

## Isotope Methods in Homogeneous Catalysis

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The use of isotope labels has had a fundamentally important role in the determination of mechanisms of homogeneously catalyzed reactions. Mechanistic data is valuable since it can assist in the design and rational improvement of homogeneous catalysts. There are several ways to use isotopes in mechanistic chemistry. Isotopes can be introduced into controlled experiments and “followed” where they go or don’t go; in this way, Libby, Calvin, Taube and others used isotopes to elucidate mechanistic pathways for very different, yet important chemistries. Another important isotope method is the study of kinetic isotope effects (KIEs) and equilibrium isotope effect (EIEs). Here the mere observation of where a label winds up is no longer enough – what matters is how much slower (or faster) a labeled molecule reacts than the unlabeled material. The most careful studies essentially involve the measurement of isotope fractionation between a reference ground state and the transition state. Thus kinetic isotope effects provide unique data unavailable from other methods, since information about the transition state of a reaction is obtained. Because getting an experimental glimpse of transition states is really tantamount to understanding catalysis, kinetic isotope effects are very powerful.

Direct substitution of D for H (e.g.,  $D_2$  vs.  $H_2$ , or  $D^+$  vs.  $H^+$ ) and measurement of the rate of a catalytic reaction provides a determination of the kinetic deuterium isotope effect on the *overall* reaction. While such measurements may be relatively simple to carry out experimentally, they are seldom unambiguously interpretable, since many steps contribute to the overall catalytic cycle. Even the premise that such a measurement will give information about the rate-limiting step can be incorrect, due to the potential involvement of isotopically sensitive pre-equilibria prior to the rate-limiting step. Enzymologists concerned with isotope effects also recognize this problem and have even coined a term “commitment to catalysis” to help deconvolute these effects.<sup>(1)</sup> Due to these complexities in gaining definitive mechanistic evidence about catalytic reactions, it is usually much more informative to measure the effect of deuterium substitution on the rate constant or equilibrium constant of single steps of a cycle, in isolation from the other steps of the catalytic reaction. This is typically done by model studies

where an organometallic complex chosen for detailed investigation exhibits reactivity akin to that thought to be occurring in the catalytic reaction.

This chapter will focus on reactions using isotopes, and the interpretation of these observations that are pertinent to revealing details of homogeneous catalysis. Complex mathematical and spectroscopic treatments are often required, but the coverage in this chapter will not emphasize the mathematical treatment, since lucid treatments are available in the original references cited here. Thorough coverage of the concepts and theory of isotope effects is provided in book,(2) and a chapter(3) in a book on metal hydrides gives a more focused treatment of some reactions pertinent to homogeneous catalysis.

The definitive treatment of the equilibrium isotope effect (EIE) is the classic 1947 paper by Bigeleisen and Mayer.(4) Eq. 1 uses the acronyms introduced later by Wolfsberg and

$$\text{EIE} = \text{MMI} \times \text{EXC} \times \text{ZPE} \quad (1)$$

Stern.(5) Despite the potential complexity of three factors, the interpretation is not always as difficult as it may appear, since in many cases one or more of these factors has a value close to unity, and thus no contribution to the overall isotope effect. A fourth factor, the SYM (symmetry) factor, is very often unity and will be discussed later in specific cases where it is pertinent. The MMI factor accounts for molecular masses and moments of inertia (i.e., rotational and translational partition function ratios) of the isotopic species. Isotopic substitution seldom significantly affects these parameters, but important exceptions are relatively small hydrocarbons and obviously, isotopes of dihydrogen. Several of these cases are important for catalysis and will be discussed below. In many cases, however, such as transfer of H (as a proton, hydrogen atom, or hydride) between relatively heavy atoms such as carbons or metals, this term is also satisfactorily approximated by unity. The excitation factor (EXC) arises from excitation of vibrational energy levels above the zero-point level; significant contributions from this factor are most likely when low-energy (low-frequency) isotopically sensitive vibrational modes are present.

In most cases the zero-point-energy factor (ZPE) is the dominant influence on isotope effects. Wolfsberg summarized the effects of zero-point energy differences and stated that "since frequencies tend to be higher in molecules with larger force constants ("tighter" binding), the zero-point energy and consequently also the isotope effect on the zero-point energy will tend to be larger in those molecules with tighter binding."(6) This leads to the qualitative and intuitively appealing generalization regarding the direction of equilibrium isotope effects based on the stretching frequencies of one bond being broken and the one being formed, that "the heavy isotope tends to concentrate (relative to the light isotope) in that species where it is more tightly bound."(6) As shown in Fig. 1, the deuterium-labeled isotopomer has a lower zero-point energy than its H analog. This is true for the ground state (GS), transition state (TS) and product. The magnitude and direction of the EIE is determined by the differences in  $\Delta\text{ZPE}$  for the ground state (reactant) vs. that for the product. When  $\Delta\text{ZPE}(\text{GS}) > \Delta\text{ZPE}(\text{Prod})$ , then a normal EIE occurs, meaning  $K_{\text{H}}/K_{\text{D}} > 1$ . In terms of free energies shown in Fig. 1, this corresponds to  $\Delta G_{\text{H}} < \Delta G_{\text{D}}$ . Note that the designation "normal" only signifies the *direction* of the isotope effect and

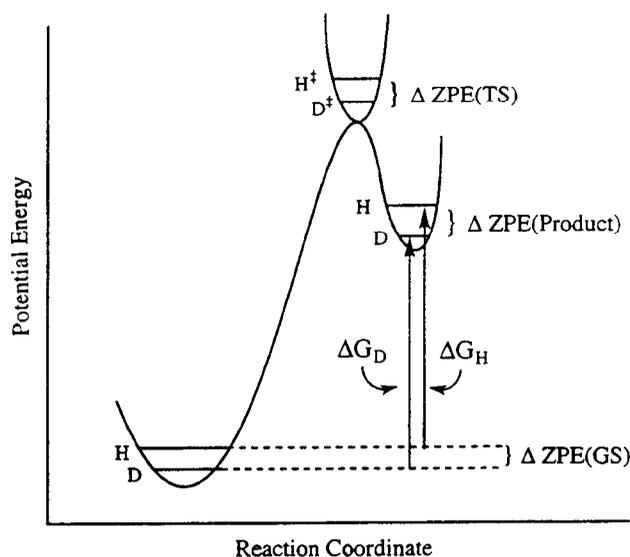


Figure 1

does not indicate that the *magnitude* of the effect is necessarily considered normal. Similarly, when  $\Delta ZPE(GS) < \Delta ZPE(Prod)$ , then  $K_H/K_D < 1$ , and an *inverse* equilibrium isotope effect occurs ( $\Delta G_H > \Delta G_D$ ). In all of these cases, several isotopically sensitive modes may contribute to the total  $\Delta ZPE$ , so the cumulative effect must account for all of these. But in many cases the analysis is not as complex as it may appear, since a single stretching frequency may dominate each term (e.g., an M-H or C-H bond being cleaved or formed).

The magnitude of the *kinetic* isotope effect is analogously dependent on the difference in zero-point-energy of the ground state [ $\Delta ZPE(GS)$ ] compared to that of the transition state [ $\Delta ZPE(TS)$ ]. Like most generalizations, this one has its limitations. In some cases it is imperative to account for all molecular degrees of freedom (especially when considering isotope effects for the binding and activation of small molecules like alkanes, dihydrogen, and alkenes). A more generally applicable rule was given by Kreevoy, that “deuterons tend to accumulate in those positions where they are most closely confined by potential barriers”(7) – this holds true whether one is considering reactant(s) vs. products, or reactant(s) vs. transition state.

Many reactions of organic compounds catalyzed by transition metals involve transfer of a hydrogen from a metal to a carbon, where an M-H bond is cleaved and a C-H bond is formed. Metal hydride bonds typically have bond dissociation energies(8) in the range of 60 – 75 kcal mol<sup>-1</sup>, with corresponding stretching frequencies of  $\nu(M-H) \approx 2000$  cm<sup>-1</sup>. Such M-H bonds are significantly weaker and have lower stretching frequencies compared to C-H bonds (bond dissociation energy  $\approx 90$  kcal/mol,  $\nu(C-H) \approx 3000$  cm<sup>-1</sup>). Although it is actually force constants rather than bond strengths that influence these isotope effects, it is still often intuitively convenient to think in terms of bond strengths, which typically correlate to a reasonable extent with force constants. A consequence of these relative force constants is that in some cases, the bond being formed (e.g., C-H) will have a higher frequency stretching vibration than the one being cleaved (e.g., M-H). As a result, several cases will be encountered where these considerations are manifested in an *inverse* isotope effect, which can have origins in a kinetic and/or thermodynamic basis. Thus some examples will be discussed where inverse kinetic

isotope effects are observed, meaning the D analog will react faster than the H analog. Analogous to the description for EIEs, a “normal” kinetic isotope effect (KIE) is one in which the unlabelled compound reacts faster than the deuterated compound ( $k_H/k_D > 1$ ). Finally, we note that the sense of “normal” and “inverse” would be interchanged if ratios were reported instead as  $k_D/k_H$  instead of as  $k_H/k_D$ ; for this reason we will follow and encourage the convention of having the lighter isotope in the numerator.

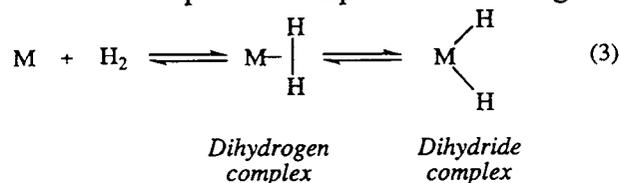
In cases where the MMI and EXC factors are close to unity, then the zero-point energy terms are dominant, and the equation for *kinetic* isotope effects according to semi-classical theory can be expressed as eq. 2, where  $N$  is the number of atoms,  $k_B$  is Boltzmann’s constant,

$$\frac{k_H}{k_D} = \exp \left\{ \frac{-hc}{2k_B T} \left[ \sum_i^{3N-7} (\bar{\nu}_{i(H)}^\ddagger - \bar{\nu}_{i(D)}^\ddagger) - \sum_i^{3N-6} (\bar{\nu}_{i(H)} - \bar{\nu}_{i(D)}) \right] \right\} \quad (2)$$

$T$  is the temperature in Kelvin,  $h$  is Planck’s constant; and  $c$  is the speed of light. Note that when this equation is applied to kinetic isotope effects, the summation is over one less vibrational mode ( $3N - 7$ ) in the transition state compared to the ground state ( $3N - 6$ ), because one vibrational degree of freedom is converted into a translational degree of freedom (i.e., the reaction coordinate) in the transition state. An analogous expression for the ZPE contribution to an equilibrium isotope effect (EIE) sums over the *same* number ( $3N - 6$ ) of vibrational modes.

An important caveat concerns the conversion of translational and rotational degrees of freedom into vibrational degrees of freedom, as for example, during a simple bimolecular reaction. In this case the sum  $N$  in the ground state will extend over  $(3n - 6) + (3m - 6)$  vibrational modes, where  $n$  and  $m$  are the number of atoms in the two reactants; in the product  $N$  extends over  $3(n + m) - 6$  vibration modes, i.e., 6 *more* vibrations than in the ground state. This important concept will be further illustrated for the case of addition of dihydrogen to organometallic complexes.

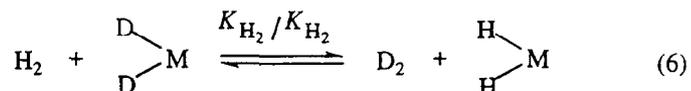
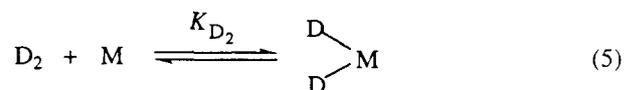
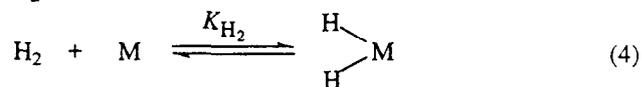
**Equilibrium Isotope Effects on Addition of  $H_2$  ( $D_2$ ) to Metal Complexes.** The discovery of dihydrogen complexes by Kubas(9) presaged the development of a new area that has become an actively studied topic(10) in organometallic chemistry. It had long been recognized that addition of  $H_2$  to metals was a crucial step in catalytic hydrogenation and other homogeneously catalyzed reactions, but the identification and characterization of dihydrogen complexes made it clear that an  $H_2$  molecule could bond to a metal prior to complete H-H cleavage.



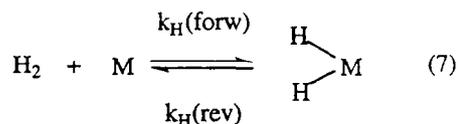
*Equilibrium isotope effects for addition of  $H_2/D_2$  to metals are typically inverse, meaning  $D_2$  binds more strongly to the metal than does  $H_2$ .* This was not fully appreciated until the 1990’s, when several well-defined examples of inverse EIEs were discovered (Table 1). Even so, the precise origin of this effect was only explained with the help of spectroscopic and computational methods.

The equilibrium constant for addition of  $H_2$  to a metal is shown in eq 4 below. This is drawn as forming a dihydride rather than a dihydrogen complex, but the equilibrium constants

will be defined in the same manner for either product. One way of experimentally determining the  $K_{H_2}/K_{D_2}$  is to compare values of  $K_{H_2}$  and  $K_{D_2}$  from separate measurements. Eq. 6 shows the definition of  $EIE = K_{H_2}/K_{D_2}$  which is the ratio of the two expressions. The equilibrium constant



$K_H$  is composed of individual forward and reverse rate constants (eq. 7), each of which can be isotopically sensitive.



**Table 1. Equilibrium Isotope Effects for Addition of  $H_2/D_2$  to Metal Complexes**

Metal Complex	Product $M(H)_2$ or $M(\eta^2-H_2)$	$K_{H_2}/K_{D_2}$ = EIE	Temp (°C)	Ref.
$W(PMe_3)_4I_2$	$W(H)_2$	0.63	60	(11)
$W(CO)_3(PCy_3)_2(N_2)$	$W(\eta^2-H_2)$	0.70	22	(12)
$Cr(CO)_3(PCy_3)_2(N_2)$	$Cr(\eta^2-H_2)$	0.65	22	(12)
$Ir(CO)Cl(PPh_3)_2$	$Ir(H)_2$	0.55	23	(13)
$Ir(PCy_3)_2HCl_2$	$Ir(\eta^2-H_2)$	0.50	-13	(14)
$Ir(P^tBu_2Me)_2(H)_2Cl$	$Ir(\eta^2-H_2)$	0.37	-13	(15)
$Os(P^iPr_3)_2(CO)ClH$	$Os(\eta^2-H_2)$	0.35	70	(16)
$Cp_2Ta(\mu-CH_2)_2Ir(CO)(PPh_3)$	$Ir(H)_2$	0.54	0	(17)

$Cp = \eta^5-C_5H_5$ ,  $Cy = \text{cyclohexyl } (C_6H_{11})$

Conclusions from studies of prototypical examples of additions of dihydrogen to metal complexes are expected to have applicability to other examples where complete spectral data or even characterization are not available. The remarkably detailed interpretations of these isotope effects are due in significant part to the complementary information provided by spectroscopic data and computations.

Bender, Kubas and co-workers reported a comprehensive analysis of the equilibrium isotope effect for addition of  $H_2/D_2$  to  $W(CO)_3(PCy_3)_2$  ( $Cy = \text{cyclohexyl}, C_6H_{11}$ ), which produces the dihydrogen complex  $(\eta^2-H_2)W(CO)_3(PCy_3)_2$ .<sup>(12)</sup> When a hydrogen molecule binds to a metal, translational and rotational degrees of freedom of the free  $H_2$  are lost, and five new

vibrational modes are created in the dihydrogen complex (Figure 2). The normal coordinate analysis carried out on this reaction (Figure 2) used spectroscopic data from IR, Raman and

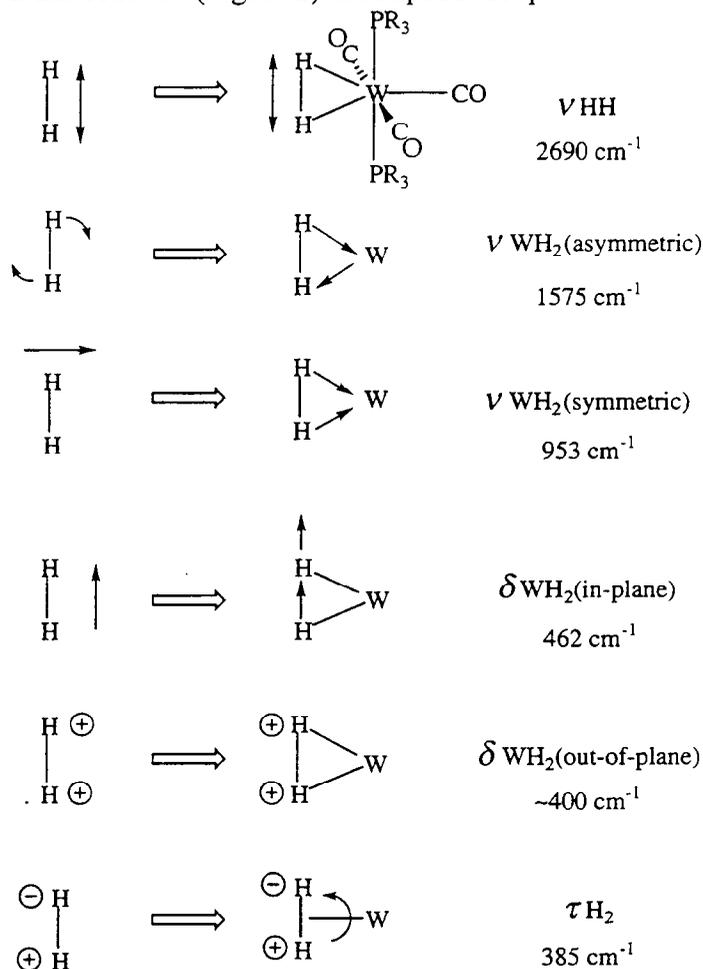


Figure 2

inelastic neutron scattering measurements. The stretching frequency for free  $\text{H}_2$  at 4395  $\text{cm}^{-1}$  (3118  $\text{cm}^{-1}$  for  $\text{D}_2$ ) is at a higher energy than that for the  $\nu(\text{HH})$  vibrational mode of bound  $\text{H}_2$  in *trans*- $\text{W}(\text{CO})_3(\text{PCy}_3)_2(\eta^2\text{-H}_2)$  at 2690  $\text{cm}^{-1}$ . If the decrease in this H-H stretching frequency were the predominant factor determining the EIE, then the EIE would be normal, not inverse. The origin of the inverse EIE found experimentally and computationally requires a more comprehensive consideration of other vibrational modes.

The individual contributions to the overall EIE were evaluated on the basis of the normal coordinate analysis for this complex. Vibrational frequencies are required for calculation of isotope effects, though the accuracy of the analysis is not dependent on the individual modes being assigned correctly. Referring to eq. 1, the MMI factor was calculated to be 5.66 from the translational and rotational energies of free  $\text{H}_2$  and  $\text{D}_2$ . Differences in mass of the  $\text{W}(\text{H}_2)$  vs.  $\text{W}(\text{D}_2)$  complexes are negligible.

Five of the individual EXC terms are inverse, but with modest magnitudes ranging from 0.996 to 0.856. The lowest energy vibrational modes, those due to bending and torsional modes,

are the ones that are most populated by thermal excitation (Boltzmann), and these are more populated for the  $W(D_2)$  complex than for the  $W(H_2)$  isotopomer, due to the lower frequencies for the deuterated complex. While none of these EXC factors *individually* has a large effect, the composite EXC factor is the product of the individual factors. The overall effect on the EIE due to the EXC factor *alone* is 0.675, a substantial contribution to the overall inverse EIE. Changes due to the ZPE contribution from the HH(DD) stretching mode give a significant *normal* factor to the EIE. If this ZPE were the sole term to consider, the EIE would be 3.2, but the contributions from the five other vibrational modes are all *inverse*. The overall ZPE factor is inverse, 0.216. The cumulative effect is that the MMI term contributes a large (5.66) normal effect, as does the ZPE term arising from the  $\nu(HH)$  stretch. The overall calculated EIE = 0.78 at 27 °C, indicating that the collective individual inverse EXC and ZPE contributions from the new vibrational modes overwhelm the normal terms, making the overall EIE inverse.

Experimental measurements(12) to compare to this calculated EIE value were precluded by the large  $K_{eq}$  for hydrogen uptake by  $W(CO)_3(PCy_3)_2$ , but a value of  $K_{H_2}/K_{D_2} = 0.70 (\pm 0.15)$  at 22 °C was measured for displacement of the nitrogen ligand of  $W(CO)_3(PCy_3)_2(N_2)$  by  $H_2$  or  $D_2$ , providing excellent agreement with the calculated value. Since the analogous Cr complex binds  $H_2$  less strongly, measurements on this complex were obtained over a range of temperatures. The  $K_{H_2}/K_{D_2} = 0.65 (\pm 0.15)$  was similar to that found for the tungsten complex. From the activation parameters, it was found that the origin of the inverse EIE is due to the enthalpic contribution overcoming the entropic term. Addition of  $D_2$  to  $Cr(CO)_3(PCy_3)_2$  is more exothermic than addition of  $H_2$  [ $\Delta H_D = -8.6(5)$  kcal mol<sup>-1</sup>;  $\Delta H_H = -6.8(5)$  kcal mol<sup>-1</sup>]. This enthalpic preference of 1.8 kcal mol<sup>-1</sup> for  $D_2$  binding overwhelms the entropic term ( $\Delta S_H - \Delta S_D = \Delta \Delta S = 5.3$  cal mol<sup>-1</sup> deg<sup>-1</sup>), which favors binding of  $H_2$ .

