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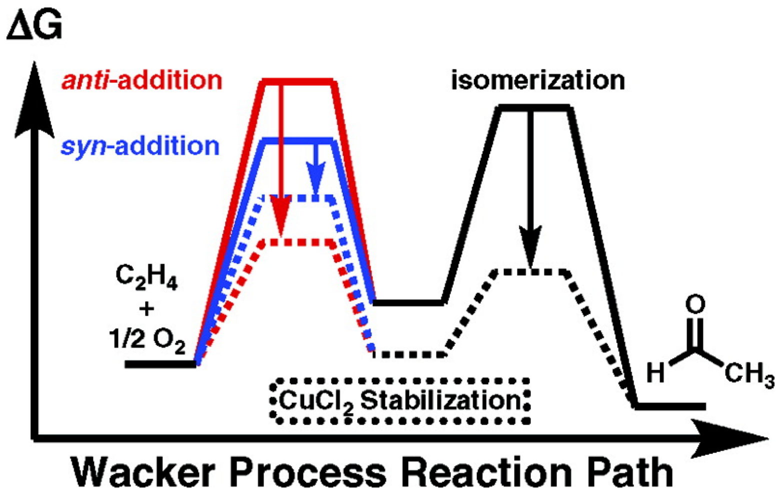

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Unraveling the Wacker Oxidation Mechanisms

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The Wacker process—olefin oxidation via a Pd(II)Cl_2 catalyst and an air-recyclable $CuCl_2$ co-oxidant (Scheme 1)—was one of the most important industrial breakthroughs in the fabrication of organic chemicals, and is widely regarded as one of the quintessential organometallic processes.[1] Besides its industrial importance, the Wacker process and its analogues are continually used in fields relating to catalysis and natural product synthesis.[2] Since its discovery in 1959,[3a] mechanistic studies have identified many important aspects;[3] however, several essential observations remain unexplained, chief of which is why the Wacker process mechanism is dependent on reaction conditions .

Experiments indicate at least two competing mechanisms, with different rate laws and different product distributions dependent on [Cl^-] and [$CuCl_2$]. Four different reaction conditions are possible, and each yields unique experimental observations.

- **LL** conditions (industrial conditions): low [Cl^-] (<1 M) and low [$CuCl_2$] (<1 M) yield only aldehyde products, via internal syn addition according to the rate law shown in eq 5.
- **HH** conditions: high [Cl^-] (>3.0 M) and high [$CuCl_2$] (>2.5 M) yield both aldehyde and chlorohydrin products, via external anti nucleophilic addition according to the rate law in eq 6.[5a]
- **HL** conditions: high [Cl^-] and low [$CuCl_2$] yield no oxidation.[5b]
- **LH** conditions: low [Cl^-] and high [$CuCl_2$] yield syn and anti products, with a combined rate law involving eqs 5 and 6 (Scheme 2).[5c]

Scheme 3 combines two mechanistic proposals that are thought to explain the experimental observations. At **LL** conditions, Henry suggested an inner-sphere process (leading to syn products), involving two fast ligand exchange reactions (**1** → **3**), followed by pre-equilibrium deprotonation (**3** → **4**), and then rate-determining syn hydroxypalladation (**4** → **5**) to yield the rate law in eq 5.[3c] Bäckvall then suggested that two facile hydride shifts (**6** → **8**) would result in an alkyl−alcohol species.[3d] Products may then undergo water-assisted reductive elimination to form acetaldehyde products.[3e]

Under **HH** conditions, an outer-sphere process was suggested (resulting in anti products) where an *external* H_2O attacks the olefin in **2**, yielding **9** after deprotonation of the intermediate $-CH_2-OH_2(+)$ cation, **9-H**.[4b] This step is thought to be rate-determining, on the basis of the rate-law in eq 6.[4b] Under **HL** conditions, experiments suggest an equilibrium between **2** and **9**, without formation of either product.[5b] Under **LH** conditions both internal and external pathways appear to be accessible.

