-}$ and $\mathrm{RuO_2}$.[34] The fact that $[\mathrm{Ru^{VII}O_4}]^{-}$ has been shown to oxidize sterically hindered alcohols such as diphenylmethanol, makes it even less likely the alcohol acts as a ligand. The outer-sphere mechanism is also consistent with our previously reported EPR results, which show that perruthenate forms an adduct with nearby species that are capable of hydrogen bonding (such as $\mathrm{NMO{\cdot}H_2O}$).

Conclusions

A comprehensive study following the oxidation of 1-octanol by TPAP and NMO (Ley–Griffith oxidation) is reported using a range of spectroscopic and in silico techniques. The role of NMO is not to form the active oxidant, but instead to rapidly rescue the $\mathrm{Ru^{V}}$ species to reform the perruthenate catalyst. NMO has also been shown, by NMR spectroscopy, to hydrogen bond to the hydroxyl proton of the alcohol. This interaction is disrupted by water, a product of the oxidation, forming an NMO hydrate which we propose hinders the ability of NMO to act as a co-oxidant. These observations explain the required use of molecular sieves. Molecular sieves remove water introduced into the reaction via hygroscopic NMO, and also remove water generated as a by-product of alcohol oxidation.

When freshly recrystallized TPAP was utilized, the oxidation proceeded slowly at the beginning of the reaction until a sufficient concentration of solid ruthenium dioxide was formed by disproportionation of the $\mathrm{Ru^{V}}$ product. In turn, $\mathrm{Ru^{V}}$ slowly escapes the rescue process as the amount of NMO co-oxidant decreases, or increasing water binds to NMO reducing its ability to reoxidize $\mathrm{Ru^{V}}$ during the reaction.

From a synthetic, laboratory-scale perspective, two important conclusions were made: 1) drying the reaction mixture prior to commencing the oxidation reduces the amount of catalyst degradation to $\mathrm{Ru^{IV}O_2}$ (via disproportionation); 2) if oxidations are not proceeding to completion, simple addition of further catalyst, or $\mathrm{NMO{\cdot}H_2O}$, is unlikely to progress the reaction further. Addition of further co-oxidant and molecular sieves to remove water from solution prior to the addition of further catalyst is a strong recommendation.

Experimental Section

Reagents: All reagents and solvents were purified prior to use according to literature methods.[50] Ruthenium(III) trichloride hydrate was obtained from Precious Metals Online. Tetra-*n*-propylammonium perruthenate (TPAP) was synthesised as previously reported.[18,34] Commercial 1-octanol and octanal were distilled under vacuum prior to use. *N*-Methylmorpholine *N*-oxide monohydrate ($\mathrm{NMO{\cdot}H_2O}$) was obtained by concentrating under reduced pressure a 50 wt/wt.-% aqueous solution of NMO (obtained from Sigma Aldrich). Anhydrous NMO solutions in acetonitrile or d_3-acetonitrile $\mathrm{CD_3CN}$ were obtained by drying a monohydrate solution over 4 Å molecular sieves for 24 hours.

Physical Methods: Time-resolved UV/Vis spectra were acquired with an Agilent 8453 diode array spectrophotometer equipped with a multi-cell holder. The cell holder was maintained at 303 K throughout with a Huber Ministat thermostatted water bath. IR spectra were measured on a Perkin–Elmer FT-IR spectrometer (Spectrum 2000). Melting points were recorded and uncorrected measurements repeated three times using a Digimelt MPA161 SRS apparatus. GC–MS was recorded using a Shimadzu GC–MS-QP5000 machine using a Restek Rtx® -5MS column and analysed using GC–MSsolutions v1.20. Microanalyses were performed by the University of Queensland Microanalytical Service.

