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Mechanistic Study of Alcohol Oxidation by the $Pd(OAc)_2/O_2$/DMSO Catalyst System and Implications for the Development of Improved Aerobic Oxidation Catalysts

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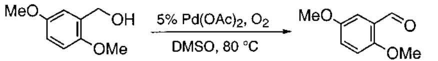
Received August 9, 2001

The development of selective oxidation reactions that employ environmentally benign and low-cost oxidants is a critical challenge for the chemical community. Although the palladium-catalyzed Wacker process (eq 1) was developed more than 40 years ago, it

$$CH_2{=}CH_2 + 1/2\ O_2 \xrightarrow{\text{Pd/Cu cat.}} CH_3CHO \qquad (1)$$

remains a rare example of a nonradical aerobic oxidation reaction in the chemical industry. Recently, a series of dioxygen-coupled oxidation reactions were reported that employ catalytic $Pd(OAc)_2$ in dimethyl sulfoxide (DMSO) as the solvent.[1] These reactions display remarkable synthetic versatility, ranging from oxidative carbon−carbon bond formation and substrate desaturation to oxidative amination and oxygenation of olefins. Unlike the Wacker process, no cocatalyst such as $CuCl_2$ is required to achieve efficient catalytic turnover. The studies outlined herein provide the first mechanistic analysis of this catalyst system and reveal that DMSO-promoted oxidation of palladium(0) by dioxygen competes with catalyst decomposition in the turnover-limiting step. The results reveal several opportunities for the development of new aerobic oxidation catalysts.

To conduct our studies, we selected the alcohol oxidation reaction in eq 2 because of its high yield, 95%, and relatively short reaction time, 12 h.[1j]

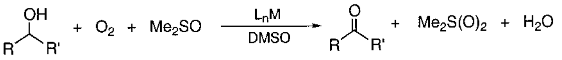


1 **2** (2)

The unique success of DMSO as the solvent in these reactions suggests several mechanistic possibilities, including the prospect that DMSO itself participates in redox chemistry. Dimethyl sulfoxide is a stoichiometric oxidant in a variety of chemical[2,3] and biological[4] oxidation reactions, yielding dimethyl sulfide as a byproduct. This possibility is readily dismissed in eq 2, however, by noting the requirement for an atmosphere of air or dioxygen to achieve catalytic turnover. At 5% catalyst loading, a 5.0(1)% yield of **2** is obtained under anaerobic conditions.

In contrast, DMSO is a reductant in certain aerobic oxidation reactions catalyzed by late transition metals (eqs 3 and 4).[5] These alcohol and dihydrogen oxidations are intimately coupled to the oxygenation of DMSO.

$$H_2 + O_2 + Me_2SO \xrightarrow[\text{DMSO}]{RhCl_3\cdot 3H_2O} H_2O + Me_2S(O)_2 \qquad (3)$$



$$RCH(OH)R' + O_2 + Me_2SO \xrightarrow[\text{DMSO}]{L_nM} RC(O)R' + Me_2S(O)_2 + H_2O \qquad (4)$$

$L_nM = RhCl_3, IrCl_3, [Cu(CH_3CN)_4]^+$

Such a mechanism does not operate for eq 2. Only a trace of dimethyl sulfone is produced during the reaction. Dioxygen uptake measurements reveal a dioxygen:substrate (**1**) stoichiometry of 0.50(3), reflecting *the use of all four oxidizing equivalents in dioxygen*. The dioxygen stoichiometry reveals that hydrogen peroxide does not accumulate during catalytic turnover as observed in other palladium-catalyzed oxidation reactions.[6,7] Attempts to use hydrogen peroxide directly as an oxidant[8] revealed that it instead undergoes rapid disproportionation under the reaction conditions (eq 5).[9]

$$H_2O_2 \xrightarrow{[Pd]} H_2O + 1/2\ O_2 \qquad (5)$$

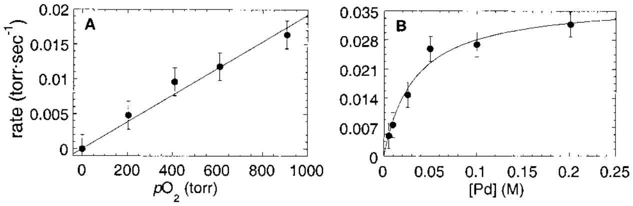


Figure 1. Dependence of the catalytic rate on initial dioxygen pressure, and catalyst and substrate concentrations at $t = 800$ s. Rates were obtained by monitoring pressure changes during catalytic turnover. The curve in B is derived from a nonlinear least-squares fit of the data to eq 7. Reaction conditions: (A) [**1**] = 1.0 M, $[Pd(OAc)_2] = 0.05$ M, $pO_2 = 0{-}908$ Torr, 2 mL of DMSO, 80 °C. (B) [**1**] = 1.0 M, $[Pd(OAc)_2] = 0.005{-}0.20$ M, 2 mL of DMSO, 80 °C, rates normalized to $pO_2 = 1000$ Torr.

