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Wacker Oxidation

The Mechanism of the Wacker Reaction: A Tale of Two Hydroxypalladations

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homogeneous catalysis · olefin oxidation ·
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Wacker process

We present a concise review on the most pertinent investigations that illuminate the complicated and elusive mechanism for the Wacker process, homogeneous olefin oxidation by palladium(II) catalysts. For more than four decades, multitudes of creative and elegant studies detailing the nucleophilic addition and other steps of the Wacker process have appeared contradictory, while in fact modern perspective has shown an intricate and colorful picture of the "textbook" organometallic reaction. A summary and critical analysis of previous studies is of great importance to explain resolved and highlight unresolved questions about this frequently misunderstood reaction.

1. Introduction

The Wacker process, olefin oxidation with $PdCl_2$ catalysts, and related processes have been a staple for organic and organometallic chemistry for half a century.[1] The overall process (Scheme 1) was discovered by Smidt and co-workers in the late 1950s at the Consortium für electrochemische Industrie, a subsidiary of and the research organization for Wacker Chemie.[1a,2]

$$\begin{array}{llll}
[PdCl_4]^{2-} + C_2H_4 + H_2O & \xrightarrow[-2\,Cl^-]{-2\,HCl} & Pd^0 + CH_3CHO & (1)\\
Pd^0 + 2\,CuCl_2 + 2\,Cl^- & \longrightarrow & 2\,CuCl + [PdCl_4]^{2-} & (2)\\
2\,CuCl + 1/2\,O_2 + 2\,HCl & \longrightarrow & 2\,CuCl_2 + H_2O & (3)\\
\hline
\text{Net:}\quad C_2H_4 + 1/2\,O_2 & \longrightarrow & CH_3CHO &
\end{array}$$

Scheme 1. Individual reactions of the Wacker process.

The oxidation reaction [Eq. (1) in Scheme 1], has been known for more than a century,[3] has received most of the mechanistic interest, and is the main focus of this review. Smidt and co-workers discovered that the formed Pd^0 could be regenerated by cupric chloride in situ [Eq. (2)], thus making the reaction a commercial success. The final step [Eq. (3)], oxidation of CuCl to $CuCl_2$, is one of the fastest reactions in inorganic chemistry.[4] These three reactions add up to the simple air oxidation of ethene to ethanal. The Wacker process is important not only in its own right, but because it also opened up the field of catalytic palladium chemistry, which proved to be very rich in both potential industrial processes and new transformations for synthetic organic chemistry.[5] An abbreviated scheme of the complete catalytic cycle of the Wacker process is shown in Scheme 2.

To maximize industrial profitability and resolve long-standing questions, many experimental and theoretical studies have attempted to define the exact mechanism of the canonical Wacker process with $PdCl_2$. Most of these studies have been imaginative and well performed, and in retrospect, have contributed favorably to understanding the reaction. However, a controversy centered on the oxidation mechanism's mode of nucleophilic attack has persisted for decades. This is partly because the original interpretations of some data, which were based on oversimplified assumptions about key inorganic and organometallic chemistry concepts, were unfortunately and readily accepted by a generation of inorganic and organometallic textbook authors. These concepts include equilibria between ligands and metal or organometallic species, ligand lability, and coordinative unsaturation. As will be shown in detail in this Minireview, metal complexes often transform into other complexes under different reaction conditions. The solvent, its pH, and the

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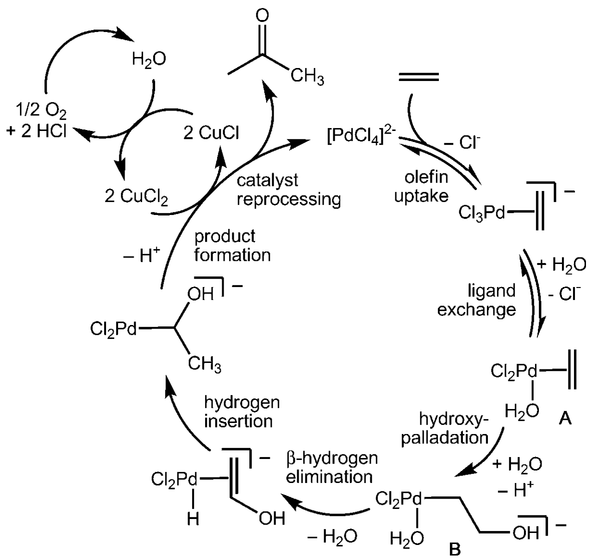


Scheme 2. Overall catalytic cycle of the Wacker process.

presence of potential ligands can all affect transition-metal catalysts.

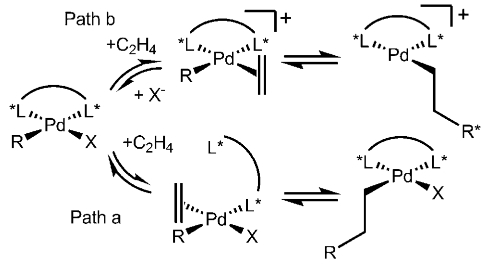
Studies of palladium(II) solutions unveiled the importance of these factors. In acetic acid in the presence of acetate ion, the Pd^{II} species can be a trimer, a dimer, or a monomer depending on the acetate ion concentration (Scheme 3).[6] In olefin acetoxylations, the dimer is by far the most reactive species.[7] Thus, if the concentration of NaOAc is increased at constant Pd^{II} concentration, the rate of ethene oxidation to vinyl acetate increases until it reaches a maximum rate at [NaOAc] = 0.2 M and then gradually decreases. At [NaOAc] = 0.2 M, the dimer concentration reaches its maximum.

$$2\,[Pd_3(OAc)_6] \underset{6\,NaOAc}{\overset{K_{32}}{\rightleftharpoons}} 3\,Na_2[Pd_2(OAc)_6] \underset{6\,NaOAc}{\overset{K_{21}}{\rightleftharpoons}} 6\,Na_2[Pd(OAc)_4]$$

$$K_{32} = 7.77\times10^{4}\,\mathrm{M}^{-5};\ K_{21} = 7.6\times10^{-4}\,\mathrm{M}^{-1}$$

Scheme 3. Equilibrium between palladium(II) acetate species in acetic acid.

Another notable example is the asymmetric arylation of olefins (the Heck reaction). In order to obtain appreciable asymmetric induction, the Pd^{II} catalyst must have, besides two sites occupied by the bidentate chiral ligand, two labile coordination sites. One site is needed for coordination of the olefin and one for the aryl group. As shown in Path a of Scheme 4, if a halide or another complexing ligand is present, a phosphorus group from the chiral biphosphine can dissociate, both making room for the olefin and rendering the asymmetric induction lost.[8] Use of a ligand more labile than halide, for example, trifluoromethanesulfonate (triflate), corrects this problem. Path b of Scheme 4 shows the reaction sequence with aryl triflate reagents. The labile triflate allows olefin coordination without displacing a phosphine ligand.



(L*-L* = chiral diphosphine; X = Cl, Br, I, triflate)

Scheme 4. The asymmetric Heck reaction.

