

Oxygen Transfer from Sulfoxides: Selective Oxidation of Alcohols Catalyzed by Polyoxomolybdates

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Benzylic, allylic, and aliphatic alcohols are oxidized to aldehydes and ketones in a reaction catalyzed by Keggin-type polyoxomolybdates, $PV_xMo_{(12-x)}O_{40}^{-(3+x)}$ ($x = 0, 2$), with DMSO as a solvent. The oxidation of benzylic alcohols is quantitative within hours and selective, whereas that of allylic alcohols is less selective. Oxidation of aliphatic alcohols is slower but selective. Further mechanistic studies revealed that, for $H_3PMo_{12}O_{40}$ as a catalyst and benzylic alcohols as substrates, the sulfoxide is in fact an oxygen donor in the reaction. Postulated reaction steps as determined from isotope-labeling experiments, kinetic isotope effects, and Hammett plots include (a) sulfoxide activation by complexation to the polyoxometalate and (b) oxygen transfer from the activated sulfoxide and elimination of water from the alcohol. The mechanism is supported by the reaction kinetics.

Introduction

The selective oxidation of alcohol substrates to aldehydes and ketones is an important goal in the development of modern and environmentally friendly methods for chemical synthesis.¹ In this context, the use of oxidants such as molecular oxygen from air and hydrogen peroxide, which are intrinsically non-waste-producing, is of special importance. Homogeneous aerobic oxidations usually proceed by a β -hydride elimination process of an alkoxy-metal intermediate or by a so-called oxometal pathway. The former pathway is often observed in reactions catalyzed by late transition metal compounds and complexes based on Ru(II),² Pd(II),³ and Cu(I/II),⁴ whereas the latter mechanism is more typical of high-valent RuO_4^- and OsO_4 .⁵ Recently, alcohol oxidation in aqueous media was shown to be possible using a water soluble palladium(II) bathophenanthroline catalyst.⁶ Aerobic alcohol oxidation is also possible by other mechanistic

schemes. First, via a free radical-type autoxidation notably using Co(III) in combination with *N*-hydroxyphthalimide,⁷ but also with soluble chromium species.⁸ Second, using stable nitroxyl radicals as catalyst precursors allows reactions to be carried out using a variety of cocatalysts.⁹

We have had an ongoing interest in the catalytic activity of polyoxometalates in oxidation reactions,¹⁰ with oxygen donors such as molecular oxygen, hydrogen peroxide, ozone, nitrous oxide, iodosobenzene, periodate, and others. In this context, it has also been found that polyoxometalates, most advantageously the phosphovanadomolybdate, $PV_2Mo_{10}O_{40}^{5-}$, Figure 1, effectively catalyze the oxidative dehydrogenation of alcohols, especially benzylic alcohols, using either active carbon supports or quinones as cocatalysts.¹¹

We have now undertaken a reinvestigation of our earlier research in this area in an effort to expand the

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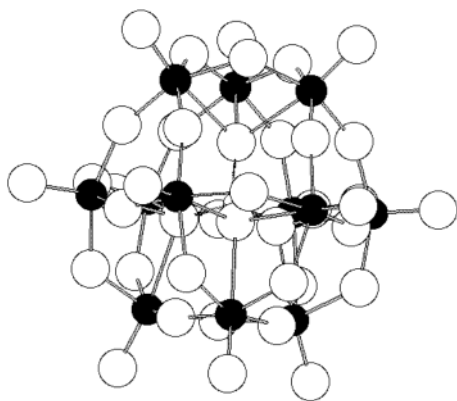


FIGURE 1. $H_{(3+x)}PV_xMo_{(12-x)}O_{40}$ polyoxometalate. Black ball = Mo, V; white ball = O; P in center (not visible).

