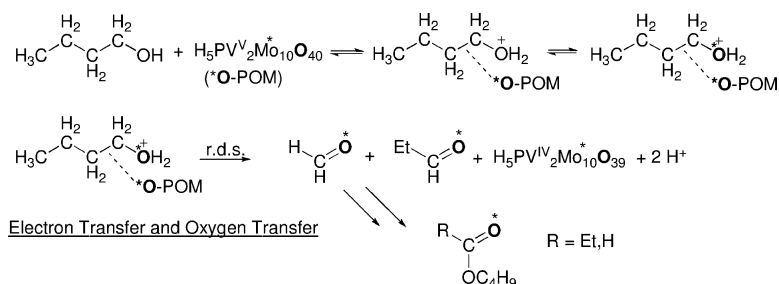Communication

Oxidative C#C Bond Cleavage of Primary Alcohols and Vicinal Diols Catalyzed by HPVMoO by an Electron Transfer and Oxygen Transfer Reaction Mechanism

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Oxidative C−C Bond Cleavage of Primary Alcohols and Vicinal Diols Catalyzed by $H_5PV_2Mo_{10}O_{40}$ by an Electron Transfer and Oxygen Transfer Reaction Mechanism

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The selective oxidation of aliphatic compounds remains a very difficult but very important research goal. In classic homogeneous liquid-phase aerobic oxidation, molecular oxygen reacts via the well-established metal-catalyzed free radical autoxidation pathways via activation of C−H bonds to yield acids, alcohols, ketones, and hydroperoxides.[1] The product selectivity depends on the catalyst, the solvent, and the reaction conditions. In the corresponding autoxidation of primary and secondary alcohols the main products are the corresponding carboxylic acids and ketones.[2] It is known that C−H bonds are more reactive than C−C bonds in free radical oxidation reactions and oxidation reactions in general, although C−C bonds have lower bond disassociation energies. This is due to steric constraints and unfavorable overlap of frontier orbitals when reactive intermediate species interact with C−C bonds in aliphatic molecules.[3] In fact, little is known about catalytic aerobic oxidative C−C bond cleavage, although this is a key step in reactions such as the degradation of the lateral chain of cholesterol by cytochrome P-450.[4] Data on C−C bond cleavage reactions in alcohol oxidation reactions are limited mainly to oxidative cleavage of tertiary alcohols by strong oxidants such as concentrated H_2O_2 in sulfuric acid,[5] Cr(VI)[6] and Ce(IV)[7] reagents, metals with persulfate,[8] or metal−hydrogen peroxide systems.[9] Recently, it was also shown that polyethylene glycols and fluorinated alcohols were oxidatively deformylated by oxygen in the presence of copper salts and base.[10] C−C bond cleavage in arylalkanol radical cations has also been reported.[11]

A survey of the earlier research on liquid phase aerobic catalytic oxidation reactions mediated by phosphovanadomolybdates of the Keggin structure, $[PV_xMo_{12-x}O_{40}]^{(3+x)-}$ particularly for $x = 2$, shows that the $[PV_2Mo_{10}O_{40}]^{5-}$ polyoxometalate, Figure 1, catalyzed oxidative dehydrogenation reactions through an electron transfer oxidation of a substrate by the polyoxometalate that is then reoxidized by oxygen.[12] Typically, free radical autoxidation reactions are inhibited by $[PV_2Mo_{10}O_{40}]^{5-}$. In parallel, aerobic oxygenation reactions catalyzed by $[PV_2Mo_{10}O_{40}]^{5-}$ have also been reported, notably including the oxygenation of inorganic sulfur compounds and thioethers,[13] the oxidative cleavage of vicinal diols to carboxylic acids,[14] and the oxidative cleavage of ketones.[15] Very little is understood about the mechanism of these reactions although Brégeault and co-workers suggested that vicinal diols were cleaved via a ternary complex between the polyoxometalate, dioxygen, and the diol that leads to simultaneous C−C and O−O bond cleavage.[14b] Additionally, several years ago we reported that activated arene and alkylated arene substrates such as anthracene and xanthene were aerobically oxygenated to the corresponding anthraquinone and xanthone via a mechanism that involved electron transfer from the substrate to the polyoxometalate followed by oxygen transfer from the reduced polyoxometalate to the organic substrate.[16] These electron and oxygen transfer (ET−OT) type
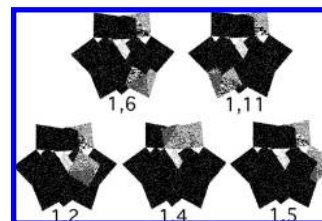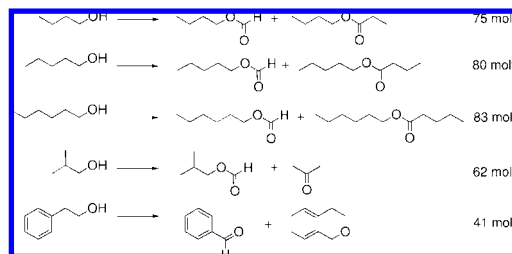

Figure 1. Polyhedral representation of the five isomers of $[PV_2Mo_{10}O_{40}]^{5-}$ (black, MoO_6; gray, VO_6; white, PO_4).