The majority of research on the Wacker mechanism has focused on identifying whether nucleophilic addition step proceeds in a *syn* or *anti* fashion. Of course, determination of this particular step is not the ultimate goal, since variants of this reaction most certainly proceed by different mechanisms. Rather, the purpose of these extensive investigations is to determine which influences cause a nucleophile to add in a particular fashion and how that determines the overall course of the reaction. Understanding the canonical Wacker reaction is an important step to understanding not only related reactions, but also the mechanisms of other processes sensitive to reaction conditions. This Minireview provides a critical analysis first of experiments and then of quantum mechanics calculations to illustrate what is known about the

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original Wacker process, a reaction that at numerous times was considered to be well understood.

2. Early Mechanistic Studies

2.1. Kinetic Studies

The Wacker reaction has been called a textbook example of a homogeneous transition-metal-catalyzed reaction since its mechanism has many intriguing facets. Its kinetics are complicated. The resting state of $PdCl_2$ under the most relevant experimental conditions is tetrachloropalladate, $[PdCl_4]^{2-}$, based on older[9] and more recent[10] studies. The rate expression [Eq. (4), Scheme 5) is first order in ethene but also exhibits a second-order chloride inhibition and a first-order proton inhibition.[11] Henry established that the second-order chloride inhibition results from two rapid equilibria [Eqs. (5) and (6), Scheme 5), where the values of K_1 and K_2 have been determined by fast reaction techniques.[11a] There is no controversy for the mechanism leading to intermediate **A**, $[PdCl_2(C_2H_4)(H_2O)]$, and on the basis of these kinetics alone, **A** was believed to be an active intermediate.

$$\text{Rate} = \frac{-\mathrm{d}\,[C_2H_4]}{\mathrm{d}t} = \frac{k\,[PdCl_4^{\,2-}][C_2H_4]}{[H^+][Cl^-]^2} \tag{4}$$

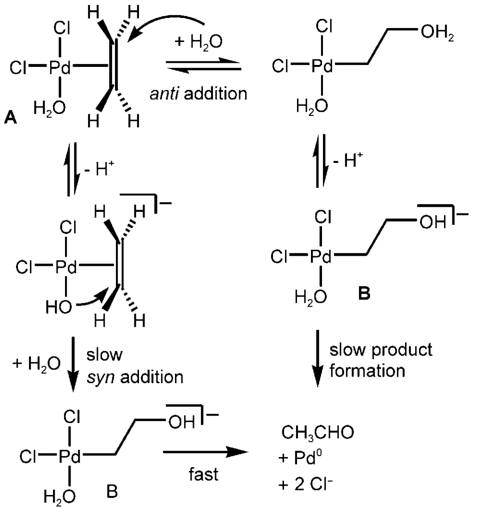
$$[PdCl_4]^{2-} + C_2H_4 \overset{K_1}{\rightleftharpoons} [PdCl_3(C_2H_4)]^- + Cl^- \tag{5}$$

$$[PdCl_3(C_2H_4)]^- + H_2O \overset{K_2}{\rightleftharpoons} \underset{\textbf{A}}{[PdCl_2(C_2H_4)(H_2O)]} + Cl^- \tag{6}$$

Scheme 5. The rate expression for the Wacker oxidation [Eq. (4)] and the origin of the chloride inhibition terms [Eqs. (5) and (6)].

Explanation of the proton inhibition term is the root of the controversy surrounding the Wacker process. A number of possible pathways starting from **A** could explain the observed proton inhibition. Fortunately, one mechanism, *anti* attack of hydroxide on **A**, can be eliminated by kinetic considerations. Using a measured value of K_1 (17.4 at 25° and $\mu = 2.0$) to deduce an estimated value for K_2 ($\approx 10^{-3}\,\text{M}$), the rate of external hydroxide attack would need to be $\approx 10^{13}\,\text{M}^{-1}\,\text{s}^{-1}$, a value $\approx 10^4$ times faster than a diffusion-controlled process.[11a] Therefore, the Wacker process was not believed to rely on an auto-ionization of H_2O, and only mechanisms explicitly involving water were considered.

Henry originally considered two possible mechanisms to explain the proton inhibition in the rate law [shown in Eq. (4)]:[11a] 1) equilibrium *anti* nucleophilic attack by water on the olefin in **A** followed by deprotonation and then rate-determining decomposition to oxidized products, or 2) equilibrium deprotonation of **A** followed by a rate-determining *syn* attack of coordinated hydroxide and then a fast decomposition (Scheme 6). Both pathways contain intermediate **B**, which is formed by distinctly different nucleophilic attacks.



Scheme 6. The two originally postulated reaction schemes for the Wacker reaction.

Note that the second mechanism makes two assumptions: first, the H_2O in **A** should be bound *cis* relative to the olefin, and second, that a Pd–OH species should be a stable intermediate under very low pH conditions. Henry deemed the first point reasonable owing to the relatively low *trans* influence of hydroxide for Pd^{II} complexes.[12] The large intrinsic activity of water in nonaqueous media was the basis for considering a Pd–OH intermediate complex.[13] Support for the second assumption is now considered somewhat less strong since recent spectrophotometry experiments by Cruywagen and Kriek indicate that Pd–OH should be quite unstable at such low pH and that the protonated Pd–H_2O complex is preferred.[10c] Henry did not explicitly address *cis* attack by solvent water (probably because of steric considerations), nor did he consider that a rate-determining nucleophilic attack by H_2O on the Pd–OH species might occur.

Numerous deuterium-labeling studies further illuminated the Wacker mechanism as well. Smidt and co-workers found that C_2H_4 oxidation in D_2O yields only CH_3CHO.[2] When Henry oxidized C_2D_4 in H_2O only CD_3CDO was formed.[11a] Thus, the Wacker reaction would appear to require an intramolecular hydrogen transfer after intermediate **B**. (This result also shows the mechanism must *not* involve the exchange of any alkyl hydrogen atoms with protons in the solvent through a keto–enol tautomerization.)

To differentiate between the *syn* and *anti* mechanisms, comparisons were made between independent oxidation rates of of C_2H_4 and C_2D_4 as well as the rates for intramolecular competitive reactions with dideuterated ethene. Since the kinetic isotope effect for the independent reactions was small ($k_H/k_D = 1.07$),[11a] this hydrogen transfer was assumed to both be fast and to be followed immediately by decomposition to ethanal products (Scheme 7).

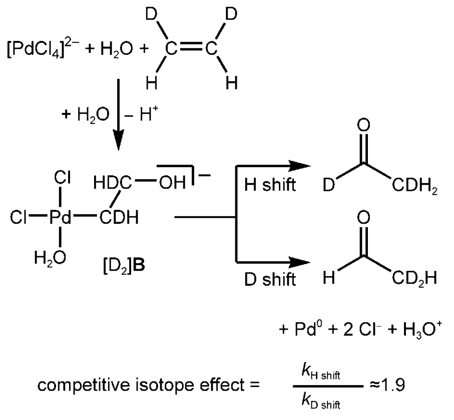
Isotope effects of simultaneous (competitive) oxidation reactions were studied by Henry using 1,2-dideuteroethene[14] and later by Saito and Shinoda using 1,1-dideuteroethene.[15] They found isotope effects of approximately 2 (Scheme 8). The fact that nonnegligible competitive isotope effects were observed suggested the rate-determining step occurs *before*

$$k_D\text{: } C_2D_4 + PdCl_4^{2-} + H_2O \xrightarrow[-2\,Cl^-]{-2\,HCl} CD_3CDO + Pd^0$$

$$k_H\text{: } C_2H_4 + PdCl_4^{2-} + H_2O \xrightarrow[-2\,Cl^-]{-2\,HCl} CH_3CHO + Pd^0$$

$$\text{kinetic isotope effect} = k_H/k_D = 1.07$$

Scheme 7. Kinetic isotope effects of the Wacker reaction with C_2H_4 and C_2D_4.



