Communication

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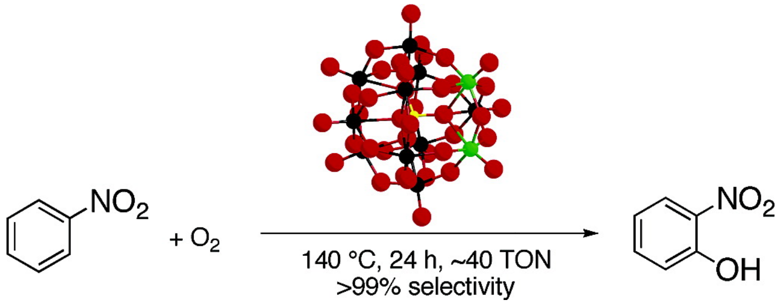
J. Am. Chem. Soc., **2005**, 127 (28), 9988-9989• DOI: 10.1021/ja051286g • Publication Date (Web): 21 June 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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Selective Ortho Hydroxylation of Nitrobenzene with Molecular Oxygen Catalyzed by the $H_5PV_2Mo_{10}O_{40}$ Polyoxometalate

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The selective liquid phase catalytic oxidation of hydrocarbons with molecular oxygen is an important research goal. Especially difficult is the selective hydroxylation of arenes to the corresponding phenols because aromatic substitution reactions are usually not regioselective, and the initial phenol products are more reactive than the arene substrate. Thus, arene hydroxylation often leads to formation of regioisomers, polyhydroxylated arenes, quinones, and tars.[1] Even rarer, in fact, apparently undocumented, is the *selective* hydroxylation of a deactivated arene substituted with electron-withdrawing moieties, such as nitrobenzene. Thus, nitrobenzene has been hydroxylated to a mixture of nitrophenol regioisomers using various hydroxy radical sources,[2] including hydrogen peroxide.[3] There is also an old report of nitrobenzene hydroxylation to a mixture of products under basic aerobic conditions,[4] as well as a report on hydroxylation by anodic electrolysis.[5]

There has been significant interest in selective oxidation and the activation of hydrocarbons catalyzed by polyoxometalates,[6] and in this context, the use of molecular oxygen as the terminal oxidant in oxydehydrogenation and oxygenation reactions catalyzed by $H_5PV_2Mo_{10}O_{40}$ is especially relevant to this report. Thus, it has been previously found that in the activation of arenes with relatively low oxidation potentials, for example, anthracene or 4-methoxytoluene, $H_5PV_2Mo_{10}O_{40}$ mediates the reaction by initially catalyzing electron transfer from the hydrocarbon to the catalyst through formation of a radical cation intermediate.[7] Therefore, one would expect that nitrotoluene with a significantly higher oxidation potential would be inactive in $H_5PV_2Mo_{10}O_{40}$-mediated oxidations. The unexpected oxygenation by dioxygen of 2- and 4-nitrotoluene catalyzed by $H_5PV_2Mo_{10}O_{40}$ versus the inactivity of toluene clearly points to a change in mechanism for such an oxidation.[8]

Perhaps even more surprising is the present finding that $H_5PV_2Mo_{10}O_{40}$ catalyzed the *selective* aerobic oxygenation of nitrobenzene to 2-nitrophenol. Thus, heating a 0.01 M solution of $H_5PV_2Mo_{10}O_{40}\cdot 34H_2O$ in *neat* nitrobenzene at 140 °C under 2 bar O_2 selectively (>99%) yielded 2-nitrophenol at a ~5% maximum yield[9] (no other product was observed by NMR or GC) with a kinetic reaction profile as shown in Figure 1. There is no reaction under Ar. Since the substrate was in large excess, it is not surprising that the reaction is pseudo (observed) zero-order in nitrobenzene. After about 30−40 h, the reaction is inhibited, although the catalyst appears to remain intact (^{31}P NMR). Further kinetic studies using different initial catalyst concentrations ($H_5PV_2Mo_{10}O_{40}$ from 5 to 20 mM) showed also that the reaction was first-order in $H_5PV_2Mo_{10}O_{40}$ (see Figure S1). Similarly, reactions carried out at oxygen pressures from 0.2 (air) to 8 bar O_2 showed that the reactions were also approximately first-order in molecular oxygen (Figure S2). Isostructural polyoxometalates, such as $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$, were inactive polyoxometalate catalysts for this reaction as was $[(n\text{-butyl})_4N]_5PV_2Mo_{10}O_{40}$. This gives a preliminary indication that, for catalytic activity, incorporation of vanadium in the polyoxomolybdate framework and the presence of an acid are required for catalysis. In fact, the relative rates of reaction for 0.01 M $H_{3+x}PV_xMo_{12-x}O_{40}$ in nitrobenzene at 140 °C under 2 bar O_2 were 1.0, 3.0, and 5.1 for x from 1 to 3, respectively (relative to $H_4PVMo_{11}O_{40}$).

