C−H Bond Activation in Aqueous Solution: A Linear Free Energy Relationship Investigation of the Rate-Limiting Step in the H/D Exchange of Alcohols Catalyzed by a Molybdocene

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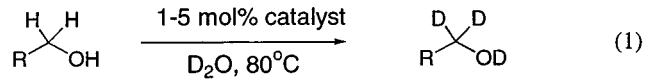
A biphasic linear free energy relationship was found for the H/D exchange reactions of the H atom bonded to the α-carbon atom in substituted benzyl alcohols catalyzed by $[Cp'_2MoOH(OH_2)]^+$ in aqueous solution. This observation is consistent with a rate-limiting step involving C−H oxidative addition. Two pathways for the C−H activation are proposed, one involving formation of a π-bonded aldehyde and the other involving a σ-bonded aldehyde. Donor groups favor the σ-bonded intermediate and withdrawing groups the π-bonded intermediate.

Introduction

We recently reported that $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2](OTs)_2$ is a catalyst for H/D exchange at the α-carbon of alcohols in aqueous solution (eq 1).[1,2] A mechanistic



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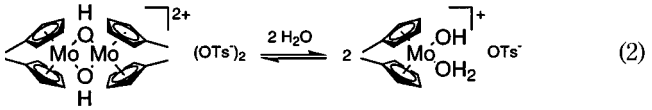

(2)

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study of this C−H bond activation showed that the active catalyst is the monomeric molybdocene species $[Cp'_2MoOH(OH_2)]^+$, which is formed by hydrolysis of $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2](OTs)_2$(**1**) (eq 2) or Cp'_2MoCl_2(**2**) in aqueous solution at neutral pH.[2,3] A mechanism for H/D exchange in alcohols, involving the active monomer, was proposed on the basis of kinetic studies (Scheme 1).[1] The proposed mechanism involves alcohol coordination to the catalyst (**3**), followed by oxidative addition of the C−H bond[4] (β-hydride transfer) to form the molybdocene η^2-ketone/aldehyde hydride complex. The hydride is then exchanged for deuterium, and reverse β-deuteride elimination subsequently forms the α-deuterated alcohol. The proposed reaction scheme[1] was supported by evidence from kinetic studies and by the isolation of key intermediates. One question that remained, however, was the identification of the rate-determining step. The kinetic isotope effect ($k_H/k_D = 2.2$)[1] showed that a hydrogen-atom bond is broken during the rate-limiting step, which leaves the C−H bond activation, step **4** → **5**-*h*, and step **5**-*h* → **5**-*d* as possible rate-limiting steps. Note that both steps are consistent with the activation parameters ($\Delta H^{\ddagger} = 19.4 \pm 0.2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -22.7 \pm 0.7$ cal mol^{-1} K^{-1}).[1] To elucidate the rate-determining step, a linear free energy relationship study was undertaken using a series of substituted benzyl alcohols as substrates in the catalytic reaction. The basis for this study was the notion that step **4** → **5**-*h* should be sensitive to substrate electronic effects but step **5**-*h* → **5**-*d* should be relatively insensitive because the reaction site in this latter step is distant from the substituents on the alcohol substrate. In this report, the resulting Hammett plot will be discussed along with likely mechanistic interpretations, including interesting results that show a change in the mechanism of the reaction.

Experimental Section

General Comments. All manipulations were carried out under a nitrogen atmosphere using standard Schlenk line or glovebox techniques. Solvents were dried over and distilled from sodium benzophenone. D_2O (99.0% D) was obtained from Cambridge Isotope Laboratories and was purged with N_2 for at least 30 min prior to use. All liquid substrates were degassed by the freeze−pump−thaw method prior to use. All substituted alcohols were obtained from Aldrich, with the exception of *p*-(trifluoromethoxy)benzyl alcohol and *p*-aminobenzyl alcohol, which were obtained from Lancaster. The *m*-ammonium benzyl alcohol was prepared by the innate protonation of *m*-aminobenzyl alcohol in a buffer solution at pH 7.2. The buffer, hemi-sodium morpholinopropanesulfonic acid salt (hemi-

(1) Balzarek, C.; Weakley, T. J. R.; Tyler, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 9427−9434.
(2) Balzarek, C.; Tyler, D. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 2406−2408.
(3) Balzarek, C.; Weakley, T. J. R.; Kuo, L. Y.; Tyler, D. R. *Organometallics* **2000**, *19*, 2927−2931.

