Stereochemistry of the Wacker Reaction: Modes of Addition of Hydroxide, Methoxide, and Phenyl at High and Low [Cl⁻]. A Study Using Chirality Transfer

Othman Hamed, Charles Thompson,*,[†] and Patrick M. Henry*

*Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626*

The Pd(II)-catalyzed oxidation of ethene in aqueous solution (Wacker reaction) gives exclusively acetaldehyde under the usual Wacker conditions of low [Cl⁻] (>1.0 M).[1] Under the same conditions, Pd(II) oxidizes α-olefins to methyl ketones and aldehydes. Thus, propene gives a mixture of acetone and propanal. At high chloride (>2.5 M) and high [CuCl₂] (>3 M) formation of ethylene chlorohydrin becomes a serious side reaction. The Wacker controversy concerns the stereochemistry of addition of the elements of Pd(II) and OH to the ethene double bond (hydroxypalladation) under the usual Wacker conditions of low [Cl⁻].

The rate expression for the oxidation of ethene to acetaldehyde, given by eq 1, is consistent with (a) syn

$$\text{rate} = k[\text{PdCl}_4^{2-}][\text{olefin}]/[\text{H}^+][\text{Cl}^-]^2 \qquad (1)$$

addition by coordinated hydroxyl on a Pd(II)−olefin π-complex to give **1** in the slow step (eq 2), or (b) anti attack by external water on the corresponding aquo-complex in an equilibrium step to give **1** (eq 3). In both

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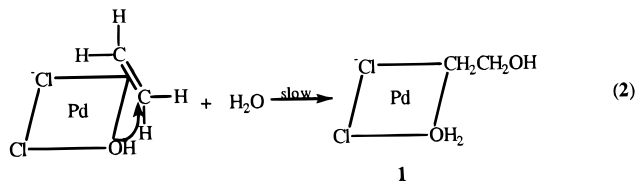
mechanisms **1** decomposes to acetaldehyde and Pd(0).

(3)
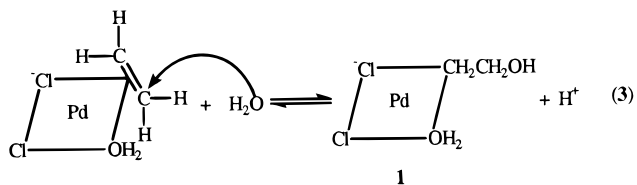
Studies under conditions far removed from those of the aqueous acyclic olefin oxidation suggest an anti mode of hydroxypalladation.[2−4] The study that uses conditions closest to those of the Wacker oxidation employs high

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† Present address: Department of Chemistry, University of Montana, Missoula, Montana 59812.

(1) For general discussion and references, see: Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel: Dordrecht, Holland, 1980; pp 41−84.

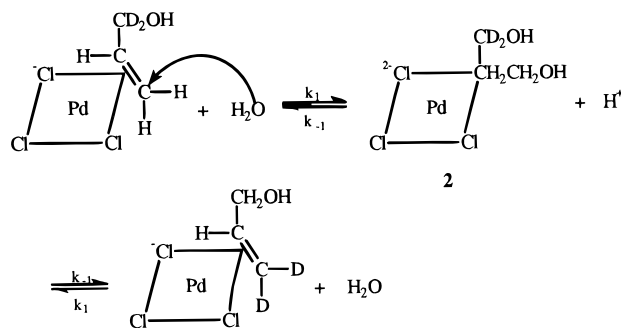(2) Stille, J. K.; James, D. E. *J. Organomet. Chem.* **1976**, *108*, 401−408.

(3) Stille, J. K.; Divakarumi, R. *J. Organomet. Chem.* **1979**, *169*, 239−248.

(4) Åkermark, B.; Söderberg, B. C.; Hall, S. S. *Organometallics* **1987**, *6*, 2608−2610.
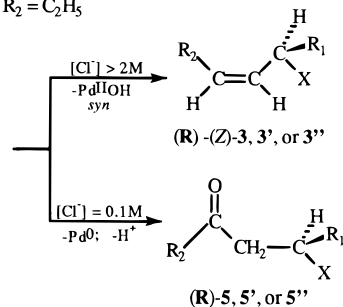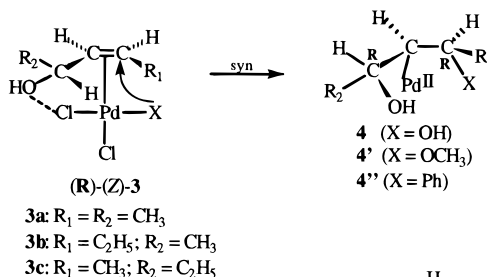
(5) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411−2416.

