Isotope Effects in C−H Bond Activation Reactions by Transition Metals

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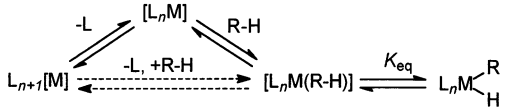
ABSTRACT
The activation of alkane C−H bonds by oxidative addition and its reverse reaction, reductive elimination, are believed to occur via transient σ-alkane complexes. This Account summarizes how isotope effects can be used to probe the nature of these intermediates and points out some pitfalls in interpreting kinetic data. Comparisons are made with arene C−H activation and other activation systems.

1. Introduction

Over the past 30 years or so, a number of examples of carbon−hydrogen bond activation by transition metals have appeared in the literature.[1] This work took on greater significance in 1982, when Bergman reported a reaction in which a "simple" oxidative addition of cyclohexane to a photochemically generated reactive Ir^{I} fragment had occurred.[2] Since then, many other transition metal complexes have been discovered that can activate alkane C−H bonds by a variety of mechanisms to give products with metal−carbon bonds. In this Account, the subject of isotope effects in some of these reactions will be examined in detail, as these effects are oftentimes quoted as having relevance to the mechanism(s) of C−H bond activation.

A general sequence for activation of a hydrocarbon C−H bond is shown in eq 1. In this process, two distinct



(1)

steps are typically proposed following generation of the reactive metal species $[L_nM]$, the first involving interaction of the hydrocarbon with the metal center to make a complex (either dissociatively, as shown, or associatively) and the second involving the actual cleavage of the C−H bond. This sequence can be used to describe a variety of hydrocarbon activations including aromatic, aliphatic, and vinylic C−H bonds. For arenes, the initial complex has been shown to be an η^2-arene complex and can be actually observed and monitored as the second step occurs.[3] For alkanes, the initial complex has been described as a "σ-complex",[4] whose structure has not been experimentally determined but which is believed to involve a three-center interaction of the metal, the carbon, and the hydrogen (η^2-C,H) after the models provided by X-ray structures of intramolecular agostic C−H interactions (Figure 1).[5] While there have been several observations of stable arene π-complexes,[6] direct observations of σ-alkane complexes are rare.[7]

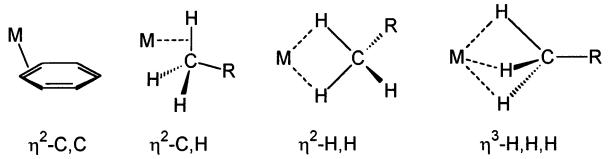
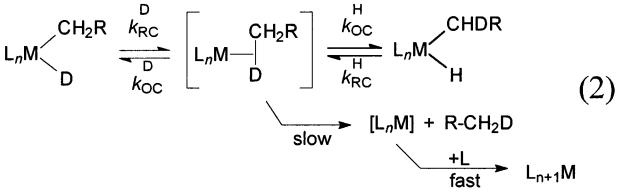


FIGURE 1. Geometries of arene π-complexes and alkane σ-complexes.

The reaction steps in eq 1 are shown as equilibria, since in many cases the formation of the alkyl or aryl hydride product is reversible. In fact, the intermediacy of an alkane σ-complex is oftentimes demonstrated by preparation of an alkyl deuteride complex, which then reversibly scrambles the deuterium into the α-hydrogens of the alkyl ligand, presumably via the unseen σ-complex. Dissociation of the alkane from the σ-complex, followed by irreversible trapping of the reactive fragment $[L_nM]$ with an external ligand, is typically observed also as a slower process (eq 2).[8]



(2)

Although the reversible formation of the σ-alkane complex is detectable in these cases by virtue of the exchange of the position of the labeled atom,[9] there is one example in which dynamic NMR exchange has been used to identify the reversible exchange.[10] Several representative examples relying on isotopic exchange are shown in Scheme 1. In addition to the reversible α-H/D exchange, an effect of isotopic substitution on the *rate of reductive elimination* was also observed. These effects were measured by comparing the rate of alkane elimination in perdeuterio vs perprotio alkyl hydride complexes. In many cases examined, the observed kinetic isotope effect, k_H/k_D, on alkane loss was *inverse*, as shown in Scheme 2.[11,12] Hence, it became common to associate an inverse isotope effect with the intermediacy of a σ-alkane com-