To elucidate the mechanisms of the Wacker process, we used hybrid density functional theory and implicit solvation methods with an empirical correction term for cationic species[6] to investigate the relevant steps shown in Scheme 3. *Surprisingly, we found that the suggested inner-sphere mechanism does not account for the experimental and theoretical observations.*

For the previously described inner-sphere (syn product) mechanism, we find that deprotonation from **3** (5.8 kcal/mol) → **4** (15.3 kcal/mol) is possible under standard conditions of pH = 0−2 (calculated $\mathbf{3}_{\mathrm{p}K_a} = 7.0$). However, this causes the *barrier* for **4** → **5** to be $\Delta G^\ddagger = 33.4$ kcal/mol. This barrier is far too high to be feasible for the Wacker process ($\Delta G^\ddagger_{\mathrm{expt}} = 22.4$ kcal/mol).

Scheme 1. The Wacker Process Reaction Equations[a]

$$C_2H_4 + Pd(II)Cl_2 + H_2O \rightarrow CH_3CHO + Pd(0) + 2\,HCl \qquad (1)$$

$$Pd(0) + 2\,Cu(II)Cl_2 \rightarrow Pd(II)Cl_2 + 2\,Cu(I)Cl \qquad (2)$$

$$2\,Cu(I)Cl + 2\,HCl + 1/2\,O_2 \rightarrow 2\,Cu(II)Cl_2 + H_2O \qquad (3)$$

$$\text{Net: } C_2H_4 + 1/2\,O_2 \rightarrow CH_3CHO \qquad (4)$$

[a] (1) olefin oxidation, (2) reprocessing of Pd(0) with Cu(II), (3) reprocessing of Cu(I) with O_2, (4) overall net reaction.

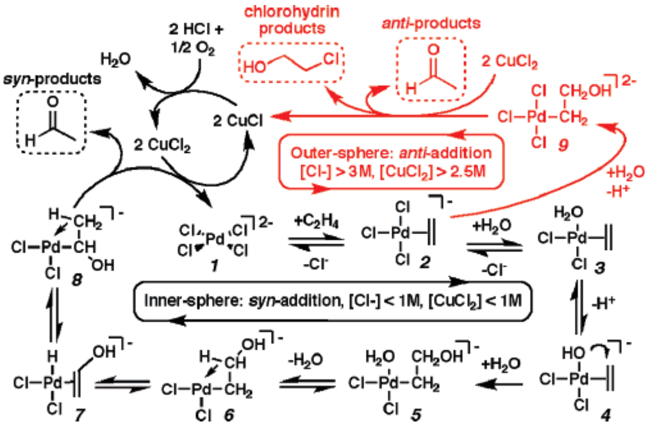
Scheme 2. The Wacker Process Rate Laws[a]

$$\mathrm{Rate}_{\mathbf{LL}} = \frac{k[PdCl_4^{2-}][\mathrm{olefin}]}{[H^+][Cl^-]^2} \qquad (5)$$

$$\mathrm{Rate}_{\mathbf{HH}} = \frac{k[PdCl_4^{2-}][\mathrm{olefin}]}{[Cl^-]} \qquad (6)$$

[a] (5) rate law at high [Cl-] and high [$CuCl_2$] (6) rate law at low [Cl-] and low [$CuCl_2$] (standard wacker process conditions).

Scheme 3. A Composite Mechanistic Scheme for Competitive Syn (black) and Anti (red) Nucleophilic Addition in the Wacker Process



However, we found two pathways with plausible barriers, all in full agreement with experimental findings. These pathways feature *three* key transition states, ranging from +22.7 kcal/mol to +23.3 kcal/mol in energy (see Figure 1).[7] These barriers are, within the margin of error, essentially equivalent in energy, and each is a possible rate-determining step (RDS).

For the inner-sphere mechanism, the first critical barrier is for the step **2** → **3**, which occurs through an associative ligand exchange (**TS-ALE1**, +23.3 kcal/mol). Note that **TS-ALE1** being the RDS is not consistent with the observed rate law under **LL** conditions (eq 5).