(6) Gregor N.; Zaw, K.; Henry, P. M. *Organometallics* **1984**, *3*, 1251−1256.

Scheme 1

Scheme 2

chloride and cupric chloride concentrations ([Cl⁻] > 3 M; [CuCl₂] > 2.5 M), conditions where the main product is 2-chloroethanol.[5] It was assumed that the same intermediate, **1**, which decomposes to acetaldehyde, is intercepted by CuCl₂ to give chlorohydrin. The present report provides evidence that the modes of addition at high and low chloride concentrations are different so the stereochemical studies at high chloride are not a valid indicator of the stereochemistry under the usual Wacker conditions of low chloride.

Oxidation of allyl alcohols occurs by the rate expression given by eq 1 at low [Cl⁻] (<1 M). The products are a mixture of hydroxyacetone and 3-hydroxypropanal, the expected Wacker oxidation products. At [Cl⁻] > 3 M the oxidation of allyl alcohol effectively ceases and nonoxidative isomerization of allyl alcohol-1,1-d_2 into its allylic isomer, allyl alcohol-3,3-d_2 predominates.[6] The rate expression for the nonoxidative isomerization, given by eq 4, is most consistent with trans attack of water on an

$$\text{rate} = k[\text{PdCl}_4^{2-}][\text{allyl alcohol}]/[\text{Cl}^-] \qquad (4)$$

allyl alcohol−Pd(II) π-complex as shown in Scheme 1. Since the isomerization shown in Scheme 1 is the predominant pathway at high [Cl⁻], it seems reasonable that a trichloro-hydroxypalladation adduct analogous to **2** is the species intercepted by CuCl₂ rather than **1**. Thus a demonstration that the stereochemistry of hydroxypalladation is different at high and low [Cl⁻] would support different mechanistic pathways for these two regions of [Cl⁻]. Since addition is anti at high [Cl⁻],[5] such

Table 1. Stereochemistry of Addition of Phenyl, Hydroxide, and Methoxide to Chiral Allylic Alcohols

| run	[Cl$^-$] (M)	X	solvent	allyl alcohol (%ee)	product (%ee)
1	0.1	Ph	CH$_3$OH	(*R*)-(*Z*)-**3a** (53)	(*R*)-CH$_3$C(=O)CH$_2$CH(Ph)CH$_3$, (*R*)-**5a″** (30%)
2	2.5	Ph	CH$_3$OH	(*S*)-(*Z*)-**3a** (74)	(*S*)-(*Z*)-CH$_3$CH=CHCH(Ph)CH$_3$, (*S*)-*Z*-**3a″** (68%)
3	0.1	OH	H$_2$O	(*R*)-(*Z*)-**3b** (66)	(*R*)-CH$_3$C(=O)CH$_2$CH(OH)C$_2$H$_5$, (*R*)-**5b** (42%)
4	2.0	OH	H$_2$O	(*R*)-(*Z*)-**3c** (76)	(*S*)-(*Z*)-C$_2$H$_5$CH=CHCH(OH)CH$_3$, (*S*)-*Z*-**3b** (76%)
5	0.1	OCH$_3$	CH$_3$OH	(*R*)-(*Z*)-**3a** (53)	(*R*)-CH$_3$C(=O)CH$_2$CH(OCH$_3$)CH$_3$, (*R*)-**5a′** (42%)
6	2.5	OCH$_3$	CH$_3$OH	(*S*)-(*Z*)-**3a** (74)	(*R*)-(*Z*)-CH$_3$CH=CHCH(OCH$_3$)CH$_3$, (*R*)-*Z*-**3a′** (68%)

a demonstration would be evidence for syn addition at low chloride concentration.

Studies in methanol at low and high [Cl$^-$] showed that the kinetics and mechanism of the Pd(II)-catalyzed reactions in this solvent are exactly analogous to those found in aqueous solution.[7,8] Oxidation to acetals obeying eq 1 occurs at low [Cl$^-$], and isomerization obeying eq 4 is found at high [Cl$^-$].

Determination of the relative modes of addition under the two regimes of chloride concentration is possible by chirality transfer. This technique employs the directing influence of the hydroxyl group in chiral allylic alcohols. This directing ability of the hydroxyl function has been shown for several reactions of allylic alcohols.[9] Previously the exchange and isomerization of chiral tetrasubstituted allylic alcohols, which cannot undergo Wacker-type oxidation, was examined. The results were consistent with different modes of addition at low and high [Cl$^-$].[10] In the present study we examine the reactions of disubstituted allylic alcohols, (**S**)-(*Z*)-3-penten-2-ol (**3a**), (*R*)-(*Z*)-3-hexen-2-ol (**3b**), and (*R*)-(*Z*)-4-hexen-3-ol (**3c**), which can undergo *both* exchange and oxidation and thus are more closely related to the allylic alcohols previously studied.

