Aerobic Oxidation of Primary Aliphatic Alcohols to Aldehydes Catalyzed by a Palladium(II) Polyoxometalate Catalyst

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Abstract: A hexadecyltrimethylammonium salt of a "sandwich" type polyoxometalate has been used as a ligand to attach a palladium(II) center. This Pd-**POM** compound was an active catalyst for the fast aerobic oxidation of alcohols. The unique property of this catalyst is its significant preference for the oxidation of primary versus secondary aliphatic alcohols. Since no kinetic isotope effect was observed for the dehydrogenation step, this may be the result of the intrinsically higher probability for oxidation of primary alcohols attenuated by steric factors as borne out by the higher reactivity of 1-octanol versus 2-ethyl-1-hexanol. The reaction is highly selective to aldehyde with little formation of carboxylic acid; autooxidation is inhibited. No base is required to activate the alcohol. The fast reactions appear to be related to the electron-acceptor nature of the polyoxometalate ligand that may also facilitate alcohol dehydrogenation in the absence of base.

Keywords: alcohols; oxidation; oxygen; palladium; polyoxometalates

The catalytic oxidation of alcohols using ground state molecular oxygen, O₂, as a primary oxidant has been a "hot" topic in recent years, expressly motivated by the apparent ecological advantage that such a transformation would have compared to other methods.^[1] There are three general rules of thumb that may be used when describing the reactivity and selectivity in these oxidation reactions. (i) Benzylic alcohols are the most reactive substrates, allylic alcohols have intermediate reactivity and saturated aliphatic alcohols are the least reactive. (ii) Typically secondary alcohols are more reactive than primary alcohols and (iii) while oxidation of secondary alcohols is typically selective to ketones, the selective oxidation of primary (nonbenzylic) alcohols to aldehydes is more difficult and over-oxidation to carboxylic acids is not uncommon.^[1] Specifically in the context of the present research that was aimed at the selective oxidation of primary aliphatic alcohols to the corresponding aldehydes, there are some notable examples of catalysts that are selective for this transformation which also clearly show specificity for primary versus secondary alcohols. Perhaps the most studied systems are those that combine metal catalyts with nitroxyl radicals, typically TEMPO, as co-catalysts. In these catalytic systems an in situ formed nitrosonium cation oxidizes alcohols to aldehydes and the hydroxylamine formed is re-oxidized by O_2 in the presence of an additional metal catalyst.^[2] Other important examples include: A Cu(II)-iminosemiquinone catalyst that oxidizes primary alcohols to aldehydes with formation of H₂O₂ and where secondary alcohols do not react,^[3] cocatalytic systems comprised of Ru(PPh₃)₃Cl₂/hydroquinone,^[4] water-soluble diruthenium complexes,^[5] nitrosylruthenium-salen catalysts with photo-irradiation,^[6] Os-Cr and Ru-Cr heterobimetallic complexes,^[7] and Au-Pd supported on TiO₂ although here the results are equivocal since 3-octanol was as reactive as 1-octanol, but 2-octanol was not reactive.^[8]

A very significant body of research in the area of aerobic oxidation of alcohols has been based on the use of Pd complexes and also Pd colloids as catalyst in mostly homogeneous but also heterogeneous reaction systems.^[9] The mechanism^[1a] (Scheme 1) of palladium(II)-catalyzed oxidations of alcohols with O₂ is generally thought to involve (a) the ligation of the alcohol by reaction of the conjugate alkoxide with the transition metal, followed by, (b) β -elimination to yield the carbonyl (ketone or aldehyde) product and a two electron reduced Pd(0) and/or Pd(II)–H complex.^[10] The rate-determining step is often the re-oxidation step with O₂,^[11] (c) and involves the intermediate formation of H₂O₂ which is typically decomposed





Scheme 1. Mechanistic scenarios in the literature for the aerobic oxidation of alcohols by Pd(II) complexes.

by disproportionation.^[12] Notably, basic conditions are beneficial for the formation of alkoxides and therefore to initiate the catalytic cycle.^[13] Also, there appear to be no reports on the preference for the oxidation of primary *versus* secondary aliphatic alcohols coupled with selective formation of aldehydes with palladium-based catalysts although there are examples of the oxidation of primary alcohols to aldehydes.

