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Comment on “Mechanism and Kinetics of the Wacker Process: A Quantum Mechanical Approach”

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Comment on “Mechanism and Kinetics of the Wacker Process: A Quantum Mechanical Approach”

Recently, a paper (“*Mechanism and Kinetics of the Wacker Process: A Quantum Mechanical Approach*” by S. Ali Beyramabadi, Hossein Eshtiagh-Hosseini, Mohammed R. Housaindokht, and Ali Morsali) appeared in *Organometallics* which concludes that anti-nucleophilic attack is the rate-determining step for the Wacker process (aerobic olefin oxidation via PdCl₂ and CuCl₂ in aqueous hydrochloric acid solution) under standard conditions.¹ This paper also claims that these conclusions are consistent with experimental observations. In fact, as shown below, these conclusions dramatically contradict both experimental observations and other more complete calculations. Because of the importance of the Wacker process to the chemical industry and the many controversies and inconsistencies that confused the understanding of this system, we felt it important to bring to the attention of the *Organometallics* community that ethylene and olefin oxidation via PdCl₂ and CuCl₂ under standard conditions (low [Cl⁻] and low [CuCl₂]) almost certainly proceeds via syn-nucleophilic attack.

Since the late 1950s, several research groups have contributed to an expansive set of experimental work to elucidate this fundamental organometallic process.² Despite this formidable body of work, several key questions have remained uncertain, including the actual chemical reaction mechanisms involved in olefin oxidation. Experiments have not yet provided a conclusive picture of this mechanism, making it a target for modern quantum mechanics (QM) simulations.

Most challenging here is to resolve the apparently contradictory results from previous experimental studies. In particular, there was a debate whether nucleophilic attack proceeds via a syn (generally presumed inner sphere)³ or an anti (generally presumed outer sphere)⁴ mechanism. Available experimental evidence had been interpreted to support either of these mechanisms. More recently, experimental kinetics and stereochemical investigations by Henry and co-workers determined that *both* processes could occur, depending on the ion concentrations under which the reaction is run.⁵

Using alkyl-group-substituted olefins, Henry and co-workers showed that a syn-nucleophilic attack process dominates under standard conditions (low [Cl⁻] and low [CuCl₂], here abbreviated **LL**), while an *isomerization* process dominates under high [Cl⁻] and low [CuCl₂] (**HL**) conditions. Furthermore, although substituted olefins are oxidized with the same rate law as ethylene under **LL** conditions (eq 1), it was found that ethylene

and allyl-alcohols are oxidized via *anti*-nucleophilic attack and chlorohydrin products at **HH** conditions (where both [Cl⁻] and [CuCl₂] are high).

It is important to note here that the oxidation equation contains a first order inhibition in protons and second order inhibition in [Cl⁻].

$$\text{rate}_{\text{LL}} = \frac{k[\text{PdCl}_4][\text{olefin}]}{[\text{H}^+][\text{Cl}^-]^2} \quad (1)$$

Under **HL** conditions, both substituted and unsubstituted olefins isomerize according to the rate law in eq 2, which now only contains a first-order inhibition in [Cl⁻].

$$\text{rate}_{\text{HL}} = \frac{k[\text{PdCl}_4][\text{olefin}]}{[\text{Cl}^-]} \quad (2)$$

This second rate law is believed to resemble the rate law for chlorohydrin formation under **HH** conditions; however, the complicated oxidation rate laws under **HH** conditions have not yet been fully characterized.

Summarizing, the three following experimental observations have been established when reaction conditions are altered.

- (A) In changing from **LL** to **HL** conditions, the dominant processes for substituted allyl alcohols change from syn oxidation according to eq 1 to isomerization according to eq 2.
- (B) In changing from **LL** to **HH** conditions, the dominant process for oxidations of substituted allyl alcohols changes from syn nucleophilic attack (presumably via an inner-sphere mechanism) to anti nucleophilic attack products (presumably via an outer-sphere mechanism) and chlorohydrin products.
- (C) Reactions with ethylene under **HH** conditions yield a mixture of anti nucleophilic attack ethanal products and chlorohydrin.

Henry and co-workers never explicitly demonstrated the mode of nucleophilic attack for ethylene oxidation under **LL** conditions; however, the observations (A–C) suggest that it should be via a syn nucleophilic attack mechanism.

The Wacker process mechanism was established as dependent on the concentrations of two ions ([Cl⁻] and [CuCl₂]), and thus there are *four* critical conditions whose observations must be explained in a viable mechanism:

- **LL** conditions: reactions with low [Cl⁻] (<1.0 M) and low [CuCl₂] (<1.0 M) almost exclusively yield acetaldehyde products generated from syn-nucleophilic attack.⁵ The reaction consumes olefin according to the rate law in eq 1.

- **HH** conditions: reactions with high [Cl⁻] (>3.0 M) and high [CuCl₂] (>2.5 M) yield two unique oxidized products, acetaldehyde products generated from an anti nucleophilic attack mechanism and chlorohydrin products.^{5,6} The complete rate law for these processes is complicated and still unknown.

(1) Beyramabadi, S. A.; Eshtiagh-Hosseini, H.; Housaindokht, M. R.; Morsali, A. *Organometallics* **2008**, *27*, 72–79.