The detailed analysis of the of the vibrational spectra of  $W(CO)_3(PCy_3)_2(\eta^2-H_2)$  provided insight into the nature of the bonding in the dihydrogen complex. The M–H stretching frequencies are an inseparable combination of M–H and H–H interactions. In other words, the HH stretch has significant WH character and is not an isolated HH mode. The force constants for the MH and HH modes are of comparable magnitude, and the interaction between them is strong, so that stretching the H–H bond strengthens the W–H bond. As a consequence of this strong interaction, the vibrational bands of an  $\eta^2$ -HD complex appear at frequencies *intermediate* between those of the corresponding  $\eta^2$ - $H_2$  and  $\eta^2$ - $D_2$  complexes, rather than being superimposed on the  $M(H)_2/M(D)_2$  bands as is found for dihydride/dideuteride complexes. These interactions between the two H atoms of the product are not present in additions of hydrogen to metals where complete oxidative addition and H–H bond rupture occurs, resulting in the formation of two M–H bonds. The EIEs of such additions of  $H_2$  are also inverse.

In 1993 Parkin and co-workers reported the oxidative addition of  $H_2$  to  $W(PMe_3)_4I_2$ , which gives the 8-coordinate dihydride complex  $W(PMe_3)_4I_2(H)_2$ .(11, 18) Analysis of the temperature-dependence of the equilibrium constants for  $H_2$  vs.  $D_2$  addition showed the enthalpic origin of the EIE. ( $\Delta H_H - \Delta H_D = \Delta \Delta H = 1.9$  kcal mol<sup>-1</sup>, Table 1, EIE = 0.63 at 60 °C). The D–D bond of free  $D_2$  (bond dissociation energy (BDE) = 106.0 kcal mol<sup>-1</sup>) is 1.8 kcal mol<sup>-1</sup> stronger than the H–H bond (104.2 kcal mol<sup>-1</sup>), but the W–D bonds being formed [ $D(WD) = 63.8(7)$  kcal mol<sup>-1</sup>] are stronger than the W–H bonds [ $D(WH) = 62.0(6)$  kcal mol<sup>-1</sup>]. As in the case discussed

above forming the *dihydrogen* complex, the inverse EIE on formation of this *dihydride* complex would not have been predicted on the basis of considering just the zero-point energies of the WH/WD vs. HH/DD stretching frequencies alone. The difference in zero-point energies of D<sub>2</sub>/H<sub>2</sub> is 630·cm<sup>-1</sup>, which exceeds the ~550 cm<sup>-1</sup> difference in zero-point energies from two W–H/W–D stretching frequencies. The reason for the inverse EIE is again due to important contributions from the four new bending modes that are isotopically sensitive. While each of these individually contributes only a small amount, the *cumulative* effect of all four of these provides a significant lowering of the zero-point energy of W(PMe<sub>3</sub>)<sub>4</sub>I<sub>2</sub>(D)<sub>2</sub> relative to W(PMe<sub>3</sub>)<sub>4</sub>I<sub>2</sub>(H)<sub>2</sub>, so that the overall EIE is inverse.

A classic example of oxidative addition of hydrogen in organometallic chemistry involves addition of H<sub>2</sub> to Vaska's complex, *trans*-Ir(CO)Cl(PPh<sub>3</sub>)<sub>2</sub>, to give the dihydride (H)<sub>2</sub>Ir(CO)Cl(PPh<sub>3</sub>)<sub>2</sub>. Krogh-Jespersen and Goldman reported a theoretical study of the deuterium EIE for this reaction.(13) Their calculated EIE of 0.46 is in good agreement with their experimentally measured value of EIE = 0.55 (±0.06) obtained from reaction of *trans*-Ir(CO)Cl(PPh<sub>3</sub>)<sub>2</sub> with an H<sub>2</sub>/D<sub>2</sub> mixture. The inverse EIE was revealed by their calculations to be compromised of a large normal MMI term (5.66) which is offset by inverse contributions from the excitation (EXC = 0.84) and an even larger magnitude inverse contribution from the zero-point energy term (ZPE = 0.10). The importance of the contributions from the four Ir–H bending modes was emphasized; when their frequencies are eliminated from the calculations, then the computed EIE is large and normal (EIE = 4.6).

It was mentioned earlier that a symmetry factor also contributes to the EIE, but seldom has any significant contribution to the EIE, since it is usually unity. SYM is a ratio of symmetry numbers for the isotopic species. Symmetry numbers are defined as "the number of different values of rotational coordinates which correspond to one orientation of the molecule, remembering that identical atoms are indistinguishable."(6) Thus σNH<sub>3</sub> = 3; σH<sub>2</sub> = σH<sub>2</sub>O = σD<sub>2</sub>O = 2; σHD = σHDO = σNH<sub>2</sub>D = 1. An interesting example of an influence from this SYM term comes from calculations on addition of H<sub>2</sub>/D<sub>2</sub> to the metal hydride Ir(CO)H(PPh<sub>3</sub>)<sub>2</sub> to give *cis*-Ir(CO)H<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub>. The calculated EIE = 0.33 is more inverse than that calculated for the analogous chloride complex.(13) Statistical reasons favor reductive elimination of H<sub>2</sub> from the trihydride *cis*-Ir(CO)H<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub>, making it twice as fast as reductive elimination of D<sub>2</sub> from *cis*-Ir(CO)HD<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>. This symmetry factor has no influence on the formation of the *trans* isomer, *trans*-Ir(CO)HD<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (calculated EIE = 0.73).

**Kinetic Isotope Effects on Oxidative Addition and Reductive Elimination of H<sub>2</sub> (D<sub>2</sub>).** Over 30 years ago, Chock and Halpern determined a small kinetic isotope effect (k<sub>H<sub>2</sub></sub>/k<sub>D<sub>2</sub></sub> = 1.22 at 30 °C) for reaction of H<sub>2</sub>/D<sub>2</sub> with *trans*-Ir(CO)Cl(PPh<sub>3</sub>)<sub>2</sub> to produce the dihydride complex (H)<sub>2</sub>Ir(CO)Cl(PPh<sub>3</sub>)<sub>2</sub>.(19) The temperature dependence of this kinetic isotope effect was reported by San Filippo and co-workers(20) to range from k<sub>H<sub>2</sub></sub>/k<sub>D<sub>2</sub></sub> = 1.18 at 0 °C to k<sub>H<sub>2</sub></sub>/k<sub>D<sub>2</sub></sub> = 1.06 at 30 °C. These results were interpreted in terms of a triangular transition state, with side-on approach of H<sub>2</sub> to Ir, as opposed to end-on approach. A reactant-like transition state was proposed, with a substantial amount of quantum mechanical tunneling.

More recently, computational studies by Goldman and Krogh-Jespersen(21) characterized the transition state for model Vaska-type complexes *trans*-Ir(CO)X(PH<sub>3</sub>)<sub>2</sub> (X =

halogen, etc.). Their calculations predicted that the reaction would become more exothermic in going to heavier halogens, with the fluoride complex being the least exothermic. This trend was explained in terms of  $\pi$ -donation from the halogens being greatest for fluoride and weakest for iodide; the thermodynamics of the oxidative addition of  $H_2$  are more favorable when there is less  $\pi$ -donation by the heavier halogens. The amount of  $\pi$ -donation was also found to be the dominant factor in the kinetic barrier to the reaction, with the barrier being highest for fluoride.

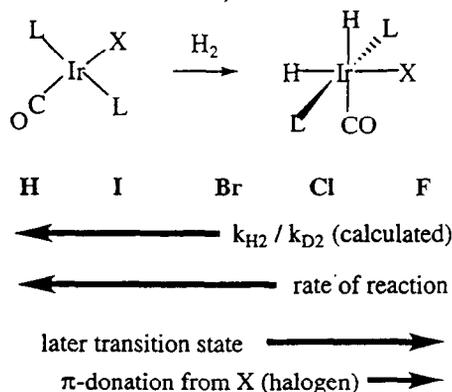


Figure 3

The calculated transition states were in accord with the Hammond(22) postulate, being more reactant-like (early transition state) for the reactions that were most exothermic, and more product-like (later transition state) for those that were thermodynamically less favorable. An interesting trend found in this study was that the *larger* KIEs were associated with the *earlier* transition states. The computed KIE was lowest ( $k_{\text{H}_2}/k_{\text{D}_2} = 1.13$ ) for the fluoride complex, which has the latest transition state and the most lengthened H–H bond in its transition state. The iodide complex had a larger computed KIE ( $k_{\text{H}_2}/k_{\text{D}_2} = 1.44$ ). Compared to the halide complexes, the hydride complex  $\text{Ir}(\text{CO})\text{H}(\text{PH}_3)_2$  had a more exothermic reaction, the earliest transition state, and the largest computed kinetic isotope effect ( $k_{\text{H}_2}/k_{\text{D}_2} = 1.69$ ). No significant contribution (<10%) to the rate from tunneling was found in this study. The calculations revealed many of the same factors influencing the KIE of this reaction as were found to be significant in the calculations of the EIEs discussed above. Thus a large normal contribution from the MMI term (5.66) is counterbalanced in large part by inverse components from the excitation term (ranging from 0.70 for F to 0.49 for H) as well as inverse contributions from the ZPE term (ranging from 0.28 for F to 0.61 for H). As was discovered for the EIEs for  $H_2$  addition, the inverse EXC terms is influenced substantially by low frequency vibrational modes that are significantly more populated in the activated complex for the  $D_2$  reaction compared to the  $H_2$  reaction.

Addition of  $H_2$  to other metal complexes typically have KIEs in the range of 1-2. The transient  $\text{Rh}(\text{PPh}_3)_2\text{Cl}$  was produced by flash photolysis of  $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$ , and its reaction with  $H_2$  showed  $k_{\text{H}_2}/k_{\text{D}_2} = 1.5$  at 23 °C.(23) Flash photolysis was also used in studies of  $\text{Cr}(\text{CO})_6$ . Loss of CO was followed by weak coordination of cyclohexane; the relative rates of reaction of the transient alkane complex  $\text{Cr}(\text{CO})_5(\text{C}_6\text{H}_{12})$  with  $H_2/D_2$  gave  $k_{\text{H}_2}/k_{\text{D}_2} = 1.9$  at room temperature for generation of the dihydrogen complex  $\text{Cr}(\text{CO})_5(\eta^2\text{-H}_2)$ .(24) The KIE for disappearance of  $\text{Cr}(\text{CO})_5(\eta^2\text{-H}_2)$  was 5 times larger than that for the analogous  $\eta^2\text{-D}_2$  complex. Flash photolysis of  $\text{Fe}(\text{CO})_5$  in the gas phase gave  $\text{Fe}(\text{CO})_4$ , which reacted with  $H_2$  to give

$\text{H}_2\text{Fe}(\text{CO})_4$  ( $k_{\text{H}_2}/k_{\text{D}_2} = 0.9$  at 23 °C).(25) The KIE for reductive elimination of  $\text{H}_2/\text{D}_2$  from  $\text{H}_2\text{Fe}(\text{CO})_4$  was  $k_{\text{H}_2}/k_{\text{D}_2} = 1.1$ . Larger normal KIEs were found for elimination of  $\text{H}_2/\text{D}_2$  from an iridium complex containing two terminal hydrides in addition to a bound dihydrogen ligand. Dissociation of  $\text{H}_2/\text{D}_2$  from  $\text{Ir}(\text{H})_2(\eta^2\text{-H}_2)\text{Cl}(\text{P}^t\text{Bu}_2\text{Me})_2$  to give  $\text{Ir}(\text{H})_2\text{Cl}(\text{P}^t\text{Bu}_2\text{Me})_2$  had  $k_{\text{H}_2}/k_{\text{D}_2} = 1.8$  at 20 °C and  $k_{\text{H}_2}/k_{\text{D}_2} = 6$  at -50 °C.(15)

No kinetic isotope effect was found for reaction of  $\text{H}_2$  with  $\text{W}(\text{PMe}_3)_4\text{I}_2$  in the absence of added  $\text{PMe}_3$ .(11) Kinetic and mechanistic studies showed that dissociation of  $\text{PMe}_3$  is required before oxidative addition of  $\text{H}_2$  can occur. Thus the intermediate that reacts with hydrogen ( $k_{\text{H}_2}/k_{\text{D}_2} = 1.2$  at 60 °C) is five-coordinate  $\text{W}(\text{PMe}_3)_3\text{I}_2$  rather than the six-coordinate starting material  $\text{W}(\text{PMe}_3)_4\text{I}_2$ . Loss of  $\text{H}_2$  from  $\text{W}(\text{H})_2(\text{PMe}_3)_4\text{I}_2$  also requires prior dissociation of  $\text{PMe}_3$ ; the KIE for  $\text{H}_2/\text{D}_2$  elimination was  $k_{\text{H}_2}/k_{\text{D}_2} = 2.0$  at 60 °C.(11) This well-studied case of oxidative addition and reductive elimination of  $\text{H}_2$  from a tungsten center is an unusual example where the EIE can be measured directly, as well as the KIEs for both the forward and reverse reactions. The agreement between these provides an internal check on the results, but in few cases is it possible to find suitable experimental conditions for each of these three quantities to be separately measured. In many cases, measurement of two of these has been used to evaluate the third; e.g., measurement of the EIE together with the KIE of the forward rate constant gives an indirect determination of the KIE of the reverse rate constant. It is important to recognize that an inverse EIE does not require that the KIE for either the forward or reverse rate constants be inverse. As exemplified in this case, an inverse EIE can result from the KIE for both the forward and the reverse steps being normal, with the *magnitude* of the reverse KIE being larger than that of the forward KIE.

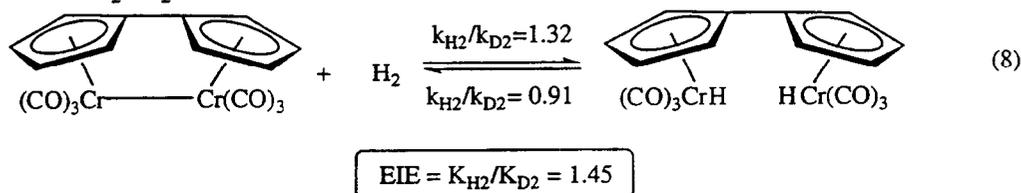
Hydrogen adds reversibly to the trimetallic cluster  $(\mu\text{-H})_2\text{Ru}_3(\text{CO})_8(\mu\text{-P}^t\text{Bu}_2)_2$  to give  $(\mu\text{-H})_2\text{Ru}_3(\text{CO})_8(\text{H})_2(\mu\text{-P}^t\text{Bu}_2)_2$  which contains two terminal Ru-H bonds. The KIE for  $\text{H}_2/\text{D}_2$  addition at 30 °C was  $k_{\text{H}_2}/k_{\text{D}_2} = 1.30$ .(26) It may seem surprising that a complicated reaction involving metal-metal bond cleavage in a cluster would exhibit a KIE similar to those discussed above for addition of  $\text{H}_2$  to single metal centers, but the kinetic study carried out on this cluster reaction provided evidence that the actual hydrogen addition step occurred at a *single* metal site, following generation of a vacant coordination site through CO dissociation. The reverse reaction,  $\text{H}_2$  elimination, was also found to be preceded by CO loss, and it had a KIE of  $k_{\text{H}_2}/k_{\text{D}_2} = 1.39$ .(26)

An inverse kinetic isotope effect of  $k_{\text{H}_2}/k_{\text{D}_2} = 0.45 \pm 0.10$  at 21 °C was determined for loss of  $\text{H}_2/\text{D}_2$  from the dihydride complex  $(\text{PMe}_3)_2\text{Pt}(\text{H})_2$ .(27) It was suggested that the H-H bond may be nearly completely formed in the transition state, possibly through pre-equilibrium formation of an  $\eta^2\text{-H}_2$  complex.

**Additions of  $\text{H}_2$  in Systems Involving Metal Radical Intermediates.** The examples of addition of hydrogen to diamagnetic complexes discussed above are the most commonly observed oxidative additions of  $\text{H}_2$ , but some examples are known to proceed by an entirely different pathway involving metal-centered radicals. Halpern discovered that reaction of  $\text{H}_2$  with the Co(II) complex  $\text{Co}(\text{CN})_5^{3-}$  is second-order in metal and first order in hydrogen.(28) Wayland and co-workers found(29) a similar overall third-order rate law for conversion of the 17-electron rhodium radical complex  $(\text{TMP})\text{Rh}\cdot$  to  $(\text{TMP})\text{RhH}$  from reaction with  $\text{H}_2$  ( $\text{TMP} =$

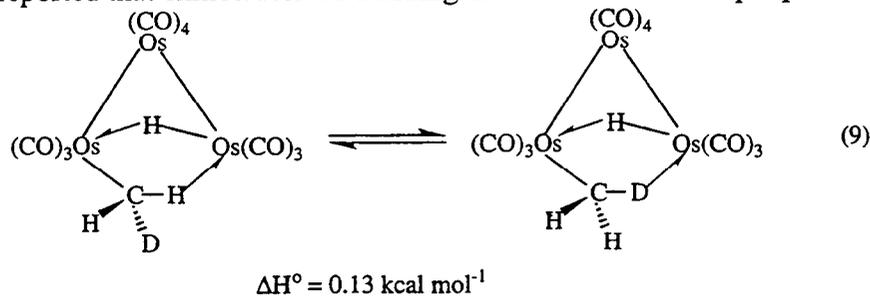
tetramesitylporphyrin); a kinetic isotope of  $k_{\text{H}_2}/k_{\text{D}_2} = 1.6$  was found at 23 °C. The chromium complex  $\text{Cp}^*(\text{CO})_3\text{Cr}\cdot$  ( $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$ ) undergoes a similar reaction with hydrogen and has  $k_{\text{H}_2}/k_{\text{D}_2} = 1.18$  at 20 °C.(30) These interesting third-order reactions have low activation enthalpies ( $\Delta H^\ddagger \approx 0 - 5 \text{ kcal mol}^{-1}$ ), reflecting M-H bond formation significantly compensating for the rupture of the H-H bond. Large negative entropies of activation ( $\Delta S^\ddagger \approx -40$  to  $-55 \text{ cal mol}^{-1} \text{ deg}^{-1}$ ) are indicative of significant ordering of the transition state. The data for these reactions are consistent with a four-center transition state  $\text{M}\cdots\text{H}\cdots\text{H}\cdots\text{M}$ , but another possibility has been suggested involving a pre-equilibrium association of hydrogen to give a 19-electron dihydrogen complex that produces product through reaction with a second metal radical.(30) These reactions are pertinent models for catalytic hydroformylations and hydrogenations, where the conversion of  $\text{Co}_2(\text{CO})_8$  to  $\text{HCo}(\text{CO})_4$  under  $\text{H}_2$  may follow a similar mechanism.

A Cr complex bridged by a fulvalene ligand catalyzes the hydrogenation of conjugated dienes, and this is proposed to occur by a radical mechanism.(31) The addition of  $\text{H}_2$  to this complex gave  $k_{\text{H}_2}/k_{\text{D}_2} = 1.32$  at 20 °C for addition of  $\text{H}_2$ .(32) This KIE is similar to those

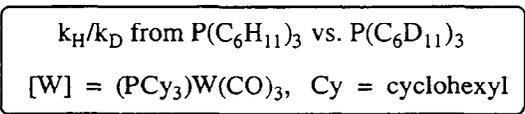
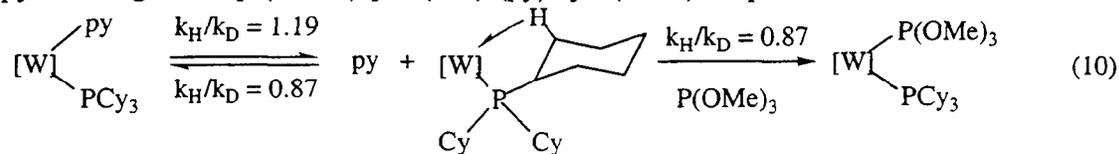


discussed above for related complexes where metal-centered radicals react with  $\text{H}_2$ . The KIE for reductive elimination of hydrogen is inverse ( $k_{\text{H}_2}/k_{\text{D}_2} = 0.91$ ), so that the EIE for hydrogen addition is normal ( $K_{\text{H}_2}/K_{\text{D}_2} = 1.45$ ). This result stands in contrast to the inverse EIEs observed and calculated for the addition of  $\text{H}_2/\text{D}_2$  to mononuclear complexes, and the precise reasons for this remain unclear.