UV/Vis/GC–MS of the Ley–Griffith Oxidation of 1-Octanol: To a solution of commercial obtained TPAP in acetonitrile (0.8 mM, 2.5 mL) was added NMO from a stock solution (0.24 mM final concentration, $\mathrm{NMO{\cdot}H_2O}$ or dried with 4 Å molecular sieves for 24 h) followed by addition of 1-octanol (0.16 mM). The solution was then separated into two volumes, one for UV/Vis spectroscopy and one for GC–MS. The sample used for GC–MS (2.0 mL) spectra, were recorded every 7 min (beginning at 3 min), and concentrations of 1-octanol and octanal determined for each spectra by use of standard curves of 1-octanol and octanal.

Computational Methods: All calculations were conducted with the Gaussian09 software (revision A.02).[51] Head-Gordons' long range corrected functional, ωB97XD/6-31G(d),[47] with the LANL2DZ basis set on Ru was used throughout this study. Implicit solvation (in acetonitrile) was modelled using Truhlar's SMD method.[48] All stationary points were confirmed by frequency analysis.

CCDC 1846870 (for TPAP **3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Keywords: TPAP · Ley-Griffith · Oxidation · Perruthenate · Mechanism

[1] G. Tojo, M. Fernandez, *Oxidation of Alcohols to aldehydes and Ketones: A Guide to Current Common Practice* (Basic Reactions in Organic Synthesis); Springer, **2006**.
[2] M. B. Smith, J. March, *March's Advanced Organic Chemistry; Reactions, Mechanism, and Structure*, Sixth Edit.; John Wiley & Sons, Ltd, **2006**.
[3] R. Larock, *Comprehensive Organic A Transformations, Guide to Functional Group Preparations*, Two Volume Set, 2nd Edit.; Wiley, **2010**.
[4] L. Kurti, B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier, **2005**.
[5] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647.
[6] J. C. Collins, W. W. Hess, F. J. Frank, *Tetrahedron Lett.* **1968**, *9*, 3363.
[7] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651.
[8] a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; b) M. J. Gallen, R. Goumont, T. Clark, F. Terrier, C. M. Williams, *Angew. Chem. Int. Ed.* **2006**, *45*, 2929; *Angew. Chem.* **2006**, *118*, 2995.
[9] T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656; *Angew. Chem.* **2005**, *117*, 3722.
[10] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
[11] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.
[12] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, *21*, 1625.
[13] W. P. Griffith, S. V. Ley, *Aldrichim. Acta* **1990**, *23*, 13.
[14] W. P. Griffith, *Chem. Soc. Rev.* **1992**, *21*, 179.
[15] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, *1994*, 639.
[16] P. Langer, *J. Prakt. Chem.* **2000**, *342*, 728.
[17] M. Pagliaro, S. Campestrini, R. Ciriminna, *Chem. Soc. Rev.* **2005**, *34*, 837.
[18] P. W. Moore, C. D. G. Read, P. V. Bernhardt, C. M. Williams, *Chem. Eur. J.* **2018**, *24*, 4556.
[19] B. Hinzen, *Synthesis* **1998**, *1998*, 977.
[20] R. Lenz, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3291.
[21] I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566.
[22] M. Hasan, M. Musawir, P. N. Davey, I. V. Kozhevnikov, *J. Mol. Catal. A* **2002**, *180*, 77.
[23] I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C. J. Urch, S. M. Brown, *J. Am. Chem. Soc.* **1997**, *119*, 12661.
[24] C. D. G. Read, P. W. Moore, C. M. Williams, *Green Chem.* **2015**, *17*, 4537.