Although **3** → **4** → **5** is not a feasible process (see previous), we find that the syn hydroxypalladation can occur in a water-catalyzed process (**TS−INT**, +18.0 kcal/mol)[7] where a solvent water simultaneously deprotonates the coordinating water in **3** to form **10** (+15.9 kcal/mol). This can be considered a neutral

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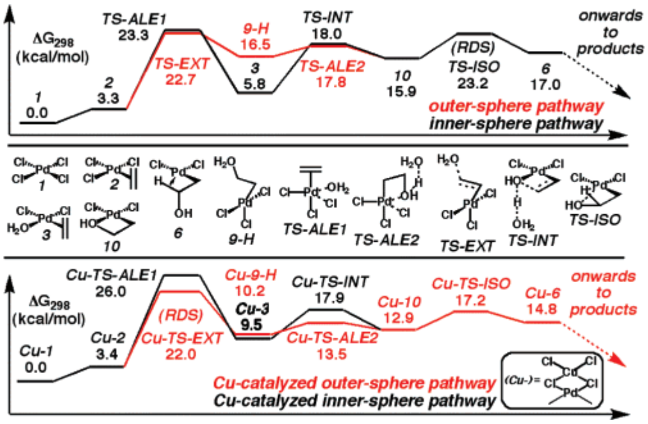

Figure 1. Calculated results on the Wacker process mechanism without $CuCl_2$ (top, black) and with $CuCl_2$ (bottom, red). Listed energies are ΔG_{298} in kcal/mol. See Supporting Information for additional details.

analogue of **4** → **10**, but avoids both the cost of deprotonating the reactant and the high energy of forming a non-coordinating (+)-H_2O-R cation.[8] The energy for **TS−INT** without the extra water is +43.5 kcal/mol.

Subsequently, a 120° rotation around the C−C bond converts **10** → **6** (+17.0 kcal/mol). We find that the barrier for this conversion, **TS−ISO** (+23.2 kcal/mol), is another critical barrier and is potentially a RDS. Contrary to **TS-ALE1**, if **TS−ISO** were the RDS of the inner-sphere process, the resulting rate law would correspond to eq 5. From **6**, the mechanism may then proceed as outlined earlier in Scheme 3 (i.e., **6** → **7** → **8** → → **1**).

For the external mechanism, we find an external nucleophilic attack transition state (**TS-EXT**, +22.7 kcal/mol) which connects **2** → **9**-H (+16.5 kcal/mol).[7] Entropic effects of water play a crucial role in **TS-EXT** since $\Delta H^{\ddagger}$ is low (8.7 kcal/mol).[3f] **TS-EXT** being the RDS of the outer-sphere mechanism is in agreement with the rate-law in eq 6 and previous deductions by Henry.[5] **9**-H may proceed directly to **10** via another water-catalyzed step, **TS-ALE2** (+17.8 kcal/mol).[7] At **10**, both pathways have converged and exit via **TS−ISO** and then **6**.

The close relative energies of the three critical barriers are in one sense encouraging, as we know from experiment that the energies of the competing steps must be quite close. Unfortunately, this also means that we cannot differentiate the mechanisms solely on the basis of our calculated energies. However, by comparing our calculated mechanisms with the experimental results, we can present a model that explains the controversial experimental observations. In the internal attack, the sequence [**1** → **2** → **TS-ALE1** → **3** → **TS−INT** → **10** → **TS−ISO** → **6** → products] yields syn addition products according to eq 5 with **TS−ISO** as the RDS. In the external attack, the sequence [**1** → **2** → **TS-EXT** → **9-H** → **TS-ALE2** → **10** → **TS−ISO** → **6** → products] yields anti addition products according to eq 6 with **TS-EXT** as the RDS.

This model assumes that our calculated energy of **TS-EXT** is slightly too low, as **TS-EXT** should be >**TS−ISO**, and that the energy of **TS-ALE1** is slightly too high, as it should be <**TS−ISO**. The differences are well within the margin of error, however.

That the mechanisms shift from syn to anti addition products when [Cl^-] increases is apparent from eqs 5 and 6, as is the complete inhibition at high [Cl^-]. However, these rate expressions do not explain why $CuCl_2$ re-enables the mechanism at high [Cl^-].