The Pd(II)-polyoxometalate complex (**Pd-POM**) was obtained by reaction of one equivalent of PdCl₂ (DMSO)₂ with two equivalents the hexadecyltrimethylammonium salt of the "sandwich" polyoxometalate^[14] Q₁₂{[WZn₃(H₂O)₂][(ZnW₉O₃₄)₂]} where $Q = C_{16}H_{33}(CH_3)_3N^+$ in a CH₂Cl₂ solution. A 1:2 ratio of PdCl₂(DMSO)₂ to Q₁₂{[WZn₃(H₂O)₂][(ZnW₉O₃₄)₂]} was used because it gave slightly better results in the catalytic oxidation of alcohols (see below), than when the catalyst was prepared from a 1:1 ratio of PdCl₂(DMSO)₂/Q₁₂{[WZn₃(H₂O)₂][(ZnW₉O₃₄)₂]}.

Although in aqueous media it is known that addi-Pd(II) tion of salts to $Na_{12}[WZn_3(H_2O)_2]$ $[(ZnW_9O_{34})_2]$ led to metathetical substitution of the terminal zinc atoms in the polyoxometalate,^[15] such a mixing in an organic solvent did not yield a complex whose structure we could clearly define since the compound obtained could not be purified and analyzed by single crystal X-ray diffraction. Nevertheless, the reaction of $Q_{12}[[WZn_3(H_2O)_2]][(ZnW_9O_{34})_2]]$ with PdCl₂(DMSO)₂ was characterized by formation of a brown solution that was followed by UV-Vis spectroscopy (Figure 1).

Furthermore, ¹H NMR measurements clearly revealed that the reaction of $PdCl_2(DMSO)_2$ with $Q_{12}[[WZn_3(H_2O)_2]][(ZnW_9O_{34})_2]]$ released free DMSO into solution. Elemental analysis (see Experimental Section) was used to determine the atom composition of **Pd-POM** yielding a molecular formula $(PdCl_2)_{0.5}Q_{12}[[WZn_3(H_2O)_2]][(ZnW_9O_{34})_2]]$. One can suggest but not prove that **Pd-POM** can be described as having Pd(II) incorporated at the terminal position



Figure 1. Formation of Pd-POM followed by UV-vis spectroscopy (difference spectra) in a 0.02 mM solution in CH_2Cl_2 .

of the polyoxometalate as observed in aqueous solution. An alternate description could be that Pd(II) is supported on the polyoxometalate where oxygen atoms of the polyoxometalate replace the good leaving DMSO ligands of PdCl₂(DMSO)₂; the polyoxometalate acts as a ligand to Pd(II). Support for such a formulation also comes from the observation that $Q_{12}[[WZn_3(H_2O)_2]][(ZnW_9O_{34})_2]]$ did not react with Pd(1,10-phenanthroline)Cl₂ under similar conditions (1,10-phenanthroline being a stronger coordinating ligand) and no active catalyst was obtained from such a mixture (*vide infra*).

The aerobic oxidation of primary alcohols was first studied using 1-heptanol as a model substrate. Thus, a typical reaction was carried out by mixing 0.1 mmol 1-heptanol and 5 μ mol Pd-POM in 1 mL α,α,α -trifluorotoluene (TFT) under 2 bar O₂ at 110 °C. Typically, after 25-30 min a maximum conversion was obtained with high selectivity to *n*-heptanal. The pressure of 2 bar O_2 is optimal (Supporting Information, Figure S1). A little over-oxidation to *n*-heptanoic acid and some alcohol oxidation-alkane dehydrogenation to yield the β -unsaturated aldehyde were observed, Scheme 2. A similar reaction using a catalyst prepared from 1:1 PdCl₂(DMSO)₂:Q₁₂{[WZn₃(H₂O)₂] $[(ZnW_9O_{34})_2]$ showed a 90% conversion of 1-heptanol with a 91% selectivity to heptanal with formation of 5% heptanoic acid.

Several further observations are notable and important. (i) No base was needed for this reaction; (ii) neither $Q_{12}\{[WZn_3(H_2O)_2][(ZnW_9O_{34})_2]\}$ nor PdCl₂(DMSO)₂ alone were active catalysts for alcohol oxidation; (iii) a reaction under anaerobic conditions [50 µmol 1-heptanol and 5 µmol **Pd-POM** in 1 mL

$$C_6H_{13}CH_2OH \xrightarrow{92\%} C_6H_{13}CHO + C_6H_{13}COOH + C_4H_9CH=CHCHO$$

94% 1-2% 4-5%

Scheme 2. Aerobic oxidation of 1-heptanol catalyzed by Pd-POM.