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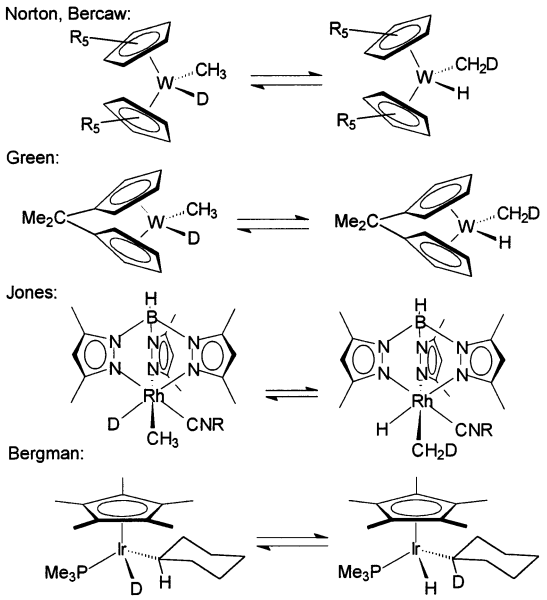
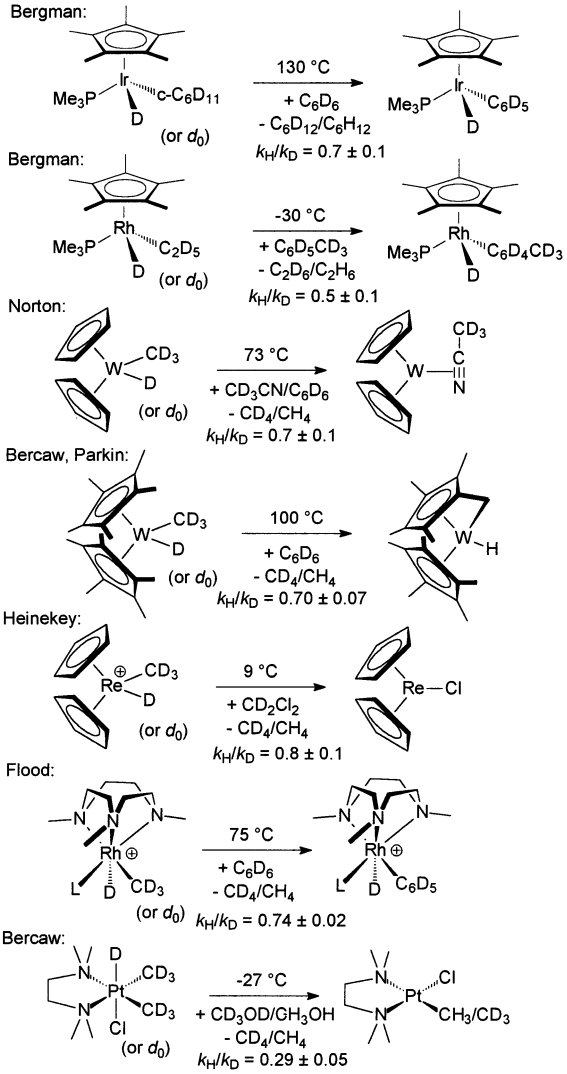
Scheme 1



Scheme 2



plex. Furthermore, since virtually all of this isotope effect would likely be associated with the C−H/C−D bond-making/bond-breaking step, rather than the alkane dissociation step, the overall isotope effect for alkane loss was attributed to an *inverse equilibrium isotope* effect (i.e., $K_{eq}^{H/D} < 1$) separating the alkyl hydride complex from the σ-alkane complex.