**Isotope Effects Involving Agostic Bonds.** A classic demonstration of the preference of D to reside in the position where it has a higher stretching frequency comes from experiments by Shapley and co-workers.(33) The Os cluster shown in eq. 9 has a partially deuterium labeled methyl group, which forms an agostic(34) interaction with one metal.  $^1\text{H}$  NMR experiments at  $-76$  °C showed that the resonance for the  $\text{CH}_2\text{D}$  appeared 0.76 ppm downfield of that for the  $\text{CH}_2\text{H}$  isotopomer. The methyl group bridges asymmetrically, and the bridging C-H(D) has a lower stretching frequency than the terminal ones, accounting for the preference for H to be located in the bridging site and D in the terminal sites. Several other examples were subsequently reported that exhibit related bonding interactions and isotopic preferences.(35)



An unusual involvement of an agostic interaction in the mechanism of a ligand displacement reaction was discovered by Hoff and co-workers (eq. 10).(36) The displacement of the pyridine ligand of  $[P(C_6H_{11})_3]_2W(CO)_3(py)$  by  $P(OMe)_3$  to produce



$[P(C_6H_{11})_3]_2W(CO)_3[P(OMe)_3]$  would appear to be a simple ligand displacement reaction, but the overall reaction showed an isotope effect ( $k_H/k_D = 1.2$ ) when the deuterated ligand  $P(C_6D_{11})_3$  was used instead of  $P(C_6H_{11})_3$ . Stopped-flow kinetics studies provided evidence for the stepwise mechanism shown in eq. 10. Dissociation of pyridine had an isotope effect of  $k_H/k_D = 1.19$ , and was interpreted in terms of a partially associative intramolecular ligand displacement, in which formation of an agostic interaction is coupled with displacement of pyridine. An inverse kinetic isotope effect of  $k_H/k_D = 0.86$  was determined for the product-forming step, in which the phosphite ligand binds to the metal, replacing the agostic interaction.

**Equilibrium Isotope Effects for the Binding of Alkanes to Metal Complexes.** Alkane  $\sigma$ -complexes mediate the making and breaking of alkane C-H bonds for certain transition-metal complexes,(37) and they may also be important for enzymatic alkane oxidation.(38) Equilibrium isotope effects (EIEs) for alkane  $\sigma$ -binding are related to more commonly measured kinetic isotope effects (KIEs) for alkane activation, but such EIEs have received less attention,(39) no doubt because of the ephemeral nature of such complexes. The numerous ways that alkanes may bond to transition metals differ chiefly in their hapticity, as shown below following the nomenclature suggested by Perutz.(37) In many cases it is unclear which bonding mode predominates (a given complex may sample more than one such structure). In principle the

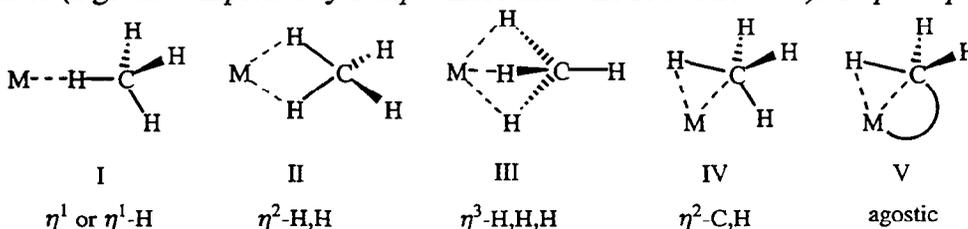
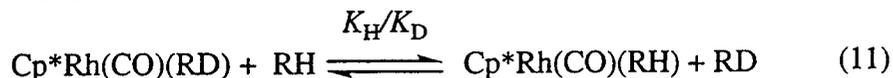


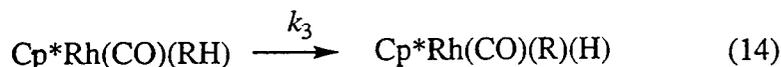
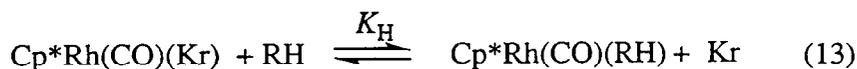
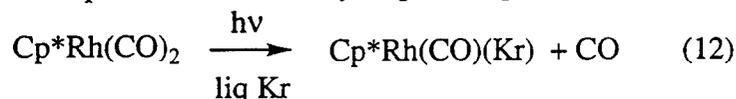
Figure 4

“frozen” structural forms should be spectroscopically distinguishable, differing as they do in local symmetry at the  $sp^3$  carbon. However, no reliable experimental technique has yet emerged to distinguish such forms, nor is it even clear whether such forms merely represent local minima on an extended potential energy surface available to a given complex. Certainly such structures might prove important as the basis of selectivity for the binding and activation of alkanes. Readers interested in how such structures might be spectroscopically distinguished are referred to a review on isoelectronic tetrahydroborate ( $BH_4^-$ ) complexes.(40)

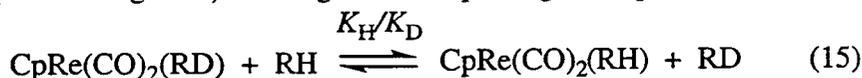
Bergman, Moore and coworkers found(41) that certain rhodium(I) complexes bind perdeuterated cyclohexane and neopentane nearly an order of magnitude better than the perprotio alkanes at  $-108\text{ }^{\circ}\text{C}$  (eq. 11); these transient alkane complexes were generated photochemically in liquid Kr or Xe solution according to eqs. 12 – 14. The equilibrium constants,  $K_{\text{H}}$  (and the corresponding  $K_{\text{D}}$ ) could not be measured directly, but were instead deduced from observed pseudo-first-order rate constants as a function of alkane concentration. The observed inverse EIE was unusual and was the opposite of what one have predicted from changes in CH(D)-stretching force constants. Presumably, a C-H(D) bond is weakened in the product, and simple zero-point energy arguments predict a normal EIE for eq. 11. The authors suggested that zero-point energy effects



from hindered rotations of the bound alkane, which would be lower in frequency for deuterated alkanes, outweighed the expected normal effect from changes in CH(D) stretching force constants. This reasoning was subsequently tested by Bender, Kubas, and Hoff for the weak  $\sigma$ -binding of dihydrogen isotopes in a molecular hydrogen complex.(12)

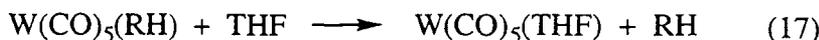
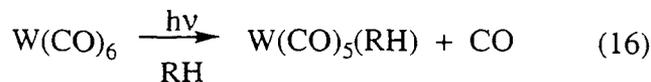


Geftakis and Ball reported the observation of an alkane  $\sigma$ -complex using a combination of low temperature photolysis and NMR detection.(42) Photolysis of  $\text{CpRe}(\text{CO})_3$  in neat cyclopentane gives rise to new NMR signals which they ascribed to  $\text{CpRe}(\text{CO})_2(\text{cyclopentane})$ . Definitive evidence for one binding mode vs. another was not available, but the authors favored an  $\eta^2\text{-C}_5\text{H}_8$  (type IV in Figure 4) bonding mode. Repeating the experiment in cyclopentane- $d_{10}$



gave rise to Cp resonances slightly shifted from those observed in cyclopentane. When the experiment was repeated in a 50/50 mixture of cyclopentane and cyclopentane- $d_{10}$ , two Cp resonances were observed; integration of those signals showed that  $\text{C}_5\text{H}_{10}$  binding was favored vs.  $\text{C}_5\text{D}_{10}$  by a ratio 1.33:1, i.e., a normal EIE, in contrast to the inverse EIE reported by Bergman for the binding of cyclohexane/cyclohexane- $d_{12}$  and neopentane/neopentane- $d_{12}$  to  $\text{Cp}^*\text{Rh}(\text{CO})$ .(41)

Schultz and co-workers used time- and temperature-resolved IR absorption spectroscopy to probe the reaction of tetrahydrofuran (THF) with  $\text{W}(\text{CO})_5(\text{solv})$  (solv = cyclohexane, cyclohexane- $d_{12}$ ) to form  $\text{W}(\text{CO})_5(\text{THF})$ .(43) In cyclohexane- $d_0$ ,  $\Delta H^\ddagger$  for displacement of alkane is  $3.6 \pm 0.2\text{ kcal mol}^{-1}$  and  $\Delta S^\ddagger = -13.7 \pm 2.5\text{ cal mol}^{-1}\text{ K}^{-1}$ ; in cyclohexane- $d_{12}$ ,  $\Delta H^\ddagger = 2.4 \pm 0.6\text{ kcal mol}^{-1}$  and  $\Delta S^\ddagger = -18.3 \pm 3.5\text{ cal mol}^{-1}\text{ K}^{-1}$ . These activation parameters are consistent with an associative mechanism for alkane ligand displacement by THF. Despite the fact that  $\Delta H^\ddagger$  for



exchange is lower for the perdeutero case, the exchange is *slower* in cyclohexane- $d_{12}$  than in cyclohexane- $d_0$  leading to a normal KIE. The entropy term governing the free energy barrier dominates: displacing  $\text{C}_6\text{D}_{12}$  is entropically more uphill than displacing  $\text{C}_6\text{H}_{12}$  because a higher density of states (a more populated vibrational manifold) for the deuterated alkane adduct must converge in the transition state than for the perprotio case. These unusual experimental results were supported by DFT calculations of vibrational frequencies and Bigeleisen KIE theory.

Another important observation by Schultz and co-workers is an experimentally deduced *inverse* EIE for the binding of cyclohexane- $d_0$  vs. cyclohexane- $d_{12}$  (Eq 18), in accord with Bergman's inverse EIE for the binding of those alkanes to  $\text{Cp}^*\text{Rh}(\text{CO})(41)$ ; the experimentally



determined (and computationally supported) EIE is 0.71 for eq 18. The differing results of Ball,(42) from those of Bergman(41) and of Schultz,(43) suggest that the simple question of whether an alkane  $\sigma$ -complex EIE is normal or inverse does not have a trivial answer!

Bender has addressed the question of how alkane binding equilibrium isotope effects can be inverse for the binding of methane to an  $\text{ML}_n$  fragment.(44) He used published vibrational frequencies calculated by Avdeev and Zhidomirov(45) for the model complex *trans*-( $\eta^2$ -H,H- $\text{CH}_4$ ) $\text{OsCl}_2(\text{PH}_3)_2$ , a complex which is predicted to bind methane in an  $\eta^2$ -H,H fashion (Type II in Fig. 4).(46, 47) Harmonic vibrational frequencies for  $\text{CH}_4$ ,  $\text{CD}_4$ , and for *trans*-( $\eta^2$ - $\text{CH}_4$ ) $\text{OsCl}_2(\text{PH}_3)_2$  and *trans*-( $\eta^2$ - $\text{CD}_4$ ) $\text{OsCl}_2(\text{PH}_3)_2$  were used to calculate the EIE using the formalism of Bigeleisen and Mayer.(4) The EIE ( $K_{\text{H}}/K_{\text{D}}$ ) for eq. 19 is around unity at ambient temperature (27 °C) and may be factored into its three components:  $\text{EIE}(0.964) = \text{MMI}(3.244) \times \text{EXC}(0.643) \times \text{ZPE}(0.462)$ . While the lack of an EIE for eq 19 is perhaps not surprising, the



prediction that the EIE can become inverse with decreasing temperature is less intuitively obvious.

The four CH-stretching modes for methane ( $A_1$  and  $3T_2$ ; Fig. 5) become two pairs stretching modes for the complex: in-phase and out-of-phase modes for each bridging and terminal pair, analogous to those observed for isostructural  $\eta^2$ -H,H- $\text{BH}_4^-$  complexes.(40) All but one of the four  $\text{CH}_2$  stretching frequencies are lowered with respect to free methane (the out-of-phase terminal  $\text{CH}_2$  stretching mode *increases* in frequency), thus zero-point energy

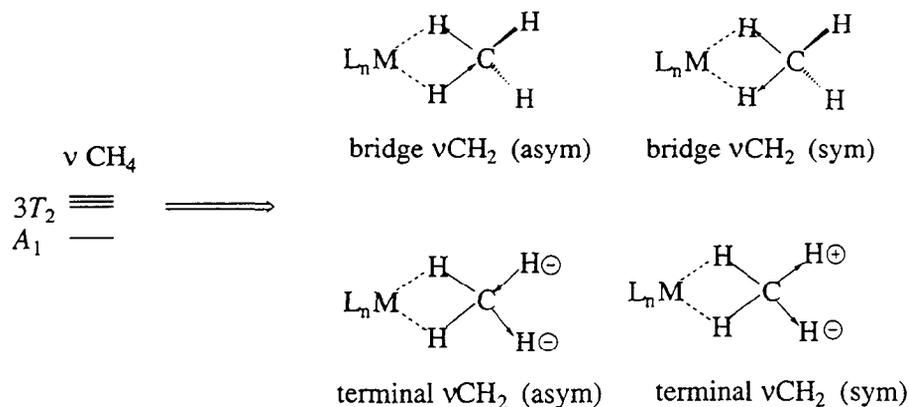


Figure 5

contributions from changes in just the CH stretching frequencies predict an EIE of about 1.3 for eq. 19, in accord with conventional wisdom. Indeed, the EIE predicted from *changes* in all nine methane vibrational frequencies (EXC  $\times$  ZPE) is 1.37 at 27 °C; at lower temperatures, an even larger EIE is predicted. But this simple analysis omits the mass and moment of inertia factor (MMI), *and* the countervailing ZPE and EXC contributions from corresponding frustrated rotations and translations of the bound methanes.

When methane and a metal-ligand fragment combine, isotopically sensitive vibrational modes for methane are shifted to higher or lower frequencies, according to changes in vibrational force constants as already described. In addition, three translational and three rotational degrees of freedom for the two molecules become six new normal mode vibrations in the complex (“frustrated” rotations and translations). These new normal modes are shown in Fig. 6 alongside their symmetry-correlated counterparts in free methane whence they derive.(48)

Three of the six new vibrational modes for *trans*-( $\eta^2$ -CH<sub>4</sub>)OsCl<sub>2</sub>(PH<sub>3</sub>)<sub>2</sub> and its *d*<sub>4</sub> analog contribute significant inverse EXC and ZPE factors to the calculated EIE. These modest EXC and ZPE contributions oppose the ZPE effects from methane frequencies changes, and more importantly, they mitigate the significant MMI factor. The MMI factor accounts for temperature-independent molecular mass and moment of inertia ratios of the isotopic species in eq. 1; in the present case MMI simply reflects the greater effect that deuterium has on the mass and moments

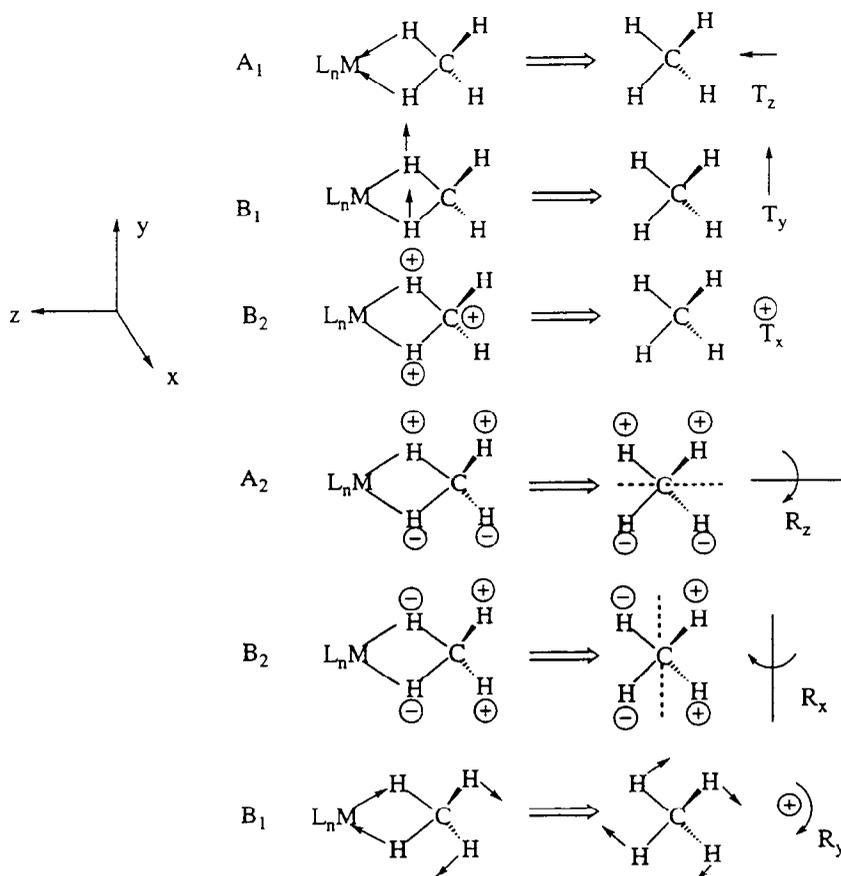
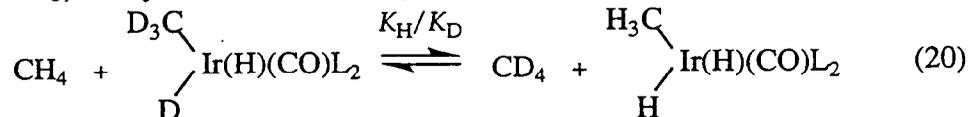


Figure 6

of inertia of methane compared with the more massive methane complex. The MMI factor may be calculated directly from molecular masses and moments of inertia for methanes and methane complexes (3.66) and independently from vibrational frequencies using the Teller-Redlich product rule (3.24). Analogous reasoning has been used by Rabinovich and Parkin,(18) and by Krogh-Jespersen and Goldman(13) to interpret EIEs for the addition of H<sub>2</sub> vs. D<sub>2</sub> to metal complexes. More recently, these ideas have been extended to EIEs for H<sub>2</sub>  $\sigma$ -bonding and metal-alkene  $\pi$ -bonding.(49) The calculated results concur with Bergman's and Schultz's experimental results: the calculated EIE for eq. 19 *at*-108°C is indeed inverse:  $K_H/K_D = 0.66$ .(50)

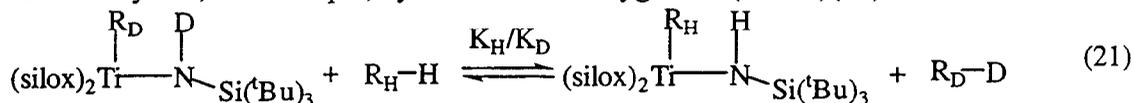
**EIEs for Alkane Oxidative Addition.** Krogh-Jespersen and Goldman calculated a *normal* EIE ( $K_H/K_D = 3.6$  at 27 °C) for the oxidative addition of CH<sub>4</sub> vs. CD<sub>4</sub> to an Ir(I) complex (eq. 20, where L = PH<sub>3</sub>). Why are the calculated (at the same temperature) EIEs for eqs. 19 and 20 so



different? As the metal fully inserts into the CH bond, several new isotopically-sensitive vibrational modes (the "frustrated" rotations and translations) as well as the nine pre-existing methane vibrational modes become the collection of metal-carbon and metal hydride and methyl bending vibrational modes. Most importantly, the isotope effect is dominated by the conversion

of a methane CH bond stretching vibration into a MH stretching vibration having a decreased force constant; this point has long been appreciated, as already discussed for agostic CH bonding.(33)

In the most comprehensive study to date, Wolczanski and coworkers have experimentally measured inter- and intramolecular EIEs for the reversible addition of various small hydrocarbons to the transient species,  $({}^t\text{Bu}_3\text{SiO})_2\text{Ti}=\text{NSi}{}^t\text{Bu}_3$  (eq 21).(51) Such alkane additions across transition metal-main group element multiple bonds are not strictly analogous to oxidative additions of alkanes to a metal centers to form an metal alkyl hydrides. On the other hand, such “1,2 additions” may more closely mimic the mechanism of alkane activation actually employed by certain enzymes, for example, by methane monooxygenase (MMO)(52)



silox = OSi<sup>t</sup>Bu<sub>3</sub>

EIEs were measured (26.5 °C) by <sup>1</sup>H and <sup>2</sup>H NMR in hydrocarbon solution. Experimental results were compared with EIEs calculated using (HO)<sub>2</sub>Ti=NH and its corresponding alkane adducts as vibrational models. They reported a statistical mechanical treatment equivalent to the Bigeleisen-Mayer treatment (except that the MMI factor was approximated by the corresponding ratios for methanes alone).(13) The calculated EIEs were factored into their MMI, EXC, and ZPE(53) contributions. The results for intermolecular EIEs are shown in Table 2.

**Table 2. Experimentally Observed and Calculated Intermolecular Equilibrium Isotope Effects for 1,2 Additions of Alkanes, Alkenes, and Arenes to  $({}^t\text{Bu}_3\text{SiO})_2\text{Ti}=\text{N}{}^t\text{Bu}$**

substrate	EIE <sub>obs</sub> <sup>a</sup>	EIE <sub>calc</sub> <sup>a</sup>	MMI	EXC	ZPE
CH <sub>4</sub> /CD <sub>4</sub>	2.00 ± .06	1.88	3.95	0.500	0.950
C <sub>2</sub> H <sub>6</sub> /C <sub>2</sub> D <sub>6</sub>	2.22 ± .08	1.93	2.69	0.551	1.299
c-C <sub>3</sub> H <sub>6</sub> /c-C <sub>3</sub> D <sub>6</sub>	1.71 ± .04	1.48	2.04	0.616	1.177
C <sub>2</sub> H <sub>4</sub> /C <sub>2</sub> D <sub>4</sub>	1.41 ± .11	1.34	2.45	0.591	0.924
C <sub>6</sub> H <sub>6</sub> /C <sub>6</sub> D <sub>6</sub>	1.22 ± .07	1.26	1.49	0.702	1.200
C <sub>7</sub> H <sub>8</sub> /C <sub>7</sub> D <sub>8</sub> <sup>b</sup>	1.59 ± .06 <sup>c</sup>	1.55 <sup>c</sup>	1.52	0.822	1.240
η <sup>2</sup> -C <sub>2</sub> H <sub>4</sub> / η <sup>2</sup> -C <sub>2</sub> H <sub>4</sub> <sup>d</sup>	0.879 ± .11	0.893	2.45	0.766	0.476

<sup>a</sup>26.5 °C (exp) and 24.8 °C (calc) except for the toluene cases. <sup>b</sup>Refers to benzyl activated products and isotopologues. <sup>c</sup>50 °C. <sup>d</sup>Refers to metallacyclic product  $({}^t\text{Bu}_3\text{SiO})({}^t\text{Bu}_3\text{SiN})\text{TiCH}_2\text{CH}_2$  and its isotopologue.