Scheme 8. Competitive kinetic isotope effects in the Wacker reaction with dideuteroethene.

the last steps of the reaction, which were at first thought to be coupled hydrogen-transfer and product-formation steps (see Scheme 2).[11a] Since the *anti*-addition pathway requires a rate-determining step after hydroxypalladation, these details implicated Henry's proposed *syn* mechanism, and the *anti*-hydroxypalladation mechanism with water was ruled out. Thus, the *syn*-hydroxide insertion from the coordination sphere of Pd^{II} was believed to be the correct Wacker mechanism by default, even though neither *syn* nor *anti* products had yet been observed.

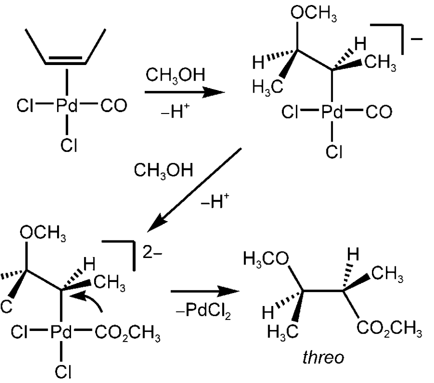
2.2. Stereochemical Studies

2.2.1. Stereochemical Studies under Non-Wacker Conditions

Typical products of the Wacker oxidation of acyclic olefins are aldehydes and ketones, and stereochemical studies require modified reaction conditions to form saturated products whose stereochemistry can be determined. Earlier stereochemical studies[16] (that all notably indicated *anti* addition) are mentioned here briefly. The general assumption in early stereochemical studies was that changes in reaction conditions do not change the mode of addition. As we will now explain, this is not a valid assumption for any of these studies.

Early stereochemical studies by Stille and co-workers[16a–d] used wet acetone or CH_3CN as reaction media. These solvents differ substantially from water, however, and their experiments resulted in an environment so removed from standard conditions that the expected resting state, $[PdCl_4]^{2-}$, was never formed. Thus, these studies, while noteworthy, may not be relevant to the canonical Wacker chemistry.

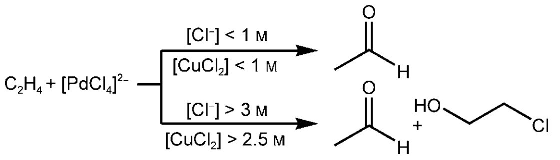
Other experiments also may not be appropriate models for Wacker chemistry when extra coordinated ligands in the coordination sphere of Pd^{II} may easily prevent the introduction of a nucleophile necessary for *syn* addition. Stille et al. undertook one study in methanol solvent under a CO atmosphere, conditions otherwise close to standard Wacker chemistry conditions.[16c,d] Indeed, methanol behaves similarly to water in the palladium(II) oxidation of olefins.[17] (*E*)- and (*Z*)-2-butene were the olefinic substrates, and the stereochemistry of the oxidized products, methyl 3-methoxy-2-methylbutanoates (Scheme 9) were consistent with *anti* addition. However, since CO is a very strongly bonding ligand, CO coordination will almost certainly prevent methanol coordination, a requisite for *syn* addition. Effects of ligand binding strength and solvents may account for *anti* nucleophilic attack observed in two noteworthy studies, one by Majima and Kurosawa on $[Pd(Cp)(PPh_3)]^+$ in dichloromethane[16e] and the other by Åkermark et al. with nonchelating diolefins.[16f] The degree that these influences may alter the course of a reaction has not yet been addressed, however.



Scheme 9. Hydroxypalladation of (*Z*)-2-butene under a CO atmosphere.

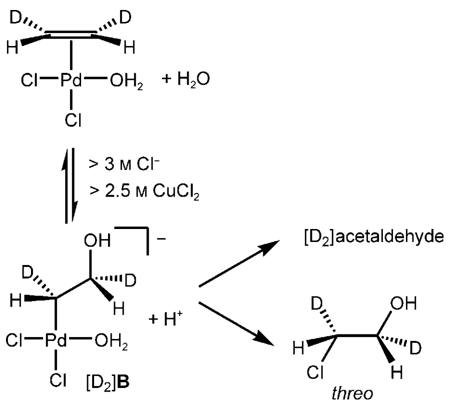
2.2.2. Stereochemical Studies in Aqueous Solutions with High Concentrations of Cl^- and $CuCl_2$

Soon after these early stereochemical studies, Bäckvall et al. presented results for a study that at first glance was conducted in the actual medium for the Wacker reaction.[18] Stangl and Jira earlier reported that under standard Wacker conditions of low Cl^- ($<1\,\text{M}$) and $CuCl_2$ concentrations ($<1\,\text{M}$), ethene is oxidized to ethanal, but at high Cl^- ($>3\,\text{M}$) and $CuCl_2$ ($>2.5\,\text{M}$) concentrations both ethanal and a new product, 2-chloroethanol, appear (Scheme 10).[19] Bäckvall and co-workers, using the latter conditions, sophisticatedly determined the stereochemistry of hydroxypalladation for the reaction pathway leading to 2-chloroethanol and assumed the stereochemistry was the same for the reaction pathway leading to ethanal.[18] They used specifically deuterium-labeled ethene and determined the stereochemistry of their product with microwave spectroscopy. They rationalized that equilibrium nucleophilic attack causing a proton inhibition in



Scheme 10. Ethene oxidation at low and high Cl^- concentrations.

the rate law would be followed by a rate-determining Cl^- dissociation, thus in full agreement with the kinetic rate law in Equation (4). Scheme 11 outlines their postulated reaction sequence.



Scheme 11. Oxidation of [D_2]ethene at high Cl^- and high $CuCl_2$ concentrations.

At the time, their work appeared to clearly implicate the *anti* pathway that was previously ruled out by kinetics experiments. Although the extension of these results to the Wacker process is still the root of heated controversy, in retrospect this study almost definitely establishes that hydroxypalladation at high Cl^- concentration is *anti*. Rationalization of this will be discussed shortly.

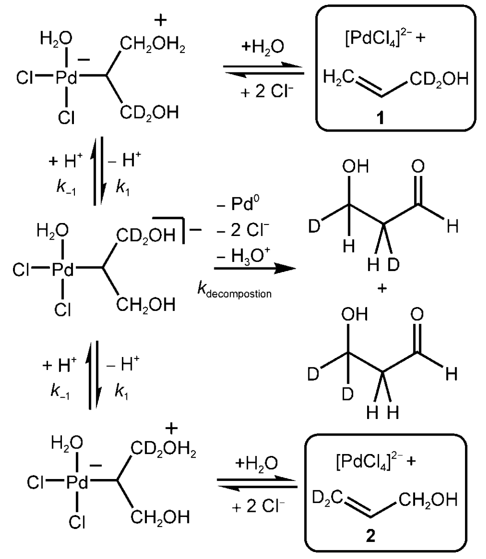
3. Later Mechanistic Investigations

3.1. Kinetic Studies

3.1.1. Allyl Alcohol with [PdCl$_4$]$^{2-}$

The collection of stereochemical studies all implicating *anti* attack made a convincing argument that was accepted by many in the chemistry community. If one disregards the incongruity of the stereochemical studies with competitive kinetic isotope experiments, testing one straightforward issue would clarify that the *anti* mechanism was valid. Recall that Henry's *syn* and Bäckvall's *anti* mechanistic pathways have a distinguishing characteristic: nucleophilic attack is an equilibrium process in the latter, but not in the former. If the nucleophilic attack were found to be an equilibrium process, then the Bäckvall mechanism would be correct.

