

## Experimental and Computational Study of a Direct O<sub>2</sub>-Coupled Wacker Oxidation: Water Dependence in the Absence of Cu Salts

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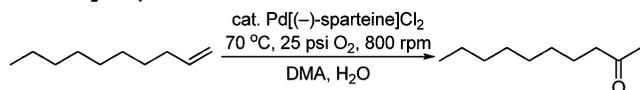
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**Abstract:** The kinetics of the Pd[(-)-sparteine]Cl<sub>2</sub> catalyzed oxidation of decene using oxygen as the sole oxidant have been studied in the absence of copper salts and high [Cl<sup>-</sup>]. Saturation kinetics are observed for [decene] as well as a third order dependence on [water]. A mechanism is proposed involving the dissociation of two chlorides and rate-limiting formation of a three-water hydrogen bridged network and subsequent oxypalladation as supported by computational studies.

Over 50 years ago Smidt and co-workers at Consortium für elektrochemische Industrie, the research organization for Wacker Chemie, reported the Pd-catalyzed oxidation of olefins to give aldehydes and ketones using molecular oxygen as the terminal oxidant.<sup>1</sup> The so-called Wacker Process has been used commercially since then to convert ethylene to acetaldehyde.<sup>2</sup> A key to developing the Wacker process into an industrial success was using CuCl<sub>2</sub>, which efficiently links the redox cycle of Pd<sup>0</sup> and Pd<sup>II</sup> to one involving O<sub>2</sub>. Initial mechanistic details determined by Smidt and co-workers showed that the oxygen atom in the product's carbonyl arises from water and not O<sub>2</sub>, while the protons are conserved from the starting olefin. Additionally, α-olefins give the Markovnikov addition product, and exogenous Cl<sup>-</sup> inhibits the reaction. This seminal work has inspired chemists through the decades to understand the details of the mechanism and develop improved synthetic methodology.<sup>3–9</sup> Herein, we report experimental and computational mechanistic studies on olefin oxidation with a unique variant of the Wacker oxidation in the absence of copper salts.

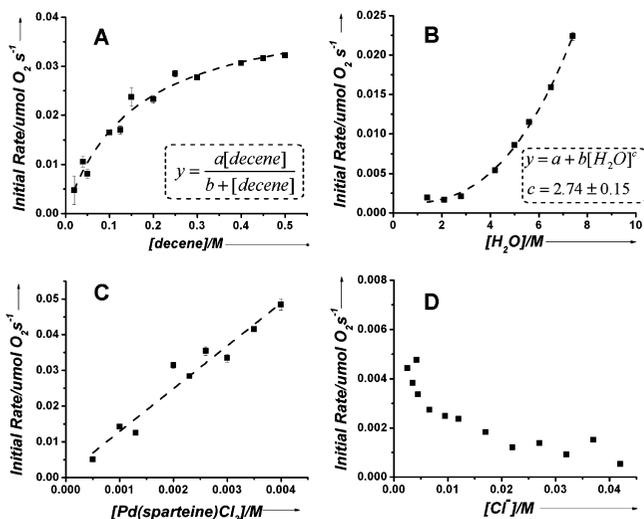
### Direct O<sub>2</sub>-Coupled Wacker Oxidation



**Figure 1.** Copper-free Pd-catalyzed aerobic oxidation of decene to 2-decanone.

Traditional Wacker chemistry and most of its related reactions use a Cu cocatalyst whose role in the chemistry is usually assumed to be only the regeneration of the Pd<sup>II</sup> catalyst. This assumption has been called into question.<sup>10</sup> Unlike classical Wacker studies,<sup>3a,b,e</sup> we have recently reported a copper-free oxidation of olefins to methyl ketones using O<sub>2</sub> as the sole oxidant and well-defined catalyst precursor Pd[(-)-sparteine]Cl<sub>2</sub> (Figure 1).<sup>11</sup> Although copper-free systems are less studied, they remove many complications due to Cu salts or high [Cl<sup>-</sup>] that may affect the mechanism.