(4) (a) It is interesting that of the three types of C−H bond activation (oxidative addition, σ-bond metathesis, and electrophilic substitution),[4b,c] electrophilic substitution seems most prominent in protic solvents,[4d−f] whereas oxidative addition is well established in nonprotic, organic solvents. However, the proposed step **4** → **5**-*h* suggests an oxidative addition in the protic solvent, water. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047−1055. (c) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154−162. (d) Stahl, S.; Labinger, J.; Bercaw, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2181−2192. (e) Stahl, S.; Labinger, J.; Bercaw, J. *J. Am. Chem. Soc.* **1996**, *118*, 5961−5976. (f) Sen, A. *Acc. Chem. Res.* **1998**, *31*, 550−557.

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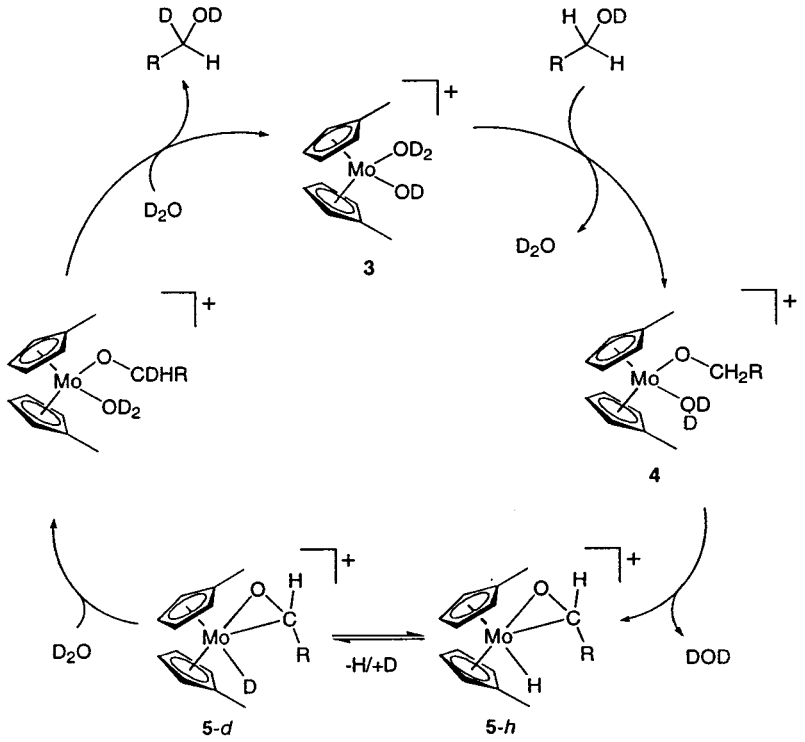
Scheme 1. Catalytic Cycle for the H/D Exchange of Alcohols[a]



[a] R = C_6H_5X, where X = H, OCH_3, NH_3^+, CH_3.

sodium MOPS), was used as received from Fluka. $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2](OTs)_2$ was prepared according to literature procedures.[2] ^1H and ^2H NMR spectra were recorded using a Varian Inova 300 (299.95 MHz for ^1H, 46.04 MHz for ^2H) or a GE 500 (500.13 MHz for ^1H, 76.77 MHz for ^2H) spectrometer. All NMR samples were prepared in the glovebox and were flame-sealed while frozen in liquid N_2 prior to heating. Samples were heated and maintained at 80 °C in a temperature-controlled oil bath or in the NMR probe by use of the variable-temperature (VT) controller. After the reaction was complete, pH measurements were obtained with a Corning NMR microelectrode, d = 3 mm, and an Orion 230A+ pH meter. All pH meter readings in D_2O are reported uncorrected.