scope of the alcohol oxidative dehydrogenation and to better understand the mechanism of such polyoxometalate-catalyzed reactions. During our search for a suitable solvent for such a mechanistic investigation, we discovered that dimethyl sulfoxide (DMSO) was by far a superior solvent for polyoxomolybdate-catalyzed oxidation of alcohols. Such success with DMSO has been reported in the past for $Pd(OAc)_2$ -catalyzed reactions,¹² and it has just recently been shown that in that case the solvent acts as a ligand to prevent $Pd(0)$ aggregation.¹³ Since DMSO activated by a variety of electrophilic reagents is a well-known stoichiometric oxidant of significant synthetic importance,¹⁴ it becomes clear that the present mechanistic investigation must also consider the possibility that the sulfoxide is a catalytically activated oxygen donor in such systems.¹⁵

Results and Discussion

The initial oxidation reaction that was surveyed was the aerobic oxidation of benzylic alcohols catalyzed by the $H_5PV_2Mo_{10}O_{40}$ polyoxometalate in DMSO as a solvent, Table 1. From Table 1 one may observe that reactions with a 0.1 mol % catalyst load are quantitative and highly selective within 4 h, except for that with 4-pyridinemethanol, which required 10 h, at 135 °C. The following additional points connected to the results described in Table 1 are worth noting: (a) even though the medium is acidic, no byproduct formation of dibenzylic ether was observed; (b) DMSO was a unique solvent, compared to other polar and nonpolar solvents such as benzonitrile, nitroethane, *N*-methylpyrrolidone, sulfolane, nitrobenzene, and xylene, which yielded significantly lower conversions and selectivity (mostly formation of dibenzylic ether); (c) oxidation of benzyl alcohol under identical

TABLE 1. Aerobic Oxidation of Benzylic Alcohols Catalyzed by $H_5PV_2Mo_{10}O_{40}$ in DMSO^a

substrate	product	conversion, mol %
benzyl alcohol	benzaldehyde	~100 (85) ^c
4-methylbenzyl alcohol	4-methylbenzaldehyde	~100
4-methoxybenzyl alcohol	4-methoxybenzaldehyde	~100 (84) ^c
4-bromobenzyl alcohol	4-bromobenzaldehyde	~100
4-nitrobenzyl alcohol	4-nitrobenzaldehyde	~100 (86) ^c
2-phenylethanol	acetophenone	98
benzhydrol	benzophenone	100
4-pyridinemethanol ^b	4-pyridinecarboxaldehyde	100 (81) ^c

^a Reaction conditions: 1 M benzylic alcohol, 1 mM $H_5PV_2Mo_{10}O_{40}$ in 1 mL DMSO under 1 atm of O_2 at 135 °C for 4 h. ^b Reaction time = 10 h. ^c Isolated yields.

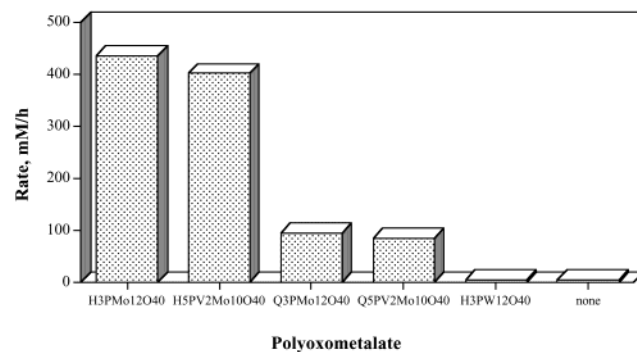


FIGURE 2. Rate of oxidation of benzyl alcohol catalyzed by various polyoxometalates. Reaction conditions: 1 mmol of benzyl alcohol, 1 μ M polyoxometalate in 1 mL of DMSO at 135 °C under 1 atm of O_2 .

but anaerobic conditions stopped within 2.5 h of reaction at ~40% conversion (400 turnovers) with formation of a dark blue reduced form of the polyoxometalate; (d) dimethyl sulfide was formed in the reaction, on average ~0.6 mol of dimethyl sulfide per mol of benzylic aldehyde.