Reaction rates of the Pd-catalyzed oxidation of decene in the absence of Cu salts were measured using a gas uptake system originally



**Figure 2.** Plots of initial rate vs [reactant] (B, C, and D at 0.3 M [decene]).

designed by Steinhoff and Stahl.<sup>12,13</sup> O<sub>2</sub> consumption was monitored simultaneously in up to six reaction wells, and the substrate conversion was independently confirmed by gas chromatographic analysis. Decene was utilized as the standard substrate in DMA/H<sub>2</sub>O solvent mixtures. Importantly, the reaction was found to be independent of O<sub>2</sub> pressure above 20 psi. Subsequent reactions were performed at 25 psi O<sub>2</sub> and stirred at 800 rpm.<sup>14</sup> Initial rates were measured up to 2% conversion.

The oxidation reaction exhibits saturation kinetics in [decene] (Figure 2A), so subsequent studies were performed under two limiting conditions: first order in [decene] (0.1 M) and zero order in [decene] (0.3 M). Substrate saturation kinetics have not been observed in previous studies of ethylene oxidation.<sup>4</sup> A first order dependence in Pd[(-)-sparteine]Cl<sub>2</sub> is observed (Figure 2C), and the oxidation reaction is inhibited by addition of NaCl although a noninteger dependence is observed (Figure 2D, vide infra). Unfortunately, we were unable to measure the dependence on [HCl] because catalyst decomposition occurs presumably due to protonation of the ligand, (–)-sparteine, under the reaction conditions. Furthermore, an approximate third order dependence on [H<sub>2</sub>O] was observed (Figure 2B), consistent with organization of three waters prior to or at the rate-limiting step.<sup>15</sup> As further evidence of the role of water, a  $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$  of  $2.6 \pm 0.1$  at high [decene] and  $1.6 \pm 0.1$  at 0.1 M [decene] is observed.<sup>16</sup> The empirical rate laws at low and high [decene] are depicted in eqs 1 and 2 respectively.

$$v_{\text{obs}} = \frac{[\text{Pd}(-) - (\text{sparteine})\text{Cl}_2][\text{decene}][\text{H}_2\text{O}]^3}{[\text{Cl}^-]^x} \quad \text{at low [decene]} \quad (1)$$

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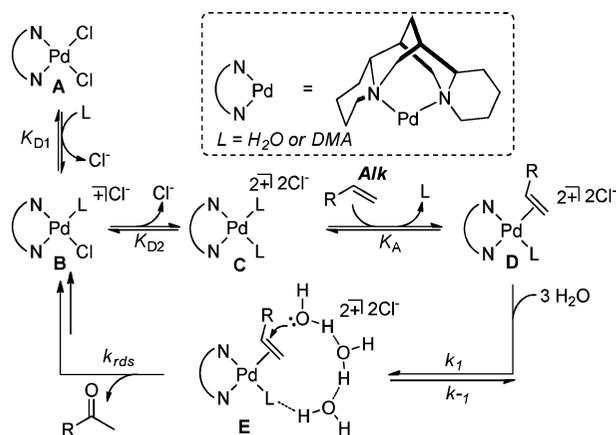
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$$v_{\text{obs}} = \frac{[\text{Pd}(-) - (\text{sparteine})\text{Cl}_2][\text{H}_2\text{O}]^3}{[\text{Cl}^-]^x} \quad \text{at high [decene]} \quad (2)$$

Chloride dissociation was measured in DMA/water electrochemically for Pd(-)-sparteine]Cl<sub>2</sub> revealing dissociation of one chloride.<sup>17</sup> Density functional theory (DFT) calculations<sup>18</sup> indicate that binding enthalpy of water and DMA to Pd(II) is stronger than that of Cl<sup>-</sup> and H<sub>2</sub>O by ~4 and ~8 kcal/mol, respectively. Since the free energies of these species in such mixed solvents cannot straightforwardly be obtained, an analysis of reaction free energies is not currently possible. Nevertheless, the calculated enthalpies alone indicate a particularly strong affinity between palladium and DMA, implicating that DMA will bind to the catalyst in the resting state.