Henry investigated this point with more kinetics experiments by measuring the rates of isomerization and oxidation of a simple isotopically substituted olefin capable of showing isotopic scrambling, [D_2]allyl alcohol (**1**).[20] Since the kinetics for allyl alcohol oxidation obeyed the same rate law as that shown in Equation (4), **1** was believed to be a suitable substrate for probing the Wacker mechanism. The rate of deuterium scrambling was thought to assess the rate of hydroxypalladation versus that of oxidation (Scheme 12). If hydroxypalladation is reversible, a 50:50 mixture of isomers **1** and **2** would be formed soon after the reaction is underway. If it is not reversible, only isomer **1** would be present throughout the course of the reaction.



Scheme 12. Proposed mechanism for the isomerization of [D_2]allyl alcohol. If isomerization of **1** and **2** would be observed, nucleophilic attack would be an equilibrium process. Isomerization of **1** and **2** was not observed.

The first compound tested was allyl alcohol itself.[21] Initially, the oxidation was examined at low Cl^- concentrations (0.1–0.7 M). The main products were the expected Wacker oxidation products $HOCH_2CH_2CHO$ (40 %) and $CH_3C(=O)CH_2OH$ (12 %). The experiments were repeated using the two deuterium-substituted allylic alcohols, **1** and **2**, in separate experiments. At about 50 % conversion only the pure starting deuterium-labeled alcohols were detected. The results provided evidence that the rate of the back reaction (k_{-1}) in Scheme 12 is slow, implicating that hydroxypalladation is *not* an equilibrium process. The observed lack of scrambling showed that the *anti* mechanism for Wacker oxidation is invalid, but it did not rigorously confirm the *syn* pathway, nor did it help explain why *anti* products had been observed.

In further kinetic studies the isomerization of [D_2]allyl alcohol was investigated (as pictured in Scheme 12). Hydroxypalladation of **1** and **2** was also not an equilibrium reaction under standard Wacker conditions. Since oxidation at low concentrations of Cl^- and $CuCl_2$ appeared to require passage through intermediate **A**, high Cl^- and low $CuCl_2$ concentrations were expected to halt oxidation by preventing the formation of **A**. Indeed, olefin oxidation was almost completely suppressed at high Cl^- concentration (> 1.5 M, half the concentration of Cl^- that was used in the stereochemical studies described in Section 2.2.2![18]). However, under these conditions a new reaction came into play: the non-oxidative isomerization of **1** into **2**. The new rate equation [Eq. (7)] for

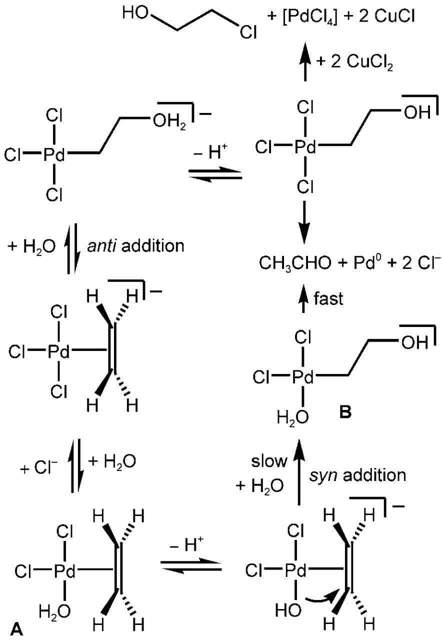
$$\text{rate} = \frac{-d[C_2H_4]}{dt} = \frac{k[PdCl_4^{2-}][C_2H_4]}{[Cl^-]} \qquad (7)$$

the isomerization contains a single term for chloride inhibition but none for proton inhibition. The chloride inhibition almost certainly results from formation of the π complex [Eq. (5)], and since there is no other chloride inhibition, the reacting species would most likely be an anionic analogue to **B**, a trichloropalladium(II) π complex. A mechanism similar to that in Scheme 12, but with a suppressed decomposition pathway, is likely at play.

One clue to the role of chloride may be the change in reactivity in complexes in which Pd^{II} is positioned β to a heteroatom and a hydrogen.[22] At low Cl^- concentration, β-hydrogen elimination should be permitted, affording ethanal. At high Cl^- concentration β-heteroatom removal is believed to occur, leading to chlorohydrin products. At high Cl^- concentration a hydroxypalladation should take place, but the intermediate normally reverts back to olefin and Pd^{II} instead of leading to oxidation. However, the trichloro analogue of **B** formed at high Cl^- concentration could then be intercepted by $CuCl_2$ to produce 2-chloroethanol. This theory is supported by studies involving allyl alcohols discussed below.

These combined results support the hypothesis that at least two hydroxypalladation reactions are active: one reaction leads to a stabilized adduct that has a long enough lifetime to be intercepted by $CuCl_2$ to produce chlorohydrins, while the other addition reaction predominates at low Cl^- concentration, leads to Wacker oxidation products, and does not require $CuCl_2$ to proceed. Stangl and Jira's experiments showed that the first mode of addition requires high concentrations of both Cl^- and $CuCl_2$,[19] and although thorough kinetics experiments have been too complicated to undertake thus far, stereochemical observations by Bäckvall and co-workers clearly implicated an *anti*-addition process for 2-chloroethanol under these conditions.[18] The second pathway had not been characterized with stereochemical methods, but kinetics experiments at low concentrations of Cl^- and $CuCl_2$ ruled out an equilibrium *anti*-addition pathway leading to oxidized products. The salient points are that under standard conditions, the *anti*-addition adduct does not appear to lead to ethanal, and that the route leading to 2-chloroethanol only appears at high concentrations of Cl^- and $CuCl_2$ and does not appear to involve *syn* addition (Scheme 13).