In Figure 2 the initial rate of oxidation of benzyl alcohol catalyzed by various polyoxometalates is presented. Surprisingly, $H_3PMo_{12}O_{40}$, which was inactive in other alcohol oxidation systems¹¹ and other solvents, gave results that were even slightly superior to those observed with $H_5PV_2Mo_{10}O_{40}$. Important here, however, is the observation that ~1 mol of dimethyl sulfide per mol of benzylic aldehyde was formed in catalysis by $H_3PMo_{12}O_{40}$. Neutral $Q_5PV_2Mo_{10}O_{40}$ or $Q_3PMo_{12}O_{40}$ (Q = tetra-*n*-butylammonium) was significantly less effective as a catalyst, while $H_3PW_{12}O_{40}$ was ineffective.

It was also possible using $H_5PV_2Mo_{10}O_{40}$ or $H_3PMo_{12}O_{40}$ under aerobic conditions to oxidize aliphatic and allylic alcohols, Table 2. However, as may be observed, reactivity in the case of aliphatic alcohols is reduced but selectivity is retained, whereas for allylic alcohols, reactivity is high but selectivity is lower.

The results mentioned above, that ~0.6 mol of dimethyl sulfide per mol of benzylic aldehyde was formed in aerobic oxidation with $H_5PV_2Mo_{10}O_{40}$ but ~1 mol of dimethyl sulfide per mol of benzylic aldehyde was formed in aerobic oxidation with $H_3PMo_{12}O_{40}$, indicated that for $H_3PMo_{12}O_{40}$ the sulfoxide was the only oxidant, whereas when $H_5PV_2Mo_{10}O_{40}$ was used both oxygen and the sulfoxide were oxygen donors. Indeed, *anaerobic* oxidation of benzylic alcohols to quantitative yields was

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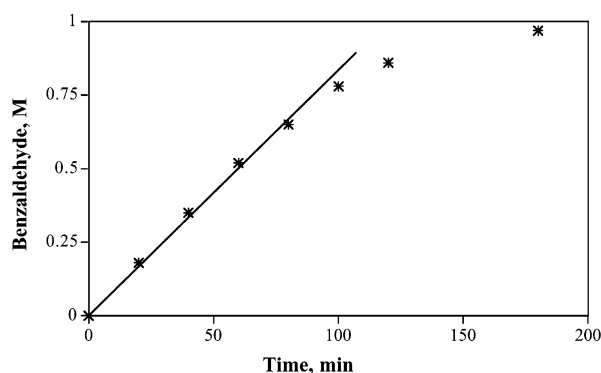
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TABLE 2. Aerobic Oxidation of Aliphatic and Allylic Alcohols Catalyzed by H₃PV₂Mo₁₂O₄₀ in DMSO^a

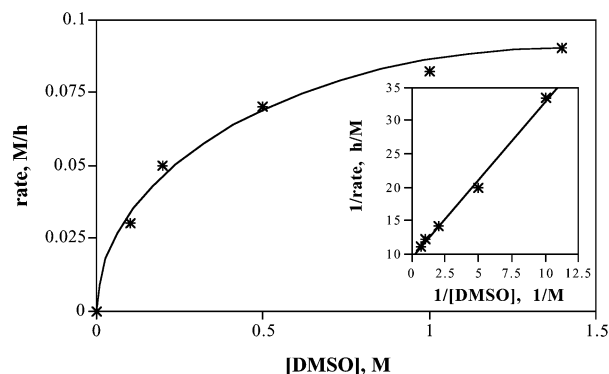
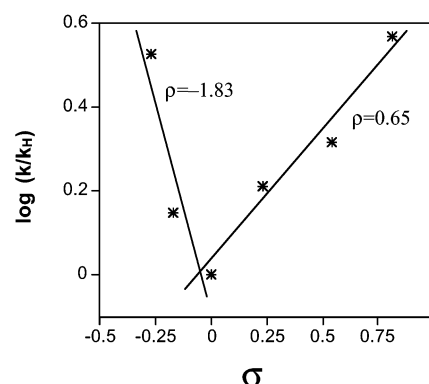
substrate	time, h	product (selectivity, mol %) ^b	conversion, mol % ^c
cinnamyl alcohol	0.75	cinnamaldehyde (100)	~100
(<i>E</i>)-2-hexen-1-ol	2	(<i>E</i>)-2-hexenal (82)	79
(<i>Z</i>)-2-hexen-1-ol	2	(<i>Z</i>)-2-hexenal (78)	83
1-octen-3-ol	3	1-octen-3-one (90)	80 (48) ^d
cyclohexen-2-ol	0.5	cyclohexen-2-one (52)	82
carveol	3	carvone (75)	96
geraniol	10	citral (43)	61
cyclooctanol	24	cyclooctanone (100)	77
cyclohexanol	24	cyclohexanone (100)	30
3-octanol	24	3-octanone	25