One explanation for the origin of the inverse equilibrium isotope is that the σ-alkane complex contains an intact, strong C−H or C−D bond, whereas the alkyl hydride complex has a weaker M−H or M−D bond. Consideration of the zero-point energy differences associated with the stretching frequencies for these bonds leads to the expectation of an inverse equilibrium isotope effect.[13] That is, with metal−hydrogen stretching frequencies being about two-thirds those of aliphatic C−H bonds, a smaller difference in zero-point energies is expected in the alkyl hydride complex compared to the σ-alkane complex. There are two possibilities to be considered for the transition state separating these two complexes. In one case, shown in Scheme 3a, the zero-point energy difference in the transition state is assumed to be intermediate between those of the reactant and product. In the second case, shown in Scheme 3b, the C−H/C−D stretching frequency is assumed to disappear as it becomes the reaction coordinate to break the bond. In the first case (a), one expects an inverse kinetic isotope effect for the conversion of the alkyl hydride complex to the σ-alkane complex (k_{RC}^{H}/k_{RC}^{D}), but a normal kinetic isotope effect for the reverse reaction (k_{OC}^{H}/k_{OC}^{D}). In the second case (b), one expects normal kinetic isotope effects in both directions, with the magnitude of the kinetic isotope effect being larger for the conversion of the σ-alkane complex into the alkyl hydride complex.

There are a few important points to be recognized immediately. First, *both* of these situations are consistent with an inverse equilibrium isotope effect separating the alkyl hydride complex from the σ-alkane complex, since the transition state does not affect the equilibrium. Second, the observation of an inverse kinetic isotope effect for the loss of alkane from an alkyl hydride/deuteride complex cannot, in itself, distinguish between these two cases. Third, to determine which of the two cases pertains to any given system, one must determine two of the three related isotope effects, since the equilibrium isotope effect is really just the ratio of the forward and reverse kinetic isotope effects (eq 3).

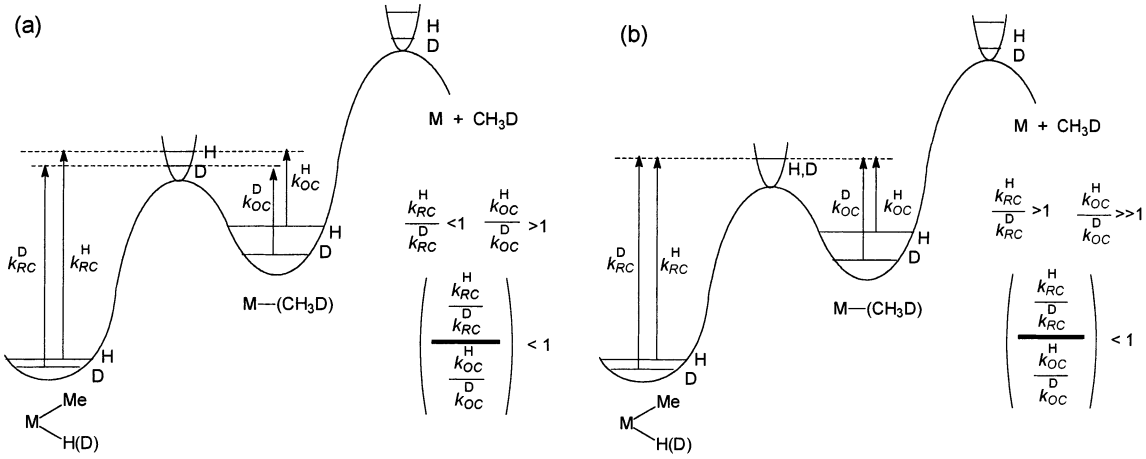
$$K_{eq}^{H/D} = \frac{k_{RC}^{H}/k_{RC}^{D}}{k_{OC}^{H}/k_{OC}^{D}} \qquad (3)$$

With this somewhat lengthy introduction, we are now ready to describe a system that is the first to establish which of the two cases described above leads to the inverse equilibrium isotope effect. We then offer commentary on related systems described in the literature.