Lastly, with regards to $CuCl_2$, there is not enough information to rule that the role of copper in the oxidation process also may be dependent on reaction conditions. For more than 100 years it has been known that Equation (1) proceeds in water without $CuCl_2$. However, Hosokawa and co-workers found crystallographic evidence that copper may play a direct role in alkene oxidation mechanisms with *N*,*N*-dimethylformamide (DMF) solvent.[23] Additionally, recent calculations have suggested the kinetic rate law for the *anti* pathway will be directly dependent on the $CuCl_2$ concentration.[24]

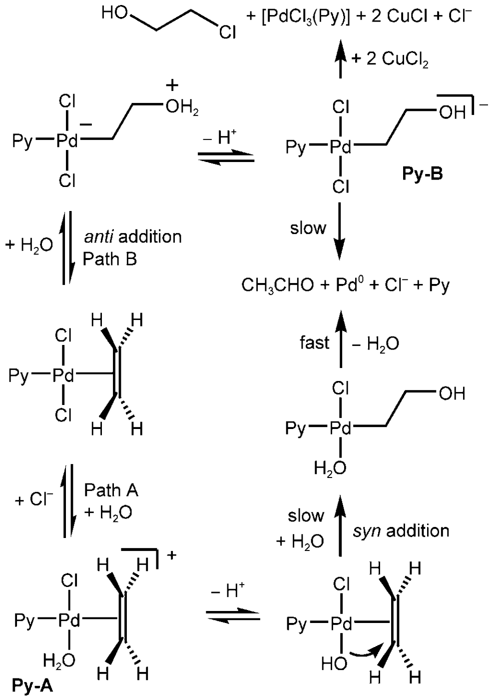


Scheme 13. Complete reaction sequence for the Wacker process as deduced from kinetic and stereochemical studies.

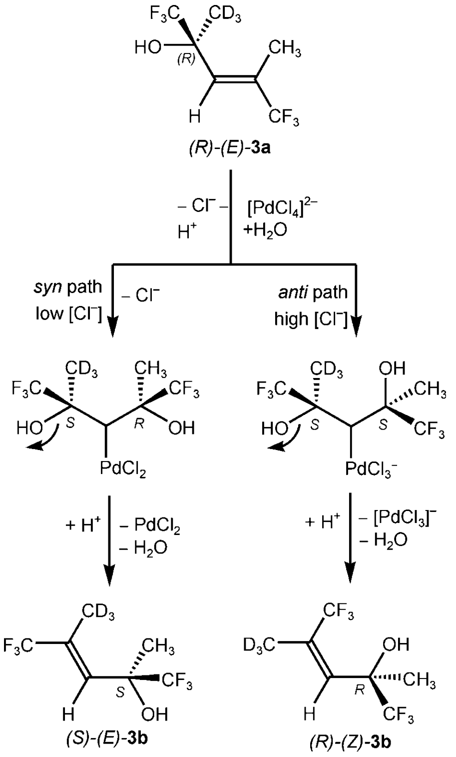
3.1.2. Ethene with Catalysts Containing Neutral Ligands

CO ligands greatly change the reactivity of Pd^{II} complexes, and so investigations involving a neutral ligand bound to Pd^{II} seemed worthwhile. Henry utilized a catalyst involving neutral pyridine (Py), and unsurprisingly, $[PdCl_3(Py)]^-$ was found to have quite different reactivity than $[PdCl_4]^{2-}$.[25] This catalyst's rate expression was found to be identical to the Wacker expression shown in Equation (4), but the rate of oxidation to ethanal was decreased by a factor of 750. Second, the $CuCl_2$-promoted reaction that yielded 2-chloroethanol became the main reaction at $[Cl^-] = 0.2$ M, a concentration under which $[PdCl_4]^{2-}$ would not have led to 2-chloroethanol under Wacker conditions. This behavior may be attributed to the stability of the hydroxypalladation adduct formed in the reaction using $[PdCl_3(Py)]^-$.

Scheme 14 represents a possible sequence for the reaction of $[PdCl_3(Py)]^-$ involving both *syn* and *anti* additions consistent with previous experimental observations. In path A of Scheme 14, the cation **Py-A** is formed after the chloride–water exchange from $[PdCl_2(Py)(C_2H_4)]$. This should be an unfavorable process as the dissociation of Cl^- from neutral $[PdCl_2(Py)(C_2H_4)]$ is expected to be less facile than from anionic $[PdCl_3(C_2H_4)]^-$, and thus oxidation by *syn* hydroxypalladation would be comparatively hindered. On the other hand, anionic **Py-B** may have a long enough lifetime to be intercepted by $CuCl_2$ to form 2-chloroethanol. The negative charge on **Py-B** may also facilitate chloride dissociation,



Scheme 14. Possible routes in the Wacker reaction with $[PdCl_3(Py)]^-$.



Scheme 15. Possible reaction paths for the isomerization of (*R*)-(*E*)-**3a**.

opening a labile coordination site for β-hydrogen transfer to produce ethanal by the *anti*-hydroxypalladation pathway.

3.2. Stereochemical Studies

3.2.1. Tri- and Tetrasubstituted Allylic Alcohols

The two mechanisms in Scheme 13 were consistent with previous experiments. Valid stereochemical results showing *syn* addition in ketone and aldehyde formation and *anti* addition in isomerization would greatly strengthen this proposed mechanism, however. Recall that previous stereochemical results definitively supporting *anti* addition avoided ketone formation and required conditions substantially different from those in industrial Wacker chemistry. Another approach would be needed to test the stereochemistry of Wacker products under low Cl^- and $[CuCl_2]$ concentrations. Henry used chirality-transfer experiments for this purpose.

An initial set of experiments invoking chirality transfer employed tetrasubstituted allylic alcohol substrates that cannot undergo oxidation and undergo only undergo isomerization. 2-[D_3]Methyl-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol was used (**3a** in Scheme 15).[26] The CF_3 groups were thought to provide hydrolytic stability and steric bulk to the system. The possible reaction sequence using one enantiomer of the substrate is shown in Scheme 15. The Pd^{II} center must add to the central carbon atom of the allyl fragment since steric hindrance would prevent it from adding to the adjacent positions having CH_3 and CF_3 substituents. Isomerization kinetics was followed by ^2H NMR spectroscopy.

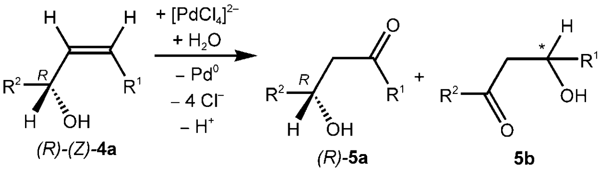
Objections to these experiments were raised because highly electronegative fluorine may favor *syn* attack just as other substrates and ion concentrations were found to favor *anti* attack. Nevertheless, both observed kinetic and stereochemical outcomes were in concordance with the postulated reaction sequence discussed in Scheme 15. At low Cl^- concentration the rate expression was identical to that for the Wacker oxidation shown in Equation (4), and the stereochemistry of the product was consistent only with *syn* addition (path A). At high Cl^- concentration (path B) the kinetics were identical to that for isomerization [Eq. (7)], and the stereochemistry of the final product was consistent only with *anti* addition. Note that the determination of the absolute configurations is not required for these studies. That a given optical isomer gives different enantiomers at low and high chloride concentrations indicates two different modes of addition under two sets of conditions. The stereochemical results of Bäckvall and co-workers[18] show that addition is *anti* at high Cl^- concentration, so if a different enantiomer is formed at lower Cl^- concentrations, the mode of addition from which it came from should be *syn*.