Figure 2. Reaction profile for the oxidation of 1-heptanol (*left*) and 2-octanol (*right*). *Reaction conditions:* 0.1 mmol substrate, 5 µmol **Pd-POM**, 1 mL TFT, 2 bar O₂, 110 °C.

 α,α,α -trifluorotoluene (TFT) under 1 bar Ar at 110°C] showed the immediate (1 min) formation of 2.5 µmol heptanal (5% conversion) consistent with a two-electron oxidation of 1-heptanol by Pd(II).

The preference for the oxidation of primary versus secondary alcohols catalyzed by **Pd-POM** is observable from the reaction profiles of the respective oxidation reaction as shown in Figure 2. Maximum conversions of 92% for 1-heptanol (30 min) and 44% for 2-octanol (360 min) were obtained. The reaction appeared to stop due to deactivation of the catalyst through formation of palladium black at the given time as is well-documented also for other palladium catalysts.^[1a,11] A compilation of results for the aerobic oxidation of various additional primary and secondary alcohols to the respective aldehydes and ketones is presented in Table 1. For primary linear alcohols, the results show a similar profile as presented in

Table 1. Oxidation of saturated aliphatic alcohols.

Substrate ^[a]	Primary Alcohol Conv. (Selectivity) ^[c]	Secondary Alcohol ^[b] Conv. (Selectivity) ^[d]
C ₄ H ₉ OH	65 (99)	3 (>99)
C ₆ H ₁₃ OH	88 (95)	27(>99)
C ₇ H ₁₅ OH	92 (94)	23 (>99)
C ₈ H ₁₇ OH	89 (91)	31 (>99)
C ₉ H ₁₉ OH	89 (88)	24 (>99)
$C_{10}H_{21}OH$	81 (89)	27 (>99)
$c-C_6H_{11}OH$		34 (>99)
c-C ₈ H ₁₅ OH		58 (>99)

- [a] Reaction conditions: 0.1 mmol substrate, 5 μmol Pd-POM, 1 mL TFT, 2 bar O₂, 110 °C.
- ^[b] For the acyclic secondary alcohols the hydroxy group is at the 2-position.
- [c] Conversion based on GC and given as mol%. The byproducts were β-unsaturated aldehyde and carboxylic acid formed in similar amounts. Selectivity is given as mol% of all products.
- ^[d] Conversion based on GC and given as mol%. The corresponding ketones were the only observed products.

Scheme 2. Corresponding secondary alcohols were oxidized to ketones in essentially 100% selectivity. Shorter chain alcohols tended to give significantly lower conversions for reasons yet unknown.

The regiospecificity of the aliphatic alcohol oxidation reactions was also manifested in the comparative conversion observed using four octanol isomers as substrates. Thus, 1-octanol, 2-ethyl-1-hexanol, 2-octanol, and 3-octanol showed reaction profiles similar to those presented in Figure 2 and conversions of 89, 76, 21 and 15 mol%, respectively, after 30 min (0.1 mmol substrate, 5 µmol Pd-POM, 1 mL TFT, 2 bar O_2 , 110 °C) demonstrating both the preferred reactivity of primary alcohols over secondary ones as well as additional preferred reactivity of less hindered alcohols, 1octanol > 2-ethyl-1-hexanol and 2-octanol > 3-octanol.

Expectedly, benzylic alcohols such as PhCH₂OH, 4-CH₃OC₆H₄CH₂OH, $4-CF_{3}C_{6}H_{4}CH_{2}OH,$ and PhCHOHCH₃ were also reactive (0.1 mmol substrate, 5 µmol Pd-POM, 1 mL TFT, 2 bar O₂, 110 °C, 20 min) all yielding the corresponding benzaldehyde derivatives (acetophenone) with >95% yields with no observed by-products. Interestingly, in the reaction of unsaturated substrates, the maximum conversions obtained for secondary alcohols were higher than those reached for primary alcohols, Table 2. cis-Isomers were isomerized to trans-products. As is noticeable from the formation of saturated aldehydes and ketones as by-products, the isomerization of the double bond competed with the alcohol oxidation reaction. No significant amounts of carboxylic acids were formed.

Since the significant preferential oxidation of aliphatic primary alcohols compared to secondary alcohols is novel for Pd(II)-catalyzed reactions and base

Table 2. Oxidation of unsaturated aliphatic alcohols.