2. Kinetic Isotope Effect on Reductive Coupling

We use the term "reductive coupling" to describe the conversion of an alkyl hydride complex into a σ-alkane

Scheme 3

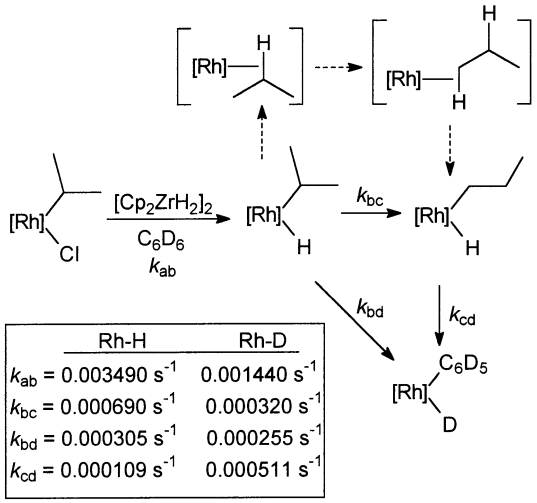


complex without loss of alkane. We first set out to measure the isotope effect on reductive coupling in a methyl hydride complex but found that, just as in the earlier examples of isotopic scrambling, the experiments described a combination of isotope effects rather than the isotope effect on a single, isolated step. We were fortunate to succeed by identifying a complex in which the reductive coupling step is *irreversible*, unlike the case with other alkyl hydride complexes. The work centers on the reactive metal fragment [Tp*Rh(CNR)] (Tp* = tris(3,5-dimethylpyrazolyl)borate, R = neopentyl), which we have shown to activate a variety of alkane and arene C−H bonds via oxidative addition.[14,15] The alkyl hydrides are stable for a few hours at room temperature before they undergo reductive elimination, allowing convenient study of their rearrangements. In benzene solvent, alkane loss is immediately followed by benzene activation to give the thermodynamically stable phenyl hydride complex, Tp*Rh(CNR)(phenyl)H.

Treatment of Tp*Rh(CNR)(*i*-Pr)Cl with $[Cp_2ZrH_2]_2$ in C_6D_6 leads to a rapid metathesis of chloride and hydride ligands to generate the secondary alkyl hydride complex, Tp*Rh(CNR)(*i*-Pr)H. This complex converts to the *n*-propyl isomer over the course of about 30 min, which is concomitant with the loss of propane to quantitatively give Tp*Rh(CNR)(C_6D_5)D after a few hours. Kinetic modeling of this sequence could be accomplished only if direct propane loss from the isopropyl hydride complex was included, as the initial rate of formation of Tp*Rh(CNR)(C_6D_5)D was faster than the initial rate of formation of Tp*Rh(CNR)(*n*-Pr)H. This requirement also makes sense in that the conversion of the isopropyl to the *n*-propyl isomer is proposed to occur via a sequence involving formation of a σ-propane complex bound at the secondary CH_2 group, followed by migration to a terminal methyl group, followed by insertion into the methyl C−H bond; it is reasonable to propose that propane dissociation could be competitive with the alkane migration. The modeling provides observed rate constants for the conversion of one species into the next, as shown in Scheme 4.

This same experiment was conducted with $[Cp_2ZrD_2]_2$, producing initially Tp*Rh(CNR)($CHMe_2$)D. Over time, Tp*Rh(CNR)(CH_2CHDCH_3)H is seen first, and then

Scheme 4

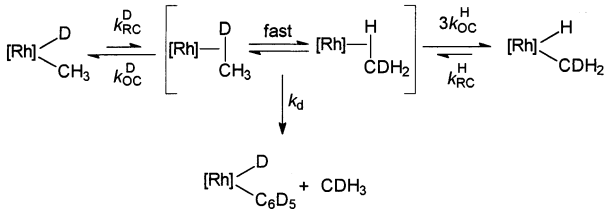


CH_3CHDCH_3 and Tp*Rh(CNR)(C_6D_5)D are observed. At no time was Tp*Rh(CNR)($CDMe_2$)H observed, the result of reversible reductive coupling and oxidative cleavage at the secondary C−H (or C−D) bond of CH_3CHDCH_3. Since the reductive coupling step from the isopropyl hydride (or deuteride) is irreversible, the observed rate constants for disappearance of Tp*Rh(CNR)($CHMe_2$)H (or D), $k_{bc} + k_{bd}$, must represent the fundamental rate for just the reductive coupling step itself, k_{RC}. Since this rate constant could be determined with both the rhodium deuteride and the rhodium hydride complexes, the ratio k_{RC}^{H}/k_{RC}^{D} could be obtained directly. From the rate constants obtained in the least-squares simulations in Scheme 4, a kinetic isotope effect for reductive coupling of $k_{RC}^{H}/k_{RC}^{D} = 2.1$ was obtained...*a normal kinetic isotope effect*.