^a Reaction conditions: 1 M alcohol, 1 mM H₃PV₂Mo₁₀O₄₀ in 1 mL of DMSO under 1 atm of O₂ at 135 °C. ^b Mol % of aldehyde product of all products. ^c Mol % of substrate reacted. ^d Isolated yield.

**FIGURE 3.** Reaction profile for oxidation of benzyl alcohol in DMSO catalyzed by H₃PMo₁₂O₄₀. Reaction conditions: 1 mmol of benzylic alcohol, 5 μmol of H₃PMo₁₂O₄₀, 1 mL of DMSO at 135 °C under Ar.

possible with H₃PMo₁₂O₄₀ (1 M benzylic alcohol, 1 mM H₃PMo₁₂O₄₀ in 1 mL of DMSO under 1 atm of Ar at 135 °C for 4 h). It was decided to investigate this anaerobic oxidation of benzylic alcohols with the sulfoxide as an oxidant more carefully. Under the conditions used, i.e., 1 mmol of benzylic alcohol, 1 of μmol H₃PMo₁₂O₄₀ in 1 mL (~14 mmol) of DMSO under 1 atm of Ar at 135 °C, the reactions show a linear dependence of conversion as a function of time, up to a conversion of 75–80% and thus are concluded to be of an *apparent or observed* zero order with respect to the benzylic alcohol, Figure 3. Notably, at higher conversions, i.e., at benzylic alcohol concentrations < 0.20 M), there is curvature in the plot, indicating a change in the rate equation at low benzylic alcohol concentrations.

Generally, reactions were carried out in DMSO as a solvent. Under such conditions, i.e., excess DMSO, the reaction kinetics are by definition pseudo zero order with respect to DMSO. To find the true reaction order in DMSO, it was necessary to use an alternative solvent and DMSO as a limiting reagent. Thus, initial rates were found for reactions carried out in nitroethane (a polar nonprotic solvent similar to DMSO) at the following conditions: 1 mmol of benzylic alcohol, 1 μmol of H₃PMo₁₂O₄₀, 0.1–1.5 mmol of DMSO in 1 mL of nitroethane under 1 atm of Ar at 135 °C. As may be observed, Figure 4, the reaction is clearly of a Michaelis–Menton type (note the excellent correlation in the Lineweaver–Burk

**FIGURE 4.** Rate of reaction as a function of DMSO concentration (inset: the corresponding Lineweaver–Burk plot). Reaction conditions: 1 mmol of benzylic alcohol, 1 μmol of H₃PMo₁₂O₄₀, 0.1–1.5 mmol of DMSO in 1 mL of nitroethane under 1 atm of Ar at 135 °C.**FIGURE 5.** Hammett plot of the oxidation of benzylic alcohols in DMSO catalyzed by H₃PMo₁₂O₄₀. Reaction conditions: 1 mmol of benzylic alcohol, 5 μmol of H₃PMo₁₂O₄₀, 1 mL of DMSO at 135 °C under Ar. $k_{\text{obs}} = 1.92 \pm 0.24 \text{ min}^{-1}$ (R = H); $2.72 \pm 0.32 \text{ min}^{-1}$ (R = Me); $6.5 \pm 0.42 \text{ min}^{-1}$ (R = OMe); $3.04 \pm 0.32 \text{ min}^{-1}$ (R = Br); $4.01 \pm 0.38 \text{ min}^{-1}$ (R = CF₃); $7.3 \pm 0.51 \text{ min}^{-1}$ (R = NO₂).

plot) as a function the DMSO concentration. In other words, the reaction order changes from first order with respect to DMSO at low concentration to zero order at higher DMSO concentrations.

