The Mechanistic Studies of the Wacker Oxidation

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Introduction

- Oxidation of ethene by Pd (II) chloride solutions (Phillips, 1894)
  - First used as a test for alkenes (Pd black was the indicator)
  \[ C_2H_4 + Pd(II)Cl_2 + H_2O \rightarrow C_2H_4O + Pd(0) + 2HCl \]

- Later Smidt and co-workers employed cupric chloride to regenerate the Pd (0) catalyst (Smidt, 1962)
  \[ C_2H_4 + Pd(II)Cl_2 + H_2O \rightarrow C_2H_4O + Pd(0) + 2HCl \]
  \[ Pd(0) + 2CuCl_2 \rightarrow Pd(II)Cl_2 + 2CuCl \]

- What made Smidt’s process applicable to large scale production was the final recycling of CuCl back to Cu(II)Cl₂ by air
  \[ 2 CuCl + 1/2 O_2 + 2 HCl \rightarrow 2CuCl_2 + H_2O \]
Introduction

- Adding up the three reactions gives the Wacker Oxidation Reaction:

\[
PdCl_4^{2-} + C_2H_4 + H_2O \rightarrow Pd(0) + CH_3CHO + 2 HCl + 2 Cl^- \quad (1)
\]

\[
Pd(0) + 2 CuCl_2 + 2 Cl^- \rightarrow PdCl_4^{2-} + 2 Cu(I)Cl \quad (2)
\]

\[
2 Cu(I)Cl + 2 HCl + 1/2 O_2 \rightarrow 2 Cu(II)Cl_2 + H_2O \quad (3)
\]

**Net:**

\[
C_2H_4 + 1/2 O_2 \rightarrow CH_3CHO \quad (4)
\]

Wacker Oxidation Reaction

- Why is it called the Wacker Oxidation?

  - Smidt and co-workers discovered the reaction at Consortium Fur Elektrochemie Industrie G.M.BH., Munich, Germany (a subsidiary of Wacker Chemie)

- Industrial Importance:

  - Plants with production capacity of 15,000 tons of acetaldehyde per year have been developed
Introduction

Rate Equation:

\[
\text{Rate} = \frac{-d[\text{olefin}]}{dt} = \frac{k \left[ \text{PdCl}_4^{2-} \right] [\text{olefin}]}{[\text{H}^+] [\text{Cl}^-]^2}
\]

- First order in Pd and alkene
- Chloride squared inhibition term
- Proton inhibition term

Chloride Inhibition:

\[
PdCl_4^{2-} + C_2H_4 \xrightleftharpoons[K_1]{K_2} PdCl_3(C_2H_4)^{1-} + Cl^{1-} \\
PdCl_3(C_2H_4)^{1-} + H_2O \xrightleftharpoons[K_2]{K_1} PdCl_2(C_2H_4)(H_2O) + Cl^{1-}
\]

1/[Cl\textsuperscript{-}] term

Proton Inhibition:

\[
\text{Rate} = \frac{-d[\text{olefin}]}{dt} = \frac{k \left[ \text{PdCl}_4^{2-} \right] [\text{olefin}]}{[\text{H}^+] [\text{Cl}^-]^2}
\]

- First order in Pd and alkene
- Chloride squared inhibition term
- Proton inhibition term
Early Evidence for Inner-Sphere Mechanism: KIEs

- Observed Kinetic Isotope Effects

\[
\begin{align*}
\text{C}_2\text{D}_4 & + \text{PdCl}_4^{2-} + \text{H}_2\text{O} & \rightarrow & \text{CD}_3\text{CDO} & + & \text{Pd(0)} & + & 2 \text{HCl} & + & 2 \text{Cl}^- & k_D \\
\text{C}_2\text{H}_4 & + \text{PdCl}_4^{2-} + \text{H}_2\text{O} & \rightarrow & \text{CH}_3\text{CHO} & + & \text{Pd(0)} & + & 2 \text{HCl} & + & 2 \text{Cl}^- & k_H
\end{align*}
\]