Based on these results, we propose the following mechanism (Scheme 1). From the dissociation constant for Pd(-)-sparteine]Cl<sub>2</sub>, **A**, the catalytic cycle is initiated with the cationic Pd-species **B**, which loses another chloride to form **C** prior to reversibly binding the olefin. Intermediate **D**, the expected precursor to the rate-determining step, then will incorporate three water molecules to account for the [water] dependence and the water isotope effect. No kinetic isotope effect was observed when using 2-deutero-undec-1-ene as the substrate, suggesting the rate-determining step occurs before β-hydride elimination.

**Scheme 1.** Proposed Mechanism for the Wacker Reaction in the Absence of Cu Salts



Using the above mechanistic proposal, a rate law was derived with the assumption that the formation of the three-water chain and subsequent oxypalladation involving water hydrogen bonding are rate determining. The rate of the reaction can then be expressed as shown in eq 3.

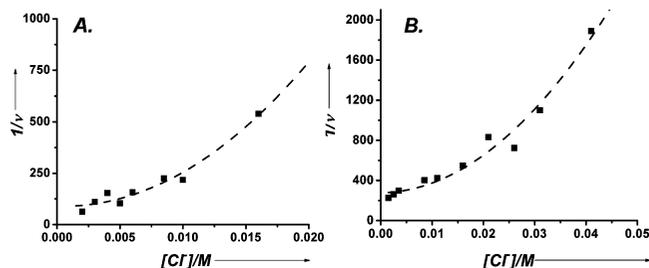
$$v = k_{\text{rds}}[\text{D}][\text{H}_2\text{O}]^3 \quad (3)$$

Due to the observed saturation kinetics, the Pd mass balance must be solved for **[D]** using the equilibrium expressions for the two chloride dissociations and the olefin association ( $K_{\text{D1}}$ ,  $K_{\text{D2}}$ ,  $K_{\text{A}}$  respectively).<sup>16</sup> The derived rate law (eq 4) is consistent with our experimental observations and shows third order dependence on [water], first order in [Pd], saturation in [decene], and inhibition by Cl<sup>-</sup>.

$$v = \frac{k_{\text{rds}}k_1K_{\text{D2}}K_{\text{A}}[\text{Alk}][\text{Pd}]_T[\text{H}_2\text{O}]^3}{(k_{-1} + k_{\text{rds}})[\text{Cl}^-](X)} \quad (4)$$

$$X = \left( 1 + \frac{[\text{Cl}^-]}{K_{\text{D1}}[\text{L}]} + \frac{K_{\text{D2}}[\text{L}]}{[\text{Cl}^-]} + \frac{K_{\text{A}}K_{\text{D2}}[\text{Alk}]}{[\text{Cl}^-]} + \frac{k_1K_{\text{A}}K_{\text{D2}}[\text{H}_2\text{O}]^3[\text{Alk}]}{(k_{-1} + k_{\text{rds}})[\text{Cl}^-]} \right)$$

A key question is whether one or two chlorides dissociate during catalysis. We derived the rate law assuming that both chlorides dissociate