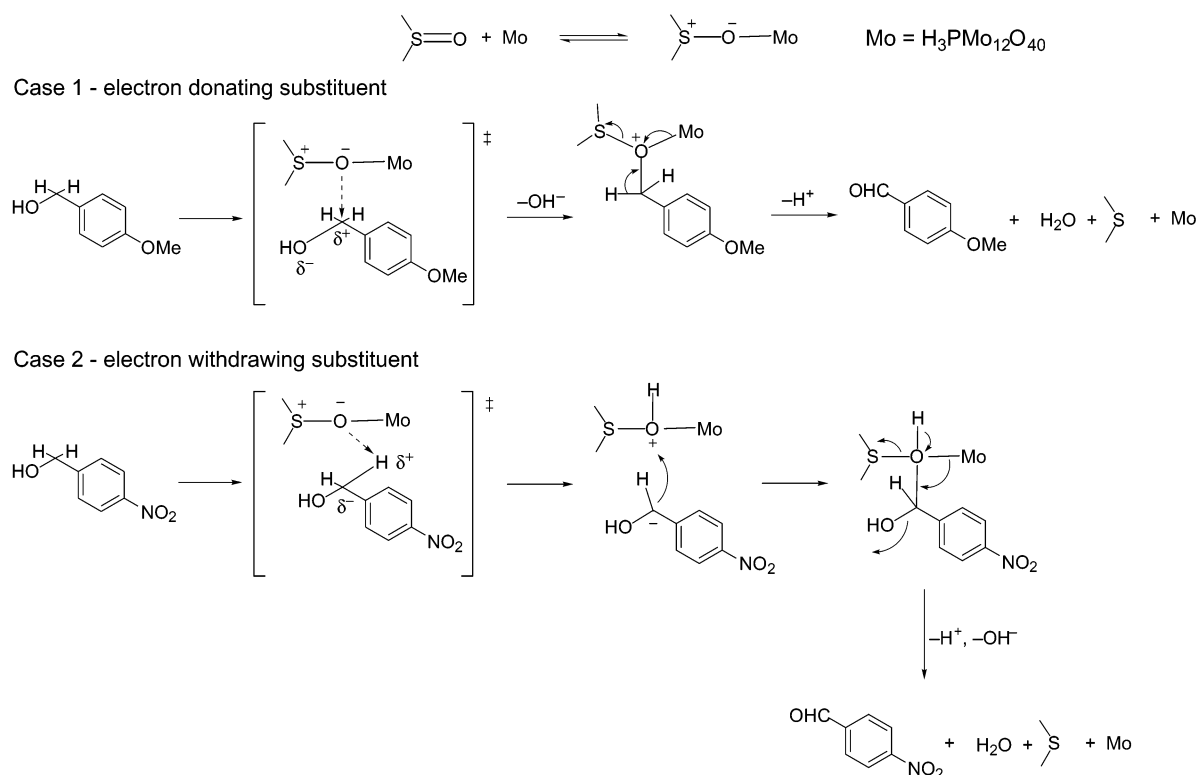
The *observed* or empiric rate equation may be summarized as eq 1.

$$d[\text{aldehyde}]/dt = -d[\text{alcohol}]/dt = k_{\text{obs}}[\text{POM}]^1[\text{DMSO}]^{1-\rho}[\text{alcohol}]^{0-\rho} \quad (1)$$

In Figure 5 are presented as a Hammett plot the results of the kinetics of the benzylic alcohol oxidation with DMSO. The results indicate two mechanistic regimes, one with a ρ value of -1.83 for electron-donating substituents, 4-OCH₃ and 4-CH₃ relative to H, and another with a ρ value of 0.65 for electron-withdrawing substituents, 4-NO₂, 4-CF₃, and 4-Br relative to H. Thus, electron-donating substituents stabilize a positively charged transition state and electron-withdrawing substituents stabilize a negatively charged transition state.