Observed KIE = \( \frac{k_H}{k_D} = 1.07 \)

- Competitive isotope effect:

\[
\begin{align*}
\text{CH}_2=\text{CHD} & + \text{PdCl}_4^{2-} + \text{H}_2\text{O} & \xrightarrow{H^+} & \text{Cl}_2(\text{OH}_2)\text{Pd} & \xrightarrow{H\text{H}_2\text{O}} & \text{C}_{-}\text{C}_{-}\text{OH} & \rightarrow & \text{CH}_2\text{DCDO} \\
\text{CH}_2=\text{CHD} & + \text{PdCl}_4^{2-} + \text{H}_2\text{O} & \xrightarrow{H\text{H}_2\text{O}} & \text{C}_{-}\text{C}_{-}\text{OH} & \rightarrow & \text{CHD}_2\text{CHO}
\end{align*}
\]

Competitive isotope effect = \( \frac{k_H}{k_D} = 1.9 \)

- No deuterium incorporation is observed when reaction is run in D\(_2\)O

GROUP EXERCISE
Early Evidence for Inner-Sphere Mechanism: KIEs

- Inner-sphere was initially proposed based on observed kinetics in combination with kinetic isotope effect (circa 1964)

- Outer-sphere was disfavored because RDS is after hydroxypalladation reasonable to assume a KIE would be observed

- Stereochemical probe of the reaction is needed
Evidence For Outer-Spere Addition: Stille Study

- Trapping hydropalladated intermediate with CO

\[
\text{[D\-H\-H]}_{2} \quad \text{NaOAc} \quad \text{CH}_{3}\text{CN} \rightarrow \quad \text{[D\-H\-H]}_{2} \quad \text{CO} \quad \text{retentive insertion}
\]

Problems:
- Solvent is CH\textsubscript{3}CN not water
- Previous studies have shown that dimeric Pd(II) complexes were prone to anti addition
- Strong CO binds Pd strongly and could prevent coordination of H\textsubscript{2}O

Trans stereochemistry confirmed by \textsuperscript{1}H-NMR coupling constant
Evidence for Outer-Sphere: Backvall Study

- Product distribution depends on chloride and CuCl₂ concentrations:

\[
\text{H}_2\text{C} = \text{CH}_2 + \text{PdCl}_4^{2-} + \text{H}_2\text{O} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CO} + \text{H}_2\text{O}
\]

\[
\begin{align*}
[\text{Cl}^-] &< 1 \text{M} \\
[\text{CuCl}_2] &< 1 \text{M} \\
\rightarrow & \quad \text{Stereochemistry is lost}
\end{align*}
\]

\[
\begin{align*}
[\text{Cl}^-] &> 3 \text{ M} \\
[\text{CuCl}_2] &> 2.5 \text{ M} \\
\rightarrow & \quad \text{Stereochemistry is retained (potentially)}
\end{align*}
\]

- Major Assumptions:
  - Chlorohydrin and ethanal are formed from the same intermediate: \((\text{PdCl}_2(\text{H}_2\text{O})(\text{C}_2\text{H}_4))\)
  - Steric course of the reaction is not altered by running at higher chloride and cupric chloride concentrations
Evidence for Outer-Spere: Backvall Study

- Stereochemical course of trans-addition (outer-sphere):

\[
\text{PdCl}_4^{2-} 
\rightarrow 
\begin{array}{c}
\text{H}_2\text{C} = \text{C} \text{D} \\
\text{Cl-Pd-OH}_2 \\
\text{Cl}
\end{array} 
\]

\[
\rightarrow 
\begin{array}{c}
\text{H}_2\text{C} = \text{C} \text{D} \\
\text{Cl-Pd-OH}_2 \\
\text{Cl}
\end{array} 
\]

\[
\rightarrow 
\begin{array}{c}
\text{L}_3\text{Pd} \\
\text{trans}
\end{array} 
\]

\[
\rightarrow 
\begin{array}{c}
\text{Cl} \\
\text{OH}
\end{array} 
\]