Substrate ^[a]	Conv. (time) ^[b]	Selectivity ^[c]
2-propen-1-ol	95 (15)	55
2-Me-2-propen-1-ol	42 (25)	96
E-2-hexen-1-ol	44 (30)	93 ^[d]
Z-2-hexen-1-ol	21 (30)	91 ^[d]
Z-3-hexen-1-ol	28 (30)	99 ^[d]
1-buten-3-ol	74 (25)	80
cyclohexen-3-ol	74 (30)	86
1-octen-3-ol	93 (30)	88

 [a] Reaction conditions: 0.1 mmol substrate, 5 μmol Pd-POM, 1 mL TFT, 2 bar O₂, 110 °C.

- ^[b] Conversion based on GC and given as mol%. Time is in minutes.
- ^[c] The selectivity is given (mol%) for the major product which was the β -unsaturated aldehyde or ketone, respectively. The only significant by-products were the saturated aldehdyes or ketones, for example, propanal, hexanal, butanone and so forth.
- ^[d] The *E*-2-hexenal was the major product.



Scheme 3. Oxidase/dehydrogenation pathways for the aerobic oxidation of alcohols by Pd-POM.

was not required to initiate the reaction, we were curious as to the possible mechanistic reason for these results. The lack of significant over-oxidation to carboxylic acid and the formation of small amounts of dehydrogenated aldehdyes, Scheme 2, suggested a typical dehydrogenation/oxidase mechanism rather than an autooxidation reaction where aldehydes are more reactive than alcohols.^[16] Possible mechanistic pathways in this context are presented in Scheme 3. On the right is presented the "consensus" mechanistic pathway^[1a] with the two proposed pathways for re-oxidation of an intermediate Pd(II)-H species as mentioned above. On the left we also consider the possibility of the oxidation of the Pd(II)-H to a protonated reduced polyoxometalate species $(H^+_2POM^{2-})$ wherein the electrons from the hydride are transferred to the polyoxometalate, which is known to act as an electron acceptor.^[17] This is in contrast to the "consensus" pathway where oxidation of the hydride leads to formation of Pd(0). The reoxidation of reduced polyoxotungstates with O_2 to yield H_2O_2 has been studied in the past.^[18]

In order to gain some experimental insight related to this mechanistic proposal, a kinetic isotope experiment performed anaerobically under stoichiometric reaction conditions (20 μ mol 1:1 C₄H₉OH/C₄D₉OH, 5 µmol Pd-POM, 1 mL TFT, 1 bar Ar, 110°C) resulted in a $k_{\rm H}/k_{\rm D} = 1$ indicating that the β -elimination step is not rate-determining in the oxygen-independent dehydrogenation part of the catalytic cycle. This result is very much in contrast to other Pd(II)-catalyzed alcohol oxidations where KIEs of 1.3-6.8 have been measured.^[9f-i] This result, together with the higher reactivity of primary alcohols, suggests that reactivity is mostly determined by the number of reactive C-H bonds that favors oxidation of primary alcohols (2:1) which is somewhat attenuated by steric effects (1-octanol is more reactive than 2-ethyl-1-hexanol) because of the bulk of the polyoxometalate ligand.^[19] The polyoxometalate ligand to the Pd(II) active site probably plays a key part in facilitating the dehydrogenation reaction in the absence of base through the electron-withdrawing effect the polyoxometalate has on the coordinated alcohol. $^{\left[17\right] }$

Importantly, in an aerobic reaction a kinetic isotope effect was observed, $k_{\rm H}/k_{\rm D} = 1.2$ (100 µmol 1:1 C₄H₉OH/C₄D₉OH, 5 µmol Pd-POM, 1 mL TFT, 2 bar O₂, 110 °C). This would appear to indicate that the rate-determining step of the reaction involves one of the possible transformations of the Pd(II)-H intermediate species, that is, Pd-H bond scission. Rather strangely in a competitive reaction between 1-heptanol and 2-octanol (100 µmol 1:1 1-heptanol/2-octanol, 5 μ mol **Pd-POM**, 1 mL TFT, 2 bar O₂, 1 h, 110 °C) the reaction still favored the oxidation of the 1-heptanol versus 2-octanol but to a lesser degree than was observed with each substrate separately (see Supporting Information, Figure S2). Since, the mechanistic pathways shown in Scheme 3 indicate a variety of possibilities including formation of inactive $Pd(0)_n$ aggregates, which occurs sooner for primary alcohols than secondary alcohols (Figure 2), the different reactivity of 1heptanol:2-octanol separately or together is likely the result of a complicated interplay of reaction pathways.

