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Inaccessibility of β-Hydride Elimination from −OH Functional Groups in Wacker-Type Oxidation

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β-Hydride elimination (BHE) is one of the most fundamental reaction classes in organometallic chemistry. The required conditions for this [1,2] rearrangement are considered to be well understood, namely the presence of a hydrogen on an atom β to a metal with a vacant coordination site. BHE is well documented for cases in which the β atom is a carbon, but it has also been postulated for alcohols, specifically in regards to the Wacker process.[1] Though some references do suggest alternative mechanisms,[2] most reports,[3a,b] reviews,[3c,d] and even textbooks[3e−g] present BHE as the final step of the Wacker reaction (**1** → **2**, see Scheme 1), illustrating the pervasiveness of the notion of this BHE. It should be noted that this communication focuses *exclusively* on this step, leaving the other parts of this complicated mechanism[4] for future investigation.

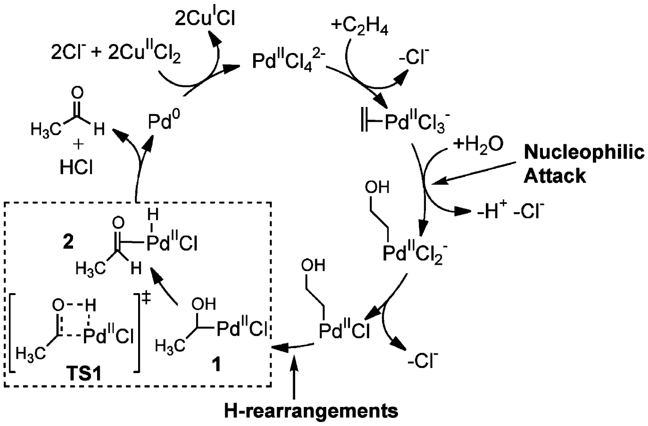
During quantum mechanics studies of the Wacker reaction, we were surprised to find a prohibitively high barrier for BHE (36.3 kcal/mol) when the β-group is −OH (i.e., in the step **1** → **2**). We searched for experimental evidence supporting BHE from −OH groups but found only the speculations mentioned above. Furthermore, a recent report by Cornell and Sigman[5] suggests this seemingly plausible BHE as a possibility for a related reaction. While they conclude that BHE is not operating in their system, this prompted us to further explore our findings.

We show here through DFT calculations that BHE should be eliminated as a possible mechanistic step for this stage of the standard Wacker process. We instead present a possible pathway similar to a reductive elimination that is much lower in energy.

We used both the B3LYP and MPW1K flavors of density functional theory (DFT) with the LACVP**++ basis set, using an effective core potential to describe the core electrons of Pd (leaving 18 explicit electrons). Energies cited in the text of the communication are from B3LYP. We used the PBF Poisson−Boltzmann continuum solvent method to simulate the aqueous environment (ϵ = 80.37 and probe radius = 1.40 Å). All calculations used the Jaguar 6.0 quantum chemistry package.[6] Quoted energies are solvent-corrected enthalpies at 0 K (including zero-point energy corrections) (Table 1). B3LYP and MPW1K results were very similar in all cases, with MPW1K barriers consistently 3−4 kcal/mol higher in energy.

To undergo BHE, an aqua-saturated **1** must first dissociate one aquo ligand, generating **1′**. Our calculations show that this process is exothermic by 2.3 kcal/mol, due to internal coordination from the −OH group (Pd−O = 2.40 Å, Pd−H = 2.79 Å). Control calculations with the other aqua ligand replaced by a second chloride yielded a slightly higher energy pathway. After dissociation, rotation around the C−O bond enables the BHE.

Scheme 1. Traditional Representation of the Wacker Cycle[a]



[a] Product formation steps (**1** → **2**) in box. Aquo ligands eliminated for clarity.

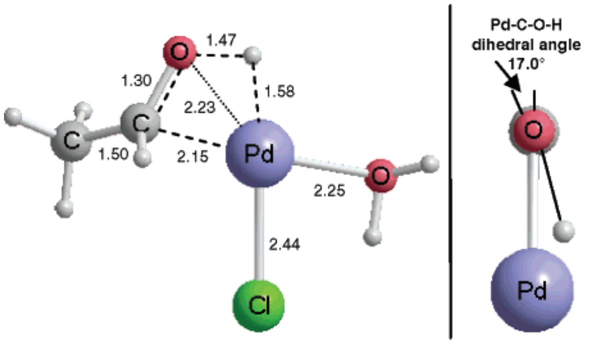


Figure 1. (Left) Optimized transition state geometry for β-hydride elimination (TS1). Distances in Å. (Right) Top view of TS1 with the Pd−C−O−H dihedral angle illustrated.

The optimized BHE transition state **TS1** (Figure 1) has Pd−H = 1.58 Å (very close to the product distance, 1.52 Å), a very long Pd−C bond (2.15 Å), and a short O═C bond (1.30 Å), indicating a very late transition state with a trapezoidal geometry. This leads to an activation enthalpy of 36.3 kcal/mol compared to **1′**. This is nearly double the experimental activation energy for the Wacker reaction, 19.8 kcal/mol,[2a] thus indicating that if our calculations are correct, an alternative lower-energy pathway for carbonyl generation must exist.

The transition state has a Pd−C−O−H dihedral angle of 17°, indicating a twisting to overlap the proton more with the lone pair of the O. This contrasts with normal BHEs, which require substantial alignment of the Pd−H bond with the π-system of the forming double bond. Ideally, the reacting atoms would be coplanar, although steric factors normally lead to slight deviations (e.g., a calculated Pd−C−C−H dihedral angle of 8° for the β-carbon analogue of **TS1**,[7] which has a barrier of 2.1 kcal/mol).