- Stereochemical course of cis-addition (inner-sphere):

\[
\text{PdCl}_4^{2-} 
\rightarrow 
\begin{array}{c}
\text{H}_2\text{C} = \text{C} \text{D} \\
\text{Cl-Pd-OH}_2 \\
\text{Cl}
\end{array} 
\]

\[
\rightarrow 
\begin{array}{c}
\text{H}_2\text{C} = \text{C} \text{D} \\
\text{Cl-Pd-OH}_2 \\
\text{Cl}
\end{array} 
\]

\[
\rightarrow 
\begin{array}{c}
\text{L}_3\text{Pd} \\
\text{cis}
\end{array} 
\]

\[
\rightarrow 
\begin{array}{c}
\text{Cl} \\
\text{OH}
\end{array} 
\]

Similarly,

\[
\text{(Z)-d}_2\text{-ethene} 
\rightarrow 
\begin{array}{c}
\text{Cl} \\
\text{OH}
\end{array} 
\]

\[
\text{erythro}
\]

\[
\text{(Z)-d}_2\text{-ethene} 
\rightarrow 
\begin{array}{c}
\text{Cl} \\
\text{OH}
\end{array} 
\]

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\]
Evidence for Outer-Spere: Backvall Study

- Control experiments:
  1. (Z)/(E) isomerization was less than 1%
  2. Confirmed cleavage of 1° palladium-carbon bond by CuCl₂-LiCl proceeded with inversion
  3. Confirmed chlorohydrin was not being obtained from an epoxide intermediate

- Independent preparation of a hydroxypalladated ethene

- Stereochemistry predicted for chlorohydrin via epoxide intermediate

- 40% yield > 96% threo
Evidence for Outer-Sphere: Backvall Study

Model for anti addition predicts:

\[
\text{(E)-ethene-d}^2 \rightarrow \text{(Z)-ethylene oxide-d}^2 \\
\text{(Z)-ethene-d}^2 \rightarrow \text{(E)-ethylene oxide-d}^2
\]

- Results clearly indicate that under these reaction conditions an outer-sphere mechanism is operative
Evidence for Outer-Sphere: Backvall Study

- Backvall Outer-Sphere Mechanism:

$$
\text{PdCl}_4^{2-} + \text{C}_2\text{H}_4 \xrightleftharpoons{\text{H}_2\text{O}} 2\text{[Cl]}^{-} \quad \text{1}
$$

$$
\begin{align*}
\text{Cl-Pd-CH}_2\text{H}_2 + \text{H}_2\text{O} & \xrightarrow{\text{K}_3} \left[ \text{Cl-Pd-OH}_2 \right]^{-} + \text{H}^{+} \\
& \xrightarrow{\text{RDS}} \left[ \text{Cl-Pd-OH}_2 \right]^{-} + \text{H}^{+} \\
& \xrightarrow{\text{RDS}} \text{Cl-PdOH}_2 \\
& \xrightarrow{\text{fast}} \text{Cl-Pd-CH}_2\text{OH} \\
& \xrightarrow{\text{RDS}} \text{Cl-PdOH}_2 \\
& \xrightarrow{\text{fast}} \text{Cl-PdOH}_2 \\
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Reevaluation of Inner and Outer Sphere Mechanisms

- Kinetically, the main difference between the mechanisms is the position of the rate-determining step:
  - Outer-sphere: Trans-hydroxypalladation is in equilibrium (proton inhibition) and RDS occurs downstream of this step
  - Inner-sphere: Proton inhibition results from Acid/Base equilibrium prior to cis-hydroxypalladation and the RDS is the hydroxypalladation

- Distinguishing the mechanisms requires an olefin that will undergo an experimentally observable change if the hydroxypalladation is in equilibrium
Evidence for Inner-Sphere: Isomerization of Allylic Alcohol