**Figure 3.** Quadratic fit to the inverse rate vs [NaCl]: (A) at 0.1 M [decene] and (B) at 0.3 M [decene].

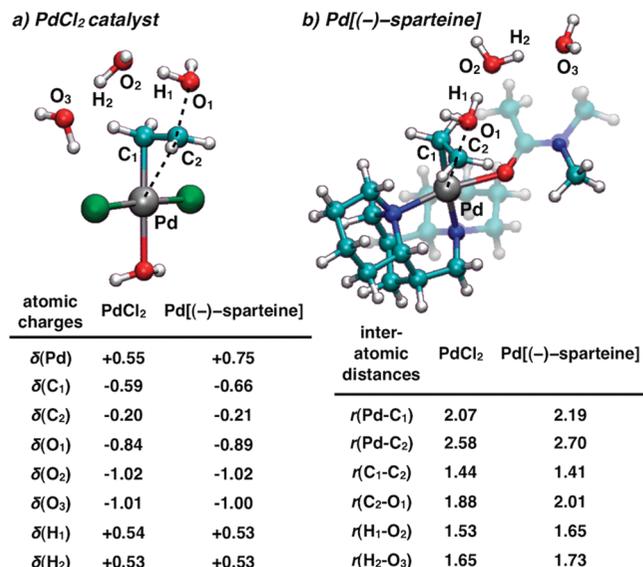
because a simple inverse first order dependence on [Cl<sup>-</sup>] is not revealed. Indeed, the derived rate law can be rearranged to solve for [Cl<sup>-</sup>] resulting in a quadratic relationship to 1/rate (general expression is eq 5).<sup>16</sup> Fitting this equation to the observed [Cl<sup>-</sup>] dependence results in an excellent fit ( $R^2 = 0.97$ ) and is consistent with both chlorides dissociating prior to the rate-limiting step (Figure 3).

$$\frac{1}{v} = a[\text{Cl}^-]^2 + b[\text{Cl}^-] + c \quad (5)$$

An intriguing aspect of the current catalytic process is that one can experimentally determine its rate dependence on [H<sub>2</sub>O]. The observation that multiple water molecules play a role in Wacker catalysis is consistent with previous computational reports<sup>9a,d,f</sup> that have all suggested the lowest-energy oxypalladation process in the Wacker process occurs via *anti*-attack with a three- or four-water hydrogen-bonded chain analogous to our mechanistic proposal (Scheme 1). Note that none of these simulations included Cu salts, and it may not be a coincidence that our experimental results find a related dependence on water for this nucleophilic attack. Indeed, low-energy enthalpic barriers (5–10 kcal/mol) for external nucleophilic attack were first believed to show nucleophilic attack was an equilibrium process in the classic Wacker reaction.<sup>9a</sup> Inclusion of free energy contributions from water in solution raise these barriers considerably, however.<sup>9c</sup> Furthermore, recent state-of-the-art CPMD simulations on the classic Wacker system by Stirling and Ujaque show *anti*-nucleophilic attack is potentially rate-determining in the absence of Cu.<sup>9f</sup> With the Pd(-)-sparteine]Cl<sub>2</sub> catalyst, the enthalpic barriers for this nucleophilic attack are low: +5.2 and +11.9 kcal/mol in continuum solvation models for H<sub>2</sub>O and DMA, respectively. Although free energy contributions cannot readily be calculated, it is possible these will play a significant role in raising the barrier for nucleophilic attack to be a rate-determining process.

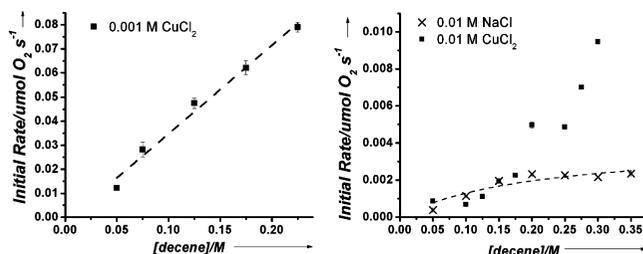
Some comparisons to the classical Wacker process studies deserve mention here. The decades-long controversy surrounding the mode of attack for the nucleophilic addition is challenging to unequivocally settle due to sensitivity of the mechanism with respect to reaction conditions.<sup>3e</sup> In this report, we use a Pd catalyst with a bidentate amine ligand in a DMA/water mixture while the classical Wacker reaction uses a PdCl<sub>4</sub><sup>2-</sup> catalyst in an aqueous environment with low concentrations of [CuCl<sub>2</sub>]. Kinetics studies indicate that both complexes release two Cl<sup>-</sup> ions into solution in order for the reaction to proceed. Given the presence of relatively strongly coordinating DMA ligands, an outersphere reaction mechanism would be expected.<sup>3c</sup>

Figure 4 compares the structures and calculated NBO charges of our *anti*-oxypalladation processes with those of Pd[ethene]Cl<sub>2</sub>, the complex used in previous theoretical studies.<sup>9</sup> Despite the fact the current process involves a dication while theoretical studies on the classic Wacker process involve a neutral complex, only very minor differences are seen between the two transition states. Calculated geometries depict a slightly earlier transition state, but surprisingly, partial atomic charges (except for Pd) are nearly identical.