Chart 1. Oxidative Cleavage of Primary Alcohols with $H_5PV_2Mo_{10}O_{40}^a$

^{a} Primary alcohol (1 M), $H_5PV_2Mo_{10}O_{40}\cdot34H_2O$ (60 mM) in sulfolane at 80 °C for 5 h under argon. The products were formed in a 1:1 ratio and were the only products observed by GC. Identification was by GC-MS and with reference standards.

reactions, known in high temperature gas phase oxidations as Mars−van Krevelen reactions,[17] are rare under low temperature homogeneous reaction conditions.[16]

Here we present our study on the oxidative carbon−carbon bond cleavage reaction of primary alcohols by the acidic $H_5PV_2Mo_{10}O_{40}$ and show that they appear to proceed by an ET−OT reaction mechanism. This is an atypical oxidation of alcohols. By corollary, we show that vicinal diols are oxidized by a similar mechanism. Primary alcohols were reacted with $H_5PV_2Mo_{10}O_{40}\cdot34H_2O$ in dioxotetrahydrothiophene (sulfolane)[18] under strictly anaerobic (Schlenk) conditions to yield the products presented in Chart 1 in a 1:1 ratio. The polyoxometalate was reduced. Secondary and tertiary alcohols were dehydrated under these reaction conditions yielding the corresponding alkenes and no C−C bond cleaved products.

One may note from these reactions that in all cases there was a $C_\alpha-C_\beta$ bond cleavage reaction, the products of which may react with the excess primary alcohol to yield the compounds noted in Chart 1 (see below for full explanation). Since the reactions were carried out under anaerobic conditions one may assume the new oxygen atoms in the products originated from $H_5PV_2Mo_{10}O_{40}$. This was indeed verified in two cases. Thus, the reaction of *dehydrated*

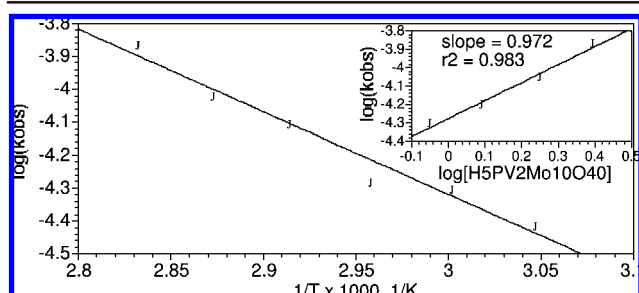**Figure 2.** Arrhenius plot for the oxidation of 1-butanol (500 mM) by $H_5PV_2Mo_{10}O_{40} \cdot 34H_2O$ (2.5 mM) in sulfolane under argon. (Insert) Plot of the observed rate constant as a function of the concentration of $H_5PV_2Mo_{10}O_{40}$ (500 mM 1-butanol, 0.9–2.5 mM $H_5PV_2Mo_{10}O_{40} \cdot 34H_2O$, 80 °C, in sulfolane under argon).

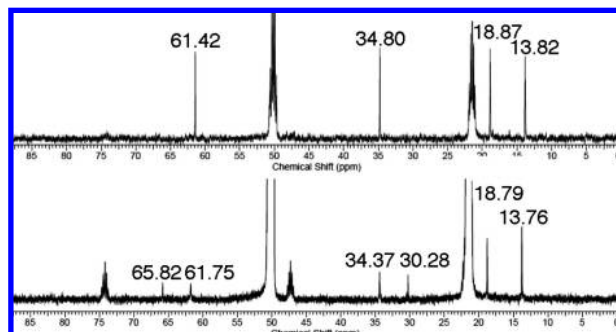**Figure 3.** ^{13}C NMR spectra of 1-butanol in sulfolane-d_8 (top) and after addition of 0.33 equiv of $H_5PV_2Mo_{10}O_{40} \cdot 34H_2O$ and heating for 3 h at 50 °C (bottom).