- Isomerization of deuterated allyl alcohol

\[
\begin{align*}
\text{D} & \quad \text{D} \\
\text{H} & \quad \text{H} \\
\text{1a} & \\
\begin{array}{c}
\text{\textbf{D}} \\
\text{\textbf{H}} \\
\text{\textbf{H}} \\
\text{\textbf{D}} \quad \text{\textbf{H}} \\
\text{\textbf{H}}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad + \quad \text{PdCl}_4^{2-} \\
& \quad + \quad \text{H}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Pd(II)} \\
\text{Oxidation Products}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{O} & \quad + \quad \text{PdCl}_4^{2-} \\
& \quad + \quad \text{HO} \\
\begin{array}{c}
\text{D} \\
\text{D} \\
\text{H} \\
\text{D} \quad \text{D} \\
\text{H}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{1b} & \\
\begin{array}{c}
\text{D} \\
\text{D} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array}
\end{align*}
\]

Experimental Predictions

**Inner-sphere mechanism:**
- \( k_2 \gg k_{-1} \)
- At early conversion very little isomerization will be observed

**Outer-sphere mechanism:**
- \( k_2 << k_{-1} \)
- At early conversion isomerization will be observed
Evidence for Inner-Sphere: Isomerization of Allylic Alcohol

- Directing influence of hydroxyl group

\[
\begin{align*}
\text{Me} & \quad + \quad \text{PdCl}_4^{2-} \\
\text{Me} & \quad + \quad \text{PdCl}_4^{2-} \\
\text{Me} & \quad + \quad \text{PdCl}_4^{2-}
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Evidence for Inner-Sphere: Isomerization of Allylic Alcohol

Control Experiments:

- No detectable isomerization observed in the absence of Pd (II)
- Kinetic study revealed that the oxidation of allyl alcohol obeyed the same rate expression as observed for ethene (eqn 1)

Initial Result:

\[
\begin{align*}
\text{D-CH=CHCHOH} & + \text{PdCl}_4^{2-} + \text{H}_2\text{O} \\
\text{std. kinetic rxn conditions} & \rightarrow \text{Oxidation Products}
\end{align*}
\]

Less 3% isomerization observed in recovered starting material after oxidation had proceeded to 50% conversion

Evidence for Inner-Sphere: Isomerization of Allylic Alcohol

\[
\begin{align*}
\text{D} & \quad \text{D} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
1a & & \text{PdCl}_4^{2-} \\
& \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\end{align*}
\]

\[ [ \text{LiCl} ] = 0.2-3.3 \text{ M} \]
\[ [ \text{HClO}_4 ] = 0.2-2.0 \text{ M} \]
\[ [ \text{PdCl}_4^{2-} ] = 0.01-0.10 \text{ M} \]

Quinone, H_2O

\[ \text{Isomerization} \]

\[ \text{oxidation} \]

\[
\begin{align*}
\text{D} & \quad \text{D} & \quad \text{H} & \quad \text{H} \\
\text{Me} & & \text{O} & \quad \text{H} & \quad \text{OH} \\
\end{align*}
\]

**Kinetic Data for Isomerization**

<table>
<thead>
<tr>
<th>run</th>
<th>[PdCl_4^{2-}]</th>
<th>[H^+]</th>
<th>[Cl^-]</th>
<th>10^3t_{1/2}, \text{s}^{-1}</th>
<th>10^5k_{\text{obsd}}, \text{s}^{-1}</th>
<th>10^3(k_i \text{ or } k_{\text{ex}}), \text{d}^{-1} \text{s}^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01</td>
<td>1.0</td>
<td>0.2</td>
<td>5.4</td>
<td>6.4</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>1.0</td>
<td>1.0</td>
<td>5.6</td>
<td>6.1</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>0.10</td>
<td>1.0</td>
<td>1.5</td>
<td>3.5</td>
<td>10.0</td>
<td>1.5</td>
</tr>
<tr>
<td>10</td>
<td>0.02</td>
<td>0.5</td>
<td>3.3</td>
<td>40</td>
<td>0.87</td>
<td>1.4</td>
</tr>
</tbody>
</table>