Henry also investigated these reactions with $[PdCl_3(Py)]^-$ as the catalyst.[26] As expected, this catalyst behaved quite differently from $[PdCl_4]^{2-}$. In the range $[Cl^-] = 0.2–1.0\,\text{M}$, the rate expression obeyed Equation (4) and at $[Cl^-] = 0.2\,\text{M}$, (*R*)-(*E*)-**3a** gave (*R*)-(*Z*)-**3b**, and (*S*)-(*E*)-**3a** gave (*S*)-(*Z*)-**3b**. These results were consistent with *anti* addition, in agreement with the finding that this process predominates at higher concentrations of Cl^-. At $[Cl^-] = 0.05\,\text{M}$ the mechanism became dramatically more convoluted. The kinetics became complicated: a chloride inhibition between first and second order suggested that isomerization of (*R*)- and (*S*)-(*E*)-**3a** occurs by both *syn*- and *anti*-addition processes. The trisubstituted olefin (*E*)-4-methyl-1,1,1,5,5,5,-hexafluoro-3-penten-

2-ol underwent oxidation as well as isomerization. Analysis of the oxidation products indicated that *syn* addition would lead to oxidation, while *anti* addition can lead either to isomerization *or* oxidation. Recall that with $[PdCl_4]^{2-}$ the *anti* pathway was believed to lead only to chlorohydrin. These results warrant scrutiny since at $[Cl^-] = 0.05\,M$ the state of $[PdCl_3(Py)]^-$ is uncertain. The actual palladium(II) species, possibly a dimer or an aquo form of the catalyst, may behave quite differently from $[PdCl_3(Py)]^-$. Thus it may not be an adequate model of Wacker chemistry. New, better suited reagents should be investigated to determine if these observations are general.

3.2.2. Disubstituted Allylic Alcohols

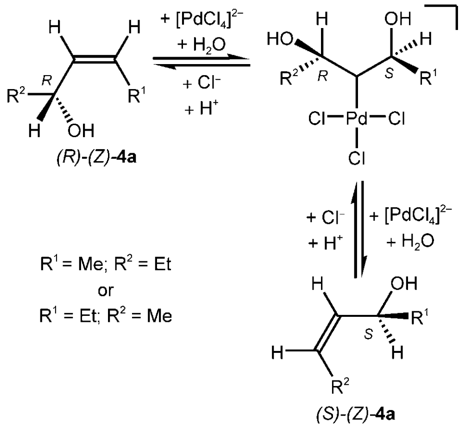
Further establishment of the "dual-mechanism" hypothesis required simpler asymmetric olefins that can oxidize to ketones at low Cl^- concentration and lead to isomerization at high Cl^- concentration. In the case of the Wacker chemistry, the problem was made more difficult since two ketones can form, only one of which (**5b** in Scheme 16) provides stereochemical evidence of the nucleophilic attack.[27] Oxidation of an asymmetric allylic alcohol to separate the two ketones was believed to be possible. In practice, the allylic alcohol **4a** with $R^1, R^2 = Me$, Et was chosen. Based on Scheme 16, the presence of (*R*)-**5b** provided the information needed to identify that the hydroxypalladation occurred by a *syn* process. In Scheme 17, formation of (*S*)-(*Z*)-**4a** indicated an *anti* hydroxypalladation.



Scheme 16. Oxidation of (*R*)-(*Z*)-**4a** at low Cl^- concentration.

Before concluding the discussion of these experiments, one should note that the directing influence of hydroxide as well as other functional groups in epoxidations, hydrogenations, and oxidations has been reviewed and confirmed by Hoveyda, Evans, and Fu.[28] That review does not provide specific examples of nucleophilic attack on coordinated olefins; however, in analogous reactions one might expect that the hydroxide groups on allylic alcohols could play a role directing the nucleophile towards a particular face of the olefin. Although one cannot rule this possibility out without experimental confirmation, consideration of the two following scenarios makes this unlikely:

1) If the directing influence arises from the allylic OH group and its direct coordination to Pd^{II}, an additional Cl^- ion must be removed to allow a vacant site for the transferring nucleophile; this would result in a different kinetic rate law than that for ethylene. As previously mentioned, the rate laws for allyl alcohols and ethylene are similar [Eq. (4)].



Scheme 17. Isomerization of (*R*)-(*Z*)-**4a** at high Cl^- concentration.

2) If the directing influence comes from a hydrogen bond between the allylic OH group and a coordinated Cl^- ligand, coordination on one particular side of the olefin would not be expected owing to the C_s symmetry of the Pd^{II} complex (e.g. $[PdCl_4]^{2-}$, $[PdCl_3(H_2O)]^-$).

To summarize this section, experimental investigations on the Wacker reaction have afforded a very complicated, but equally interesting view of the mechanism. A few questions remain, however. Notably, the validity of the most recent stereochemical studies that play an essential role in summarizing the Wacker mechanisms is still somewhat uncertain. Future experimental work should test the validity of these studies and address the potentially important role of copper in the corresponding rate laws for Equations (1) and (2).

4. Theoretical Studies

Since the early 1980s, questions about the Wacker process have intrigued computational chemists. For more than a decade, limited ab initio studies attempted to shed light on key qualitative bonding concepts that could help explain experimental observations. By the middle 1990s, successful applications of density functional theory (DFT) and implicit solvation methods began to provide improved simulations of homogeneous catalysis processes in general. Several notable reviews and book chapters provide detailed overviews on this subject.[29]

4.1. Early Theoretical Treatments

Most theoretical studies from this period have been reviewed in depth by Dedieu in a comprehensive perspective of early calculations on olefin oxidation.[30] This book chapter focuses on molecular orbital analyses of Wacker process mechanisms based on comparative analysis from different simulations. Key studies pertaining to the canonical Wacker reaction, almost all of which implicate an *anti*-nucleophilic attack, are mentioned here.

To the best of our knowledge, the earliest theoretical study explicitly studying Wacker chemistry was conducted by

Shinoda and Saito,[31] who used an extended Hückel approach to investigate the early stages of proposed β-hydrogen elimination for both Pd^{II} and Hg^{II} complexes. They concluded that the similar energies for the σ and π complexes of Pd^{II} support a *cis* orientation, which in turn should support *syn* migrations.

Eisenstein and Hoffmann were two of the first to investigate nucleophilic addition to metal-coordinated olefins with extended Hückel theory.[32] The degree that η^2-coordinated olefins slip to η^1 coordination was determined in terms of molecular orbital populations. Their results did not distinguish *syn* and *anti* additions for the Wacker mechanism; however, they provided a useful illustration of simultaneous metal–olefin bond activation and olefin–nucleophile bond deactivation still used today. Extended Hückel calculations involving metals now are rarely relied on for good reason: they give qualitatively poor descriptions of fundamental steps of the Wacker process.[33] Furthermore, while Eisenstein and Hoffmann's study was conceptually interesting, its use of free OH^- as a model nucleophile is perhaps not relevant to understanding Wacker chemistry since earlier kinetic studies[11a] ruled out this nucleophile (see Section 2.1).