In summary, the Pd-POM catalyst has shown several unique and notable properties, especially for the aerobic oxidation of saturated aliphatic alcohols. These include: (i) a significant preference for the oxidation of primary versus secondary aliphatic alcohols. This may be the result of the intrinsically higher probability (more C–H bonds) for oxidation of primary alcohols attenuated by steric factors. (ii) The reaction is highly selective to aldehyde with little formation of carboxylic acid; autooxidation is inhibited. (iii) No base is required to activate the alcohol. (iv) The fast reactions appear to be related to the electron acceptor nature of the polyoxometalate ligand that probably facilitates alcohol dehydrogenation and also may lead to an atypical [for Pd(II)-catalyzed alcohol oxidation] catalyst re-oxidation pathway.

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Experimental Section

Catalyst Preparation

The quaternary ammonium salt of the polyoxometalate, $Q_{12}[WZn_3(H_2O)_2][(ZnW_9O_{34})_2]\}$ where $Q = C_{16}H_{33}(CH_3)_3N^+$, was prepared by dropwise addition of 1 mmol of the parent polyoxometalate, $Na_{12}[WZn_3(H_2O)_2]$ $[(ZnW_9O_{34})_2]]\cdot46H_2O$,^[15] dissolved in 10 mL H₂O to 12 mmol of $C_{16}H_{33}(CH_3)_3N^+Cl^-$ (25% aqueous solution). The precipitate formed was separated by centrifugation, filtered off and dried overnight under vacuum at 80°C. Thermogravimetric analysis showed no water was present. Elemental analysis found (calculated) %: C 33.02 (32.76), H 6.24 (6.03), N 1.98 (2.01).

The Pd(II)-supported polyoxometalate catalyst was prepared by dropwise addition of 0.167 g (0.5 mmol) of $Pd[(CH_3)_2SO]_2Cl_2^{[20]}$ dissolved in 4 mL of CH_2Cl_2 to a solution of 8.36 g (1 mmol) of $Q_{12}\{[WZn_3(H_2O)_2][(ZnW_9O_{34})_2]\}$ in 50 mL CH₂Cl₂ at 35 °C. The rate of addition of Pd[(CH₃)₂SO]₂Cl₂ was controlled by observation and dissolution of a transient precipitate as the solution turned yellow and then brown. After stirring the solution for another 10 min, the solvent was removed and the residue dried under vacuum overnight. The resulting brown solid was used as a catalyst without further purification and from elemental analysis has a molecular formula of $(PdCl_2)_{0.5}Q_{12}\{[WZn_3(H_2O)_2][(ZnW_9O_{34})_2]\}$. Elemental analysis found (calculated) %: Pd 0.62 (0.63), W 40.02 (41.35), Zn 3.68 (3.87), C 32.79 (32.42), H 6.22 (6.06), N 2.11 (1.99).

Instrumental Techniques

Oxidation reaction products were characterized and quantified using reference compounds when available by use of GLC (HP-6890 gas chromatograph) with a flame ionization detector and a 30 m×0.32 mm 5% phenylmethylsilicone (0.25 µm coating) capillary column and helium carrier gas. Products whose initial identities were questionable were unambiguously identified using a gas chromatograph equipped with a mass selective detector (GC-MS HP 5973) and the same column described above. The IR spectra were recorded on a Nicolet 6700 FTIR spectrometer as KBr pellets. UV-visible spectra were recorded on Agilent 89090 A spectrophotometer. ¹H NMR spectra were measured on a Bruker Avance DPX 500 spectrometer using TMS as external standard. Elemental analyses were performed on a FlashEA 1112 Elemental Analyzer for carbon, hydrogen and nitrogen and on a EX-310 LC Jordan Valley XRF Spectrometer, using the corresponding salts as calibrating standards for palladium, zinc and tungsten.

Oxidation Reactions

All the reactions were carried out in 20-mL glass pressure tubes equipped with a pressure valve and a stirring bar. The tubes were loaded with substrate, catalyst and solvent and were gently flushed several times with oxygen. Then the pressure was brought to 2 bar and the reaction vessels were placed in a thermostatted oil bath adjusted to appropriate temperature. Reaction mixtures were analyzed using GC and GC-MS. Kinetic isotope effects were measured in competitive reactions by reacting equimolar concentrations of deuturated and protonated substrates. Peaks were quantified by comparing molecular peak intensities of the starting materials and the oxidized products.

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