The above results exclude mechanisms that involve DMSO redox chemistry. The essential role of DMSO as a solvent therefore appears to be associated with its palladium-coordination ability. Access to both hard (*O*-) and soft (*S*-) ligand donor atoms perhaps facilitates the redox cycling between palladium(II) and palladium(0) in these reactions.[10,11]

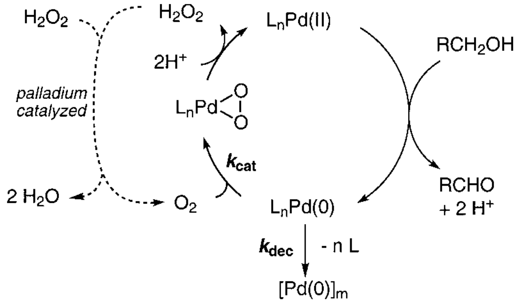
Kinetic studies revealed additional insights into the catalytic mechanism. The reaction rate diminishes steadily over time, correlating with the gradual precipitation of palladium black. Despite this potential complication, the dependence of the reaction rate on both pO_2 and [Pd] (Figure 1), and lack of a dependence on [alcohol] (data not shown) supports a mechanism in which oxidation of palladium(0) by dioxygen constitutes the turnover-limiting step (k_{cat}, Scheme 1). This step alone, however, predicts a linear, first-order rate dependence on [Pd]. The saturation [Pd] dependence (Figure 1B) is accommodated by invoking a bimolecular catalyst decomposition step, k_{dec}, that competes with k_{cat}. The rate law for such a mechanism (eq 7) fits the experimental [Pd] dependence (Figure

$$\frac{d(pO_2)}{dt} = k_{cat}[Pd]_t \cdot pO_2; \quad [Pd]_t = \frac{[Pd]_0}{1 + [Pd]_0(k_{dec}\cdot t)} \qquad (7)$$

1B),[12] and the corresponding integrated rate law fits well to an extended reaction time course (Figure 2). According to this scheme, the deviation from linearity in Figure 1B becomes more pronounced at higher catalyst concentration because of the bimolecular dependence of the decomposition step on [Pd].

10.1021/ja016806w CCC: $22.00

Scheme 1. Catalytic Mechanism



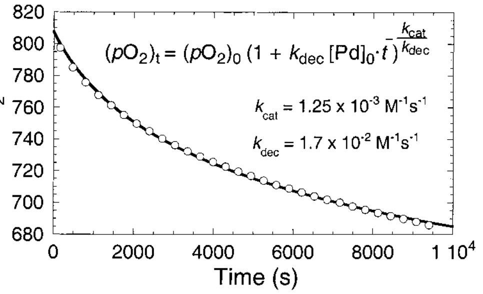


Figure 2. A 10 000 s time-course (○) for the catalytic oxidation of **1** (30 of 9500 data points shown). The fit (—) is based on integration of the rate expression in eq 7 (see inset). Reaction conditions: $[\mathbf{1}] = 1.0$ M, $[Pd]_0 = 0.05$ M, $(pO_2)_0 = 807$ Torr, 2 mL of DMSO, 80 °C.

The lack of a rate dependence on [alcohol] (eq 7) is consistent with the independent observation that stoichiometric alcohol oxidation by $Pd(OAc)_2$ occurs within seconds under anaerobic reaction conditions, i.e., much faster than the initial catalytic turnover rates, 4−5 h^{-1}. Although we obtained no direct evidence for the intermediate formation of peroxopalladium(II) (Scheme 1), such reactivity has substantial precedent.[13] Rapid protonolysis of the peroxo ligand releases hydrogen peroxide and generates the active palladium(II) catalyst.[7] That addition of both weak and strong acids, CH_3CO_2H and H_2SO_4, to the reaction mixture has no beneficial effect on the rate confirms protonolysis of the peroxo species does not limit the catalytic turnover rate.

According to Scheme 1, palladium(II) releases the peroxo ligand prior to substrate oxidation. This sequence differs from biological oxygenases and related model systems in which substrates react directly with activated dioxygen intermediates.[14] The use of dioxygen simply as a two-proton, two-electron acceptor in the $Pd(OAc)_2/O_2$/DMSO reactions functionally mimics biological oxidases. Thus, these reactions may be defined mechanistically as “chemical oxidases”.

The mechanistic studies outlined above clearly define the challenge in developing a more active aerobic oxidation catalyst system, namely, enhancing the rate of palladium(0) oxidation, particularly with respect to competing palladium(0) aggregation. This challenge has traditionally been addressed by employing redox mediators to enhance the kinetics of palladium(0) oxidation. The present work, however, suggests an alternative strategy: ligand-promoted direct oxidation of palladium(0) by dioxygen. The role of DMSO as a favorable ligand in the present system suggests that other ligands might further enhance k_{cat}. Ideal ligands will simultaneously diminish k_{dec}, thereby promoting higher catalyst lifetime as well as catalytic rates. This principle appears consistent with the recent use of pyridine and chelating nitrogen ligands in aerobic palladium oxidation reactions that lack redox mediators,[15] including an asymmetric oxidation reaction.[16]

Acknowledgment. We thank Prof. C. R. Landis and his group for generous access to their gas-uptake kinetics apparatus and Profs. C. P. Casey and C. R. Landis for insightful discussions and suggestions. We gratefully acknowledge financial support from the University of Wisconsin—Madison, the Camille and Henry Dreyfus Foundation (New Faculty Award), Merck Research Laboratories, and the National Science Foundation (CAREER Award). S.R.F. was supported by a Chemistry Biology Interface NIH training grant.

Supporting Information Available: Experimental procedure and discussion of the hydrogen peroxide experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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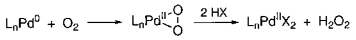

(6)

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(11) Catalytically active, DMSO-stabilized palladium colloids have been isolated from aerobic oxidation reactions similar to eq 2 (ref 1c).

(12) The magnitude of k_{dec} can vary by factors of 2 to 5, depending on the stock of $Pd(OAc)_2$; however, k_{cat} remains constant. This result suggests palladium(0) aggregation may be catalyzed by trace impurities.

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JA016806W