\[
\text{Rate} = \frac{-d[\text{olefin}]}{dt} = k_{\text{ox}} \frac{[\text{PdCl}_4^{2-}][\text{olefin}]}{[\text{H}^+][\text{Cl}^-]^2} \quad (1) \quad \text{Rate expression for oxidation}
\]

\[
\text{Rate} = \frac{-d[\text{olefin}]}{dt} = k_i \frac{[\text{PdCl}_4^{2-}][\text{olefin}]}{[\text{Cl}^-]} \quad (2) \quad \text{Rate expression for isomerization}
\]
Evidence for Inner-Sphere: Isomerization of Allylic Alcohol

• Question: Why is isomerization the predominate process at high [Cl\textsuperscript{-}]?

\[
\text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_2\text{OH} \quad \text{H}_2\text{O} \quad \leftrightarrow \quad \text{HOH}_2\text{C} \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_2\text{OH} \quad + \quad \text{H}^+ \quad \leftrightarrow \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_2\text{OH} \quad + \quad \text{Cl}^- \quad \downarrow \text{Unfavorable at high [Cl\textsuperscript{-}]} \quad \text{HOH}_2\text{C} \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{Cl} \quad \text{CH}_2\text{OH} \quad + \quad \text{Cl}^- \quad \downarrow \text{Labile coordination site}
\]

• Compare to proposed wacker intermediates that lead to oxidation

\[
\text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{Cl} \quad \text{OH}_2 \quad + \quad \text{H}_2\text{O} \quad \leftrightarrow \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{OH}_2 \quad + \quad \text{H}^+ \quad \rightarrow \quad \text{CH}_3\text{CHO} \quad \quad (\text{Slow})
\]

\[
\text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{Cl} \quad \text{OH} \quad + \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{Cl} \quad \text{Pd} \quad \text{Cl} \quad \text{OH}_2 \quad + \quad \text{H}^+ \quad \rightarrow \quad \text{CH}_3\text{CHO} \quad \quad (\text{Labile coordination site})
\]
Evidence for Inner-Sphere: Kinetic Probe

• Design a kinetic probe in which RDS is hydroxypalladation

Assumption:
- Exchange is completely symmetric then $k_1 = k_{-1}'$ and $k_{-1} = k_{-1}'$, then the rate of isomerization only depends on the rate of formation of 3, not on its equilibrium conc.

Prediction:
- Kinetics will follow rate equation (1) if syn hydroxypalladation is operative (b/c proton equilibrium is prior to RDS)
- Kinetics will follow rate equation (3) if trans hydroxypalladation is operative

$$\text{Rate} = \frac{k_i \left[ \text{PdCl}_4^{-2} \right] [\text{olefin}]}{[\text{Cl}^{-}]^2 [\text{H}^+]} \quad (1)$$
$$\text{Rate} = \frac{k_i \left[ \text{PdCl}_4^{-2} \right] [\text{olefin}]}{[\text{Cl}^{-}]^2} \quad (3)$$
Evidence for Inner-Sphere: Kinetic Probe

Results:

**Kinetic Data**

<table>
<thead>
<tr>
<th>run</th>
<th>[PdCl$_4^{2-}$]</th>
<th>[H$^+$]</th>
<th>[Cl$^-$]</th>
<th>$10^8k_{obsd}, s^{-1}$</th>
<th>$10^8(k_i$ or $k_{ex}) d, s^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.007</td>
<td>0.05</td>
<td>0.5</td>
<td>7.7</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>0.015</td>
<td>0.05</td>
<td>0.5</td>
<td>13</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>0.008</td>
<td>0.10</td>
<td>0.25</td>
<td>15</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>0.016</td>
<td>0.10</td>
<td>1.0</td>
<td>1.3</td>
<td>0.81</td>
</tr>
<tr>
<td>5</td>
<td>0.008</td>
<td>0.05</td>
<td>0.5</td>
<td>6.0</td>
<td>0.94</td>
</tr>
<tr>
<td>6</td>
<td>0.008</td>
<td>0.15</td>
<td>0.5</td>
<td>2.1</td>
<td>0.98</td>
</tr>
<tr>
<td>7</td>
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<td>0.20</td>
<td>0.5</td>
<td>1.5</td>
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</tr>
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<td>10</td>
<td>0.004</td>
<td>0.10</td>
<td>0.50</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>11</td>
<td>0.032</td>
<td>0.40</td>
<td>0.50</td>
<td>3.5</td>
<td>1.1</td>
</tr>
<tr>
<td>12</td>
<td>0.008</td>
<td>0.10</td>
<td>0.5</td>
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<td>1.47</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**Isomerization**

**18O Exchange**

- Kinetic data shows clear inverse dependence on [H$^+$]
- The value of $k_i$ was calculated from eqn 1 and remains fairly constant over range of Pd, Cl and H concentrations

\[
\text{Rate} = \frac{k_i [\text{PdCl}_4^{-2}][\text{olefin}]}{[\text{Cl}^{-}]^2[H^+]} \quad (1)
\]

\[
\text{Rate} = \frac{k_i [\text{PdCl}_4^{-2}][\text{olefin}]}{[\text{Cl}^{-}]^2} \quad (3)
\]

- Kinetic data is consistent with syn hydoxypalladation, what about stereochemistry of isomerization
Evidence for Inner Sphere: Kinetic Probe

- Prediction on stereochemical outcome of the isomerization
  - Syn should lead to inversion and Anti should give retention

Isomerization Results:

<table>
<thead>
<tr>
<th>substrate</th>
<th>% ee</th>
<th>[Cl^-]</th>
<th>catalyst</th>
<th>% isomerization</th>
<th>% S^d</th>
<th>% R^d</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>100</td>
<td>0.10</td>
<td>PdCl_4^{2-}</td>
<td>30</td>
<td>32.5*</td>
<td>67.5</td>
</tr>
<tr>
<td>R</td>
<td>100</td>
<td>0.05</td>
<td>PdCl_4^{2-}</td>
<td>48</td>
<td>50.0*</td>
<td>50.0</td>
</tr>
<tr>
<td>S</td>
<td>100</td>
<td>0.10</td>
<td>PdCl_4^{2-}</td>
<td>25</td>
<td>72.5</td>
<td>27.5*</td>
</tr>
<tr>
<td>S</td>
<td>100</td>
<td>0.05</td>
<td>PdCl_4^{2-}</td>
<td>50</td>
<td>50.0</td>
<td>50.0*</td>
</tr>
</tbody>
</table>

- Stereochemistry of isomerization is also consistent with a syn hydroxypalladation
- Downside this alkene is not a good model of an actual Wacker substrate
Evidence for Inner Sphere: Transfer of Chirality

- Chirality Transfer to study modes of addition

![Chemical structures](image)

- Study stereochemistry of products at both high and low chloride concentrations

- Anti-addition at low chloride will give the opposite absolute stereochemistry
Evidence for Inner Sphere: Transfer of Chirality

Controls:

1. Test a nucleophile whose mode of addition is known to be syn regardless of chloride concentration

\[
\text{Me} \quad \text{H} \quad \text{C} = \text{C} \quad \text{H} \quad \text{Me} \quad \text{HO}
\]

\((R)-Z-3a\) (53% ee)

\[
\text{Li}_2\text{PdCl}_4, \text{NEt}_3 \quad \text{CuCl}_2, \text{PhHgCl} \quad \text{MeOH}
\]

\[
\begin{align*}
\text{O} & \quad \text{Me} & \quad \text{H} \\
\text{Me} & \quad \text{H} & \quad \text{Ph}
\end{align*}
\]