Deuteration of Substituted Benzyl Alcohols. On the benchtop, 145 mg (16.4 mmol) of $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2](OTs)_2$ and 445 mg (202 mmol) of hemi-sodium MOPS buffer were measured into 5 mL volumetric flasks. The volumetric flasks were transferred into the glovebox. In the glovebox, at least three solutions of different aliquots between 200 and 1000 mg (20−100 mL, 200−800 mmol) of the aromatic alcohol (benzyl alcohol, *m*-methoxybenzyl alcohol, *m*-methylbenzyl alcohol, *p*-methoxybenzyl alcohol, or *m*-ammonium benzyl alcohol) were added to volumetric flasks. D_2O was added to each volumetric flask, bringing the total sample volume to 5 mL. This produced samples with 0.0033 M $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2](OTs)_2$, 0.404 M buffer solution, and variable concentrations of alcohol. Samples were mixed until homogeneous. The solution was transferred to five 5 mm NMR tubes, which were capped, removed from the glovebox, and flame-sealed as described above. Samples could be stored in a refrigerator at 10 °C for 1 week without appreciable H/D exchange. The reaction was monitored by ^1H and ^2H NMR. Many other substrates, which were found to be unsuitable for the reaction conditions, were tested and are discussed in the Supporting Information. Each sample's pH, measured after the reaction was complete, ranged from 6.9 to 7.2.

The reaction rate was determined from the first-order exponential decay fit[5] of alcohol concentration vs time.[1] The first-order rate equation is applicable in this situation because the concentration of the catalyst remains constant over the reaction period. Each alcohol was studied for evidence of substrate inhibition, and the initial substrate concentration was determined from the integration of the alcohol peaks (4.75−4.55 ppm, 2H) vs the buffer (3.9−3.7 ppm, 4H) after the temperature equilibration. The initial rate (M/s) was plotted against the initial substrate concentration to investigate substrate inhibition.

Table 1. Rate Constants of H/D Exchange in Substituted Benzyl Alcohol Substrates

substrate	σ	obsd rate constant (k_{obs}, s^{-1})	std dev	ln k_{obs}
p-methoxybenzyl alcohol	−0.27	2.8×10^{-5}	3.3×10^{-6}	−10.48
m-ammonium benzyl alcohol	0.86	4.7×10^{-5}	8.7×10^{-6}	−9.96
m-methylbenzyl alcohol	−0.07	1.9×10^{-5}	2.8×10^{-6}	−10.86
m-methoxybenzyl alcohol	0.12	2.5×10^{-5}	5.6×10^{-6}	−10.61
benzyl alcohol	0	1.7×10^{-5}	3.7×10^{-6}	−10.97

Results and Discussion

The H/D exchange reaction in Scheme 1 occurs in aqueous solution, and thus it was necessary to use water-soluble alcohols as the substrates. The substituted benzyl alcohols used in this study were *p*-methoxybenzyl alcohol, *m*-methoxybenzyl alcohol, *m*-methylbenzyl alcohol, *m*-ammonium benzyl alcohol, as well as benzyl alcohol (Table 1). Each of these substrates is water-soluble, and they do not undergo side reactions or form unproductive complexes with the catalyst under the experimental conditions, as determined by NMR. The equilibria involving aqueous molybdocenes are pH dependent.[3] Consequently, to eliminate possible pH changes caused by the substituent on the phenyl ring,

(5) The equation used was $[A] = [A]_0 e^{-0.5kt}$, where A is the alcohol and the value 0.5 is due to the need for both protons to be exchanged in subsequent reaction cycles. (The second cycle is only productive half of the time.) See ref 1. In this case, $k = k'K_{eq}$[catalyst].

the pH of the reaction solutions was controlled with hemi-sodium MOPS (pK_a 7.2).