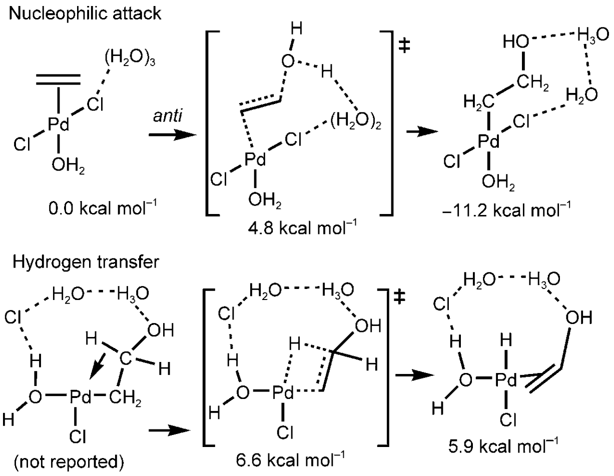
Bäckvall et al. investigated *syn*-nucleophilic attacks on olefins with ab initio SCF calculations in tandem with frontier molecular orbital theory.[34] They compared orbital energies of Pd–nucleophile complexes for several nucleophiles (Nu = H^-, CH_3^-, OH^-, F^-) in *trans*-$[Pd(Nu)_2(C_2H_4)(H_2O)]$ to estimate the reactivity of the coordinated nucleophile for *syn* additions. For Nu = H^- and CH_3^-, they reported a much smaller HOMO–LUMO energy gap (both on the order of ≈7 eV) than for OH^- (≈10 eV) or F^- (≈12 eV). Frontier molecular orbital theory thus suggested the latter nucleophiles would not undergo *syn* addition, in agreement with the discrepancy between observed *cis* attacks on olefins by H^- and CH_3^-, and the lack of *cis* attacks found with OH^- and F^- ligands. Before this study can be a valid argument against *syn* hydroxypalladation by OH^-, these conclusions merit reevaluation. Customary for calculations in the early 1980s, the authors employed minimal-sized pseudopotentials with no atomic polarization functions. Omission of these basis functions could easily lead to qualitatively different results, especially for more electronegative atoms such as oxygen or fluorine, which require substantial polarization.

Other MO calculations have appeared, notably the work of Fujimoto and Yamasaki,[35] who used coupled fragment molecular orbital method with similarly small basis sets and determined that internal hydroxypalladation was prohibited. The model and method from this work has been utilized again in more recent studies that help explain the regioselectivity of aldehyde formation in the Wacker oxidation.[36]

Only one reported study using semiempirical MNDO methodology has supported *syn*-nucleophilic attack.[37] Here, plots of $\log(k_{rel})$ for $PdCl_2$ vs. ionization protentials and calculated HOMO and LUMO energies for different substituted and non-substituted ethenes all yielded very slightly negative slopes. The authors claimed this data is consistent with a nucleophilic process as the rate-determining step, which would implicate *syn* hydroxypalladation for the Wacker process. Apart from this theoretical study, all other theoretical studies focusing on the Pd–OH species found *syn* hydroxypalladation energetically forbidden.

4.2. Modern Theoretical Treatments

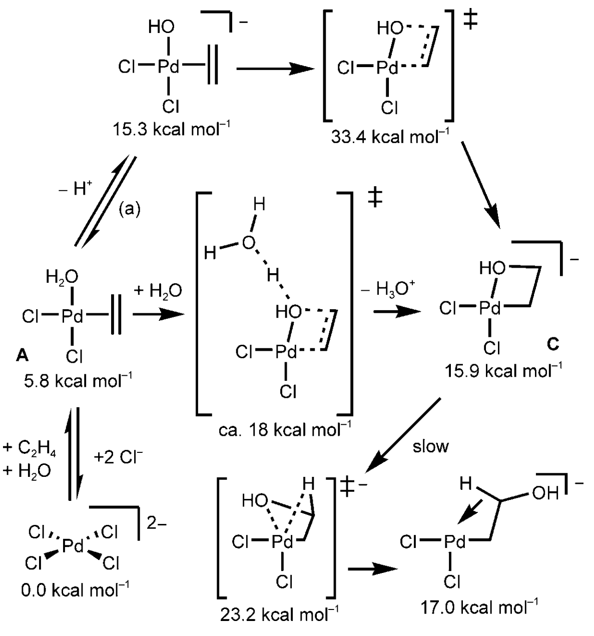
P. E. M. Siegbahn was a major contributor to theoretical studies of the Wacker process. He was the first to study the Wacker process with moderate electronic correlation with DFT and a prototype-implicit solvation method. He also brought attention to two important mechanistic steps: external nucleophilic attack by water and the β-hydrogen elimination leading to vinyl alcohol (Scheme 18). Siegbahn obtained energetic convergence when he used three explicit water molecules (in a "water chain") combined with an implicit solvation treatment.[33b] These calculations showed two intriguing results. First, solvent polarization effects favor the external *anti*-nucleophilic attack pathway more than the *external syn*-nucleophilic attack pathway. Therefore, *syn* attack by solvent water is unlikely. Second, the enthalpic barrier for *anti* attack of water was more than 10 kcal mol^{-1} lower than the barrier for β-hydrogen elimination, showing that nucleophilic attack should be an equilibrium process. This result, however, contradicts the observed lack of isotopic scrambling of allyl alcohols reported by Henry (Section 3.1.1). Kinetic isotope effects in Scheme 7 suggest β-hydrogen elimination is not rate-determining, and so the only other posible rate-determining step would be chloride dissociation as first suggested by Bäckvall and co-workers.



Scheme 18. Mechanistic steps investigated by Siegbahn.

Ten years later, Goddard and co-workers[24] used a more robust solvation treatment by incorporating electronic relaxation due to solvent at each step of the geometry optimization. This technique was used in lieu of determining the often complicated conformations of explicit water molecules around the complex. The authors found the barrier to *anti* attack to be low ($\Delta H^{\neq} = 8.7$ kcal mol^{-1}) for *trans*-**A** and in qualitative agreement with Siegbahn's value ($\Delta H^{\neq} = 4.8$ kcal mol^{-1}). However, when entropy and free energy contributions of solvent water were incorporated, the resulting free energy barrier was much higher ($\Delta G^{\neq} = 18.7\ \mathrm{kcal\,mol^{-1}}$). This calculated barrier does not quite agree with kinetic (experimental $\Delta G^{\neq} = 24.2\ \mathrm{kcal\,mol^{-1}}$) and isomerization observations, but this value is at the cusp of expected accuracy for these simulations ($\approx 5\ \mathrm{kcal\,mol^{-1}}$). One should probably not eliminate the possibility that the barrier to external *anti*-nucleophilic attack is higher than previously believed, and that accurate solvation treatments are crucial to analyze this particular mechanism.

Goddard and co-workers also investigated the barrier for internal *syn* hydroxypalladation.[24] Unlike simulation of a nucleophilic attack, which presents technical problems from treatment of proton solvation and zwitterionic species, this process remains anionic and can be calculated straightforwardly. The authors found the barrier to Henry's *syn*-hydroxypalladation pathway was $+33.4\ \mathrm{kcal\,mol^{-1}}$, far too high to be a feasible mechanistic step, and in qualitative agreement with previous theoretical studies that suggested this would be a prohibitive step. The unanimous agreement between diverse theoretical methods calls the original *syn* mechanism into question. Goddard presented an alternative pathway that did not involve explicit hydroxide, but if true would show the same characteristics previous experiments identified (Scheme 19).



Scheme 19. Mechanistic steps investigated by Goddard and co-workers.