Kinetic isotope effects were measured for the oxidation of XPhCD₂OH/XPhCH₂OH (X = H, 4-OCH₃, 4-NO₂) under the following reaction conditions: 0.5 M XPhCD₂-

SCHEME 1



OH, 0.5 M XPhCH₂OH, 3.0 mM H₃PMo₁₂O₄₀ in 1 mL of DMSO at 135 °C. Kinetic isotope effects of 2.4–2.6 ± 0.1 were obtained for all three substituents. Additional isotope-labeling experiments also yielded significant insight. First, the ¹⁷O NMR of a solution of 1.4 M DMSO-¹⁷O (~0 ppm, ~5% enriched) and 2.8 mM ⁴Q₃[PMo₁₂O₄₀] in nitroethane, heated at 120 °C for 1 h, showed only a new peak at 182 ppm, indicating a coordination interaction between DMSO and the polyoxomolybdate. This chemical shift is distinctly different compared to chemical shifts for bridging and terminal oxygens appearing at ~500 and ~900 ppm,¹⁶ respectively, and rules out oxygen exchange between the sulfoxide and ⁴Q₃[PMo₁₂O₄₀]. Second, a reaction between 1 mmol of DMSO-¹⁸O (85% enriched), 1 mmol of benzyl alcohol, and 3.3 μmol of Q₃PMo₁₂O₄₀ in 1 mL of nitroethane at 135 °C under Ar yielded benzaldehyde with 40% ¹⁸O enrichment.¹⁷ Furthermore, a reaction between 1 M benzaldehyde-¹⁶O with 1 M H₂¹⁸O (95% enrichment) in DMSO-¹⁶O at 135 °C under Ar in the presence or absence of Q₃PMo₁₂O₄₀ yielded after a few minutes benzaldehyde with ~40% ¹⁸O enrichment, which remained unchanged over time; however, the DMSO remained unlabeled. Finally, a reaction using DMSO-*d*₆ (1 M benzyl alcohol, 1 mM H₃PMo₁₂O₄₀ in 1 mL of DMSO-*d*₆ under 1 atm of Ar at 135 °C for 4 h) yielded only dimethyl sulfide-*d*₆ and no dimethyl sulfide-*d*₅. The latter is formed in Swern-type reactions, ruling out such a mechanism in this case. Furthermore, the use of diphenylsulfoxide as a solvent is possible in these reactions; reaction rates are up to 70% faster compared to DMSO.

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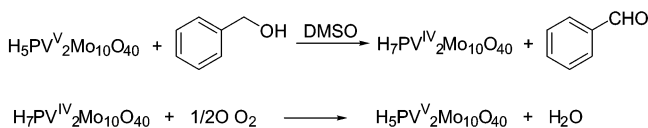
(17) ⁴Q₃[PMo₁₂O₄₀] was used instead of H₃PMo₁₂O₄₀, despite the lower rates, because the latter is a hydrate, which would complicate the interpretation of the results.

From the experimental evidence a possible reaction pathway for the oxidation may be postulated as follows. First, a H₃PMo₁₂O₄₀–sulfoxide complex is formed that polarizes the S–O bond as evidenced by the ¹⁷O NMR, although there is no change in the ³¹P NMR of H₃PMo₁₂O₄₀ in the presence of DMSO. Additional support of such a complex was obtained by heating DMSO and H₃PMo₁₂O₄₀ in acetonitrile. Despite the fact that each component by itself is soluble in acetonitrile, a precipitate was formed whose elemental C,H analysis best fits a complex of the formula (DMSO)₉H₃PMo₁₂O₄₀ [exptl (calcd): C 8.78 (8.54); H 2.26 (2.25)]. The Hammett plot indicates that oxidation of benzylic alcohols by the DMSO–polyoxomolybdate complex proceeds via different transition states for electron-donating and electron-withdrawing substituents. The negative ρ value for electron-donating substituents, e.g., methoxy, indicates a transition with a partial positive charge at the benzylic carbon, whereas the positive ρ value for electron-withdrawing substituents, e.g., nitro, indicates a transition state with a partial negative charge at the benzylic carbon. From this we propose, in general terms, oxidation of benzylic alcohol in two different ways as presented in Scheme 1.