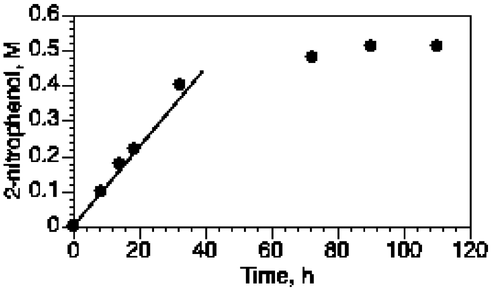

Figure 1. Reaction profile for selective oxygenation of nitrobenzene; 0.01 M $H_5PV_2Mo_{10}O_{40}\cdot 34H_2O$ in $PhNO_2$, 140 °C, 2 bar O_2.

Further kinetic experiments included the following: (i) A kinetic isotope experiment (0.01 M $H_5PV_2Mo_{10}O_{40}$ in 1:1 $C_6H_5NO_2/C_6D_5NO_2$ at 140 °C under 2 bar O_2) yielded a $k_H/k_D = 2.5 \pm 0.1$.[10] (ii) A reaction using labeled $^{18}O_2$ (0.01 M $H_5PV_2Mo_{10}O_{40}$ in $C_6H_5NO_2$ at 140 °C under 2 bar $^{18}O_2$ (96.1% ^{18}O)) yielded ^{18}O-labeled 2-nitrophenol with 86% ^{18}O at the phenolic oxygen. (iii) A reaction in the presence of $H_2{}^{18}O$ (0.01 M $H_5PV_2Mo_{10}O_{40}$, 0.5 M $H_2{}^{18}O$ (94.3% ^{18}O) in $C_6H_5NO_2$ at 140 °C under 2 bar $^{16}O_2$) yielded no ^{18}O-labeled 2-nitrophenol. (iv) Nitrobenzene at 140 °C under 2 bar O_2 for 24 h in the presence of 1 mol % 1,1′-azobis(cyclohexanecarbonitrile) as radical initiator yielded a mixture of 2-, 3-, and 4-nitrophenol (0.056 M) in a nearly statistical distribution (~1:0.9:0.45 ratio).

We sought to forward an explanation for the described unusual selective hydroxylation to 2-nitrophenol. Considering its high oxidation potential, it would appear unlikely that activation of nitrobenzene proceeded by its oxidation via electron transfer. In fact, nitrobenzene has been observed to be a mild oxidative dehydrogenating agent under both acidic and basic conditions.[11] Additionally, the possibility of obtaining hydroxylation in the presence of a radical reaction initiator, the value of the kinetic isotope effect in a competitive experiment, and the finding, using labeled oxygen reagents, that the source of the phenolic oxygen in the product was derived from molecular oxygen indicated the possibility of initial formation of a radical intermediate formed through an *intramolecular regioselective process and oxidation* as opposed to a nonregioselective autoxidation in the presence of 1,1′-azobis(cyclohexanecarbonitrile). A rough scheme of such a reaction scenario is provided in Scheme 1.

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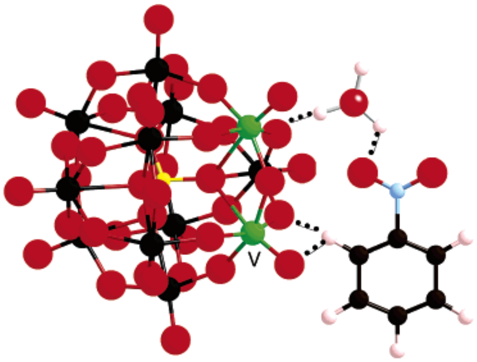
10.1021/ja051286g CCC: $30.25 © 2005 American Chemical Society

Scheme 1. Cartoon Representation of the Interaction of Nitrobenzene with the Acidic $H_5PV_2Mo_{10}O_{40}$ Polyoxometalate (just one of the five $H_5PV_2Mo_{10}O_{40}$ isomers is presented for simplification)