3. Kinetic Isotope Effect on Oxidative Bond Cleavage and Equilibrium Isotope Effects

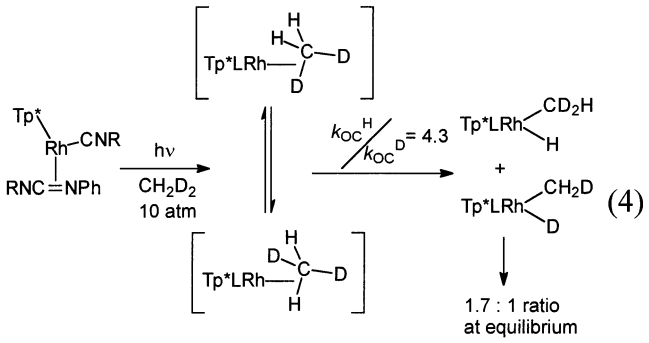
We use the term "oxidative cleavage" to describe the unimolecular conversion of a σ-alkane complex into an alkyl hydride complex. An experiment was designed to probe the kinetic isotope effect for the oxidative cleavage reactions, which is the microscopic reverse of the reductive coupling. For this experiment, we would need to

Scheme 5



observe the rate at which the σ-alkane complex converts to the alkyl hydride or deuteride product.

This measurement would prove difficult, however, because it would require observing the coordinatively unsaturated intermediate [Tp*Rh(CNR)] and monitoring its rate of disappearance in deuterio- or protioalkane. Instead, we chose to generate the [Tp*Rh(CNR)] fragment in the presence of CH_2D_2. Rapid coordination of the hydrocarbon would generate the σ-methane complex of CH_2D_2, which contains equal numbers of C−H and C−D bonds; we could then monitor the kinetic selectivity for formation of Tp*Rh(CNR)(CHD_2)H vs Tp*Rh(CNR)(CH_2D)D. This was accomplished by irradiation of the precursor complex Tp*Rh(CNR)(RN=C=NPh) in the inert solvent C_6F_6 under 10 atm CH_2D_2 at low temperature.[15] The ratio of the kinetically formed products was 4.3:1, and over time at 10 °C the ratio was seen to adjust to ~1.7:1 (eq 4). Based



(4)

upon the initial ratio, the kinetic isotope effect for oxidative cleavage is therefore k_{OC}^{H}/k_{OC}^{D} = 4.3...a normal isotope effect, but larger than that seen in the reductive coupling. Consequently, in this system involving the activation of alkanes by the [Tp*Rh(CNR)] fragment, it is clearly determined that the situation depicted in Scheme 3b applies, and the *the inverse equilibrium isotope effect arises as a result of two normal isotope effects of different magnitudes that oppose each other*.

Furthermore, one calculates an equilibrium isotope effect of 2.1/4.3 = 0.49 from eq 3. This compares reasonably well with the observed value of 1/1.7 = 0.59 from the equilibration seen in eq 4. Also, the reductive coupling isotope effect (k_{RC}^{H}/k_{RC}^{D}) was determined for the isopropyl hydride complex, but it is reasonable to expect a similar isotope effect with the methyl hydride complex.