Furthermore, the Mulliken charge on the H in **TS1** is +0.23, whereas it is −0.10 for the product, suggesting a transition state more akin to a proton transfer. Molecular orbital analysis with Pipek−Mezey localized orbitals shows that the two reacting MOs are both destabilized in **TS1** compared to the reactant. In the allowed

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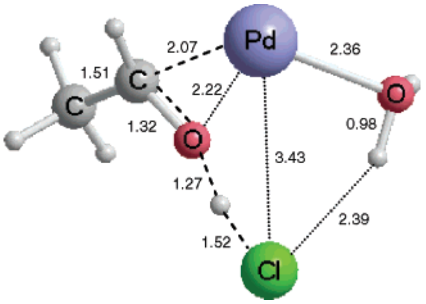
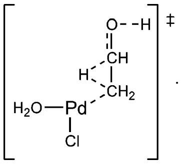


Figure 2. Optimized transition state geometry for direct reductive elimination (TS2) in the Wacker oxidation process. Distances are in Å.

β-carbon analogue BHE, the reacting orbitals are correlated: one is stabilized while the other destabilized, which facilitates the favorable orbital interactions. Thus, both electronic and structural deviations from the β-carbon analogue indicate that **TS1** is not the pericyclic rearrangement expected for BHE.

Because **TS1** is prohibitively high in energy, we explored other mechanisms, such as the α-hydride shift first suggested by Henry[2a] and also postulated by others, including Cornell and Sigman.[5] Such a transition state was located, but because this barrier is high as well ($\Delta H^{\ddagger} = +42.8$ kcal/mol) this mechanism was not studied further.



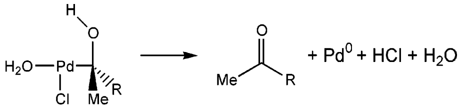
Instead, we found a low-energy pathway through **TS2** (see Figure 2). We consider this a chloride-mediated reductive elimination (RE), where HCl and Pd(0) form directly. In **TS2**, the Cl removes the hydrogen from the OH as it dissociates (O−Cl = 3.43 Å). It also features a partial O−H bond (1.27 Å versus 0.97 Å in the reactant) and a partial Cl−H bond (1.52 Å versus 1.35 Å in the product). The new O═C bond is half formed (1.32 Å versus 1.38 Å in the reactant and 1.29 Å in the product). The increased distance between H_2O and Pd (2.36 Å) and the movement of the H_2O toward the Cl (2.39 Å) indicates that Pd(0) binds them less tightly than Pd(II).

We find an activation energy of 18.7 kcal/mol for **TS2**, just half that for the BHE mechanism. Molecular orbital analysis shows that formation of both the C−O π-bond and Cl−H bond correlate with the destabilization of the breaking O−H bond. Intrinsic reaction coordinate (IRC) calculations confirm that **TS2** does connect the Pd(II)(Cl)(H_2O)($CHCH_3$−OH) transition state with both the Pd(0) product and the Pd(II) reactant.

We also evaluated the reaction energetics for the phenyl-substituted olefin considered by Cornell and Sigman.[5] These calculations (Table 1) suggest a similarly prohibitive barrier for BHE (29.9 kcal/mol) compared to a quite accessible barrier for RE (12.5 kcal/mol). While our conditions are sufficiently dissimilar to prevent any mechanistic conclusions, this does imply that a reinterpretation of Cornell and Sigman's results might be warranted.

Because the Wacker reaction is run under aqueous conditions, we considered the possibility that an explicit solvent molecule could play a role in assisting H-transfer from −OH to Pd−H formation (in the case of BHE) or direct elimination of HCl (in the case of RE). We found that the explicit water does lower the overall barriers for both mechanisms; nevertheless, the BHE pathway forming Pd−H is still higher than the RE pathway (25.0 versus 17.2 kcal/mol). Preliminary calculations indicate that further waters do not alter these barriers. All structures and details of the energies can be found in the Supporting Information. We also considered the possibility of effects by other external elements such as chloride ions or $CuCl_2$ but could find no catalytic or concentration effects of note.

Table 1. Barrier Heights (in kcal/mol) of Transition States TS1 and TS2[a]



$\Delta H^{\ddagger}$ (kcal/mol)	BHE (TS1) B3LYP	BHE (TS1) MPW1K	RE (TS2) B3LYP	RE (TS2) MPW1K
R = H	36.2	40.6	18.8	22.5
R = H (+H_2O)	25.0	29.7	17.2	20.9
R = Ph	29.9	34.3	12.5	15.4

[a] (+H_2O) denotes simulations with an explicit water molecule bridging the H-transfers.

With a barrier of 25.0 kcal/mol, it is expected that in a protic solvent the BHE-type mechanism is feasible, yet the difference in $\Delta H^{\ddagger}$ of 7.8 kcal/mol is more than enough to suggest that the BHE-type mechanism is not competitive even in pure water.

In summary, DFT calculations on mechanisms relevant to the Wacker process indicate that the barrier for BHE from −OH groups is prohibitively high (36.2 kcal/mol), compared with an RE process that eschews Pd−H formation (18.8 kcal/mol). In addition, we showed that the α-hydride process is prohibitively high (42 kcal/mol), and we carried out preliminary calculations on several other possible mechanisms. However, it should be noted that the presence of alternative low-energy pathways cannot be completely excluded. Our calculations also showed that explicit water catalyzes both mechanisms, leading to barriers of 25.0 and 17.2 kcal/mol, respectively, but the BHE type mechanism is still not expected to be competitive.

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Supporting Information Available: Molecular structures, energies, zero-point energies, IRC outputs, and DFT functional comparisons. This material is available free of charge via the Internet at http://pubs.acs.org.

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