For reactions accelerated by electron-donating moieties, the activated oxygen atom of the sulfoxide reacts by nucleophilic attack at the benzylic carbon leading to formation of a new carbon–oxygen bond (as indicated by the isotope-labeling experiments) with the hydroxide anion as a leaving group. Subsequently, dimethyl sulfide, a proton, and polyoxometalate are eliminated as shown with formation of the benzylic aldehyde. For reactions accelerated by electron-withdrawing moieties, the significantly higher acidity (many orders of magnitude)¹⁸ of

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SCHEME 2



the benzylic hydrogen leads to a partial negative charge at the benzylic carbon. We put forth the possibility of proton abstraction from benzylic alcohol by the DMSO–polyoxometalate complex. The protonated DMSO complex¹⁹ then may recombine with a carbanionic species leading to formation of the new carbon–oxygen bond. We believe that this reaction is possible *vis-à-vis* (re)-protonation because the polyoxomolybdates are powerful electron acceptors or oxidants leading to formation of an electrophilic oxygen. As in the previous case, similar subsequent elimination of a proton, hydroxide, dimethyl sulfide, and the polyoxometalate leads to formation of the benzylic aldehyde. In all cases, use of ¹⁸O-labeled sulfoxide leads to labeled aldehyde; however, the coformation of water and the fast reaction of the latter with the aldehyde leads to ¹⁸O to ¹⁶O exchange and a lower ¹⁸O content. From the kinetic isotope effect values for deuterated benzylic alcohols it is clear that the carbon–hydrogen bond is being broken in the rate-determining step in both postulated pathways, although at different stages of the reaction. Since the DMSO oxygen donor first reacts with the H₃PMo₁₂O₄₀ catalyst to form a H₃PMo₁₂O₄₀–sulfoxide complex, Michaelis–Menton-type kinetics, Figure 4, are expected and indeed observed for DMSO. Also, at the beginning of the reaction, the benzylic alcohol substrate is in large excess with respect to the initial amount of H₃PMo₁₂O₄₀ and the H₃PMo₁₂O₄₀–sulfoxide complex. Thus, initially, the reaction is effectively zero order in benzylic alcohol, Figure 3, but as the amount of benzylic acid is lowered, the bimolecular interaction between the H₃PMo₁₂O₄₀–sulfoxide complex and the benzylic alcohol is elicited in the rate equation. The observed reaction kinetics as described in eq 1 support the mechanism.

An interesting observation noted above is that with H₅PV₂Mo₁₀O₄₀ as a catalyst instead of H₃PMo₁₂O₄₀ under anaerobic conditions the reaction for benzyl alcohol stops at ~40% conversion, whereas for H₃PMo₁₂O₄₀, the reaction is completed. Our explanation for this finding is that H₅PV₂Mo₁₀O₄₀ can also oxidize alcohols without the direct involvement of the sulfoxide in the oxidation reaction (~0.6 mol of dimethylsulfide formed per mol of benzyl alcohol reacted and DMS not oxidized to a significant amount under reaction conditions), Scheme 2. However, under anaerobic conditions, this oxidation pathway leads to a reduced heteropolyblue species that is apparently catalytically inactive and was not reoxidized directly with DMSO.

Conclusion

Polyoxomolybdates catalyze the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, with sulfoxides as oxygen donors. DMSO is activated by complexation to the polyoxometalate.