In a separate examination of the above isotope effects, the complex Tp*Rh(CNR)(CH_3)D was synthesized and allowed to equilibrate with Tp*Rh(CNR)(CH_2D)H, similar to other cases that have been reported in the literature. Scheme 5 summarizes the kinetics for the complex, and

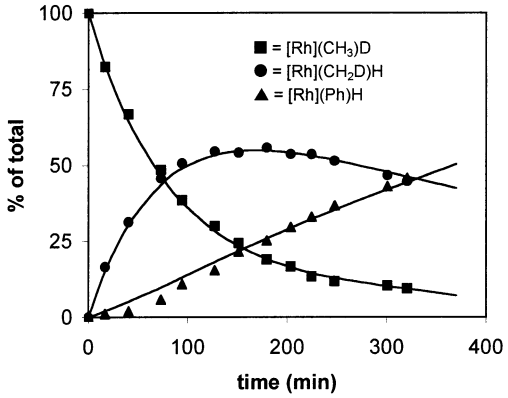


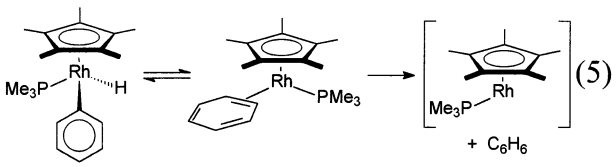
FIGURE 2. Scrambling of deuterium in Tp*Rh(CNR)(CH_3)D at 26 °C.

Figure 2 shows the distribution of species. From the figure, one can see that the methyl deuteride and methyl-d_1 hydride complexes are nearly equilibrated after about half of the methane has been lost, and that $K_{eq} \approx 6.3$. In this example, the complex Tp*Rh(CNR)(CH_2D)H would be favored statistically by a factor of 3 over Tp*Rh(CNR)(CH_3)D. In addition, there should be an equilibrium isotope effect of 2.05 (= $(k_{OC}^{H}/k_{OC}^{D})/(k_{RC}^{H}/k_{RC}^{D})$ = 4.3/2.1). With the combination of these two effects, one expects an equilibrium ratio of these two complexes of about 6.1:1. The excellent agreement in this independent experiment indicates that the assumptions made about the isotope effects transfer reasonably well from one Tp*Rh(CNR)(alkyl)H complex to another.

In addition, it was possible to simulate in detail the microscopic kinetics of the Tp*Rh(CNR)(CH_3)D system, as described previously in detail.[15] The data treatment allowed the determination of relative rate constants in this system, but not absolute rate constants for any reaction stemming from the σ-methane complex (since no σ-methane complex is directly observed). The fitted rate constants provide a value for the oxidative bond formation isotope effect, k_{OC}^{H}/k_{OC}^{D}, of 4.8, compared with the direct observation of 4.3 from eq 4. Again, good agreement is seen. The fitted rate constants also give a value for K_{eq} of 7.1, comparing well with the observed value of 6.3 toward the end of the reaction in Figure 2.

4. Isotope Effects in Arene Activation by [Cp*Rh(PMe$_3$)]

Just as H/D scrambling has been taken as evidence for the intermediacy of σ-alkane complexes, H/D scrambling in aryl deuteride complexes has been taken as providing evidence for η^2-arene complexes (eq 5). The η^2-benzene



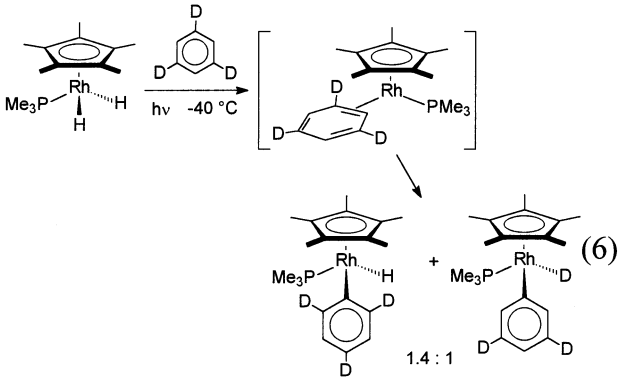
(5)

complex can be seen in transient absorption experiments, and with naphthalene, the equilibrium is such that both η^2-arene and aryl hydride complex can be directly ob-

served.[3] In addition, reductive elimination reactions of aryl hydride/deuteride complexes can give inverse isotope effects. Do these systems correspond to the picture in Scheme 3a or 3b with regard to isotope effects?