There is reasonable agreement between experiment and theory, and after careful consideration of the sources of random and systematic error, the differences were attributed to experimental difficulties. For each intermolecular case, a significant normal MMI factor is attenuated by an inverse EXC factor, and also by inverse ZPE factors from vibration modes which are not present in the free hydrocarbons, although the *overall* ZPE factor in several cases is normal, due to changes CH vs NH bending and stretching modes.

Intramolecular EIEs ( $K_H/K_D$ ) may also be formulated using eq. 21, but in so doing  $R_H-H$  and  $R_D-D$  become equivalent and therefore all contributions from the “free” hydrocarbon are eliminated from consideration. Therefore, MMI factors along with attenuating EXC and ZPE factors, which were significant in the intermolecular cases, are absent in the intramolecular cases; the calculated intramolecular EIEs in Table 3 are determined by *changes* in zero-point (and to a lesser extent by EXC) factors when deuterium occupies sites with different force constants within the same molecular species. Heinekey has discussed this phenomenon in the context of non-classical hydrides.(54) Symmetry factors are important for bookkeeping purposes, but because they alone cannot lead to isotope fraction,(2a) the observed and calculated EIEs in Table 3 have been corrected for these statistical factors. The authors note that in organic systems, MMI and EXC factors are generally ignored, or at least assumed to be equal to unity; they maintain that because MMI and EXC factors compensate one another, both factors may be ignored without consequence the present cases, and isotopically sensitive vibrations that are absent in intramolecular cases are primarily responsible for the greater intermolecular EIEs.

**Table 3. Experimentally Observed and Calculated Intramolecular Equilibrium Isotope Effects for 1,2 Additions of Representative Alkanes, Alkenes, and Arenes to  $(^t\text{Bu}_3\text{SiO})_2\text{Ti}=\text{N}^t\text{Bu} \rightleftharpoons$**

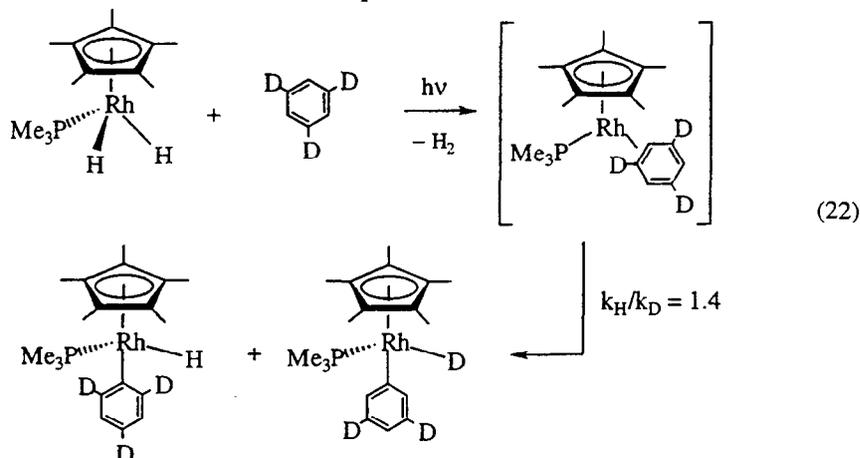
substrate	EIE <sub>obs</sub> <sup>a</sup>	EIE <sub>calc</sub> <sup>a</sup>	SYM	EXC	ZPE
intramolecular <sup>b</sup>	/SYM	/SYM			
(ND)CH <sub>3</sub> ⇌ (NH)CH <sub>2</sub> D	1.05 ± 0.08	0.867	3	0.956	0.908
(ND)CDH <sub>2</sub> ⇌ (NH)CHD <sub>2</sub>	1.13 ± 0.08	0.911	1	0.925	0.976
(ND)CHD <sub>2</sub> ⇌ (NH)CD <sub>3</sub>	1.17 ± 0.08	0.909	1/3	0.925	0.982
(ND)CD <sub>2</sub> CH <sub>3</sub> ⇌ (NH)CH <sub>2</sub> CD <sub>3</sub>	1.53 ± 0.03	1.44	1	0.969	1.482
(ND)( <i>c</i> -CDCH <sub>2</sub> CH <sub>2</sub> ) ⇌ (NH)( <i>c</i> -CHCH <sub>2</sub> CD <sub>2</sub> )	1.29 ± 0.03	1.27	2	0.869	1.457
(ND)(3,5-C <sub>6</sub> H <sub>3</sub> D <sub>2</sub> ) ⇌ (NH)(2,4,6-C <sub>6</sub> H <sub>2</sub> D <sub>3</sub> )	1.27 ± .04	1.25	1	0.855	1.460
(ND)(CH <sub>2</sub> Ph) ⇌ (NH)(CHDPh) <sup>c,d</sup>	1.03 ± .01	0.99	2	0.867	1.143

<sup>a</sup>26.5 (3) °C (exp) and 24.8°C (calc) except for the toluene cases. <sup>b</sup>For the intramolecular case, the MMI term is approximated as unity. <sup>c</sup>Refers to benzyl activated products and isotopologues. <sup>d</sup>50 °C.

**KIEs For Oxidative Addition of Alkanes.** Discovery and development of homogeneous catalysts capable of selective functionalization of alkanes is a goal that has spawned intense efforts by many groups. Well before precise kinetic isotope effects for the activation of alkanes measured and interpreted, H/D exchange itself was used to establish that CH bonds were indeed being reversibly cleaved by certain metal complexes, notably those of Pt(II) in acidic media.(55) In the early 1980’s Bergman and co-workers discovered that alkyl hydride complexes of Ir are generated by photolysis of Cp\*(PMe<sub>3</sub>)Ir(H)<sub>2</sub>, which loses H<sub>2</sub> to produce highly reactive [Cp\*(PMe<sub>3</sub>)Ir] which reacts with alkanes. Reaction of Cp\*(PMe<sub>3</sub>)Ir(H)<sub>2</sub> with cyclohexane

(vs.  $C_6D_{12}$ ) with gave  $k_H/k_D = 1.38$ .(56) A similar KIE ( $k_H/k_D = 1.2$ ) was found for oxidative addition of hexane to the Rh intermediate  $Cp^*(PMe_3)Rh$  at  $-60^\circ C$ .(47)

Isotope effects have also played a major role in the mechanistic understanding of addition of C-H bonds of *arenes* to unsaturated metal centers. Jones and Feher found a very small *intermolecular* isotope effect ( $k_H/k_D = 1.05 \pm 0.06$ ) from photolysis of  $Cp^*(PMe_3)Rh(H)_2$  in  $C_6H_6/C_6D_6$ .(57) A larger *intramolecular* isotope effect ( $k_H/k_D = 1.4 \pm 0.1$ ) resulted from experiments with 1,3,5- $d_3$ -benzene, where the photochemically generated Rh intermediate selects between C-H or C-D bonds in the same arene. The different isotope effects in these two experiments required that an intermediate be present, and eq. 22 shows the  $\eta^2$ -arene intermediate implicated on the basis of this and other experiments. Burk and Crabtree discovered an Ir system



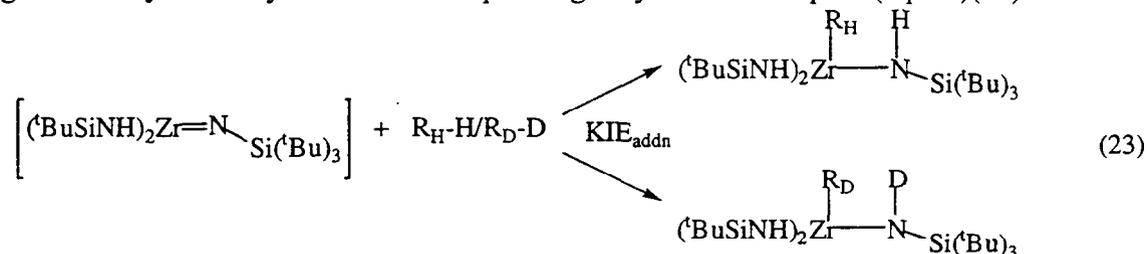
that catalyzes dehydrogenation of alkanes to alkenes.(58) They found a larger KIE ( $k_H/k_D = 4.5 \pm 0.1$ ) for reaction of  $C_6H_6/C_6D_6$  with  $IrH_2(O_2CCF_3)[P(C_6H_4-p-F)_3]_2$ , and suggested that this KIE reflected the lower reactivity (higher selectivity) of their intermediate compared to  $Cp^*Ir(PMe_3)$ .(56)

Goldman and co-workers studied the mechanism of photochemical dehydrogenation of alkanes and found a large KIE of  $k_H/k_D = 5.3$  when *trans*- $Rh(PMe)_2(CO)Cl$  was photolyzed with  $C_6H_{12}/C_6D_{12}$ .(59) They suggested that this KIE was inconsistent with C-H activation as the rate-limiting step, and that it resulted instead from the two isotopically sensitive steps – the combination of an EIE on oxidative addition of the C-H bond to the metal, followed by a KIE on the subsequent  $\beta$ -elimination step. Jones and Feher found an EIE of  $K_H/K_D = 2.7$  for addition of the C-H/C-D bond of benzene to  $Cp^*(PMe_3)Rh$ .(57) This shows the expected preference of D to occupy the site of higher force constant ( $\nu_{CD} > \nu_{MD}$ ). Thus a similar EIE is present in the Rh reaction by Goldman, coupled with a KIE of about 2 for the  $\beta$ -elimination step, would account for their observed  $k_H/k_D = 5.3$ .

Flood and co-workers reported detailed kinetics studies for oxidative addition of alkyl and aryl C-H bonds to osmium complexes. After dissociation of  $PMe_3$  from  $(PMe_3)_4Os(H)(CH_2CMe_3)$ , oxidative addition of benzene occurs with  $k_H/k_D = 3.3 \pm 0.3$  at  $80^\circ C$ .(60) The most unusual isotope effect observed in this study was not of the C-H activation step itself, but was an isotope effect observed on the rate constant for ligand dissociation.(60) Experiments at  $65^\circ C$  showed that dissociation of  $P(CH_3)_3$  from  $[P(CH_3)_3]_4Os(H)(CH_2CMe_3)$  was faster ( $k_H/k_D = 1.27$ ) than dissociation of  $P(CD_3)_3$  from  $[P(CD_3)_3]_4Os(H)(CH_2CMe_3)$ ! This

was proposed to be due to a steric isotope effect. Since C-D bonds are shorter than C-H bonds (by about 0.003 Å), steric crowding is more pronounced in the P(CH<sub>3</sub>)<sub>3</sub> complex compared to the P(CD<sub>3</sub>)<sub>3</sub> analog, leading to faster dissociation in the non-deuterated phosphine complex. While this steric isotope effect may appear to be surprisingly large, note that since there four phosphines containing a total of 36 H (or D) atoms, the effect per hydrogen atom is about 1.009, which is in accord with the magnitude of steric isotope effects in organic systems.

Wolczanski and coworkers have measured KIEs for the addition of methane isotopomers to a transient Zr(IV) imido species, (tBu<sub>3</sub>SiNH)<sub>2</sub>Zr=NSi<sup>t</sup>Bu<sub>3</sub>, a highly reactive species that may be generated by thermolysis of the corresponding alkyl amido complex (eq. 23)(61)



Trapping experiments with deuterated methanes revealed that primary KIEs for *intermolecular* CH/CD activation were significantly greater than the corresponding *intramolecular* primary KIEs; thus CH<sub>4</sub> is trapped ten times faster than CD<sub>4</sub>: KIE = 11.2 ± 1.7, while the CH bond reacts only five times faster than the CD bond in CH<sub>2</sub>D<sub>2</sub>: KIE = 5.1 ± 0.6 (both KIEs were measured at 95 °C). The authors noted that an *intermolecular* KIEs contains a rotational partition ratio for CD<sub>4</sub>/CH<sub>4</sub> (a factor of 2√2 or ≈ 2.83) which is not present in the intramolecular case.

Inter- vs intramolecular KIEs were reexamined by Wolczanski in a subsequent collaboration with Cundari as part of thorough study including EIEs which was mentioned above.(51) From knowledge of experimentally measured EIEs and corresponding KIEs for the elimination step, KIEs for the *addition* of hydrocarbons to (silox)<sub>2</sub>Ti=NSi<sup>t</sup>Bu<sub>3</sub> may be inferred by rearranging the simple expression EIE = KIE<sub>addn</sub>/KIE<sub>elim</sub>; see eq. 24. This remarkable collection of results is summarized in Table 4.



silox = OSi<sup>t</sup>Bu<sub>3</sub>

Several trends are apparent from the comparison of KIEs for closely related hydrocarbons in Table 4: first, alkane KIEs (cf. entries 1-6, 13) are typically greater than alkene (cf. entries 9, 10) or arene (entries 11, 12) KIEs, despite the generally *stronger* CH stretching force constants for the latter two; secondly, cyclopropane KIEs (entries 7,8) are more alkene-like, perhaps consistent with the unusual carbon hybridization characteristic of that strained ring;(62) thirdly, intermolecular KIEs are on the whole greater than corresponding intramolecular KIEs, a result which parallels the trends found in the EIEs; lastly, several intermolecular KIEs (cf. entries 1, 5, 6) are *substantially* greater than the commonly accepted “semi-classical maximum” of ≈ 7 for primary CH bond-breaking at 25 °C.(2b)

**Table 4. Experimentally Inferred Intermolecular and Intramolecular Kinetic Isotope Effects ( $KIE_{\text{addn}}$ ) for 1,2-hydrocarbon-addition to  $(\text{silox})_2\text{Ti}=\text{NSi}^t\text{Bu}_3$ .<sup>a,b</sup>**

entry	Intermolecular	Intramolecular	EIE <sub>obs</sub> /SYM	KIE <sub>elim</sub>	KIE <sub>addn</sub> (exp) <sup>c</sup>
	R <sub>H</sub> H/R <sub>D</sub> D	RH/RD			
1	CH <sub>4</sub> /CD <sub>4</sub>		2.00 ± 0.06	14.7 ± 1.7	29.4 ± 3.5
2		CDH <sub>3</sub>	1.05 ± 0.08	13.4 ± 1.0	14.1 ± 1.5
3		CD <sub>2</sub> H <sub>2</sub>	1.13 ± 0.08		15.1 ± 1.6
4		CD <sub>3</sub> H	1.17 ± 0.07		15.7 ± 1.5
5	C <sub>2</sub> H <sub>6</sub> /C <sub>2</sub> D <sub>6</sub>		2.22 ± 0.08	14.3 ± 0.7	31.7 ± 1.9
6		CD <sub>3</sub> CH <sub>3</sub>	1.53 ± 0.03		21.9 ± 1.2
7	c-C <sub>3</sub> H <sub>6</sub> /c-C <sub>3</sub> D <sub>6</sub>		1.71 ± 0.04	9.0 ± 0.5	15.4 ± 0.9
8		1,1-c-C <sub>3</sub> H <sub>4</sub> D <sub>2</sub>	1.29 ± 0.03		11.6 ± 0.7
9	C <sub>2</sub> H <sub>4</sub> /C <sub>2</sub> D <sub>4</sub>		1.41 ± 0.01	7.8 ± 0.4	11.0 ± 0.1
10		<i>trans</i> -HDC=CHD	1.00 ± 0.02		7.8 ± 0.4
11	C <sub>6</sub> H <sub>6</sub> /C <sub>6</sub> D <sub>6</sub>		1.22 ± 0.07	7.4 ± 0.3	9.0 ± 0.6
12		1,3,5-C <sub>6</sub> H <sub>3</sub> D <sub>3</sub>	1.273 ± 0.004		9.4 ± 0.4
13	C <sub>7</sub> H <sub>8</sub> /C <sub>7</sub> D <sub>8</sub>		1.59 ± 0.06	10.5 ± 0.7 <sup>d</sup>	16.7 ± 1.3
14		PhCH <sub>2</sub> D	1.03 ± 0.01		10.8 ± 0.7

<sup>a</sup>All KIE<sub>elim</sub> values refer to the 1,2-R<sub>H</sub>H-elimination from  $(\text{silox})_2(^t\text{Bu}_3\text{SiNH})\text{TiR}_\text{H}$  and  $k_\text{D}$  refers to 1,2-R<sub>H</sub>D-elimination from  $(\text{silox})_2(^t\text{Bu}_3\text{SiND})\text{TiR}_\text{H}$ . <sup>b</sup> EIE<sub>obs</sub> at 26.5 ± 0.3, EIE<sub>calc</sub> at 24.8 °C; KIE<sub>elim</sub> at 24.8 °C for R = Me, Ph, CH<sub>2</sub>Ph; KIE<sub>elim</sub> at 26.5 °C for R = Et, CH=CH<sub>2</sub> and <sup>c</sup>Pr. <sup>c</sup>All inferred KIE<sub>addn</sub>(exp)'s calculated according using the EIE<sub>obs</sub>/SYM and the experimental KIE<sub>elim</sub>. <sup>d</sup>EIE<sub>obs</sub> at 50.0 °C; KIE<sub>elim</sub> at 52.4 °C.

The large intermolecular KIEs observed for methane and ethane (~30) are similar to those observed for methane oxidation by soluble methane monooxygenases (sMMO). Lipscomb and co-workers reported(63) KIEs of ~50-100 for the hydroxylation of CH<sub>4</sub> vs CD<sub>4</sub> by sMMO isolated from *Methylosinus trichosporium* OB3b; Lippard and co-workers found a similarly large KIE of ~28 for the same reaction catalyzed by *Methylococcus capsulatus* (Bath).(64) Many factors can *decrease* observed KIEs,(2c) but only two factors may significantly *increase* them – secondary effects and quantum mechanical tunneling. To obtain a KIE of around 30 for CH<sub>4</sub> vs. CD<sub>4</sub> means that more than just the zero-point energy for a single CH stretch must be lost in the transition state – the zero-point energy for one or two bending modes must be lost as well. In other words, the reaction coordinate for transferring H(D) nucleus (whether as H<sup>+</sup>, H-atom or hydride) does not resemble the textbook linear three-centered atom or proton transfer,(2b) for which bending frequencies present in the ground state are also present in the transition state. Therefore, the usual arguments as well as the usual upper limit of ~7 do not model these 1,2 additions, so further theoretical modeling of the transition state and its attendant vibrational frequencies are required for a full understanding.

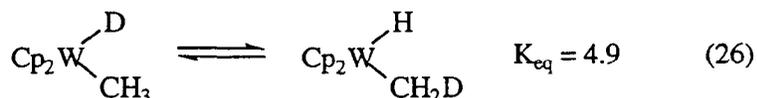
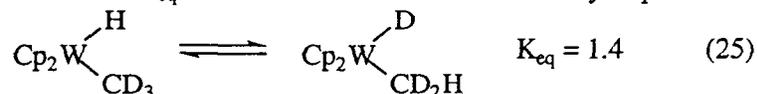
Quantum mechanical tunneling plays a well-established role in the H-atom abstraction from CH bonds in condensed phases(65) and is now recognized in enzymatic catalysis as

well.(66) But unusually large KIE's need not signify tunneling; Kreevoy(67) proposed experimental criteria for recognizing tunneling based on deviations from predicted Arrhenius temperature behavior. Clearly, temperature-dependent KIE studies, despite their experimental difficulty, are extremely worthwhile! The role of tunneling in organometallic systems has begun to receive theoretical attention,(68) but is beyond the scope of this review.

KIEs have been reported for highly electrophilic metal centers that react with hydrocarbons or C-H bonds of ligands. The lutetium complex  $\text{Cp}^*_2\text{LuCH}_3$  exchanges with methane, and its reaction with benzene (vs.  $\text{C}_6\text{D}_6$ ) to give  $\text{Cp}^*_2\text{LuPh}$  and  $\text{CH}_4$  has  $k_{\text{H}}/k_{\text{D}} = 5.5$  at  $70^\circ\text{C}$ .(69) Even larger KIEs were found by Marks and co-workers, who reported detailed studies of  $\text{Cp}^*_2\text{ThR}_2$  complexes and found  $k_{\text{H}}/k_{\text{D}}$  values as high as 10 for reactions of some thorium complexes with C-H bonds.(70)

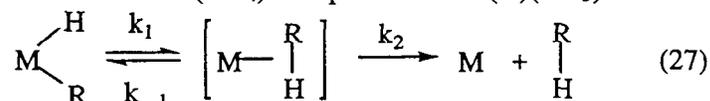
In contrast to these reactions that proceed through diamagnetic intermediates, Sherry and Wayland found that the stable rhodium radical  $(\text{TMP})\text{Rh}\cdot$  ( $\text{TMP}$  = tetramesitylporphyrin) reacts with methane to give  $(\text{TMP})\text{RhH}$  and  $(\text{TMP})\text{RhCH}_3$ .(71) A large KIE of  $k_{\text{H}}/k_{\text{D}} = 8.6$  at  $23^\circ\text{C}$  was found for  $\text{CH}_4$  vs.  $\text{CD}_4$ , and a termolecular four-centered transition state ( $\text{Rh}\cdots\text{C}\cdots\text{H}\cdots\text{Rh}$ ) was proposed.