**Figure 4.**  $\text{PdCl}_2$  and  $\text{Pd}[(\text{-})\text{-sparteine}]$  *anti*-oxypalladation transition states. Table inset lists partial natural bond order charges ( $\delta$ ) in atomic units and interatomic distances ( $r$ ) in Å.

Last, we sought to investigate the effect of copper salts on our Wacker oxidation system. Previous studies have assumed these to be unimportant in the olefin oxidation. Interestingly, the addition of  $\text{CuCl}_2$  has a dramatic effect on the reaction mechanism (Figure 5). At low concentration of  $\text{CuCl}_2$  (0.001 M, 1:1 Cu/Pd), the rate dependence on [decene] is first order, but at higher concentrations of  $\text{CuCl}_2$  (10:1 Cu/Pd) a greater than second order dependence on [decene] is observed.<sup>19</sup> If NaCl is substituted for  $\text{CuCl}_2$ , saturation kinetics are observed similar to results in the absence of  $\text{CuCl}_2$  demonstrating that the effect of  $\text{CuCl}_2$  does not arise from  $[\text{Cl}^-]$  inhibition. As proposed by Hosokawa,<sup>10</sup> these results strongly suggest that Cu salts play a complex role in Wacker chemistry and are influential in the alkene oxidation process.



**Figure 5.** Plots of initial rate vs [decene] in the presence of 0.001  $\text{CuCl}_2$  (left) and 0.01 M  $\text{CuCl}_2$  or NaCl (right).

In summary, the kinetics of the  $\text{Pd}[(\text{-})\text{-sparteine}]\text{Cl}_2$  catalyzed oxidation of decene using oxygen as the sole oxidant have been investigated in the absence of copper salts and high  $[\text{Cl}^-]$ . Our reaction conditions differ from the original Wacker conditions in that our Pd-catalyst contains a bidentate amine ligand and the reactions were performed in a DMA/water mixture. From the kinetic analysis, a mechanism is proposed involving dissociation of both chlorides followed by rate-limiting organization of a three-water hydrogen-bond bridged chain and subsequent oxypalladation. While our studies do not directly address the long-standing mechanistic question of *syn* or *anti* oxypalladation, the observed experimental kinetics and theoretical

calculations are consistent with other calculations on the Wacker process without copper that suggest oxypalladation proceeds through an *anti* attack from a three-water hydrogen-bond bridged network. Of particular interest, the presence of  $\text{CuCl}_2$  in the reaction mixture has a dramatic effect on the mechanism. Current studies are ongoing to better understand the oxypalladation step and the precise role of copper salts in the Wacker oxidation and to apply this information to the design of new alkene oxidation catalysts.

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**Supporting Information Available:** Kinetic data, rate law derivation, and computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (14) The reaction stir rate was kept above 800 rpm to avoid mass transfer problems.
- (15) Note that this experiment requires an ~10% change in [DMA].
- (16) See Supporting Information for more details.
- (17) No change of the dissociation constant for  $\text{Pd}[(\text{-})\text{-sparteine}]\text{Cl}_2$  was observed when the ratio of  $\text{H}_2\text{O}/\text{DMA}$  was altered.
- (18) Calculations were carried out with Jaguar 7.5 using the B3LYP/LACV3P\*\*++ level with implicit solvation parameters for DMA. See Supporting Information for more details.
- (19) Similar kinetic results were obtained if  $(\text{-})\text{-sparteine}$  was added to chelate  $\text{CuCl}_2$  ruling out ligand exchange processes affecting catalysis.
- (20) Calculations were run on the bwGRiD (<http://www.bw-grid.de>), member of the German D-Grid initiative funded by the Ministry for Education and Research (Bundesministerium für Bildung und Forschung) and the Ministry for Science, Research and Arts Baden-Württemberg (Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg).

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