One system that has been investigated in detail uses $Cp^*Rh(PMe_3)(Ph)H$, in which H/D exchange is seen by virtue of isotopic exchange between the hydride and the other positions around the arene ring.[16] This exchange occurs sequentially, first in the ortho, then in the meta, and then in the para position, as expected for a mechanism involving reversible formation of an η^2-arene complex (Scheme 6). At equilibrium, a 2.7:2:2:1 ratio of the four isomers is observed. Since there are two ortho and two meta hydrogens, this corresponds to an equilibrium isotope effect of $K_{eq} = 1/2.7 = 0.37$ (favoring deuterium on carbon).

The kinetic isotope effect on oxidative cleavage has also been determined. The coordinatively unsaturated fragment $[Cp^*Rh(PMe_3)]$ was created photochemically from the dihydride in the presence of 1,3,5-trideuteriobenzene at low temperature. Only one η^2-arene complex is possible, and the intermediate must choose between cleavage of a C−H or C−D bond (eq 6). The kinetic isotope effect on oxidative cleavage was found to be $k_{OC}^H/k_{OC}^D = 1.4$.



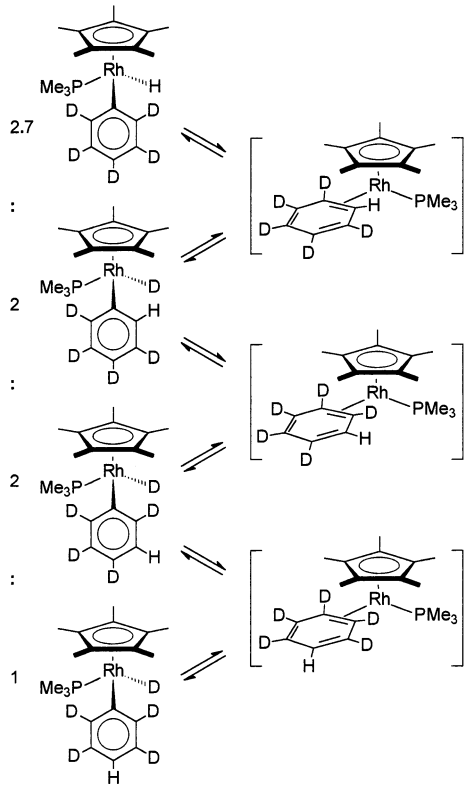
(6)

We now have two isotope effect measurements for the interconversion of the aryl hydride complex and the η^2-arene complex, so the system is determined. One can calculate the kinetic isotope effect for reductive coupling from $(k_{OC}^H/k_{OC}^D)K_{eq}$, and one obtains $k_{RC}^H/k_{RC}^D = 0.52$, *an inverse kinetic isotope effect.* Consequently, this aromatic system can be described using Scheme 3a, with an η^2-arene complex replacing the σ-alkane complex, and in which the transition state for reductive coupling has an intermediate zero-point energy associated with it.

5. Comments on Some Isotope Effects in the Literature

The above analysis can be applied widely to systems in which there is an equilibrium followed by a rate-determining step. Determination of two of the three isotope effects allows determination of the third. Likewise, the system is "undefined" with regard to Scheme 3 if only one isotope effect has been measured. In the reported systems involving alkane H/D scrambling, none of them (except the Tp*Rh(CNR) system) measures more than one

Scheme 6



isotope effect (usually for alkane loss), and therefore the origin of an inverse isotope effect remains undefined.[17]