(19) It is conceivable that the proton is delocalized around the polyoxomolybdate.

Experimental Section

Materials and Equipment. Alcohol substrates and DMSO were all from commercial sources, of the highest purity available, and used without further purification. H₃PMo₁₂O₄₀·H₂O was purchased commercially, and H₅PV₂Mo₁₀O₄₀·32H₂O was prepared according to the literature procedure.²⁰ Q₃-PMo₁₂O₄₀ and Q₅PV₂Mo₁₀O₄₀ were prepared by adding dropwise 5 mmol of the polyoxometalate dissolved in 20 mL water to 20 (30) mmol of *n*-(C₄H₉)₄N⁺Br⁻ dissolved in 25 mL of water. The precipitated product was thoroughly washed with water and dried under vacuum at 80 °C. ¹⁷O- and ¹⁸O-labeled DMSO were prepared using H₂¹⁷O (10.2% ¹⁷O) and H₂¹⁸O (95% ¹⁸O) using the procedure described in the literature.²¹ 4-Methoxybenzyl alcohol- α,α -d₂ (97% enrichment) was prepared by reduction of 4-methoxybenzoic acid with LiAlD₄ in THF. 4-Nitrobenzyl alcohol- α,α -d₂ (97% enrichment) was prepared by reduction of 4-nitrobenzoyl chloride with NaBD₄ according to the literature method.²² Nitroethane was dried and distilled over CaH₂. ¹⁷O NMR was measured at 54.25 MHz on a Bruker Avance 400 instrument with H₂¹⁷O (2%) as an external standard. Isotope incorporation into substrates and products was measured by GC-MS (HP 5973). Reactions were quantified by GLC (HP 6890) using a 30 m 5% phenylmethyl silicone capillary column with an ID 0.32 mm and 0.25 μ m coating (Restek 5MS).

General Procedure for Oxidation of Alcohols. Reactions were carried out in 20 mL glass pressure tubes for aerobic reactions and in 20 mL Schlenk flasks for reactions under anaerobic conditions (Ar). Typically, the tubes or flasks were loaded with the polyoxometalate, sulfoxide, and substrate, degassed by three successive “freeze–pump–thaw” cycles, and loaded with Ar or O₂. The solution was brought to the appropriate temperature in a thermostated oil bath. After the reaction was completed and the mixture cooled, GLC and GC-MS analyses were performed on aliquots withdrawn directly from the reaction mixture.

Detailed Procedure for Oxidation of Benzyl Alcohol. Benzyl alcohol (5 mmol, 540 mg) and H₅PV₂Mo₁₀O₄₀·32H₂O (5 μ mol, 12.5 mg) were dissolved in 5 mL of DMSO in a 50 mL Buchi glass autoclave. The autoclave was pressurized to 1 atm of O₂, and the homogeneous mixture was magnetically stirred at 135 °C for 4 h. After the reaction mixture was cooled to room temperature, 20 mL of water was added and the benzaldehyde was extracted with two 5 mL portions of ethylacetate. The organic phase was dried with MgSO₄, and the product was purified by column chromatography (silica as a stationary phase and CHCl₃ as an eluent). The yield of benzaldehyde (>99.5% purity) was 450 mg (85%).

General Procedure for Kinetic Experiments. Reactions were carried out in 20 mL Schlenk flasks. Typically, the flasks were loaded with the polyoxometalate, sulfoxide, and substrate, degassed by three successive “freeze–pump–thaw” cycles, and loaded with Ar. Exact reaction conditions are given in the figure captions. The solution was brought to the appropriate temperature in a thermostated oil bath. At the desired time, 1 μ L aliquots were removed for GC analysis. Conversion was analyzed by evaluation of both disappearance of the substrate and appearance of the product, which were found to be in agreement within \pm 2%. Kinetic isotope effects for the oxidation of the benzylic alcohols were measured by reacting equimolar mixture of proto- and deuterio-alcohols. Peaks were quantified by comparing the molecular peak intensities (GC-MS) of the product aldehyde.

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