**H/D Site Exchange and KIEs for Reductive Elimination of Alkanes.** Intramolecular H/D scrambling between metal hydride and methyl sites in  $\text{M}(\text{H})(\text{CH}_3)$  (with deuterium labels in either site) provides additional evidence for the intermediacy of  $\sigma$ -alkane complexes in the reductive elimination of hydrocarbons from metal alkyl hydride systems. Microscopic reversibility requires the same intermediates in oxidative addition of alkanes to metal systems. In several cases equilibrium constants for this site exchange have been measured, as shown by examples in eqs. 25-26. The  $K_{\text{eq}}$  values differ from the statistically expected value of 3 due to



the EIE favoring deuterium in the C-H rather than the M-H site.(72) Related H/D exchanges were observed in other examples shown in Table 5 that exhibit inverse isotope effects.

The  $\sigma$ -alkane complexes enable scrambling of H and D between MH and  $\text{CH}_3$  sites, since the bound  $\text{CH}_4$  complex is thought to readily equilibrate among different forms. These same  $\sigma$ -alkane complexes account for the inverse isotope effects often found (Table 5) in reductive eliminations from metal alkyl hydride complexes. These inverse isotope effects have their origin in pre-equilibrium reversible formation of the alkane complexes, for which the EIE is inverse. Thus the  $K_{\text{eq}}$  for formation of an  $\text{M}(\text{CD}_4)$  complex from  $\text{M}(\text{D})(\text{CD}_3)$  exceeds that of formation



of an  $\text{M}(\text{CH}_4)$  complex from  $\text{M}(\text{H})(\text{CH}_3)$ . While the H/D scrambling provides evidence for the intermediacy of  $\sigma$ -alkane complexes in the examples that have inverse isotope effects, it is

possible that  $\sigma$ -alkane complexes also form in the cases in Table 5 that have normal isotope effects. The critical feature was proposed to be "the energy of the transition state for dissociation of alkane relative to that of the transition state for  $\sigma$ -complex formation from the alkyl-hydride."(73)

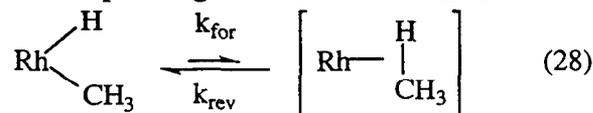
**Table 5. KIEs for Reductive Elimination of RH from M(R)(H)**

Metal Complex	$k_H/k_D$	Temp. (°C)	Ref.
(PPh <sub>3</sub> ) <sub>2</sub> Pt(H)(CH <sub>3</sub> )	3.3	-25	(74)
(tmeda)Pt(CH <sub>2</sub> Ph)(H)Cl <sub>2</sub>	3.1	-28	(75)
(PPh <sub>3</sub> ) <sub>2</sub> Pt(H)(CH <sub>2</sub> CF <sub>3</sub> )	2.2	40	(76)
(Cy <sub>2</sub> PCH <sub>2</sub> CH <sub>2</sub> PCy <sub>2</sub> ) Pt(H)(CH <sub>2</sub> CMe <sub>3</sub> )	1.5	69	(77)
(PMe <sub>3</sub> ) <sub>3</sub> Rh(H)(CH <sub>2</sub> OCH <sub>3</sub> )(Cl)	1.3	31	(78)
[Cp <sub>2</sub> Re(H)(CH <sub>3</sub> )] <sup>+</sup>	0.8	9	(79)
[Cn(PMe <sub>3</sub> )Rh(H)(CH <sub>3</sub> )] <sup>+</sup>	0.74	75	(80)
Cp*(PMe <sub>3</sub> )Ir(H)(Cy)	0.7	130	(46)
Cp <sub>2</sub> W(H)(CH <sub>3</sub> )	0.7	73	(72)
Cp* <sub>2</sub> W(H)(CH <sub>3</sub> )	0.7	100	(73)
Cp*(PMe <sub>3</sub> )Rh(H)(3,5-C <sub>6</sub> H <sub>3</sub> Me <sub>2</sub> )	0.51	51	(57)
Cp*(PMe <sub>3</sub> )Rh(H)(CH <sub>2</sub> CH <sub>3</sub> )	0.5	-30	(47)
(tmeda)Pt(CH <sub>3</sub> )(H)Cl	0.29	-27	(75)

Cy = C<sub>6</sub>H<sub>11</sub> (cyclohexyl); Cn = 1,4,7-Trimethyl-1,4,7-triazacyclononane

Referring to eq. 27, a normal KIE is found in cases where  $k_2 \gg k_1$ , and an inverse isotope effect is found when  $k_1 \gg k_2$ .

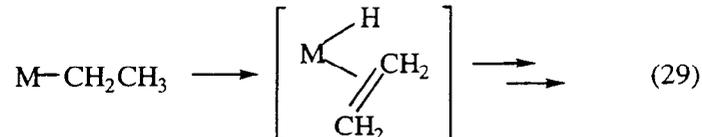
Many of these examples that have inverse isotope effects for reductive elimination of alkanes observed through kinetics measurements have their origin in inverse *equilibrium* isotope effects. Jones and co-workers provided evidence that the *kinetic* isotope effect for formation of alkane complexes was also inverse in the forward direction.(81) A thorough kinetic analysis of reductive elimination of Tp'(L)Rh(CH<sub>3</sub>)(H) [Tp' = hydridotris(3,5-dimethylpyrazolyl)borate; L = CNCH<sub>2</sub>CMe<sub>3</sub>] and related complexes gave evidence for  $k_H/k_D = 0.62$  for the forward



direction of eq. 28 (formation of the unobserved alkane complex) and  $k_H/k_D = 1.2$  for the reverse direction (oxidative addition from the bound alkane complex).

Another fascinating observation made by Jones and co-workers was that the rate constant for reductive elimination of methane from Tp'(L)Rh(CH<sub>3</sub>)(H) was slightly but reproducibly faster in benzene than in benzene-*d*<sub>6</sub> [ $k_{\text{C}_6\text{H}_6}/k_{\text{C}_6\text{D}_6} = 1.08(6)$ ].(81) This unusual effect, along with kinetics in C<sub>6</sub>F<sub>6</sub> containing varying amounts of C<sub>6</sub>D<sub>6</sub>, provided evidence for an associative component of the mechanism in which an  $\eta^2$ -benzene ligand binds to an intermediate, prior to the elimination of methane and formation of the final Tp'(L)Rh(H)Ph product.

**$\beta$ -Hydride Elimination Reactions.** Many metal alkyl complexes with  $\beta$ -hydrogens decompose by  $\beta$ -hydride elimination to give metal hydrides and alkenes. This fundamentally important



reaction is the reverse of the insertion of metal alkenes into M-H bonds. Schwartz and co-workers found a KIE of  $k_{\text{H}}/k_{\text{D}} = 2.28 \pm 0.2$  for  $\beta$ -elimination from  $(\text{PPh}_3)_2(\text{CO})\text{Ir}(n\text{-octyl})$ .(82) Thermal decomposition of  $(\text{PMe}_2\text{Ph})_2(\text{acac})\text{Co}(\text{CH}_2\text{CH}_3)_2$  [vs.  $\text{Co}(\text{CH}_2\text{CD}_3)_2$ ] gave  $k_{\text{H}}/k_{\text{D}} = 2.30 \pm 0.15$  at  $15^\circ\text{C}$ .(83) Bercaw and co-workers reported  $k_{\text{H}}/k_{\text{D}} = 2.0 \pm 0.3$  for  $\beta$ -elimination of styrene (vs. styrene- $d_1$ ) from  $\text{Cp}^*_2\text{Sc}(\text{CH}_2\text{CHDPh})$ .(84) In all of these cases  $\beta$ -elimination was proposed to be rate-limiting.

In other cases  $\beta$ -elimination reactions exhibit KIEs, but kinetic and mechanistic information indicates that the actual  $\beta$ -elimination is not always the sole cause of the KIE. Whitesides and co-workers carried out detailed kinetics studies of  $\beta$ -hydride elimination from Pt alkyl complexes.(85) A negligible KIE ( $k_{\text{H}}/k_{\text{D}} = 1.0 \pm 0.3$ ) resulted from thermolysis ( $118^\circ\text{C}$ ) of  $(\text{PEt}_3)_2\text{Pt}(\text{CH}_2\text{CH}_3)_2$  [vs.  $(\text{PEt}_3)_2\text{Pt}(\text{CD}_2\text{CD}_3)_2$ ], consistent with phosphine dissociation being rate-determining. When 0.3 M  $\text{PEt}_3$  was added,  $k_{\text{H}}/k_{\text{D}} = 3.3 \pm 0.5$  (at  $131^\circ\text{C}$ ). Scrambling of H/D was found in experiments using  $(\text{PEt}_3)_2\text{Pt}(\text{CH}_2\text{CD}_3)_2$ , indicating that  $\beta$ -hydride elimination was reversible, and it was concluded that the rate-determining step was reductive elimination of ethane from the mono-phosphine intermediate. With larger amounts (1.64 M) of added  $\text{PEt}_3$ , a lower KIE was found:  $k_{\text{H}}/k_{\text{D}} = 1.7 \pm 0.3$  (at  $157^\circ\text{C}$ ). A mechanism involving diphosphine intermediates was proposed, with the rate-determining step being either reductive elimination of ethane or loss of ethylene.

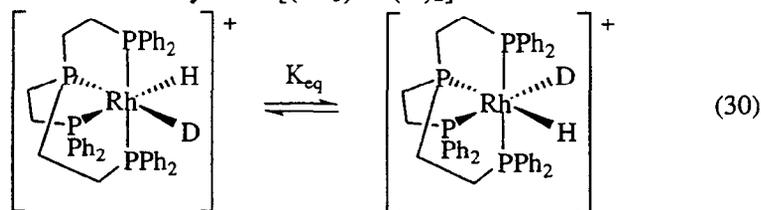
**Deuterium Effects on NMR Spectra.** Substitution of an H by D on a metal hydride typically causes a small but observable isotope effect on the  $^1\text{H}$  NMR chemical shift of the remaining hydride(s). Crabtree and co-workers reported several examples of this with partially deuterated metal polyhydrides.(86) For a series of rhenium complexes  $\text{ReH}_7\text{L}_2$  ( $\text{L}_2 =$  chelating bidentate phosphine) introduction of D in place of H led to an *upfield* shift of  $-0.002$  to  $-0.009$  ppm for each D substitution in the partially deuterated complexes  $\text{ReH}_{7-x}\text{D}_x\text{L}_2$  ( $x = 0 - 6$ ). Small isotope effects on coupling constants were found for Pt compounds, which normally have large couplings. The  $J_{\text{Pt-P}}$  of *trans*- $[\text{HPt}(\text{PEt}_3)_3]^+$  was 2055 Hz for the P trans to H, but  $J_{\text{Pt-P}} = 2031$  Hz for the analogous metal deuteride, *trans*- $[\text{DPt}(\text{PEt}_3)_3]^+$ .(87) A higher trans influence of D compared to H was found in compounds where a terminal H (or D) is trans to a dihydrogen ligand. The  $^1\text{H}$  NMR chemical shift of the HD resonance of  $[\text{Ru}(\eta^2\text{-HD})(\text{D})(\text{PMe}_2\text{Ph})(\text{diphos})]^+$  appears 0.067 downfield of the HD resonance of  $[\text{Ru}(\eta^2\text{-HD})(\text{H})(\text{PMe}_2\text{Ph})(\text{diphos})]^+$ .(88) and a similar observation was made with labeled derivatives of  $[\text{Os}(\eta^2\text{-H}_2)(\text{H})(\text{depe})_2]^+$ .(89)

One of the most definitive spectroscopic criteria for identification of a bound  $\eta^2\text{-H}_2$  ligand(10) is through  $^1\text{H}$  NMR spectroscopic studies of the corresponding  $\eta^2\text{-HD}$  complex. The observation of a 1:1:1 triplet for bound HD ligand establishes the presence of the bound dihydrogen ligand, with  $J_{\text{HD}}$  values ranging from about 10-35 Hz. These couplings are observed because some H-H (or H-D) bonding is retained in the metal complex, as opposed to dihydrides where only M-H bonds (and no H-H interaction) are present. Deuterium labels are also used in

the study of an entirely different type of coupling. Exchange couplings of quantum mechanical origin have been observed in dihydrides and polyhydride complexes.(90) These exchange couplings lead to observation of extremely large, temperature-dependent  $J_{\text{HH}}$  couplings. In one of the early examples of exchange couplings, Heinekey and co-workers reported that  $[\text{Cp}(\text{PPh}_3)\text{IrH}_3]^+$  exhibited  $J_{\text{HH}} = 260$  Hz at  $-97$  °C and  $J_{\text{HH}} = 397$  Hz at  $-77$  °C.(91) These remarkable couplings are suppressed in the partially deuterium labeled compounds, which has proven useful in the study of these remarkable observations.

Deuterium labels in ligands are advantageous in the study of paramagnetic compounds, since deuterium NMR typically gives much narrower NMR signals than those for the corresponding proton NMR. For example, Cummins and co-workers have made extensive use of deuterated ligands in the study of paramagnetic complexes, such as three-coordinate Ti complexes  $\text{Ti}(\text{NRAr})_3$  (Ar = aryl group, R =  $\text{C}(\text{CD}_3)_2(\text{CH}_3)$ , where the source of D is deuterated acetone.)(92)

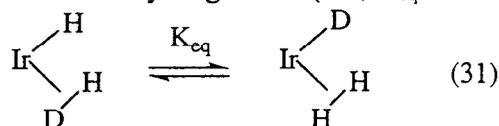
**Exchange between Dihydrogen and Terminal Hydride Ligands.** Heinekey and co-workers reported detailed low-temperature NMR studies of a series of Fe, Co, Rh and Ir dihydride complexes with the tetradentate ligand  $\text{P}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3$  (abbreviated as  $\text{PP}_3$ ). (93) In contrast to the modest *upfield* shifts normally found upon partial deuteration of polyhydrides, they found that the  $^1\text{H}$  NMR chemical shifts of the  $\text{M}(\text{H})(\text{D})$  complexes were substantially *downfield* of the corresponding  $\text{M}(\text{H})_2$  complexes. The two chemically distinct hydride sites undergo rapid dynamic exchange but can be resolved at low temperature. In the case of the cationic Rh complex shown in eq. 27, the hydride resonance of  $[(\text{PP}_3)\text{Rh}(\text{H})(\text{D})]^+$  at  $27$  °C appears 0.193 ppm downfield of that for the dihydride  $[(\text{PP}_3)\text{Rh}(\text{H})_2]^+$ . This unusual result was due to



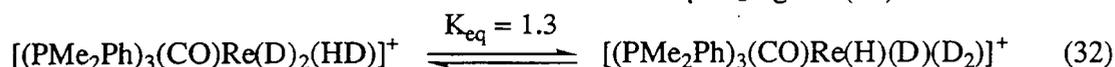
non-statistical occupation of inequivalent sites. The deuterium in the monodeuterated complex has a site preference; in the case of the Rh complex shown in eq. 30,  $K = 1.16$ . The kinetics of site exchange between the two hydride locations (intramolecular hydride rearrangement) was studied by comparison of experimental and simulated NMR lineshapes as a function of temperature for the  $\text{Rh}(\text{H})_2$  complex and its  $\text{Rh}(\text{H})(\text{D})$  analog. The KIE of  $k_{\text{H}}/k_{\text{D}} = 1.3$  shows that some changes in M-H interactions occur between ground and transition states, and it was suggested that a dihydrogen intermediate was involved. Rotation of the H-H or H-D ligand and reformation of the  $\text{Rh}-\text{H}(\text{D})$  bonds would accomplish the exchange. Hoff and co-workers found  $k_{\text{H}_2}/k_{\text{D}_2} = 1.08$  for conversion of the dihydride  $[\text{P}(\text{C}_6\text{H}_{11})_3]_2(\text{CO})_3\text{W}(\text{H})_2$  to the dihydrogen complex  $[\text{P}(\text{C}_6\text{H}_{11})_3]_2(\text{CO})_3\text{W}(\eta^2-\text{H}_2)$  complex.(94) Note that the KIE is significantly higher in the Rh case than in this W example, particularly since the Rh measurement compares  $\text{Rh}(\text{H})_2$  vs.  $\text{Rh}(\text{H})(\text{D})$  whereas the W example measured  $\text{W}(\text{H})_2$  vs.  $\text{W}(\text{D})_2$ .

The question of whether D should favor a terminal M-H site or a non-classical dihydrogen site  $\text{M}(\eta^2-\text{H}_2)$  has been addressed in several studies, but the conclusions diverge. Heinekey and co-workers prepared the cationic complex  $[\text{Tp}(\text{PMe}_3)\text{Ir}(\text{H})(\text{H}_2)]^+$  (Tp =

hydridotris(pyrazoyl)borate) and compared its NMR with that of partially deuterated analogs.(95) They found large, temperature-dependent downfield isotope shifts for the hydride resonances of the monodeuterated complex ( $\delta(\text{H}_2\text{D}) - \delta(\text{H}_3) = 0.228$  ppm at  $-58$  °C). A comprehensive study of these systems using tritium as well as deuterium labels led to the conclusion that in partially deuterated isotopomers of  $[\text{Tp}(\text{PMe}_3)\text{Ir}(\text{H})(\text{H}_2)]^+$ , D preferentially occupies the terminal rather than the dihydrogen site (i.e.,  $K_{\text{eq}}$  lies to the right in eq. 31).



Henderson and Oglieve(96) also found a preference for D in the classical tautomer of  $[\text{Cp}_2\text{W}(\text{H})_3]^+$  compared to  $[\text{Cp}_2\text{W}(\text{H})(\eta^2\text{-H}_2)]^+$ . In contrast, Luo and Crabtree found that deuterium preferentially occupies the non-classical site in a cationic Re complex shown in eq. 32, which has two terminal M-H bonds in addition to the  $\eta^2\text{-H}_2$  ligand.(97) Poliakoff and



co-workers also found a preference for D in the non-classical site of  $\text{Cp}(\text{CO})_3\text{Nb}(\text{H}_2)$  vs.  $\text{Cp}(\text{CO})_3\text{Nb}(\text{H})_2$ .(98) These studies were conducted over different temperature ranges and spanned a variety of metals and ligands, so there appears to be no general conclusion of whether D or H will preferentially reside in the terminal (classical) or non-classical (dihydrogen) site.

NMR studies have also examined exchange between terminal Os-H and Os( $\eta^2\text{-H}_2$ ) sites. A KIE of  $k_{\text{OsH}_3}/k_{\text{OsHD}_2} = 1.4(2)$  at  $-25$  °C was found for exchange between  $[\text{Os}(\eta^2\text{-HD})(\text{D})(\text{depe})_2]^+$  and  $[\text{Os}(\eta^2\text{-D}_2)(\text{H})(\text{depe})_2]^+$  (depe =  $\text{Et}_2\text{PCH}_2\text{CH}_2\text{PEt}_2$ ). (99) Analysis of  $^1\text{H}$  and  $^2\text{H}$  NMR spectra of  $\text{Os}(\text{H})(\eta^2\text{-H}_2)(\text{P}^i\text{Pr}_3)_2(\text{CO})\text{Cl}$  and  $\text{Os}(\text{D})(\eta^2\text{-D}_2)(\text{P}^i\text{Pr}_3)_2(\text{CO})\text{Cl}$  at  $60$  °C gave a much larger KIE of  $k_{\text{OsH}_3}/k_{\text{OsD}_3} = 4.6(16)$ . The  $\text{H}_2$  and H ligands are trans to each other in the ground state structure, and it was suggested that an isomerization to put these ligands in a cis arrangement would facilitate the observed exchange reaction.