(2) For a summary of experimental studies see (vide infra): (a) Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel: Boston, 1980. (b) Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: New York, 2002; Vol. 1, p 2119.

(3) Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246.

(4) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(5) (a) Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745. (b) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082.

(6) Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832.

• **HL** conditions: reactions with high $[\text{Cl}^-]$ (>3.0 M) and low $[\text{CuCl}_2]$ (<1.0 M) yield no oxidized products but rather isomerized products.⁷

• **LH** condition experiments have not yet been extensively investigated.

Reference 1 describes ethylene oxidation under standard conditions, i.e. **LL** conditions, with the corresponding rate law (eq 1.) cited. This paper concludes that anti nucleophilic attack is the dominant mechanism for the rate-determining step and it claims that this is consistent with experimental observations. While their results are consistent with the rate law in eq 1, their results are *not* consistent with the other characteristic found under **LL** conditions, as surmised from experiments by Henry et al.^{2,5-7}

In particular, ref 1 disregards the strong stereochemical evidence that hydroxypalladation proceeds by a syn process under **LL** conditions. The authors have made a tacit assumption that ethylene behaves differently than the allyl alcohol used in these studies. While it is conceivable that ethylene and substituted olefins could react via the same rate law but through different mechanisms, this is an extraordinary claim that would require substantially more evidence than presented in ref 1. Indeed, it would appear that the authors do not believe their claim that ethylene proceeds through an anti mechanism, since they (on page 73) cite studies implicating the syn mechanism (ref 14c in ref 1).⁸

Furthermore, the **Introduction** section of ref 1 does not provide an accurate description of the present state of the knowledge of the Wacker system. Two of the three studies cited as supporting the syn mechanism (CH_3OH isotope effects and thallic ion oxidation of olefins) do *not* implicate the internal syn mechanism. Additionally, the authors did not mention the important reasons to postulate the internal syn attack mechanism, including isomerization of tetrasubstituted chiral allylic alcohols (refs 17a and 23a in ref 1). Instead, the authors cite these references as proof that the β -elimination step is not rate determining, even though these alcohols cannot decompose by β -elimination since they have no β -hydrogens! The authors also fail to discuss the stereochemical results mentioned above (ref 2c in ref 1). Finally, the authors did not cite a review of recent developments in the field.^{2b} This review offers reasons why the chlorohydrin product in their ref 8b (ref 4 of this comment) does not reflect the stereochemical characteristics of the hydroxypalladation observed in Wacker chemistry and why the Bäckvall postulate of equilibrium hydroxypalladation is *not* valid under **LL** conditions.

Recently, we used QM calculations to establish a series of mechanistic steps⁹ that helps explain the experimental observations listed above. Most important, we found that $[\text{Cl}^-]$ has a strong inhibition on the syn attack pathway while having a less strong inhibition of the anti attack/chlorohydrin pathway, which

explains the different products observed at different $[\text{Cl}^-]$. Furthermore, we found that $[\text{CuCl}_2]$ stabilizes the anti attack pathway while having little effect on the syn attack pathway, which explains why **HH** yields anti Wacker oxidized products while the **HL** process only involves isomerization. This also suggests that the rate law for the **HH** processes should certainly include $[\text{CuCl}_2]$. We should note here that we also misinterpreted two aspects of the experimental results. First, we incorrectly stated eq 2 was the rate law for oxidation under **HH** conditions, when in fact this rate law has not yet been determined. However, since eq 2 is expected to resemble the rate law for chlorohydrin formation, our previous analysis still identifies the most likely causes for ion concentration dependence in the Wacker process mechanisms. Second, we originally stated that experiments under **LH** conditions showed a mixture of all products, when in fact those experiments utilized a different catalysis that included a pyridine ligand. Observations with this modified catalyst system should not be directly compared to experiments not involving the pyridine ligand.

Moreover, we have carried out additional calculations (see the Supporting Information) that find no significant difference in energies between ethylene and allyl alcohol olefin mechanisms, further supporting the logical conclusion that oxidation at **LL** conditions goes syn.

Although we were able to reproduce the calculations in ref 1 with respect to the PdCl_4^{2-} ground state, the transition state reported in ref 1 for the anti attack on $\text{cis-}[\text{Pd}(\text{Cl})_2(\text{OH})(\text{C}_2\text{H}_4)]^-$ (24.6 kcal/mol) is 1.9 kcal/mol higher in energy than anti attack on $[\text{Pd}(\text{Cl})_3(\text{C}_2\text{H}_4)]^-$ (+22.7 kcal/mol) as well as higher than processes which lead to syn products (+18.0 and +22.9 kcal/mol) previously reported.⁹ Thus, we find that anti attack on $\text{cis-}[\text{Pd}(\text{Cl})_2(\text{OH})(\text{C}_2\text{H}_4)]^-$ would not play a role in Wacker chemistry.

Our conclusions are that the results in ref 1 do not correspond to experimental observations and that ethylene oxidation under standard Wacker conditions is syn, not anti.

Supporting Information Available: Text and tables giving calculation methods, a comparison of calculated energies, and relevant energies and geometries. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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