$H_5PV_2Mo_{10}{}^{18}O_{40}$ (~50% enrichment) with 1-butanol under the conditions described in Chart 1 yielded 1-butylformate (41% ^{18}O) and 1-butylpropionate (50% ^{18}O) as determined by GC–MS. No doubly labeled products were observed. Similarly oxidation of 2-methy-1-propanol with $H_5PV_2Mo_{10}{}^{18}O_{40}$ yielded acetone (49% ^{18}O) and isobutylformate (39% ^{18}O). Kinetic isotope effect experiments in competitive reactions also under the conditions described in Chart 1 between 1-butanol/1-butan-1,1-d_2-ol, 1-butanol/1-butan-2,2-d_2-ol, and 1-butanol/1-butanol-d_{10} all showed k_H/k_D values of 1.0 ± 0.1 as measured by GC/MS indicating that C–H bond cleavage is *not* involved in the rate determining step.

The kinetics of the reaction of $H_5PV_2Mo_{10}O_{40}$ with excess 1-butanol was studied by following the reduction of the polyoxometalate by UV–vis spectroscopy under anaerobic conditions. Thus, 0.5 M 1-butanol, 0.9–2.5 mM $H_5PV_2Mo_{10}O_{40}$ in sulfolane were reacted at 80 °C. A log k_{obs} versus log $[H_5PV_2Mo_{10}O_{40}]$ plot, Figure 2, insert, gave a slope of 0.972 indicating that the reaction is first order in the polyoxometalate. Measurement of rates as a function of temperature, Figure 2, yielded the following values for the activation energy, enthalpy, entropy, and free energy of activation: $\Delta E_a = 11.2$ kcal/mol, $\Delta H^{\ddagger}_{338} = 10.5$ kcal/mol, $\Delta S^{\ddagger}_{338} = -47.2$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger}_{338} = 26.4$ kcal/mol. The high negative value of $\Delta S^{\ddagger}$ suggests that the transition state of the rate determining step reaction is highly organized and solvation of the transition state by polar solvent molecules (sulfolane) may also be involved.[19]

To obtain additional evidence on the interaction of $H_5PV_2Mo_{10}O_{40}$ and 1-butanol, ^{13}C NMR spectra were measured in sulfolane-d_8. In Figure 3 one may observe the spectrum of 1-butanol (Figure 3, top) and the spectrum after heating the alcohol for 3 h at 50 °C (no esters formed; GC) under argon in the presence of 0.33 equiv of $H_5PV_2Mo_{10}O_{40}$ (Figure 3, bottom). The spectrum of 1-butanol with peaks at 61.4, 34.8, 18.8, and 13.8 ppm for the C_{α},
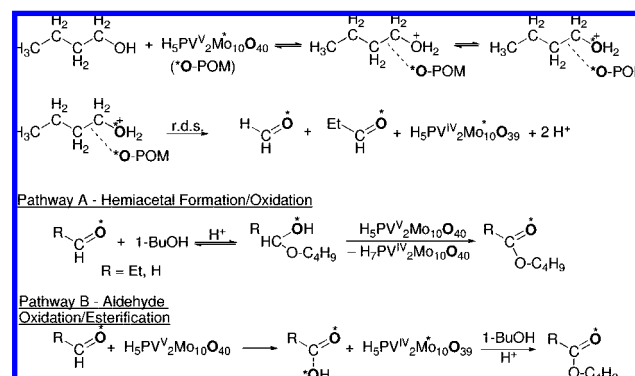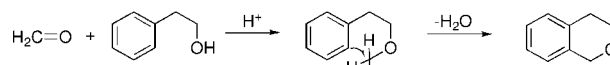
C_{β}, C_{γ}, and C_{δ} carbon atoms shows two new additional peaks at 65.8 and 30.3 ppm attributable to peaks related to the interaction of the polyoxometalate C_{α} and C_{β} atoms.[20] The peaks attributable to the C_{γ} and C_{δ} carbon atoms remain unchanged. One may also observe that the peaks of the sulfolane solvent are also partially shifted downfield presumably due to protonation of sulfolane by the acidic $H_5PV_2Mo_{10}O_{40}$.

The observed experimental information can be used to formulate a possible reaction mechanism for the observed C–C cleavage reaction. Initially, $H_5PV_2Mo_{10}O_{40}$ reacts with 1-butanol to yield a polyoxometalate–substrate prerate determining complex as supported by the ^{13}C NMR spectrum, Scheme 1. In this context, we also observed that 2,2-diphenyl ethanol and 2,2-dimethyl-1-propanol were unreactive (only a trace amount of product formed) likely due to the steric bulk of the polyoxometalate. It should also be noted that dehydration of 1-butanol to give 1-butene apparently does not occur since 1-butene was not sampled in either the gas or liquid phase; 1-alkenes did not undergo C–C bond cleavage.