The most stable π-complex intermediate in these reactions is the one in which the R$_1$ and R$_2$ groups are furthest apart. Scheme 2 outlines one possible reaction sequence involving syn addition to the most stable π-complex. As shown in Scheme 2, the face to which the Pd(II) is directed will depend on the absolute configuration of the starting alcohol. If, as shown, (*R*)-(*Z*)-**3** is the allylic alcohol, the intermediate **4** will have the (*R,R*) configuration. The products that retain this chiral center will have the (*R*)-absolute configuration. Conversely, if (*S*)-(*Z*)-**3** is the allylic alcohol, syn addition will result in products with the (*S*)-absolute configuration. Anti addition to the most stable π-complex with either (*R*)- or (*S*)-(*Z*)-**3** will give products with the opposite absolute configuration from that of the starting material. On the other hand, anti addition to the least stable π-complex will give the same absolute configuration as the starting material. The important result is *that one type of addition to a given π-complex will give both isomerization and oxidation products with the same absolute configuration.*

The approach assumes *only* that the same π-complex is attacked at high and low [Cl$^-$].[11] It would be very unlikely that one mode of addition occurs to one π-complex at low [Cl$^-$] and another mode of addition to the other π-complex at high [Cl$^-$]. To test this assumption, a nucleophile, whose mode of addition is known and is the same at both low and high chloride, is required. Such a nucleophile is the phenyl group. As shown in eq 5, the phenylation (Heck reaction) of allyl alcohol at low [Cl$^-$]

$$CH_2=CHCH_2OH + PhHgCl \xrightarrow{PdCl_2} PhCH_2CH_2CHO \qquad (5)$$
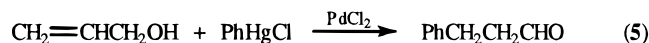
gives a β-phenyl ketone analogous to **5′**.[12] The actual reagent in the Heck reaction is "phenylpalladium" (Ph-

PdCl) formed by exchange of the PhHgCl with PdCl$_2$.[13] This nucleophile was chosen because, being a carbanoid species, it can only exist in hydroxylic solvents bonded to Pd(II). For that reason it must add syn under all experimental conditions, and syn addition has been demonstrated for this nucleophile.[14] For solubility reasons, methanol was the solvent. As discussed above, methanol behaves in the same fashion as water in Wacker chemistry.

Table 1 summarizes the results. Runs 1 and 2 provide evidence for the reaction sequence outlined in Scheme 2. *Thus, as predicted by Scheme 2, the products from syn phenylation had the same absolute configuration as the starting allylic alcohol at both high and low [Cl$^-$].* This result is strong evidence for addition to the most stable π-complex at both high and low [Cl$^-$]. The remainder of the data in Table 1 can now be interpreted in light of this analysis. The most significant result is the relative configurations of the oxidation and exchange products in runs 3 and 4. The product of oxidation of (*R*)-(*Z*)-**3b** is (*R*)-**5** while the product of isomerization of (*R*)-(*Z*)-**3c** is (*S*)-(*Z*)-**3b**. *Thus, according to Scheme 2, the stereochemistry of hydroxypalladation must be opposite at high and low [Cl$^-$]!* The results are best accommodated by syn addition at low [Cl$^-$] and anti addition at high [Cl$^-$]. This interpretation is consistent with kinetic studies discussed above and with the stereochemistry studies in the presence of CuCl$_2$.[5]

Runs 5 and 6 confirm the mechanistic similarity of water and methanol solvents. The results parallel those in water with different modes of addition at high and low [Cl$^-$]. Thus the phenylation results in runs 1 and 2 are valid models for the results in aqueous solution.

Supporting Information Available: Experimental procedure and characterization data (10 pages).

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(7) Henry, P. M.; Lee, H. B. *Can. J. Chem.* **1976**, *54*, 1726−1738.
(8) Dumlao, C. M.; Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 1400−1405.
(9) See reference 10 for a discussion of chirality transfer.
(10) (a) Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498−3503. (b) Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832−2836.
(11) A reviewer pointed out that it is also assumed that the same π-complex is attacked regardless of nucleophile. Certainly methanol and water are so similar that this assumption must be valid. Also there appears to be no reason coordinated hydroxide or methoxide would add to a different π-complex than coordinated phenyl.
(12) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526−5531.
(13) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518−5526.
(14) (a) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707−6714. (b) Henry P. M.; Ward, G. A. *Ibid.* **1972**, *94*, 673−674.