To obtain a linear free energy plot, the experimental objective was to measure the rate constant for each substrate. Toward this goal, the H/D exchange reactions were monitored by ^{1}H NMR and ^{2}H NMR. Plots of the α-H concentration (as represented by the area of the NMR peak at 4.75−4.55 ppm) over time were fit to a simple first-order exponential decay.[5−7] The observed rate constants determined from the fit of the NMR data can be described by $k_{obs} = k'K_{eq}$[catalyst], where k' is the rate constant for the rate-determining step and K_{eq} is the binding equilibrium of the alcohol to the metal (i.e., the alcohol coordination step found in reaction **3** → **4**, Scheme 1). (Note that the concentration of the catalyst was identical in each experiment.) We attempted to extract k' from k_{obs} using common procedures applicable to catalytic schemes that follow Michaelis−Menten kinetics.[8] However, because it was impossible to run the catalytic reactions under saturation conditions, the numerical solutions for k' were not unique. Although k' could not be determined explicitly, this did not matter in the interpretation of the Hammett plot because we can qualitatively correct for the effect of K_{eq} on the ρ value of k_{obs} by noting that K_{eq} is likely enhanced by electron-donating groups and will thus contribute a negative slope (ρ value) to the plot. With this point in mind, a Hammett plot using k_{obs} instead of k' should still provide a measure of the electronic sensitivity of the rate-limiting step.

The observed rate constant, k_{obs}, the natural logarithm of k_{obs}, and the σ value for each substrate are presented in Table 1. A plot of ln k_{obs} vs σ[9,10] is shown in Figure 1. Note that the plot is biphasic. It is evident that stronger electron withdrawing groups (positive σ values) enhance the reaction rate compared to benzyl alcohol and that stronger electron donating groups (negative σ values) enhance the reaction rate compared to benzyl alcohol. For each group of substrates, the slopes of the lines ($|\rho| > 1$) indicate a rate-limiting step involving an electronically sensitive transition state. Because the plot reflects ρ values for both k' and K_{eq} and because the ρ value for K_{eq} is surely negative, the slope of the right-hand section of the plot with $\rho > 1$ is less than it would be for k' alone. Likewise, the left-hand section has a somewhat more negative slope than would k' alone.

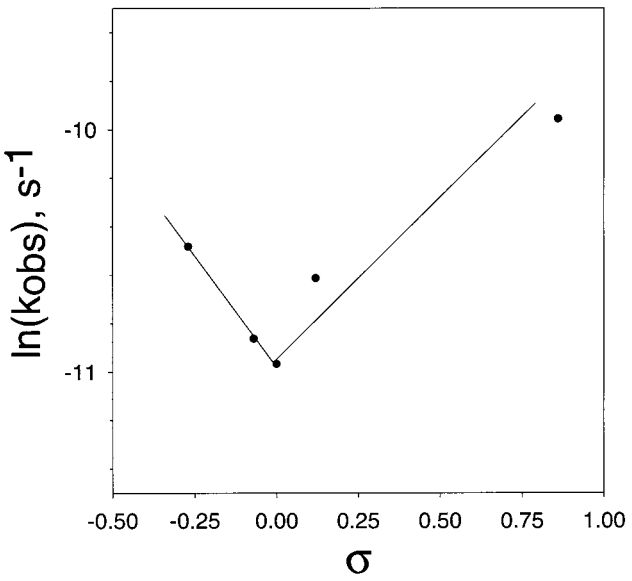
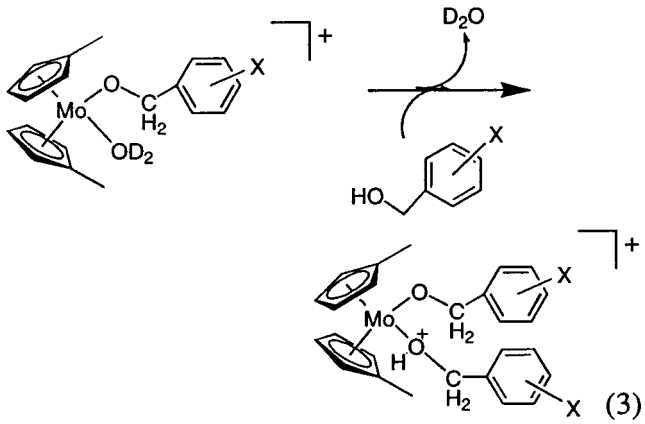