**Rhodium-Catalyzed Asymmetric Hydrogenation.** The asymmetric hydrogenation of prochiral enamides by Rh complexes with chiral diphosphine ligands has significant commercial utility, due to the continuing need for enantioselective synthetic procedures. The demonstration that the predominant product enantiomer arises from the “minor manifold” encompassing a minority of the Rh-containing complex was a triumph of mechanistic understanding.(100, 101) This has been referred to an “anti-lock-and-key” motif.(102)

Landis and Brauch reported an experimental study of the hydrogenation of methyl acetamidoacrylate (MAA), using  $[\text{Rh}(\text{norbondiene})(\text{DIPHOS})]^+ \text{BF}_4^-$  as the catalyst precursor.(103) Hydrogenations were conducted using mixtures of  $\text{H}_2$  and  $\text{D}_2$  and the H or D content of the hydrogenated product was determined by  $^1\text{H}$  NMR. An advantage of carrying out the experiments under mixed  $\text{H}_2/\text{D}_2$  is that any impurity (notably  $\text{O}_2$ ) that might be present in either separate gas would equally affect the reaction, compared to carrying out separate  $\text{H}_2$  vs.  $\text{D}_2$  experiments. An intriguing result is that there is *not* a significant kinetic isotope effect on the

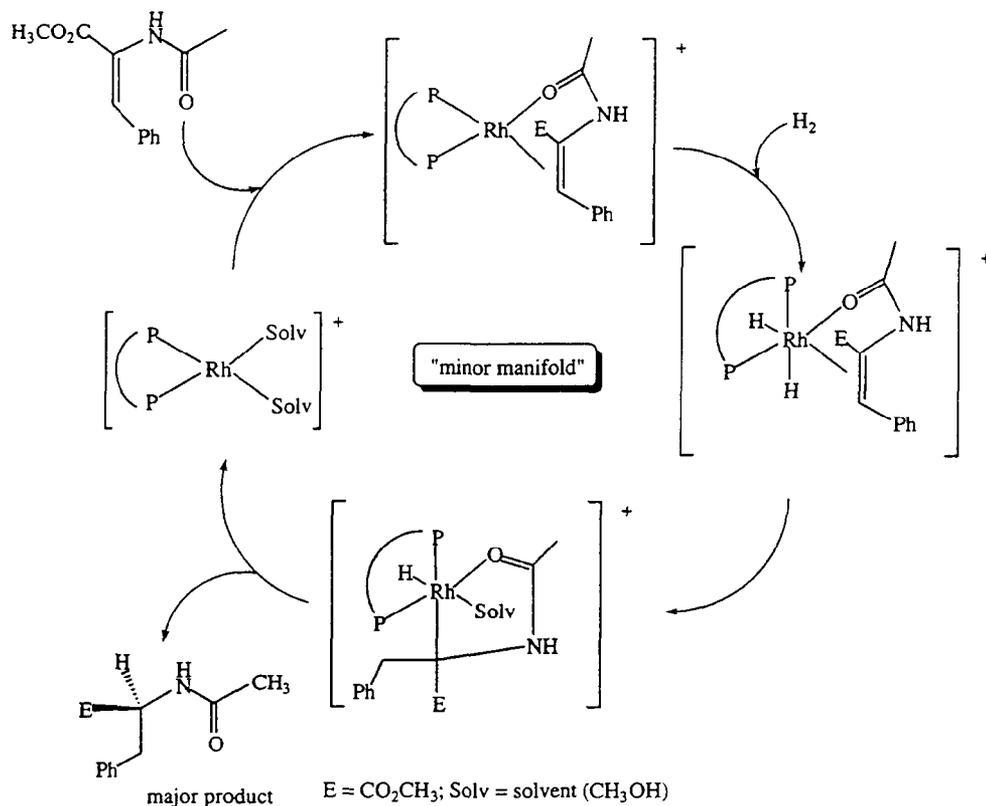
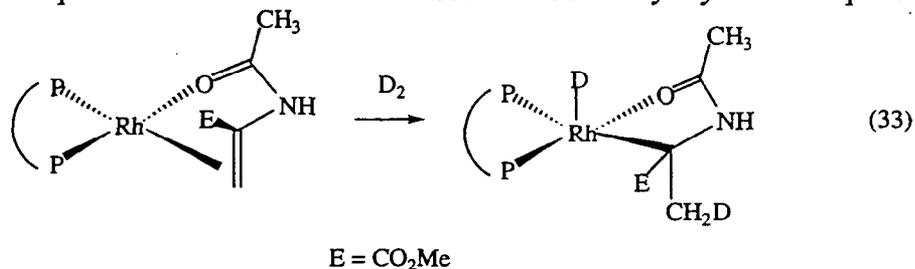


Figure 7

overall catalytic hydrogenation reaction. An average value of  $k_{H_2}/k_{D_2} = 1.04 \pm 0.05$  (corrected for 4% solubility difference of H<sub>2</sub> vs. D<sub>2</sub>) was determined on the basis of multiple measurements. A small KIE ( $k_{H_2}/k_{D_2} = 1.23 \pm 0.05$ ) had been found earlier by Brown and Parker(104) for hydrogenation of (*Z*)- $\alpha$ -acetamidocinnamic acid by  $[Rh(\text{norbornadiene})(\text{DIPHOS})]^+$ .

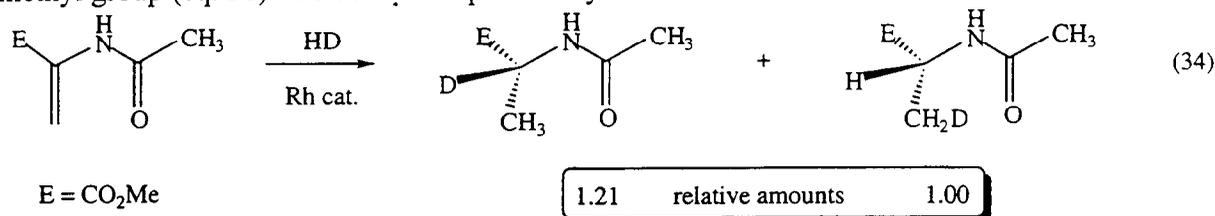
Additional isotopic probes were used to scrutinize individual steps of the reaction. As shown in Fig. 7, a critical step of the mechanism is insertion of the C=C bond into a Rh-H bond, producing a Rh alkyl hydride complex. Landis and Brauch found that catalytic hydrogenation of methyl acetamidoacrylate by D<sub>2</sub> produced the product shown in eq. 33.(103) The <sup>1</sup>H NMR integration indicating a CH<sub>2</sub>D group and the lack of any HD detected in the headspace over the reaction mixture provided evidence that the formation of the alkyl hydride complex was



irreversible. If the insertion had been reversible, then elimination of H or D from the CH<sub>2</sub>D would have occurred, providing a mechanism for H/D scrambling. Studies of this type determining the location of D labels is in the product (or recovered starting material) provide

valuable mechanistic data on catalytic reactions, without requiring a direct comparison of rate constants for a kinetic isotope effect.

The Rh-catalyzed addition of HD to methylacetamidoacrylate gave two products, since H or D can add to either position. Isotopic regioselectivity was observed, with the experimentally determined ratio of the two products being 1.21:1, with D favoring the  $\alpha$  position over the methyl group (eq. 31). To assess the possibility that addition of HD to the metal was



regioselective, HD was reacted with  $[\text{Ir}(\text{COD})(\text{DIPHOS})]^+$ , (COD = 1,5-cyclooctadiene) an Ir complex closely related to these Rh complexes. No evidence for kinetic or thermodynamic regioselectivity was observed in this oxidative addition of HD to Ir.(103) Both of the two specifically labeled Ir(H)(D) complexes (H or D trans to C=C or P) were independently prepared; H/D exchange was not observed at  $-78^\circ\text{C}$ , but complete equilibration occurred at  $-18^\circ\text{C}$ .

The potential energy surface for hydrogenations catalyzed by the achiral model complex  $[\text{Rh}(\text{PH}_3)_2]^+$  was studied by Landis and co-workers using nonlocal density functional methods.(105) Of four possible approaches of H<sub>2</sub> to a square-planar, Rh(I) enamide complex with low barriers to H<sub>2</sub> addition, one had a calculated barrier to insertion substantially less than the others. This study found no kinetic or equilibrium isotope effect for exchange of H or D between the two sites in the Rh complex, corroborating the experimental results mentioned above for addition of HD to the Ir complex  $[\text{Ir}(\text{COD})(\text{DIPHOS})]^+$ . The computational study provided evidence that  $\text{Rh}(\eta^2\text{-H}_2)$  complexes (not detected experimentally) were necessary intermediates in the formation of the dihydrides. It was noted that these dihydrogen complexes might represent “more than a shallow ‘pothole’ along the potential energy surface to oxidative addition.”(105)

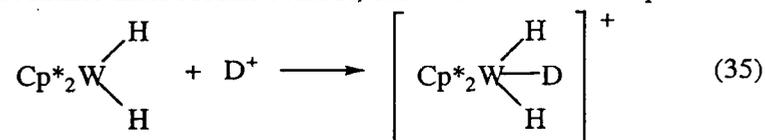
Subsequent large-scale computations(102) were carried out on a Rh complex with a “real” phosphine, (*R,R*-Me-DuPHOS),(106) rather than the model phosphine (PH<sub>3</sub>) used in earlier computations. If oxidative addition of H<sub>2</sub> is turnover-limiting, then the isotope effect for the minor pathway will be the product of the EIE for formation of the  $\text{Rh}(\eta^2\text{-H}_2)$  complex (calculated EIE = 0.615) and the KIE for oxidative addition (calculated KIE = 2.575), for a resultant calculated isotope effect of 1.584. Alternatively, if insertion of the C=C bond into the Rh-H bond is turnover-limiting, the isotope effect will be the product of three factors: the EIE for formation of the  $\text{Rh}(\eta^2\text{-H}_2)$  complex (calculated EIE = 0.615, as above), the EIE for dihydride formation (calculated EIE = 1.049) and the KIE for migratory insertion (calculated KIE = 1.561), leading to a calculated overall isotope effect of 1.007. The experimentally determined isotope effects cited above for related Rh systems, ( $k_{\text{H}_2}/k_{\text{D}_2} = 1.04 \pm 0.05$ )(103) and ( $k_{\text{H}_2}/k_{\text{D}_2} = 1.23 \pm 0.05$ )(104) tend to lie between the extremes of the computed values and thus do not definitively distinguish between the potential turnover-limiting steps. The experimentally determined isotopic regioselectivity results from reactions with HD were also between the limiting values

calculated for the two turnover-limiting steps. The computations suggest similar barriers for oxidative addition of H<sub>2</sub> to Rh and insertion of C=C into the Rh-H bond. Since the computations do not account for solvent effects, they may overestimate the barrier to insertion, which involves solvent binding as indicated in Fig. 7. Consideration of all of the experimental and computational data suggests that oxidative addition of H<sub>2</sub> to Rh is turnover-limiting. Considering the large amount of experimental and computational data on these reactions, it is clear that a variety of isotopic methods were used to understand details of a reaction which shows a negligible isotope effect for the overall reaction!

**Kinetic Isotope Effects on Enantioselective Transfer Hydrogenation.** Traditional hydrogenations catalyzed by metal complexes use H<sub>2</sub> gas, but an alternative method is transfer hydrogenations, in which the source of hydrogen is isopropanol(107) or formic acid. Leitner, Brown and Brunner studied the mechanism of the rhodium-catalyzed enantioselective transfer hydrogenation of  $\alpha,\beta$ -unsaturated carboxylic acids, in which formic acid/triethylamine is used as the hydrogen source.(108) Use of DCO<sub>2</sub>D instead of HCO<sub>2</sub>H for the hydrogenation of the C=C bond of itaconic acid gave a kinetic isotope effect of  $k_H/k_D = 3.1 \pm 0.1$  at 32 °C. This indicates that cleavage of the C-H bond of formic acid is involved in (or before) the rate-determining step, and that hydrogenation is fast compared to formic acid decomposition. The isotope effect was interpreted in terms of formation of a rhodium dihydride that is identical (or at least very similar to) the one formed during hydrogenations using H<sub>2</sub>.

**Kinetic Isotope Effects on Hydrogenolysis Reactions.** Hydrogenolysis involves reactions of H<sub>2</sub> with metal complexes in which a ligand is cleaved from the metal through the reaction with H<sub>2</sub>. Hydrogenolysis of the alkyl group of  $(\eta^5\text{-C}_5\text{Me}_5)_2\text{Th}(\text{CH}_2\text{CMe}_3)(\text{OCMe}_3)$  by H<sub>2</sub>/D<sub>2</sub> to give neopentane and a thorium hydride was studied by Lin and Marks. The kinetic isotope effect of  $k_{\text{H}_2}/k_{\text{D}_2} = 2.5$  was interpreted to indicate a transition state where H-H bond cleavage was rate-limiting.(109) The proposal that the metal-carbon bond cleavage involved a four-center polar transition state was supported by the solvent dependence, in which the hydrogenolysis was about three times faster in THF than toluene. A four-center transition state was also proposed for an earlier study of the hydrogenolysis of *n*-octyllithium, which gives LiH and octane.(110)

**Proton Transfer Reactions. Proton Transfer TO Metal Complexes.** Use of deuterium labels in protonation of metal complexes has provided an abundance of detailed mechanistic information. The predominant isotopomer of  $[\text{Cp}^*_2\text{WH}_2(\text{D})]^+$  produced from reaction of  $\text{Cp}^*_2\text{WH}_2$  with D<sup>+</sup> is the one with D in the central rather than lateral position.(111) This results from charge control rather than orbital control, since there is no occupied metal-based orbital in



the central position. The initial site of protonation is not directly at the metal center, but rather protonation at the M-H bond. Stopped-flow kinetics studies on the Cp analog, Cp<sub>2</sub>WH<sub>2</sub>, gave further confirmation that the initial site of protonation was at the M-H bond to give the intermediate dihydrogen complex  $[\text{Cp}_2\text{W}(\text{H})(\eta^2\text{-H}_2)]^+$  which converted on a slower timescale (seconds) to the trihydride complex  $[\text{Cp}_2\text{W}(\text{H})_3]^+$ .(96) The protonation reaction exhibits an inverse equilibrium isotope effect ( $K_H/K_D = 0.39$ ), meaning addition of D<sup>+</sup> is favored over

addition of H<sup>+</sup>. Conversion of the dihydrogen-hydride complex to the trihydride has an inverse isotope effect for the kinetics in the forward direction ( $k_H/k_D = 0.43$ ) and an inverse EIE ( $K_H/K_D = 0.20$ )

Very large kinetic isotope effects are found upon protonation of some bimetallic and metal cluster complexes. Knight and Mays reported  $k_{H^+}/k_{D^+}$  values of about 16 for protonation of a series of trimetallic clusters by aqueous acid. (Table 6).(112) Pribich and Rosenberg used low-temperature NMR to determine the kinetic isotope effects on protonation of  $[MCo_3(CO)_{12}]^-$

**Table 6. Kinetic Isotope Effects on Protonation of Metal Complexes by H<sup>+</sup>(D<sup>+</sup>)(112)**

Complex to be protonated	$k_{H^+}/k_{D^+}$
FeCo <sub>3</sub> (CO) <sub>12</sub> <sup>-</sup>	16.8 ± 1.0
RuCo <sub>3</sub> (CO) <sub>12</sub> <sup>-</sup>	15.4 ± 1.0
OsCo <sub>3</sub> (CO) <sub>12</sub> <sup>-</sup>	16.2 ± 1.0
Os <sub>3</sub> (CO) <sub>12</sub>	11 ± 2
[CpFe(CO) <sub>2</sub> ] <sub>2</sub>	7 ± 1

(M = Fe, Ru, Os) by FSO<sub>3</sub>H (FSO<sub>3</sub>D).(113) Initial protonation at oxygen gives a protonated bridging carbonyl complex, (μ-H)(μ-COH)Ru<sub>3</sub>(CO)<sub>10</sub>, which was characterized by <sup>1</sup>H NMR at -80 °C; oxygen-to-metal proton transfer in this complex produces the final product, (H)(μ-H)Ru<sub>3</sub>(CO)<sub>11</sub>, containing one bridging and one terminally bound metal hydride. A lower limit of  $k_{H^+}/k_{D^+} = 47$  at -40 °C was estimated(113) for the intramolecular proton transfer from oxygen to the metal core, and it was further suggested that similar initial protonation of a carbonyl ligand, followed by rate-determining proton transfer, would explain the very high kinetic isotope effects found by Knight and Mays. The very large kinetic isotope effects observed in these cases are indicative of tunneling. The likelihood of tunneling is often enhanced when there is minimal distortion in geometry in going from the ground state to the transition state, so the facile fluxionality often found in metal cluster rearrangements could contribute to the viability of this pathway.

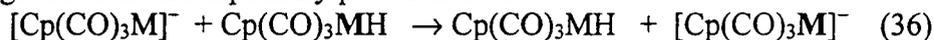
Casey and co-workers found extremely large kinetic isotope effects ( $k_H/k_D = 105 ± 20$  at -38 °C) for the acid-catalyzed (CF<sub>3</sub>CO<sub>2</sub>H/CF<sub>3</sub>CO<sub>2</sub>D) isomerization of *trans*-[CpFe(CO)]<sub>2</sub>(μ-CO)(μ-CH<sub>2</sub>) to an equilibrium *cis/trans* mixture.(114) Isotope effects of this magnitude are again strongly suggestive of tunneling. Protonation at iron was favored as a mechanistic pathway, rather than initial reversible protonation at a bridging carbonyl and subsequent protonation at the metal. It was noted that the protonated complex should be more prone to bridge opening and rotation, leading to the observed isomerization. Large kinetic isotope effects were also found in other reactions where protonation at the metal can occur; Whitesides and Nielan reported a  $k_H/k_D$  of about 27 for acid-catalyzed (CF<sub>3</sub>CO<sub>2</sub>H/CF<sub>3</sub>CO<sub>2</sub>D) *cis* to *trans* isomerization of a substituted diene ligand of an (η<sup>4</sup>-diene)Fe(CO)<sub>3</sub> complex, and rate-determining protonation at Fe was suggested.(115)

Electrophilic cleavage reactions of metal alkyl complexes by acid have been shown to exhibit large kinetic isotope effects. Cleavage of the Fe-C bond of *p*-FC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>Fe(CO)<sub>2</sub>Cp by CF<sub>3</sub>CO<sub>2</sub>H/CF<sub>3</sub>CO<sub>2</sub>D gave an isotope effect of  $k_H/k_D ≈ 15-20$ .(116) These results were interpreted as evidence for protonation at the metal followed by reductive elimination of

$\text{FC}_6\text{H}_4\text{CH}_3$ . A similar result ( $k_{\text{H}}/k_{\text{D}} \approx 20$ ) was found for acid-induced cleavage of the Mn-C bond of  $p\text{-BrC}_6\text{H}_4\text{Mn}(\text{CO})_5$ .(117)

An experimentally cogent point is that for large isotope effects, the large difference in rate constants for reactions by H and D means that more uncertainty will be introduced by small amounts of H impurity in the deuterated acid or other reagent. This will tend to underestimate the magnitude of the KIE, since the apparent rate constant for the D reaction is enhanced by the H impurity.

**Proton Transfer Reactions. Proton Transfer FROM Metal Complexes.** In contrast to the reactions discussed above where protons were transferred *to* a metal from an acid, many reactions of importance involve a proton being transferred *from* a metal complex. Most relevant to homogeneous catalysis are examples where the acid is a metal hydride or dihydrogen complex. Norton and co-workers reported proton transfer self-exchange reactions between metal hydrides and their conjugate bases, the metal anions (eq. 36; M = Cr, Mo, W)(118). Studies of self-exchange reactions are especially powerful since the



kinetics reveal information about the barrier to reaction in the *absence of a thermodynamic driving force*. Such self-exchange reactions have identical products and starting materials (except for the presence of an isotope label in most cases). It is thought that in this case the transition state is linear, and linear transition states usually result in larger isotope effects than non-linear transition states.(2) Adapting eq. 2 to determine the maximum KIE expected from rupture of an M-H/M-D bond gives eq. 37. Substitution of the observed stretching frequencies

$$\frac{k_{\text{H}}}{k_{\text{D}}} = \exp \left\{ \frac{hc}{2k_{\text{B}}T} (\bar{\nu}_{\text{MH}} - \bar{\nu}_{\text{MD}}) \right\} \quad (37)$$

for the M-H bonds leads to predicted values of  $k_{\text{H}}/k_{\text{D}} = 3.39$  for  $\text{HCr}(\text{CO})_3\text{Cp}$ , 3.38 for  $\text{HMo}(\text{CO})_3\text{Cp}$ , and 3.53 for  $\text{HW}(\text{CO})_3\text{Cp}$ . The experimentally determined kinetic isotope effects on proton transfer self-exchange for eq. 33 are  $k_{\text{H}}/k_{\text{D}} = 3.6 \pm 0.2$  for  $\text{HCr}(\text{CO})_3\text{Cp}$  and  $k_{\text{H}}/k_{\text{D}} = 3.7 \pm 0.2$  for both  $\text{HMo}(\text{CO})_3\text{Cp}$  and  $\text{HW}(\text{CO})_3\text{Cp}$ , in excellent agreement with the maximum predicted values.

Kinetic isotope effects have been measured for proton transfers from metal hydrides to amine bases.(119) A KIE of  $k_{\text{H}}/k_{\text{D}} = 4.2$  at 25 °C for proton transfer  $\text{HW}(\text{CO})_3\text{Cp}$  to aniline was reported, and it was noted that this value is surprisingly large since the reaction is thermodynamically unfavorable by 5.5 pKa units. Oxidation of metal hydrides by one electron gives radical cations, which in some cases are sufficiently long-lived for kinetic and/or spectroscopic measurements. The ruthenium radical cation  $\text{CpRu}(\text{PPh}_3)_2\text{H}^{+\bullet}$  can be generated electrochemically, and the rate constant for protonation of amines was measured. For proton transfer to pyrrolidine at 20 °C,  $k_{\text{H}}/k_{\text{D}} = 2.7$ . This reaction is thought to be approximately thermoneutral, but its kinetic isotope effect is lower than that observed for self-exchange reactions that are inherently thermoneutral.