\((R)-2\) Low Chloride

84% yield

30% ee

Similarly,

\[
\text{Me} \quad \text{Ph} \quad \text{H} \quad \text{Me}
\]

\((S)-Z-3a\) (74% ee)

High Chloride

70% yield

68% ee

Results:

<table>
<thead>
<tr>
<th>run</th>
<th>[Cl(^-)] (M)</th>
<th>X</th>
<th>solvent</th>
<th>allyl alcohol (%ee)</th>
<th>product (%ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>Ph</td>
<td>CH(_3)OH</td>
<td>(R)-(Z)-3a (53)</td>
<td>(R)-CH(_3)C(=O)CH(_2)CH(Ph)CH(_3), (R)-5a&quot; (30%)</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>Ph</td>
<td>CH(_3)OH</td>
<td>(S)-(Z)-3a (74)</td>
<td>(S)-(Z)-CH(_3)CH=CHCH(Ph)CH(_3), (S)-Z-3a&quot; (68%)</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>OH</td>
<td>H(_2)O</td>
<td>(R)-(Z)-3b (66)</td>
<td>(R)-CH(_3)C(=O)CH(_2)CH(=O)C(_2)H(_5), (R)-5b (42%)</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>OH</td>
<td>H(_2)O</td>
<td>(R)-(Z)-3c (76)</td>
<td>(S)-(Z)-C(_2)H(_5)CH=CHCH(=O)CH(_3), (S)-Z-3b (76%)</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>OCH(_3)</td>
<td>CH(_3)OH</td>
<td>(R)-(Z)-3a (53)</td>
<td>(R)-CH(_3)C(=O)CH(_2)CH(OCH(_3))CH(_3), (R)-5a' (42%)</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>OCH(_3)</td>
<td>CH(_3)OH</td>
<td>(S)-(Z)-3a (74)</td>
<td>(R)-(Z)-CH(_3)CH=CHCH(OCH(_3))CH(_3), (R)-Z-3a' (68%)</td>
</tr>
</tbody>
</table>

- Results suggest a syn hydroxypalladation at low chloride concentrations and an anti hydroxypalladation at high chloride concentrations
Computational Study of the Wacker Oxidation

- Combined catalytic cycles of the Wacker Oxidation

Wacker Conditions:

**LL** conditions (Industria): Low [Cl\(^-\)] (< 1M) and low [CuCl\(_2\)] (< 1M) yield only aldehyde via internal syn addition (rate eqn 1)

**HH** conditions: high [Cl\(^-\)] (> 3 M) and high [CuCl\(_2\)] (> 2.5M) yield both aldehyde and chlorohydrin via external anti addition (rate eqn 2)

**HL** conditions: yield no oxidation products

**LH** conditions: yield syn and anti products, and obey a combined rate law

- Employed computational models (hybrid density functional theory and implicit solvation methods) to investigate relevant steps in cycle

Computational Study of the Wacker Oxidation

Key Results (Syn pathway):

1. For the syn manifold, the calculated barrier for the deprotonation from $3$ (5.8 kcal/mol) to $4$ (15.3 kcal/mol) is plausible under the standard conditions (pH 0-2).

2. The calculated barrier for $4$ to $5$ is $\Delta G^{**} = 33.4$ kcal/mol and is far too high to be feasible for the Wacker process ($\Delta G^{**}_{\text{expt}} = 22.4$ kcal/mol).