Figure 1. Hammett plot of the H/D exchange rate constants, k_{obs}, in substituted benzyl alcohols. The substituted benzyl alcohols (σ) used were *p*-methoxybenzyl alcohol (−0.27), *m*-methylbenzyl alcohol (−0.07), benzyl alcohol (0), *m*-methoxybenzyl alcohol (0.12), and *m*-ammonium benzyl alcohol (0.86).[9]

A V-shaped Hammett plot is generally indicative of a change in the mechanism. However, before discussing this possibility, we discuss two alternative explanations, namely the possibility of substrate inhibition and experimental error. As the electron-donating ability of the substituent increases, it is possible that the coordinating ability of the alcohol increases to the point that a second alcohol could inhibit the catalytic cycle by coordinating to the metal alkoxide after dissociation of the deuterium oxide (eq 3). This would prevent the



oxidative addition step (reaction **4** → **5**-*h*, Scheme 1). To check for substrate inhibition, k_{obs} was determined using different concentrations of the alcohols. Specifically, the rate constants were determined for each alcohol at three or more concentrations. For each alcohol, a plot of the initial rate vs the initial substrate concentration was linear with a positive slope. (A representative sample is found in the Supporting Information.) Thus, there is no evidence of substrate inhibition at the concentration levels tested for any of the substrates.[11] Another artifact that might induce a discontinuity in

(6) The data from the first 2 h of heating were also fit to a linear expression to determine the initial rate of reaction. However, the precision of the data was greatly improved with the exponential decay method due to the increased number of data points for the fit.

(7) The initial data show small deviations from the first-order exponential decay. This slight error is likely the result of initial temperature equilibration.

(8) Enzyme substrate kinetics of the following form follow the initial rate equation

$$\text{enzyme} + \text{substrate} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{ES complex} \overset{k'}{\rightleftharpoons} \text{enzyme} + \text{product}$$

$$\text{rate}_0 = \frac{V_m}{(1 + K_m/[S]_0)};\ V_m = k'[\text{enzyme}],\ K_m = k' + k_{-1}/k_1$$

The rate constant k' can be extracted by a computer fit of the saturation curves or by plotting $1/(\text{rate})_0$ vs $[S]_0$.

(9) There is some discrepancy in the σ value for the ammonium substituent (0.66 vs 0.86), which is generally attributed to the positive charge of the ammonium. The σ values used herein are from: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(10) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; HarperCollins: New York, 1987.