To explore this, we added explicit $CuCl_2$ to our mechanisms and found that $CuCl_2$ stabilizes **TS−ISO** by −6.0 kcal/mol, stabilizes **TS-EXT** by −1.9 kcal/mol, but destabilizes **TS-ALE1** by +2.7 kcal/mol.[7] This causes the overall barriers to drop enough to overcome even a relatively large [Cl^-] inhibition, selectively favoring the anti addition pathway. Thus, at **LH** conditions, our model predicts both pathways will be accessible, in agreement with observations that both syn and anti products are created.[5c] At **HH** conditions, our model predicts that anti products will strongly predominate, also in agreement with experiment.[5a] Intriguingly, this result implies that eq 6 should include a [$CuCl_2$] term, while eq 5 should not. Validation of this should be possible.

The surprisingly strong stabilization by the oxidant $CuCl_2$ could also explain the observed formation of chlorohydrin products at higher [$CuCl_2$]. It is not clear exactly how this occurs, but our preliminary results indicate that forming a C−Cl bond from either reductive elimination or nucleophilic attack (S_N2) directly from **9**-H has a barrier >50 kcal/mol. Furthermore, since the ratio of chlorohydrin to aldehyde products increases with increasing [$CuCl_2$],[5c] this implies a second- (or higher) order dependence of chlorohydrin formation on $CuCl_2$. Consequently, eq 6, which only describes loss of starting material, should be replaced by the sum of two different terms, that is, eq 7, where k_1 and k_2 are the rate constants associated with the formation of aldehyde and chlorohydrin products, respectively.

$$\mathrm{Rate}_{\mathrm{HH}} = \frac{k_1[\mathrm{PdCl_4}^{2-}][\mathrm{olefin}][\mathrm{CuCl_2}]}{[\mathrm{Cl}^-]} + \frac{k_2[\mathrm{PdCl_4}^{2-}][\mathrm{olefin}][\mathrm{CuCl_2}]^2}{[\mathrm{Cl}^-]} \quad (7)$$

In summary, using theoretical methods, we have identified the two main mechanisms for the Wacker process, both of which are in full agreement with experimental observations and rate laws. At low [Cl^-] and low [$CuCl_2$], the rate determining step is not hydroxypalladation as typically believed, but isomerization from **10** → **6**, a step that is necessary for subsequent hydride transfer processes. At high [Cl^-] and high [$CuCl_2$], the rate-determining step is an external nucleophilic attack by water, which is only low-energy in the presence of [$CuCl_2$]. Consequently, the rate law at high [Cl^-] and [$CuCl_2$] should include a [$CuCl_2$] term.

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Supporting Information Available: Discussion of free-energy calculations, calculated geometries, and calculated energies terms. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Spessard, G. O.; Miessler, G. L. *Organometallic Chemistry*; Prentice Hall: Upper Saddle River, 1997.
(2) See for example: (a) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778. (b) Cornell, C. N.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 4117. (c) Lee, J. M.; Ahn, D. S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12954.
(3) (a) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem., Int. Ed.* **1959**, *71*, 176. (b) Phillips, F. C. *J. Am. Chem. Soc.* **1894**, *16*, 225. (c) Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246. (d) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. (e) Keith, J. A.; Oxgaard, J.; Goddard, W. A. *J. Am. Chem. Soc.* **2006**, *128*, 3132. (f) Siegbahn, P. E. M. *J. Phys. Chem.* **1996**, *100*, 14672.
(4) For a review of experimental studies see: (a) Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel Publishing Company: Boston, MA, 1980. (b) Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 1, p 2119.
(5) (a) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082. (b) Gregor, N.; Zaw, K.; Henry, P. M. *Organometallics* **1984**, *3*, 1251. (c) Francis, J. W.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1996**, *112*, 317.
(6) Calculations were carried out with Jaguar 6.5 using B3LYP/LACVP**++//B3LYP/LACVP** and implicit water solvation. See Supporting Information for references and additional details.
(7) See Supporting Information for details.
(8) While this contradicts a statement in ref 4b, this reference did not consider the existence of species such as **10**.

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