This scenario is supported first of all by the known formation of $PhNO_2/H^+_n$ or $PhNO_2/H_3O^+$ intermediates when nitrobenzene is mixed with Bronsted acids.[12] In confirmation of such an intermediate, a ^{15}N NMR (50.69 MHz) of ~10% $Ph^{15}NO_2$ showed line broadening from $\Delta\nu_{1/2} = 1.24$ to 1.71 Hz and a downfield shift of 8 Hz upon addition of $H_5PV_2Mo_{10}O_{40}$ (0.04 M). Second, calculations by various methods and microwave measurements[13] have shown that the C−H bond length at the ortho position is either shorter by a fraction of a picometer or practically the same as the bond lengths at the meta and para positions. Therefore, since the C−H bond strengths are similar at all positions, the regioselective hydroxylation should be the result of an intramolecular preference with the resulting thermokinetic advantage for reaction at the ortho position.

Direct evidence for the formation of a radical intermediate was obtained by an EPR spin-trap experiment. Thus, mixing a solution of 0.01 M $H_5PV_2Mo_{10}O_{40}$ and 0.1 M phenyl-*tert*-butylnitrone in nitrobenzene at room temperature under 2 bar O_2 yielded after 10 min an EPR signal at $g = 2.0$ of a spin-trapped radical intermediate with splitting constants of $A_N = 14.06$ G and $A_H = 2.55$ G (Figure 2).[14] The trapped radical may be associated to either a carbon- or oxygen-centered radical intermediate[15] formed via a polyoxometalate−nitrobenzene interaction. Replacing the $H_5PV_2Mo_{10}O_{40}$ with catalytically inactive $H_3PW_{12}O_{40}$ or $H_3PMo_{12}O_{40}$ did not yield the formation of a spin-trapped intermediate; the solution remained EPR silent.

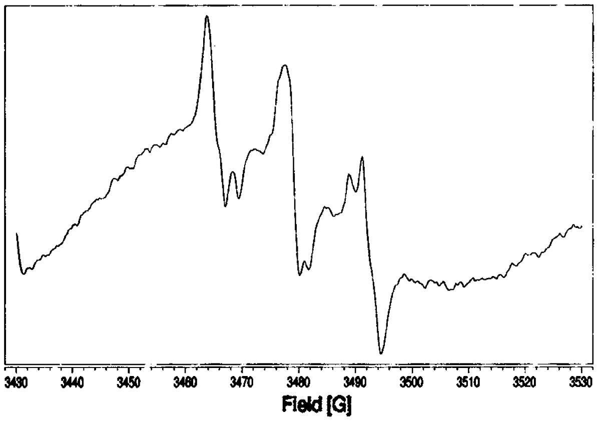


Figure 2. EPR spectrum of a radical intermediate trapped by phenyl-*tert*-butylnitrone.

The reaction orders observed in the kinetic experiments would support a reaction between the proposed polyoxometalate−nitrobenzene intermediate and molecular oxygen in the rate-determining step. The pathway for the completion of the reaction, nitrobenzene to 2-nitrophenol, after the formation of the intermediate and its reaction with oxygen remains unclear. Notably, aerobic oxidation usually is accompanied by water formation; in this case, the reaction stoichiometry shows that no protons are generated in the oxidative transformation, and it is possible that this is the cause of the reaction stopping after ~50 TON. In this context, it is valuable to note that the addition of 4 Å molecular sieves to a reaction mixture to remove water completely inhibited the reaction (Figure S3). Unfortunately, however, addition of water was also not helpful as it significantly slowed the reaction (Figure S3).

To the best of our knowledge, this is probably the first example of an (aerobic) regioselective hydroxylation of an arene; it has been achieved through an intramolecular interaction between a polyoxometalate and the substrate.

Acknowledgment. The research was supported by Israel Science Foundation and the Helen and Martin Kimmel Center for Molecular Design. R.N. is the Rebecca and Israel Sieff Professor of Organic Chemistry. Leonid Konstantinovski is thanked for his help with the ^{15}N NMR.

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

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(8) Solutions of $H_5PV_2Mo_{10}O_{40}\cdot 34H_2O$ (10 mM) in 2- or 4-nitrotoluene at 140 °C under 2 bar O_2 for 12 h yielded selective formation of 2-nitrobenzaldehyde (17 TON) and 4-nitrobenzaldehyde (19 TON), respectively.
(9) A ~10% maximum yield is possible at 20 mM polyoxometalate, which represents the boundary of solubility of the catalyst. Dilution of the reaction medium inhibits the reaction.
(10) A $k_H/k_D = 4.3$ was measured in a comparative experiment. Since the rates are low, the data for a competitive experiment were deemed more accurate.
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JA051286G