Deprotonation of the cationic metal hydride  $\text{HMo}(\text{CO})_2(\text{dppe})_2^+$  (dppe =  $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$ ) by pyridine is thermodynamically favorable but kinetically slow. The rate of deprotonation is accelerated by at least two orders of magnitude by addition of halide anions, which functioned as kinetically active proton carriers. Kinetic isotope effects determined for

deprotonation of  $\text{DMo}(\text{CO})_2(\text{dppe})_2^+$  (vs.  $\text{HMo}(\text{CO})_2(\text{dppe})_2^+$ ) by anions were  $k_{\text{H}}/k_{\text{D}} = 2.30$  for  $\text{Cl}^-$  and  $k_{\text{H}}/k_{\text{D}} = 1.86$  for  $\text{Br}^-$ .(120)

**Hydrogen Atom Transfer Reactions.** Hydrogen atom transfer from metal hydrides is a fundamental reaction pathway that is pertinent to certain hydrogenation and hydroformylation mechanisms. Isotope effects have been particularly beneficial in interpretation of mechanistic studies of the hydrogenation of  $\text{C}=\text{C}$  bonds proceeding by radical mechanisms. A classic study by Sweany and Halpern published in 1977 provided conclusive evidence that hydrogenation of  $\alpha$ -methylstyrene proceeded through a radical pathway involving hydrogen atom transfers from metal hydrides (Figure 8).(121) Particularly definitive in this and related studies is the *inverse* isotope effect observed in the kinetics. For the hydrogenation of  $\alpha$ -methylstyrene by  $\text{HMn}(\text{CO})_5$

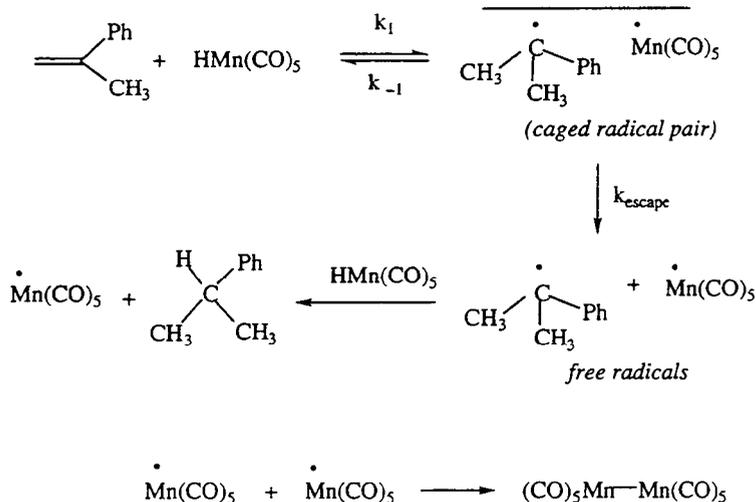
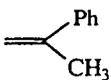
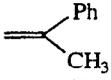
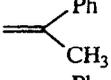
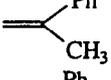
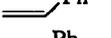
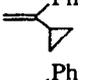
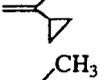
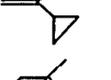
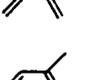
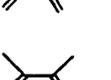
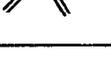


Figure 8

(vs.  $\text{DMn}(\text{CO})_5$ ) shown in Fig. 8,  $k_{\text{H}}/k_{\text{D}} \approx 0.4$  at  $65^\circ\text{C}$ . Subsequent studies on hydrogenation of substituted styrenes and dienes by several metal hydrides showed that inverse isotope effects are characteristically observed for these types of hydrogenation reaction (Table 7). The first four examples (hydrogenation of  $\alpha$ -methylstyrene by different metal hydrides) illustrate another valuable aspect of studies of isotope effects. Mechanistically related reactions such as these can exhibit similar isotope effects, even though the rate constants differ greatly, as evidenced by the  $100^\circ$  range of temperatures shown in the Table. This because stretching frequencies appear in the equation for KIEs, but the activation barrier does not. The possibility of inverse kinetic isotope effects was predicted by Bigeleisen in his original 1949 paper on the theory of kinetic isotope effects.(130) Melander has given an illuminating discussion of the effect of transition state asymmetry on isotope effects, and he stated that "a very product-like transition state could give rise to an inverse kinetic isotope effect provided that the equilibrium effect is sufficiently strong and in the proper direction. In general, this would require that a strongly endothermic reaction leads to a product in which the frequencies concerned with the atom transferred are higher than those of the reactant."(131)

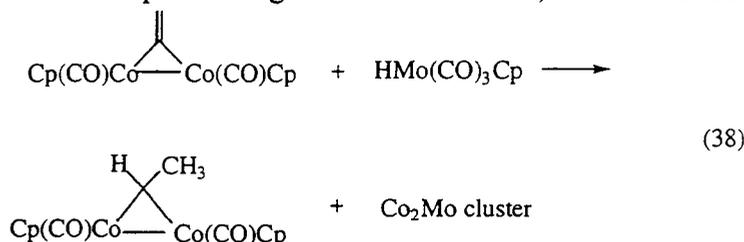
**Table 7. Kinetic Isotope Effects in Hydrogenation of Unsaturated Substrates by Hydrogen Atom Transfers**

Substrate	Metal Hydride	Major Product	$k_{MH}/k_{MD}$	T (°C)	Ref.
	HMn(CO) <sub>5</sub>		0.4	65	(121)
	HMo(CO) <sub>3</sub> Cp		0.48	65	(122)
	HW(CO) <sub>3</sub> Cp		0.65	100	(122)
	HCo(CO) <sub>4</sub>		0.68	0	(123)
	HCo(CO) <sub>4</sub>	PhCH <sub>2</sub> CH <sub>3</sub>	0.45	0	(124)
	HMn(CO) <sub>5</sub>		0.4	25	(125)
	HW(CO) <sub>3</sub> Cp	 + 	0.55	100	(126)
	HCr(CO) <sub>3</sub> Cp	 + 	0.45	68	(126)
	HFe(CO) <sub>4</sub> SiCl <sub>3</sub>	 -Fe(CO) <sub>4</sub> SiCl <sub>3</sub>	0.71	20	(127)
	HMn(CO) <sub>5</sub>	 -Mn(CO) <sub>5</sub>	0.57	55	(128)
	HFe(CO) <sub>2</sub> Cp	 -Fe(CO) <sub>2</sub> Cp	0.86	21	(129)

These criteria appear to be fulfilled by the initial hydrogen atom transfer from metal hydrides to C=C bonds. While the M-H bond being cleaved (BDE  $\approx$  60-70 kcal mol<sup>-1</sup>)(8) is weaker than the C-H bond being formed, the reaction is nevertheless endothermic since the C=C bond of the starting material is converted to a C-C bond in the carbon-centered radical. The enthalpy of the initial hydrogen atom transfer from metal hydrides to  $\alpha$ -methylstyrene has been evaluated(132) using thermochemical data; for the example shown in Fig. 8 with HMn(CO)<sub>5</sub>,  $\Delta H = 22$  kcal mol<sup>-1</sup>. Thus the initial hydrogen atom transfer is endothermic, and furthermore the stretching frequency of the bond being formed [ $\nu(\text{C-H}) \approx 3000$  cm<sup>-1</sup>] is much higher than that of the bond being cleaved [ $\nu(\text{M-H}) \approx 1800$  cm<sup>-1</sup>]. It is therefore possible that these inverse isotope effects are due to an inverse *kinetic* isotope effect on an elementary hydrogen atom transfer reaction. The late transition state would involve a significant amount of C-H bond formation.

Although this interpretation is plausible and had been anticipated by theory, the reversibility of the hydrogen atom transfer requires consideration of an alternative explanation involving *equilibrium* isotope effects. As indicated in Fig. 8, the initial hydrogen atom transfer produces a caged radical pair. In several studies listed in Table 4, the reversibility of the

hydrogen atom transfer was demonstrated by H/D exchange, through formation of M-H from reactions starting with M-D as well as the corresponding accumulation of D in the methyl group of  $\alpha$ -methylstyrene. Jacobsen and Bergman studied details of the hydrogen atom transfer from  $\text{DMo}(\text{CO})_3\text{Cp}$  to the binuclear cobalt vinylidene complex shown in eq. 38, which has  $k_{\text{H}}/k_{\text{D}} = 0.70$  at  $60^\circ\text{C}$ .(133) H/D isotope exchange was fast at  $-40^\circ\text{C}$ , and was found to occur at least



100 times faster than product formation. Since the reverse hydrogen atom transfer (carbon-to-metal in this case; analogous to  $k_{-1}$  in Fig. 8) occurs in a cage, limitations on rate constants imposed by diffusion control (often important in bimolecular reactions) are not applicable, since the radical pair is already assembled in close proximity for reaction. It was estimated that this reverse hydrogen atom transfer could occur with rate constants as large as  $10^{13} - 10^{14} \text{ sec}^{-1}$ , which is comparable to the timescale of a molecular vibration.

For this thoroughly studied case, the inverse isotope effect observed in the kinetics owes its origin to an inverse *equilibrium* isotope effect, as a consequence of the higher equilibrium constant for generation of the radical pair with D than with H.(133) This does not *require* that the KIE on the elementary step of metal-to-carbon hydrogen atom transfer be inverse. The hydrogen atom transfer equilibrium is actually established in this case (corresponding to  $k_{-1} > k_{\text{escape}}$  for the rate constants in Fig. 8), but whether or not the equilibrium is actually established is not easy to determine experimentally. It is generally difficult to confidently ascertain whether isotope effects in cases like those listed in Table 7 are controlled by an inverse kinetic isotope effect on an elementary step ( $\Delta G_{\text{D}}^{\ddagger} > \Delta G_{\text{H}}^{\ddagger}$ ), or by a higher equilibrium constant for the deuterated isotope, resulting in an inverse EIE ( $\Delta G_{\text{D}} > \Delta G_{\text{H}}$ ). Fortunately, despite these nuances of interpretation, the recognition that an inverse isotope effect is frequently observed in hydrogen atom transfers from metal hydrides to substituted styrenes, dienes, and related substrates remains a valuable kinetic probe in mechanistic studies.

Orchin and co-workers studied the hydrogenation of the C=C bonds of a series of substituted fluorenylidene complexes that proceed by sequential hydrogen atom transfers from  $\text{HCo}(\text{CO})_4$  or  $\text{HMn}(\text{CO})_5$ .(134) A progression of isotope effects from inverse to normal was found, as shown in Table 8 for hydrogenations by  $\text{HCo}(\text{CO})_4$ . While the inverse isotope effect found for ethylidene-fluorene is comparable to others listed in Table 7, the normal isotope effect found

Table 8

Hydrogenation by $\text{HCo}(\text{CO})_4$		$k_{\text{H}}/k_{\text{D}}$
		0.43
		1.22
		2.01

for bifluorenylidene was suggested to be due to the hydrogen atom transfer to bifluorenylidene being less endothermic by comparison. The ground state structure of bifluorenylidene has a considerable amount of twist, resulting in some radical character in the ground state. It was suggested that the normal isotope effect results from a relative ground state destabilization of bifluorenylidene, leading to a transition state that resembles starting materials (e.g., less C-H formation) more than in the other cases.

The product-forming step in these radical hydrogenations (Table 7) involves an exothermic hydrogen atom transfer from a metal hydride to a carbon-centered radical. Since this second hydrogen atom transfer occurs after the rate-limiting step, isotope effects on it cannot be directly measured. Use of a radical rearrangement enabled the determination of KIEs for hydrogen atom transfer from  $\text{HW}(\text{CO})_3\text{Cp}$  to two carbon-centered radicals to be determined.<sup>(126)</sup> The mechanism is analogous to that established above, and the overall

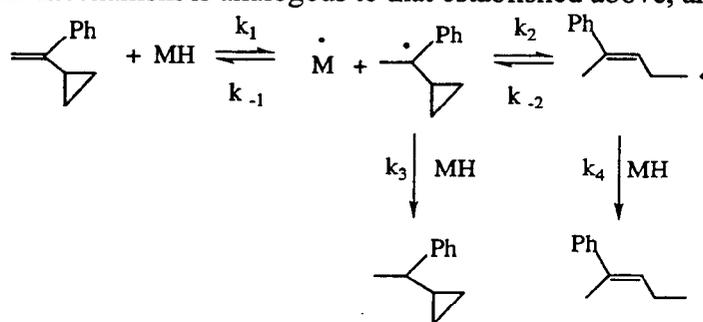
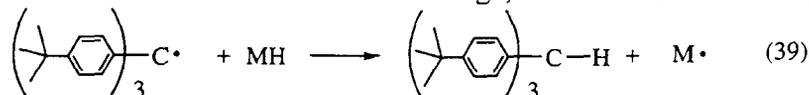


Figure 9

reaction has an inverse isotope effect ( $k_{\text{H}}/k_{\text{D}} = 0.55 \pm 0.1$  at  $100^\circ\text{C}$ ). Since the initially formed tertiary carbon-centered radical undergoes first-order rearrangement in competition with second-order trapping by metal hydride, the product ratio varies with metal hydride concentration, producing more of the unrearranged product at higher concentrations of metal hydride. Kinetic

isotope effects at 100 °C from HW(CO)<sub>3</sub>Cp (vs. DW(CO)<sub>3</sub>Cp) showed  $k_H/k_D = 2.2 \pm 0.2$  at 100 °C for the  $k_3$  step of Fig. 9, and  $k_H/k_D = 1.8 \pm 0.3$  for the  $k_4$  step of Fig. 9.(126) These were interpreted as evidence for an early transition state for this exothermic reaction.

Norton and co-workers used stopped-flow methods to determine kinetic isotope effects for hydrogen atom transfer from metal hydrides to a substituted trityl cation (eq. 36).(135) For hydrogen atom transfer from HMn(CO)<sub>5</sub>/DMn(CO)<sub>5</sub>,  $k_H/k_D = 3.18$  at 25 °C. The temperature dependence of the KIE was evaluated over a 100 ° range, and the difference in Arrhenius



activation energies was  $E_a^D - E_a^H = 0.86(7)$  kcal mol<sup>-1</sup>. There is thus no evidence for tunneling, since this difference in activation energies is not substantially higher than the 0.7 kcal mol<sup>-1</sup> difference in zero-point energies of the H-Mn and D-Mn bonds (eq. 40;  $N$  = Avogadro's number). A larger KIE was determined for hydrogen atom transfer from the osmium complex

$$\Delta E_0 = \frac{Nhc}{2} (\bar{\nu}_{\text{MD}} - \bar{\nu}_{\text{MH}}) \quad (40)$$

(H)<sub>2</sub>Os(CO)<sub>4</sub>/(D)<sub>2</sub>Os(CO)<sub>4</sub> to the substituted trityl radical ( $k_H/k_D = 4.3$  at 25 °C). It was proposed that some of the reason for the higher KIE observed in the Os compared to the Mn case was that the latter had a more symmetric transition state. The largest isotope effect is expected when the transition state is thermoneutral and symmetric.(136) In consideration of the effect of increasing the reactivity of a reagent that abstracts hydrogen, Melander and Saunders stated that the "transition state will change from product-like to symmetric to reactant-like, so that the hydrogen isotope effect will increase to a maximum at the symmetric transition state and then decrease."(2d) Based on an estimated BDE of about 81 kcal mol<sup>-1</sup> for the C-H bond being formed in eq. 36, the Os reaction is approximately thermoneutral, in comparison to the substantially exothermic hydrogen atom transfer from HMn(CO)<sub>5</sub> (Mn-H BDE ~ 68 kcal mol<sup>-1</sup>).

Hydrogen atom transfer from metal to oxygen was studied by Bakac in aqueous solution using the rhodium hydride complexes L(H<sub>2</sub>O)RhH<sup>2+</sup> (L = the macrocyclic ligand [14]aneN<sub>4</sub>). In the presence of O<sub>2</sub>, hydrogen atom transfer from L(H<sub>2</sub>O)RhH<sup>2+</sup> to the aquachromyl ion, Cr<sup>IV</sup><sub>aq</sub>O<sup>2+</sup>, leads to Cr<sub>aq</sub><sup>3+</sup> and LRhOO<sup>2+</sup> with a KIE of  $k_H/k_D = 5.4$  being found from use of the Rh deuteride.(137) No solvent isotope effect was found:  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1$ . Hydrogen atom transfer to the chromium superoxo complex Cr<sub>aq</sub>OO<sup>2+</sup> gave Cr<sub>aq</sub>OOH<sup>2+</sup> with an even larger KIE of  $k_H/k_D = 7.6$ .(138) This large KIE is suggestive of some quantum mechanical tunneling. Steric effects on the atom transfer rate are minimal due to three atoms (H•••O-O) in the transition state keeping the metals apart.

Gardner and Mayer examined oxidations of hydrocarbons by MnO<sub>4</sub><sup>-</sup>, and concluded that hydride transfer occurs in water, but that a hydrogen atom transfer pathway is operative in toluene.(139) They found  $k_H/k_D \approx 2.5$  at 45 °C for reaction of toluene (vs. toluene-*d*<sub>8</sub>) with MnO<sub>4</sub><sup>-</sup>, and attributed this to hydrogen atom transfer from a CH bond of the methyl group to an oxygen atom of MnO<sub>4</sub><sup>-</sup>.

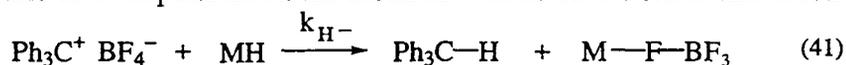
Gridnev and co-workers studied chain transfer catalysis of methyl methacrylate catalyzed by a cobalt porphyrin complex. In experiments with methyl methacrylate (vs. deuterated

monomer), an isotope effect of about 3.5 was found, indicating that hydrogen atom transfer occurs in the rate-limiting step of the polymerization.(140)

Hoff and co-workers discovered an unusual hydrogen atom transfer from a metal hydride to •NO. A  $k_H/k_D = 1.7 \pm 0.2$  was determined for reaction of •NO with  $\text{HCr}(\text{CO})_3\text{Cp}^*$  (vs.  $\text{DCr}(\text{CO})_3\text{Cp}^*$ ). (141) Since an inverse EIE was presumed [based on  $v(\text{H-NO}) > v(\text{H-Cr})$ ], and this normal KIE was interpreted as evidence for an early transition state.

**Hydride Transfer Reactions.** Darensbourg and co-workers carried out extensive studies on anionic metal carbonyl hydrides and demonstrated their utility as reducing agents for a variety of organic reactions.(142) Reduction of *n*-BuBr to butane was about twice as fast using  $\text{DW}(\text{CO})_4\text{P}(\text{OMe})_3^-$  as with  $\text{HW}(\text{CO})_4\text{P}(\text{OMe})_3^-$ .(143) Facile H/D exchange of the metal hydrides with  $\text{CH}_3\text{OD}$  or  $\text{D}_2\text{O}$  led to metal deuterides that functioned as  $\text{D}^-$  transfer reagents for conversion of acyl halides to deuterium-labeled aldehydes, or for reduction of alkyl bromides to specifically D-labeled alkanes.(144)

The rate constants for hydride transfer from a series of transition metal hydrides to  $\text{Ph}_3\text{C}^+$  (eq. 41) was found to be dependent on the metal as well as on the steric and electronic effects



of the ligand; rate constants of the kinetic hydricity spanned a range of greater than  $10^6$ .(145) The kinetic isotope effects were determined for a series of M-H/M-D pairs.(146) Three Mo hydrides [ $\text{CpMo}(\text{CO})_3\text{H}$ ,  $\text{Cp}^*\text{Mo}(\text{CO})_3\text{H}$ , and *trans*- $\text{CpMo}(\text{CO})_2(\text{PCy}_3)\text{H}$ ] all had  $k_H/k_D = 1.7 - 1.8$ . Tungsten hydrides with substituted Cp ligands had isotope effects that varied with the rate constants for hydride, with the largest value ( $k_H/k_D = 1.8$ ) being the same as that observed for the Mo hydrides.