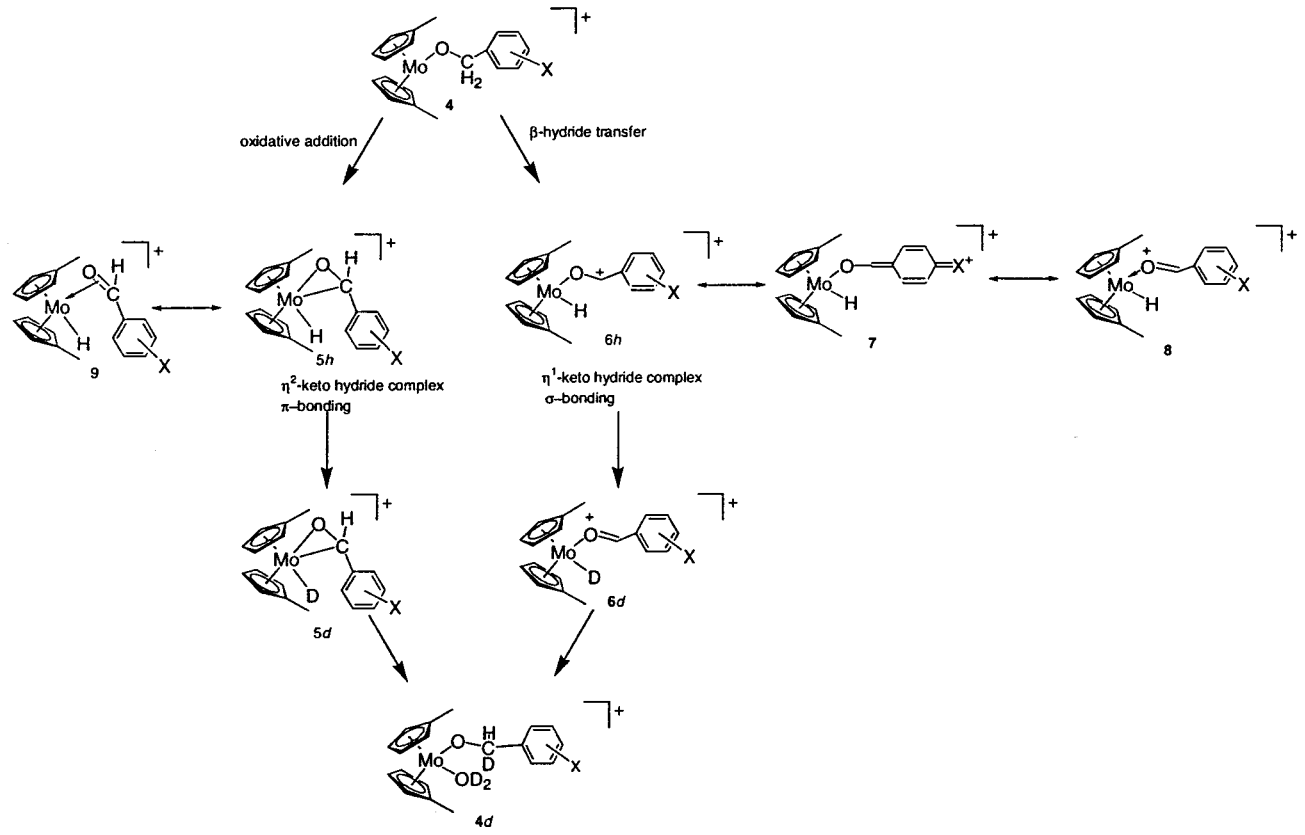


Figure 2. Two possible mechanisms for C−H bond activation in primary aromatic alcohols. β-Hydride transfer (right side) predominates for primary aromatic alcohols with electron-donating groups (X = *p*-OCH_3, *m*-CH_3). Oxidative addition (left side) predominates for primary aromatic alcohols with electron-withdrawing groups (X = *m*-OCH_3, *m*-NH_3^+).

the Hammett plot is large experimental errors in the observed rate constants; i.e., errors could inaccurately represent the Hammett plot as biphasic, when in fact it is linear or nearly linear. However, this explanation is also unlikely because the rate data are reproducible and the errors in the rate constants are small with respect to the rate constants (Table 1).[12]

Because substrate inhibition and large errors can be ruled out as reasons for the biphasic plot, it is concluded that there is a change in the reaction mechanism and that the rate-limiting step in each pathway is highly sensitive to electronic effects. Of the two possible rate-limiting steps discussed in the Introduction, the electronic sensitivity should be small or negligible for the H/D exchange of the metal hydride ligand (step **5**-*h*→**5**-*d*, Scheme 1). The basis for this statement is that the substituent on the benzyl alcohol would not produce a large change in the observed rate constant because of its distance from the reaction site and the shielding by the metal center. In contrast, step **4** → **5**-*h* in Scheme 1, the oxidative addition of the C−H bond of the α-carbon, should be sensitive to electronic effects. Numerous prior studies have shown that the α-carbon electron density in alkanes, acids, and alcohols is directly related to the rate of oxidative addition.[13−15] It is concluded, therefore, that the C−H bond activation step (**4** → **5**-*h*, Scheme 1) is the rate-limiting step.