In this pathway, rather than undergoing an equilibrium deprotonation, *cis*-**A** may undergo an inner-sphere transfer of a water molecule while simultaneously ejecting a proton into the solvent.[24] This step was found to highlight a disturbing shortcoming of quantum chemistry methodology. This work exposed that supposedly reliable methodology inaccurately depicts the energetics of protons, even in the presence of counter ions with an explicit water molecule. An approximate error bar and crude empirical correction were derived from calculated data on ion pairs involving palladium chloride complexes to determine the inaccuracy of such simulations. They reported a consistent error of $\approx 15\ \mathrm{kcal\,mol^{-1}}$ for ion pairs involving metal complexes. Clearly, calculations on zwitterionic transition states should not be quantitatively trusted, but noting this error provided a possible reaction scheme that gives the same result as *syn* hydroxypalladation. Nucleophilic attacks such as this certainly must be reinvestigated when better methodology has been established to treat deprotonations in aqueous solution.[38]

If a hydroxide group is transferred by this *syn*-addition pathway, a new intermediate is expected where the oxygen remains bound to the Pd$^{\mathrm{II}}$ center and forms a four-membered ring with the olefin (**C** in Scheme 19). An isomerization may replace the Pd–OH bond with an agostic C–H interaction; the calculated $23.2\ \mathrm{kcal\,mol^{-1}}$ barrier for this step is appropriate for a rate-determining process. If this step is assumed to be rate determining, this mechanism would be in agreement with all previous experimental observations including the kinetic rate equation.

This modeled mechanism is intriguing for several reasons. First, if this nucleophilic attack were actually an equilibrium process, the adduct **C** would not show isotopic scrambling since protonations of **C** would simply return the complex to **A**, effectively masking the equilibrium that Henry's scrambling experiments sought to identify. Second, this work also identified two mechanistic pathways dependent on Cl$^-$ and $CuCl_2$ concentrations that show how the Wacker mechanisms might switch from *syn* products under normal conditions to *anti* products and chlorohydrin under different conditions.

Under low Cl$^-$ and $CuCl_2$ concentrations the calculated reaction pathway leads to the products of *syn* nucleophilic attack. Calculations find that when the Cl$^-$ concentration is increased, the pathway to **A** is inaccessible, and so the internal nucleophilic addition is prohibited. This leaves only pathways for *anti* nucleophilic attack available, but further oxidation mechanisms should not be possible unless $[PdCl_3(C_2H_4)]^-$ and subsequent adducts are stabilized by $CuCl_2$. The experimental reasoning reported over the past decades and reviewed here speculated this, but some modern computational methods now support similar conclusions. Kinetic studies determining the dependence of $CuCl_2$ on the Wacker rate law would succinctly clarify if these predictions are worth merit.

These proposed mechanisms for nucleophilic attack are not the only possibilities, however. Recent studies by Eshtiagh-Hosseini and co-workers reported the possibility of an *anti* nucleophilic attack on ethylene that was consistent with experimental observations.[39] Here, the *cis*-$[PdCl_2(C_2H_4)(OH)]^-$ complex is attacked by water. Their proposed calculations are controversial since they assumed (without providing support) that ethylene is not comparable to longer-chain allyl alcohols, and thus previous experiments that showed *syn* addition do not hold for ethylene (see Section 3.2). As explained previously, this assumption is impossible to validate experimentally, because the mode of nucleophilic attack can be observed only with substituted olefins.

Fewer studies have probed the remaining processes for product formation. As opposed to reactions leading to nucleophilic attack, no intermediates starting from β-hydrogen elimination have been experimentally observed and reaction processes are expected to be very fast. Siegbahn's simulations on β-hydrogen elimination have already been mentioned.[33b]

Goddard and co-workers[40] also investigated steps of a non-controversial product-formation mechanism. After hydrogen transfers, ethanal formation requires the alkyl alcohol coordinated to Pd^{II} to deprotonate (Scheme 2). β-Hydrogen elimination from the OH group followed by reductive elimination to form HCl was first proposed by Heck[41] and was later incorporated into Bäckvall's mechanism,[18b] but Goddard calculated this hydrogen-transfer barrier to be $+28.4\,\mathrm{kcal\,mol^{-1}}$, again too high in energy to be a feasible non-rate-determining step of the Wacker process. A mechanism best described as a reductive deprotonation was found to be substantially lower in energy, and therefore is more likely at play. Furthermore, this pathway was believed to be lower in energy than the barrier for reductive elimination from a Pd–H species to ethanal.

Three years later, Eshtiagh-Hosseini and co-workers reported a nearly identical mechanism with the same conclusions.[42] The differences in these studies was the solvation model in the latter and that an aqueous species receives the transferring proton. Nevertheless, both studies found similar barrier heights for both β-hydrogen eliminations from an OH group and for reductive deprotonations leading to ethanal and Pd^0. Furthermore, both simulations were made before the difficulty in characterizing zwitterionic transition states coupled to deprotonations was observed. These calculated barriers should also be revisited with more accurate quantum chemical methods.

5. Conclusions

This Minireview summarizes the longstanding kinetic, stereochemical, and theoretical evidence of two distinct pathways in the Wacker oxidation reaction. This evidence points out that the Wacker process is quite sensitive to and dependant on reaction conditions, specifically Cl^- and $CuCl_2$ concentrations. Experimental results support the conclusion that *syn* hydroxypalladation leading to ethanal is the active mechanism of the Wacker process under industrial conditions (low concentrations of Cl^- and $CuCl_2$) and *anti* hydroxypalladation leading to chlorohydrin is the active mechanism under conditions with high concentrations of Cl^- and $CuCl_2$. This conclusion that two mechanism are in effect relies heavily on kinetic evidence ruling out proposed *anti*-hydroxypalladation pathways and the validity of stereochemical studies at low concentrations of Cl^- and $CuCl_2$ that some have found controversial. These conclusions have evolved over decades and provide a picture that is noticeably different or neglected in most mechanism discussions.

A general observation emerges from stereochemical data. In reactions in which Pd^{II} is in the presence of a strongly coordinating ligand such as CO, nucleophilic attack should be *anti* because the second coordination site necessary for *syn* addition is not available. Strongly complexing ligands also stabilize oxypalladation adducts similar to intermediate **B** against decomposition to oxidation products since vacant coordination sites are not available for hydrogen transfers. Thus, the same factors that favor *anti* addition also favor stable oxypalladation intermediates that may in turn undergo different reactions to form different products.

Results from theoretical calculations have clarified the mechanism somewhat. All calculations on the originally proposed *syn*-hydroxypalladation mechanism rule out internal migration of OH^- as a possible mechanism. However, a novel *syn*-hydroxypalladation mechanism involving a water transfer simultaneously coupled to a deprotonation may be consistent with current interpretations of experimental and theoretical calculations; this mechanism warrants more investigation.

Although we cannot describe the one "true" pathway of the Wacker oxidation process, we have summarized a wide variety of studies that provide strong evidence that subtle changes in experimental conditions can result in substantially different reaction mechanisms. Furthermore, this Minireview describes the current status of a conventional but controversial reaction that at different times was believed to be completely understood. Future experimental and theoretical studies should seriously consider this body of evidence implicating two reaction pathways governed by distinctly different sets of experimental conditions.

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[38] One possible solution may be DFT-based molecular dynamics simulations to explicitly treat solvent molecules and eliminate deficiencies in empirical solvation methods. However, if the reported errors are caused by an inherent problem with DFT itself, one should not be surprised if DFT-based methodologies do not provide reliable insight to intermolecular deprotonation reactions.

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