Overall for syn: $1 \rightarrow 2 \rightarrow \text{TS-ALE1} \rightarrow 3 \rightarrow \text{TS-INT} \rightarrow 10 \rightarrow \text{TS-ISO (RDS)} \rightarrow 6 \rightarrow \text{product}$
Computational Study of the Wacker Oxidation

Key Results (anti-pathway):

- Overall for anti: $1 \rightarrow 2 \rightarrow \text{TS-EXT (RDS)} \rightarrow 9$-H $\rightarrow \text{TS-ALE2} \rightarrow 10 \rightarrow \text{TS-ISO} \rightarrow 6 \rightarrow$ product

- Since anti obeys rate equation 2 there is no proton inhibition so TS-EXT being the RDS is consistent with rate law
Computational Study of Wacker Oxidation

Results: Role of CuCl₂

Stabilizing Interactions:
CuCl₂ stabilizes both TS-ISO (by -6.0 kcal/mol) and TS-EXT (by -1.9 kcal/mol)

Destabilizing Interactions:
CuCl₂ destabilizes TS-ALE1 (by +2.7 kcal/mol)
- Predicts at HH anti pathway is strongly favored
Conclusions

• Mechanism of the Wacker oxidation is dependent on the reaction conditions and is best described by two competing processes

<table>
<thead>
<tr>
<th>Inner-Sphere Hydroxypalladation</th>
<th>Outer-Sphere Hydroxypalladation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Occurs at low [Cl\textsuperscript{-}] and low [CuCl\textsubscript{2}]</td>
<td>- Occurs at high [Cl\textsuperscript{-}] and high [CuCl\textsubscript{2}]</td>
</tr>
<tr>
<td>- Rate is best described by eqn 1</td>
<td>- Rate is best described by eqn 2</td>
</tr>
<tr>
<td>- RDS is still debated</td>
<td>- RDS is still debated</td>
</tr>
</tbody>
</table>

• Kinetic and stereochemical models have been well studied and future work may need to relay more heavily on computational models
Excellent Reviews:

Initial Kinetic Studies:
(1) Smidt, J. et. al. Angew. Chem. Int. Ed. 1962, 1, 80-88

Backvall Study:
(1) Backvall, J. E. et. al. J. Am. Chem. Soc. 1979, 101, 2411-2416

Computational Studies:
(3) Siegbahn, E. M. J. Phys. Chem. 1996, 100, 14672-14680
Patrick Henry
“Give me liberty or give me death”

Updated Version
“Give me syn or give me death”

http://en.wikipedia.org/wiki/Patrick_Henry
Given that (1) is an intermediate the reaction, write a mechanism that accounts for the formation acetaldehyde observed in the KIE studies.

\[
\begin{align*}
\text{C}_2\text{D}_4 + \text{PdCl}_4^{2-} + \text{H}_2\text{O} & \rightarrow \text{CD}_3\text{CDO} + \text{Pd}(0) + 2 \text{HCl} + 2 \text{Cl}^- \\
\text{C}_2\text{H}_4 + \text{PdCl}_4^{2-} + \text{H}_2\text{O} & \rightarrow \text{CH}_3\text{CHO} + \text{Pd}(0) + 2 \text{HCl} + 2 \text{Cl}^- \\
\end{align*}
\]

Observed KIE = \( k_H / k_D = 1.07 \)

Competitive isotope effect = \( k_H / k_D = 1.9 \)

Reaction run in \( \text{D}_2\text{O} \) shows no incorporation
• Recent computational work questions ability to undergo β-Hydride elimination from -OH (see Goddard, W. A. JACS, 2006, 128, 3132 and reference therein)
Backup: Ruling out $\pi$-Allyl Pathway

Rate of exchange is equal to rate of isomerization

<table>
<thead>
<tr>
<th>run</th>
<th>$[\text{PdCl}_2]^{-}$</th>
<th>$[\text{H}^+]$</th>
<th>$[\text{Cl}^-]$</th>
<th>$10^4 \text{k}_{\text{obs}}$ $\text{s}^{-1}$</th>
<th>$10^4 (k_i$ or $k_{ex})$ $\text{s}^{-1}$</th>
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<td>0.98</td>
</tr>
<tr>
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<td>11</td>
<td>0.052</td>
<td>0.40</td>
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<td>0.05</td>
<td>1.0</td>
<td>1.47</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Rate of isomerization is equal to 1/2 rate of exchange
Backup: Schematic for Industrial Wacker Process