Change in the Rate-Determining Step. Because the C−H bond activation step is the rate-limiting step, the Hammett plot can be explained by a change in the mechanism of this step. In the proposed catalytic cycle, the C−H bond activation occurs through an oxidative addition reaction which leads to a η^2-aldehyde hydride complex (**5**-*h*; see the left side of Figure 2). The rate of this step would be increased with the introduction of electron-withdrawing groups on the substrate. However, it is the exception rather than the rule that a π-bonded η^2-aldehyde complex would occur preferentially over a σ-bonded η^1-aldehyde complex (**6**-*h*, right side of Figure 2). For example, several molybdenum aldehyde complexes were recently reported to favor σ bonding.[16] (The π/σ ratio was decreased with increasing temperature and decreasing solvent polarity.[16−19]) It is proposed that C−H bond activation also occurs through a β-hydride transfer mechanism to form an η^1-keto complex (**4**-*h* → **6**-*h*, Figure 2), which is stabilized by resonance (**6**−**7**−**8**, Figure 2).[20] The stabilization of the σ complex

(11) Walter, C. *Steady-State Applications in Enzyme Kinetics*; The Ronald Press: New York, 1965.
(12) Note that Hammett plots are typically reported without error bars.
(13) Bruno, J. W.; Smith, G. M.; Marks, T. J.; Fair, C. K.; Schulty, A. J.; Williams, J. W. *J. Am. Chem. Soc.* **1986**, *108*, 40.
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(19) Mendez, N. Q.; Mayne, C. L.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *12*, 1475−1476.
(20) Note that resonance form **7** in Figure 2 is only applicable to para-substituted alcohols. However, meta-substituted alcohols with electron-donating groups would be subject to inductive stabilization of the carbocation.

would be increased by electron-donating groups on the benzyl alcohol. Consistent with the dual pathways proposed above, it has been shown that aliphatic aldehydes and aromatic aldehydes with electron-withdrawing groups favor π bonding, and ketones and aromatic aldehydes with electron donating groups favor σ bonding.[17−19] Therefore, the change in mechanism is due to the relative amounts of π/σ stabilization of the incipient aldehyde during the C−H bond activation. Again, it is evident that C−H bond activation would be sensitive to electronic effects, consistent with the conclusion that this is the slow step of the catalytic cycle, as opposed to the hydride exchange step.

In conclusion, the rates of the H/D exchange reactions are sensitive to electronic effects, a result that suggests that the C−H bond activation step is rate limiting. The biphasic Hammett plot is consistent with a change in mechanism for the C−H bond activation step, and two pathways are proposed. One involves the intermediate formation of a π-bonded aldehyde and the other a σ-bonded aldehyde. Which pathway is followed depends on the electron donating/withdrawing ability of the substrate. Donating groups favor the σ-bonded intermediate and withdrawing groups the π-bonded intermediate. It is noteworthy that all of the previously reported kinetic data are also consistent with a pathway in which C−H bond activation, step **4** → **5**-*h* or **4** → **6**-*h*, is the rate-limiting step in the catalytic H/D exchange. Thus, the previously reported primary kinetic isotope effect ($k_H/k_D = 2.2$)[1] is consistent with both pathways, and the activation parameters ($\Delta H^{\ddagger} = 19.4 \pm 0.2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -22.7 \pm 0.7$ cal mol^{-1} K^{-1})[1] indicate that the transition state of the rate-limiting step acquires a considerable increase in order, again consistent with both pathways in Figure 2.

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Supporting Information Available: Text giving a discussion of substrate limitations and figures giving representative rate plots and substrate inhibition (concentration vs rate) plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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