[25] D. S. Brown, W. J. Kerr, D. M. Lindsay, K. G. Pike, P. D. Ratcliffe, *Synlett* **2001**, *2001*, 1257.
[26] P. W. Moore, P. M. Mirzayans, C. M. Williams, *Chem. Eur. J.* **2015**, *21*, 3567.
[27] P. W. Moore, Y. Jiao, P. M. Mirzayans, L. N. Q. Sheng, J. P. Hooker, C. M. Williams, *Eur. J. Org. Chem.* **2016**, *2016*, 3401.
[28] R. Ciriminna, L. M. Ilharco, A. Fidalgo, S. Campestrini, M. Pagliaro, *Soft Matter* **2005**, *1*, 231.
[29] R. Ciriminna, S. Campestrini, M. Pagliaro, *Org. Biomol. Chem.* **2006**, *4*, 2637.
[30] S. Campestrini, M. Carraro, L. Franco, R. Ciriminna, M. Pagliaro, *Tetrahedron Lett.* **2008**, *49*, 419.
[31] D. G. Lee, Z. Wang, W. D. Chandler, *J. Org. Chem.* **1992**, *57*, 3276.
[32] W. D. Chandler, Z. Wang, D. G. Lee, *Can. J. Chem.* **2005**, *83*, 1212.
[33] D. G. Lee, L. N. Congson, *Can. J. Chem.* **1990**, *68*, 1774.
[34] T. J. Zerk, P. W. Moore, C. M. Williams, P. V. Bernhardt, *Chem. Commun.* **2016**, *52*, 10301.
[35] K. E. German, M. S. Grigoriev, C. Den Auwer, A. Y. Maruk, Y. A. Obruchnikova, *Russ. J. Inorg. Chem.* **2013**, *58*, 691.
[36] R. E. Connick, C. R. Hurley, *J. Am. Chem. Soc.* **1952**, *74*, 5012.
[37] P. W. Moore, J. P. Hooker, A. Zavras, G. N. Khairallah, E. H. Krenske, P. V. Bernhardt, G. Quach, E. G. Moore, R. A. J. O' Hair, C. M. Williams, *Aust. J. Chem.* **2017**, *70*, 397.
[38] T. Rosenau, A. Potthast, H. Sixta, P. Kosma, *Prog. Polym. Sci.* **2001**, *26*, 1763.
[39] H. Chanzy, S. Nawrot, A. Peguy, P. Smith, J. Chevalier, *J. Polym. Sci. Polym. Phys. Ed.* **1982**, *20*, 1909.
[40] H. Chanzy, A. Peguy, S. Chaunis, P. Monzie, *J. Polym. Sci. Polym. Phys. Ed.* **1980**, *18*, 1137.
[41] E. Maia, A. Peguy, S. Pérez, *Acta Crystallogr., Sect. B Struct. Sci.* **1981**, *37*, 1858.
[42] E. Maia, S. Pérez, *Acta Crystallogr., Sect. B Struct. Sci.* **1982**, *38*, 849.
[43] H. Chanzy, E. Maia, S. Pérez, *Acta Crystallogr., Sect. B Struct. Sci.* **1982**, *38*, 852.
[44] F. Holloway, M. Cohen, F. H. Westheimer, *J. Am. Chem. Soc.* **1951**, *73*, 65.
[45] A. Leo, F. H. Westheimer, *J. Am. Chem. Soc.* **1952**, *74*, 4383.
[46] H. Rzepa, How to tame an oxidant: the mysteries of "tpap" (tetra-*n*-propylammonium perruthenate).
[47] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.
[48] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.
[49] M. L. Laury, A. K. Wilson, *J. Chem. Theory Comput.* **2013**, *9*, 3939.
[50] W. L. Armarego, D. Perrin, *Molecules* **1997**, *2*, 152.
[51] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision A*.**02**, Gaussian, Inc., Wallingford CT, **2009**.

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Ley–Griffith Oxidation Mechanism

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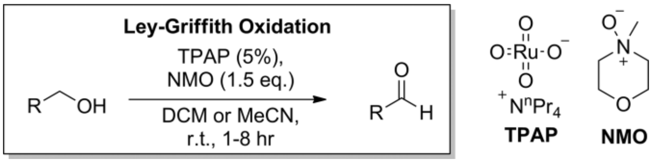
Hydrogen-Bonding Interactions in the Ley–Griffith Oxidation: Practical Considerations for the Synthetic Chemist



Further exploration of the Ley–Griffith (TPAP) oxidation has unveiled a better understanding of the role *N*-methylmorpholine *N*-oxide (NMO) plays, not just as a co-oxidant, but also a hydrogen bonding partner to the alcohol substrate and water. These additional attributes impact reaction performance, with important implications for the practicing synthetic chemist.

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