Since the protonated 1-butanol is long-lived it is likely that ^{18}O exchange occurs with the ^{18}O labeled polyoxometalate since the latter is very susceptible to such exchange with water (from protonated 1-butanol). In the rate determining reaction step electron and oxygen transfer leads to the cleavage of the C–C bond as supported by the absence of kinetic isotope effects in reactions carried out with the various deuterated 1-butanol substrates. In all, this is a two-electron oxidation coupled with oxygen transfer and the release of two protons and can be defined as an ET–OT reaction. The formation of the aldehyde(s) is supported by benzaldehyde formation in the oxidation of 2-phenylethanol and acetone formation in the oxidation of 2-methyl-1-propanol (Chart 1). Formaldehyde formation is also supported by the formation of isochroman in the oxidation of 2-phenylethanol (see below).

The formation of the observed and final product may be through either acid catalyzed formation of a hemiacetal followed by oxidation via hydrogen abstraction or proton coupled electron transfer (pathway A). Alternatively, the aldehyde may be first oxidized to the corresponding carboxylic acid followed by esterification (pathway B). There is no clear-cut evidence for either possibility although the formation of isochroman, Scheme 2, can be best explained by an intramolecular electrophilic aromatic substitution reaction via an intermediate hemiacetal; no formate ester of 2-phenylethanol was observed. Pathway A is preferred.
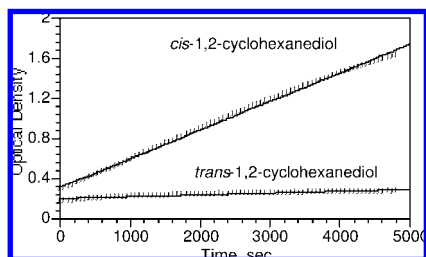
Figure 4. Interaction of *cis*- and *trans*-1,2-cyclohexanediol (50 mM) with $H_5PV_2Mo_{10}O_{40} \cdot 34H_2O$ (2.5 mM) in sulfolane at 50 °C.

Studies on the similar oxidative C—C bond cleavage of vicinal diols were also used to support the results and the mechanistic proposal made for the oxidative cleavage of primary alcohols. Thus, the oxidation of 1,2-ethanediol yielded a ~3:1 mixture of 1,3-dioxolane and 2-hydroxyethylformate. The formation of 1,3-dioxolane by reaction of formaldehyde with excess diol to yield the stable heterocyclic acetal supports the hypothesis made above that the aldehyde is the initial product in the C—C bond cleavage reaction. As stipulated above formation of a hemiacetal or oxidation of the formaldehyde directly can lead to 2-hydroxyethylformate (see Scheme 2, Pathway A or B). A KIE experiment in a competitive oxidation of $HOCH_2CH_2OH$ (1 M) and $HOCD_2CD_2OH$ (1 M), 10 mM $H_5PV_2Mo_{10}O_{40}$ in sulfolane at 80 °C for 6 h also showed no KIE. Furthermore, the activation parameters for the oxidation of 1,2-ethanediol, calculated by measuring the C—C bond cleavage reaction under anaerobic conditions, Figure S1, gave values for the activation energy, enthalpy, entropy, and free energy of activation: $\Delta E_a = 11.9$ kcal/mol, $\Delta H^{\ddagger}_{338} = 11.3$ kcal/mol, $\Delta S^{\ddagger}_{338} = -43.5$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger}_{338} = 26.4$ kcal/mol. These values are very similar to those observed for the C—C bond cleavage of 1-butanol. Coupled with the absence of a KIE, this suggests a similar rate determining step for both the C—C oxidative bond cleavage of primary alcohols and those of vicinal diols.

For diol oxidation, the formation of a pre-rds association complex was sampled by comparing the interaction of *cis*- and *trans*-1,2-cyclohexanediol with $H_5PV_2Mo_{10}O_{40}$ by its reduction by UV—vis under anaerobic conditions, Figure 4. The results show that the *cis* isomer reacted 15 times faster than the *trans* isomer as would be expected if the formation of such a complex would be required for subsequent C—C bond cleavage.

Primary alcohols are oxidized by $H_5PV_2Mo_{10}O_{40}$ in an *atypical* manner. The alcohol moiety is not directly modified. Instead, there is an oxidative cleavage between the C_α and C_β atoms via a proposed ET—OT mechanism as supported by ^{13}C NMR evidence and kinetic and labeling experiments. The initial carbonyl products formed further react with the alcohol substrate to yield esters via further oxidative transformations. Oxidative C—C bond cleavage of vicinal diols also appears to occur by an ET—OT mechanism.

Supporting Information Available: Full experimental details and the results of kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA8063233