A recent report by Keinan et al. claims to have determined that reductive coupling in a methyl deuteride complex, $TpPtMeD_2$, has an inverse kinetic isotope effect.[18] Deeper examination of the report, however, reveals that only one of the three isotope effects that determine the equilibrium between methyl hydride and σ-methane complex has been measured (the overall equilibrium isotope effect). Consequently, their claim that the reductive coupling step involves an inverse kinetic isotope effect must be rejected as arbitrary, since insufficient measurements were made to support this statement. The kinetic analysis presented erroneously assumed that the scrambling reaction was irreversible. Their treatment specifically neglected the isotope effect on oxidative cleavage (k_{OC}^H/k_{OC}^D) following the rate-determining reductive coupling step, and consequently is flawed.[19] The observed isotope effects reported by Keinan et al. are not isotope effects for fundamental steps, but actually reflect a combination of isotope effects on several steps during the approach to equilibrium, which includes both k_{RC} and k_{OC} terms. It is not possible to draw a conclusion as to whether the isotope effect on reductive coupling is normal or inverse from their data. [Note added in proof: Keinen et al. have published a correction to their earlier paper, which indicates that the isotope effect for reductive coupling is related to the isotope effect for oxidative coupling: Lo, H. C.; Haskel, A.; Kapont, M.; Keinan, E. *J. Am. Chem. Soc.* **2002**, *124*, 12626 (Addition/Correction).] Bercaw and coworkers have made similar observations with (tmeda)Pt-

$(CH_3)_2(D)(CD_3OD)$ in CD_3OD solvent, where no claims about fundamental isotope effects were made.[9f]

In another example, Bullock et al. measured an inverse kinetic isotope effect for abstraction of hydride ligand from a $CpW(CO)_3H$ complex by trityl cation. The authors support a mechanism involving a direct hydride transfer, and therefore the inverse isotope effect refers to a single reaction step. They did acknowledge, however, that if the hydride transfer is reversible, then they may be monitoring an inverse equilibrium isotope effect as opposed to a kinetic inverse isotope effect.[20] The discussion presented here would then apply.

Finally, there is one report in the literature where an isotope effect on oxidative cleavage of an alkane has been directly measured. Moore and Bergman examined the photolysis of $Cp^*Rh(CO)_2$ in cyclohexane and cyclohexane-d_{12} in liquid krypton solvent and found that they could observe by IR the conversion of the σ-alkane complex to the alkyl hydride. The values for k_{OC}^H/k_{OC}^D were about 10−15 at 163−193 K.[21] This system is somewhat different from that described in Scheme 3, since that alkane is quite labile and there is a rapid equilibrium between bound krypton and bound alkane prior to the oxidative cleavage (i.e., the "right-hand" barrier in Scheme 3 would be lower than the "left-hand" barrier). Similar results were obtained with neopentane and neopentane-d_{12}.[22]

In summary, we have found evidence that the inverse kinetic isotope effect for alkane reductive elimination in $Tp^*Rh(CNR)(alkyl)H$ compounds is due to an inverse equilibrium isotope effect separating the alkyl hydride complex from the σ-alkane complex. This inverse equilibrium isotope effect arises due to two opposing *normal kinetic isotope effects* of different magnitudes. The case is different for arenes in $Cp^*Rh(PMe_3)(aryl)H$ compounds, where the inverse equilibrium isotope effect is due to an *inverse kinetic isotope effect* opposing a small normal isotope effect. Finally, one is reminded that statements regarding isotope effects for a single step in a more complex reaction require that more than one isotope effect measurement be made.

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(11) Examples of inverse k_H/k_D: (a) $Cp^*Ir(PMe_3)(H)(C_6H_{11})$ in C_6D_6 at 130 °C, 0.7(1) (ref 9a). (b) $Cp^*Rh(PMe_3)(H)(C_2H_5)$ in toluene-d_8 at −30 °C, 0.5(1) (ref 9b). (c) $Cp_2WH(CH_3)$ in CD_3CN at 72.6 °C, 0.75-(4) (ref 9c). (d) $Cp^*{}_2WH(CH_3)$ in C_6D_6 at 100 °C, 0.77(7) (ref 9d). (e) $[Cp_2Re(H)(CH_3)][Cl]$ in CD_2Cl_2 at 9 °C, 0.8(1) (ref 8e). (f) $[CnRh(PMe_3)(H)(CH_3)][BAr_4]$ in C_6D_6 at 75 °C, 0.74(2) (ref 9 g). (g) (tmeda)-$Pt(CH_3)(H)(Cl)$ in CH_3OH at −27 °C, 0.29 (ref 9f).

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