**Table 9. Kinetic Isotope Effects For Hydride Transfer from Tungsten Hydrides with Substituted Cyclopentadienyl Ligands to  $\text{Ph}_3\text{C}^+ \text{BF}_4^-$  (25 °C).**

Metal Hydride (Deuteride)	$k_H/k_D$
$(\text{C}_5\text{H}_4\text{CO}_2\text{Me})(\text{CO})_3\text{WH}$	0.47
$(\text{C}_5\text{H}_5)(\text{CO})_3\text{WH}$	0.92
$(\text{C}_5\text{H}_4\text{Me})(\text{CO})_3\text{WH}$	1.4
$(\text{C}_5\text{Me}_5)(\text{CO})_3\text{WH}$	1.7
(Indenyl)(CO) <sub>3</sub> WH	1.8

transfer. The tungsten hydride with the largest rate constant for hydride transfer, (Indenyl)(CO)<sub>3</sub>WH, had the largest KIE ( $k_H/k_D = 1.8$ ). Tungsten hydrides with progressively less electron-donating ligands had lower rate constants *and* lower KIEs. An inverse kinetic isotope effect ( $k_H/k_D = 0.47$ ) was determined for the metal hydride that was slowest at hydride transfer,  $(\text{C}_5\text{H}_4\text{CO}_2\text{Me})(\text{CO})_3\text{WH}$ . As found for other cases discussed here, the force constants for stretching (and bending) of the C-H bond being formed is much higher than the force constants for the M-H bond being ruptured. Figure 9 qualitatively illustrates the differences in zero-point energy responsible for the inverse KIE. The summation sign indicates that more than one isotopically sensitive mode may be involved, so it is the cumulative effect of these that will determine the isotope effect. For the case of an inverse isotope effect,  $\Delta_{\text{CH/CD}} > \Delta_{\text{MH/MD}}$ , so that  $\Delta G_{\text{H}}^\ddagger > \Delta G_{\text{D}}^\ddagger$ . The progressively decreasing values of  $k_H/k_D$  were interpreted in terms of

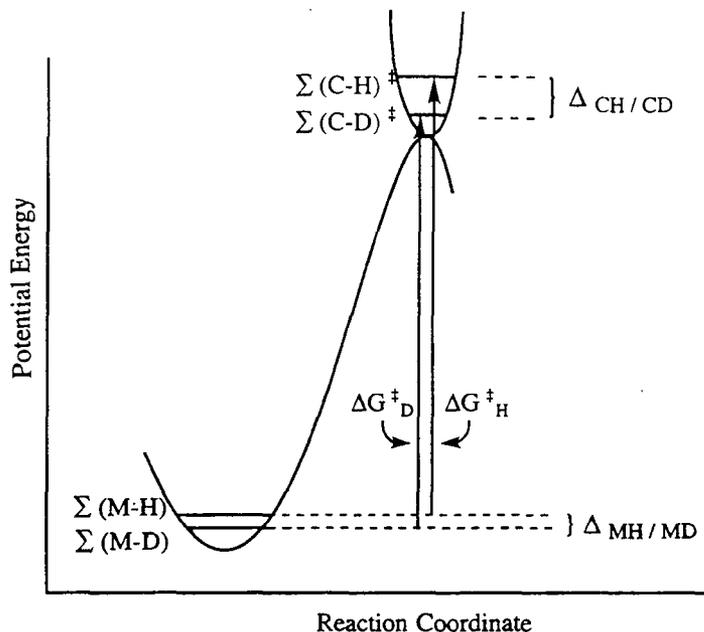
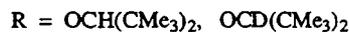
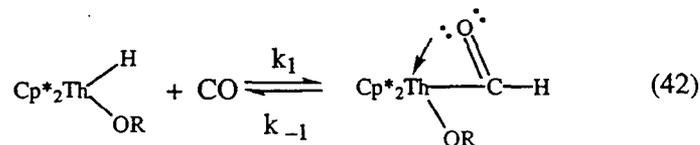


Figure 10

increasingly stronger force constants for isotopically sensitive modes of the transition state, as the reaction progresses to lower rate constants for the less electron-rich ligands. This could be due to correspondingly larger amounts of C-H bond formation (and more M-H bond cleavage) in the transition state. This interpretation is not definitively proven by the data, however. Model calculations have shown that for non-linear transition states, the magnitude of the isotope effect may not be strongly dependent on the extent of hydrogen transfer in the transition state.(147)

**Insertions Into Metal Hydrogen Bonds.** The insertion of unsaturated organic molecules into the M-H bond of a metal hydride is a required step in many homogeneously catalyzed reactions. Insertion of the C=C bonds of alkenes into M-H(D) bonds is important in hydrogenation and hydroformylation reactions. In cases where the insertion step is amenable to study, small KIEs ( $k_H/k_D = 1.1 - 1.2$ ) were found.(148, 149)

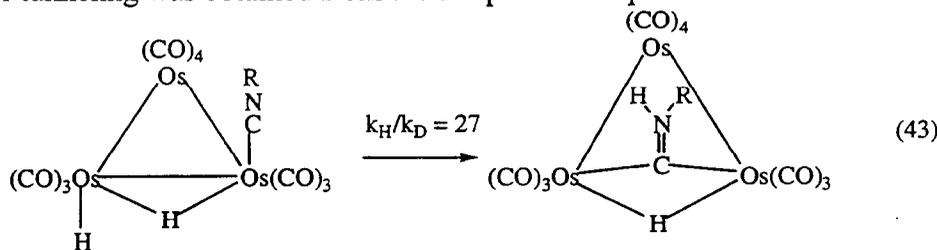
Moloy and Marks reported isotope effects on the formation of metal formyl complexes from reaction of CO with thorium complexes (eq. 42)(150) and found an EIE (Th-H vs. Th-D) of



$K_H/K_D = 0.31$  at  $-78^\circ\text{C}$ . The Th-H stretching mode [ $\nu(\text{Th-H}) = 1355 \text{ cm}^{-1}$ ] has a much lower frequency than the stretching frequency of the C-H bond being formed. The KIEs of insertion of CO ( $k_H/k_D = 2.8$  for  $k_1$  eq. 42) and its reverse reaction ( $k_H/k_D = 4.1$  for  $k_{-1}$ ) were determined at  $-58^\circ\text{C}$ . Both of these KIEs were normal, providing another example where an inverse EIE results from normal KIEs for the forward and reverse reaction, with the reverse KIE having a larger magnitude.

The insertion of CO<sub>2</sub> into the Re-H bond of *fac*-HRe(CO)<sub>3</sub>(bipy) gives *fac*-Re(CO)<sub>3</sub>(bipy)OC(O)H.(151) There was a large solvent dependence on this reaction, with the rate constants increasing with the dielectric constant of the solvent (e.g., over 200 times faster in acetonitrile vs. THF). Comparison of rate constants for Re-H/Re-D showed an inverse KIE for the insertion reaction ( $k_H/k_D = 0.58 \pm 0.03$  in THF;  $k_H/k_D = 0.52 \pm 0.05$  in acetonitrile). A highly polar transition state was proposed, in which hydride transfer occurs from the metal to carbon. The kinetics of extrusion of CO<sub>2</sub> from a metal formate complex, Cp(NO)(PPh<sub>3</sub>)ReOC(O)H, were studied at 112 °C.(152) The KIE of this decarboxylation reaction was  $k_H/k_D = 1.55 \pm 0.19$ .

The KIE for the osmium to nitrogen transfer of hydrogen shown in eq. 43(153) was temperature-dependent, ranging from  $k_H/k_D = 27 \pm 3$  at 32 °C to  $4.2 \pm 0.4$  at 70 °C. Further evidence for tunneling was obtained from the temperature dependence of the Arrhenius

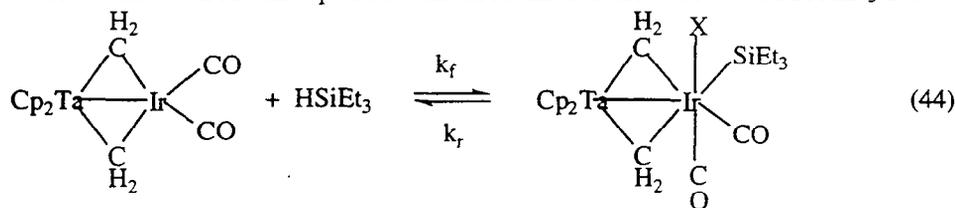


parameters, in which the  $E_a^D$  (30.6 kcal mol<sup>-1</sup>) was about 8 kcal mol<sup>-1</sup> larger than  $E_a^H$  (22.6 kcal mol<sup>-1</sup>).

In contrast to the spectacularly large kinetic isotope effects found above for metal clusters, Rosenberg and co-workers reported detailed studies of hydride mobility on Ru and Os clusters and found small isotope effects ( $k_H/k_D = 1.4 - 2.0$ ) for several dynamical processes that could be studied by low-temperature <sup>1</sup>H and <sup>13</sup>C NMR.(154) Among the processes showing KIEs in this relatively narrow range were migrations of hydrides on the face of the trinuclear cluster (e.g., conversion between a bridging hydride and a terminal hydride), often in connection with mobility of hydrocarbon ligands on the clusters.

**Secondary Isotope Effects on Oxidative Additions.** Primary isotope effects, where the bond being broken affects the rate constant, are most commonly studied, but secondary isotope effects have been studied for some reactions pertinent to homogeneous catalysis. In the addition of H<sub>2</sub> to the Ir in Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)(PPh<sub>3</sub>), the inverse EIE of 0.54 reported in Table 1 is actually a composite isotope effect incorporating the effect of H<sub>2</sub> vs. D<sub>2</sub> addition to the metal, but additionally including the effect of the bridging ligand being CH<sub>2</sub> vs. CD<sub>2</sub>. Since rapid H/D exchange occurs between the H<sub>2</sub>/D<sub>2</sub> and CH<sub>2</sub>/CD<sub>2</sub>, measurement of H<sub>2</sub> to the Ta(CD<sub>2</sub>)<sub>2</sub>Ir complex could not be determined. Isotope effects were also informative in understanding mechanistic details of the reactions of the closely related complex, Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub>, which is a homogeneous catalyst for hydrogenation and hydrosilation of ethylene.(155, 156) NMR measurements showed that the oxidative addition of HSiEt<sub>3</sub>/DSiEt<sub>3</sub> to Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub> had an inverse EIE ( $K_H/K_D = 0.53(4)$  at 0 °C.) This again is a composite of primary and secondary isotope effects due to fast exchange under conditions used in these NMR experiments. Use of UV-vis spectroscopy to measure the rate of this reaction enabled separate measurements to distinguish the primary vs. secondary effects. The primary kinetic

isotope effect on addition of HSiEt<sub>3</sub>/DSiEt<sub>3</sub> to Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub> was k<sub>H</sub>/k<sub>D</sub> = 1.13; the same value was obtained from independent measurements on addition of HSiEt<sub>3</sub>/DSiEt<sub>3</sub> to



*Primary Effects*

*H-Si vs. D-Si*

$$K_{\text{H/D}} = 0.78 \text{ (calculated)}$$

$$k_{\text{H}}^f / k_{\text{D}}^f = 1.13$$

$$k_{\text{H}}^r / k_{\text{D}}^r = 1.45$$

*Secondary Effects*

*H-Si + Ta(CH<sub>2</sub>)<sub>2</sub>Ir vs. Ta(CD<sub>2</sub>)<sub>2</sub>Ir*

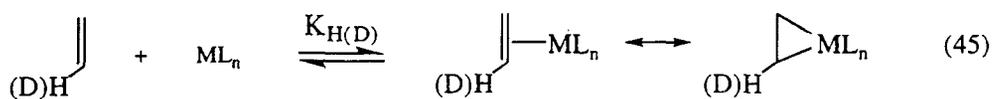
$$K_{\text{H/D}} = 0.70 \text{ (calculated)}$$

$$k_{\text{H}}^f / k_{\text{D}}^f = 0.875$$

$$k_{\text{H}}^r / k_{\text{D}}^r = 1.25$$

Cp<sub>2</sub>Ta(μ-CD<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub>. The secondary isotope effect was determined in this system by comparing the rate constants for addition of HSiEt<sub>3</sub> to Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub> vs. Cp<sub>2</sub>Ta(μ-CD<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub>. This secondary isotope effect occurs due to changing H or D in the bridging methylene, rather than isotopic changes to the H-Si bond being cleaved. These measurements showed an inverse secondary isotope effect of k<sub>H</sub>/k<sub>D</sub> = 0.874 ± 0.032. Since there are four deuteriums in Cp<sub>2</sub>Ta(μ-CD<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub>, the effect due to each deuterium is (0.874)<sup>1/4</sup> = 0.967. The effect of deuteration at the bridging methylene is to provide a small acceleration in the rate constant for reaction with HSiEt<sub>3</sub>. The normal KIE on the oxidative addition is small, but its magnitude is about equal (but opposite direction) to that of the secondary kinetic isotope effect. Estimates of the primary and secondary contributions to the EIE were calculated from IR bands of the Ir-H and Si-H bonds, with the assumption that K<sub>H/D</sub>(total) = K<sub>H/D</sub>(primary) K<sub>H/D</sub>(secondary). As shown in eq. 39, both contributions are inverse for the EIE. The inverse EIE, together with a small KIE on the forward reaction, then requires that the KIE on the reverse reaction be normal and of higher magnitude. The secondary KIE was also studied for oxidative addition of CH<sub>3</sub>I vs. CD<sub>3</sub>I to Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub>, which gives Cp<sub>2</sub>Ta(μ-CH<sub>2</sub>)<sub>2</sub>Ir(CO)<sub>2</sub>(CH<sub>3</sub>(I)). This KIE was also inverse, but with a larger magnitude: k<sub>H</sub>/k<sub>D</sub> = 0.752 ± 0.018, corresponding to an effect of 0.931 per D. Several explanations were considered to account for the origin of these secondary isotope effects; inductive effects were favored as a more likely explanation than hyperconjugation, hybridization changes or steric differences. The inductive effect is due to deuterium being a better electron donor than hydrogen. We shall encounter such inductive effects below in the discussion of isotope effects and the binding/activation of olefins.

**Isotope Effects in Catalysis Involving Alkenes.** Alkene binding and activation, like H<sub>2</sub> binding and activation, is fundamental to homogeneous catalysis. And while countless transition metal complexes bind olefins (eq. 45), some also functionalize them in useful ways. Many of the important discoveries, concepts and processes involving metal-olefin complexes have been tested and verified to some extent using isotope effects.



Secondary deuterium isotope effects for binding constants were first observed in the 1950's and much of the literature prior to 1972 was reviewed by Hartley.(157) Such secondary effects (wherein attack or binding occurs at the C=C double bond) are usually inverse (deuterated olefins are bound better or react faster) and supporting theoretical treatments have implicated changes in zero-point energies (specifically for out-of-plane bending frequencies) as the olefin carbons rehybridize from  $sp^2$  to  $sp^3$  as the underlying cause of these observed inverse effects;(158) this interpretation is essentially the same one introduced by Streitwieser for  $\alpha$ -secondary deuterium kinetic isotope effects at  $sp^3$  carbons for solvolyses of cyclopentyl tosylates.(159)

Other possible causes of inverse equilibrium isotope effects for alkene binding may be steric and inductive (electronic).(2e) Because the mean vibrational amplitude of a CD bond is less than that for a CH bond, deuterium is a "smaller" carbon substituent. A carbon atom bonded to deuterium has been considered to be more electropositive (electron-releasing) than a carbon bonded to protium --"D is a better donor than H," such inductive isotope effects were introduced by Halevi.(160) Because the average C-H bond distance is longer than the average C-D bond distance, the average electron distribution is somewhat different for the two isotopic bonds, and this may lead to slightly different electrostatic interactions for isotopic bonds. And while these treatments use concepts more familiar to organic chemists than the notion of zero-point energies, both treatments are consistent with the original Bigeleisen-Mayer theory.(2f)

**Equilibrium Isotope Effects for the Binding of Olefins.** Cvetanovic and others observed isotope effects on the retention times of  $C_2H_4$  and  $C_2D_4$  and other simple olefins when passed through ethylene glycol solutions of  $AgNO_3$  on a stationary GLC support;(161) they interpreted their results as an EIE for those alkenes binding to  $Ag(I)$  and established that binding is favored for  $C_2D_4$  (e. g.,  $K_H/K_D$  for binding = 0.89 at 25 °C.) The EIEs were attributed to an increase in the out-of-plane bending force constant upon binding, a conclusion that paralleled the explanation of the origin of secondary deuterium isotope effects for organic systems.(159) Both  $\alpha$ - and  $\beta$ -secondary effects were distinguished and discussed.

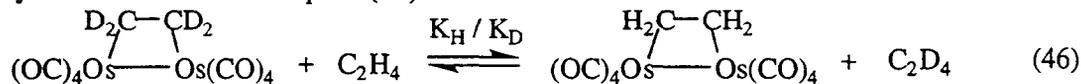
Jung and coworkers attempted to quantify the origin(s) of inverse EIEs for ethylene binding to  $Ag(I)$  complexes and carried out normal coordinate vibrational analyses of  $Ag^+(C_2H_4)$  and  $Ag^+(C_2H_3D)$  complexes.(162) They measured EIEs for ethylene and mono-deuterated ethylene binding to  $Ag(I)$  impregnated GC columns and compared the experimental value to the EIE calculated from the Bigeleisen equation. They concluded that the EIE arose from ZPE changes for several modes, some of which contributed inverse factors and some of which contributed normal. No single dominant contribution was identified.

More recently, Jung and coworkers examined the EIE for the binding of  $C_2H_4$  and  $C_2H_3D$  to  $Rh(I)$  complexes bound to a stationary GC chromatography support.(163) The experimentally observed EIE was compared to the EIE calculated from vibrational frequencies obtained from normal coordinate analyses of  $Rh(C_2H_4)$  and  $Rh(C_2H_3D)$  complexes. Reasonable

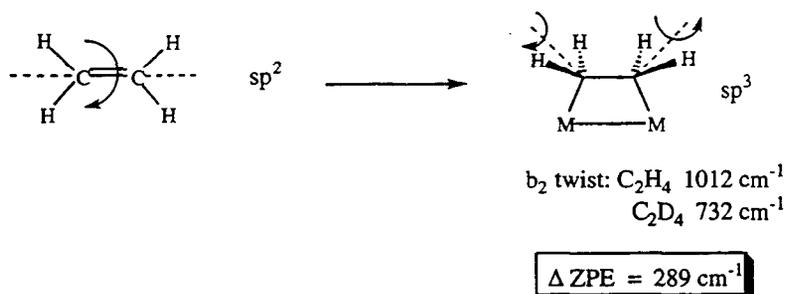
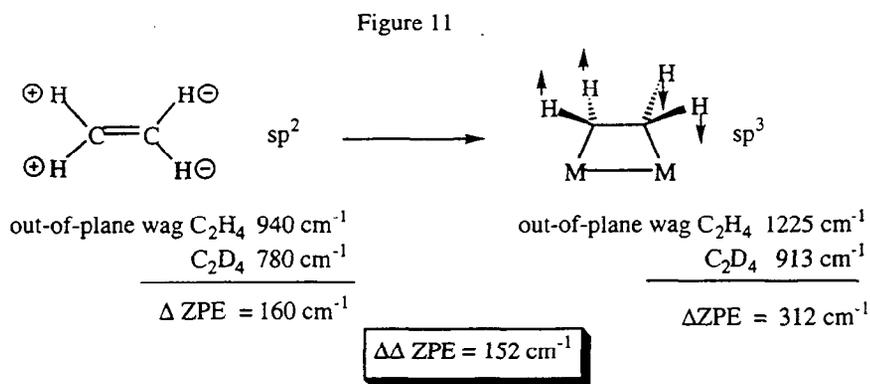
agreement was found between calculated and experimental EIEs, and the authors concluded that the inverse EIE was attributable to olefin rehybridization as in Ag(I) ethylene complexes.

Strausz et al. challenged(164) the idea that secondary deuterium isotope effects for simple additions to olefins arise from changes in out-of-plane bending motions (i.e., rehybridization), an idea having widespread currency in organic chemistry.(165) They analyzed the secondary deuterium KIE for the addition of ground state sulfur atoms S(<sup>3</sup>P) to a 50/50 mixture of C<sub>2</sub>H<sub>4</sub> and C<sub>2</sub>D<sub>4</sub> to give thiirane and thiirane-*d*<sub>4</sub>. Analysis of product ratios gave an inverse KIE of 0.877 – a result consistent with the general notion that deuterium favors sp<sup>3</sup> hybridization in the transition state. Strausz and coworkers compared the experimental KIE to that calculated from the full Bigeleisen equation using various transition-state vibrational models. The authors argued that the observed KIE arose not from force constant changes from any particular mode, but rather from an *increase* in the number of isotopically sensitive normal modes when ethylene encounters sulfur in the transition state.

Bender used analogous reasoning in his analysis of an *equilibrium* isotope effect for the reversible binding of C<sub>2</sub>H<sub>4</sub> and C<sub>2</sub>D<sub>4</sub> to a dinuclear osmium cluster. He used gas phase IR to directly measure the EIE in eq. 46.(49)

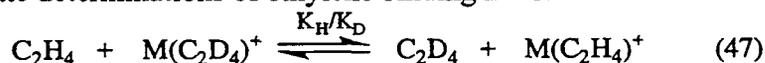


The secondary deuterium EIE for the reversible binding of ethylene in eq. 46 is inverse:  $K_H/K_D = 0.7(1)$  at 40 °C; the KIE for ethylene replacement in the same diosmacyclobutane system has been measured and discussed.(166) Previously published vibrational assignments for (C<sub>2</sub>H<sub>4</sub>)Os<sub>2</sub>(CO)<sub>8</sub> and (C<sub>2</sub>D<sub>4</sub>)Os<sub>2</sub>(CO)<sub>8</sub> as well as literature values for C<sub>2</sub>H<sub>4</sub> and C<sub>2</sub>D<sub>4</sub> allowed the calculation of the same EIE. The calculated EIE is also inverse and has a value of 0.711 at 40 °C. The calculated EIE was resolved into a mass and moment of inertia factor (MMI = 2.27), a vibrational excitation factor (EXC = 0.882), and a zero-point energy factor (ZPE = 0.355) (eq. 1). Using symmetry correlation rules, contributions to the EXC and ZPE factors from changes in ethylene vibrational modes for individual modes were then determined. The analysis revealed that most of the EIE was not due to *changes* in vibrational frequencies for any single mode when ethylene carbons rehybridize from sp<sup>2</sup> to sp<sup>3</sup> but was instead primarily due to zero-point energy from a vibrational mode which correlates with a “whole molecule” rotation in free ethylene. These ideas are shown in Figure 11.



The ethylene out-of-plane bending frequency increases from 940 cm<sup>-1</sup> (780 cm<sup>-1</sup> for C<sub>2</sub>D<sub>4</sub>) to 1225 cm<sup>-1</sup> (913 for C<sub>2</sub>D<sub>4</sub>) on going from sp<sup>2</sup> to sp<sup>3</sup> hybridization (Figure 11, upper); this leads to a *net* zero point energy change of 152 cm<sup>-1</sup>. Conversion of a molecular rotational degree of freedom into a vibrational mode incurs a zero-point energy difference of 289 cm<sup>-1</sup> between C<sub>2</sub>H<sub>4</sub> and C<sub>2</sub>D<sub>4</sub> complex, a value nearly twice the ΔΔ ZPE for *changes* out-of-plane bending mode.

Recently, Schröder and coworkers carried out a thorough experimental and theoretical study(167) of EIEs for the binding of ethylenes to the triad of coinage metal cations in the gas phase (eq. 47). Careful attention to possible sources of experimental errors ultimately gave very precise and accurate determinations of ethylene binding EIEs.



**Table 10. Experimental and Calculated EIEs for the Binding of Ethylene to Coinage-Metal Cations (eq. 47)**

Metal	EIE (expt)	EIE (calc)	ΔH <sub>dissoc</sub> for M(C <sub>2</sub> H <sub>4</sub> ) <sup>+</sup>
Cu	0.86 ± 0.02	0.86	+48 ± 3 kcal/mol
Ag	0.83 ± 0.02	0.83	+34 ± 2 kcal/mol
Au	0.74 ± 0.02	0.74	+65 ± 3 kcal/mol

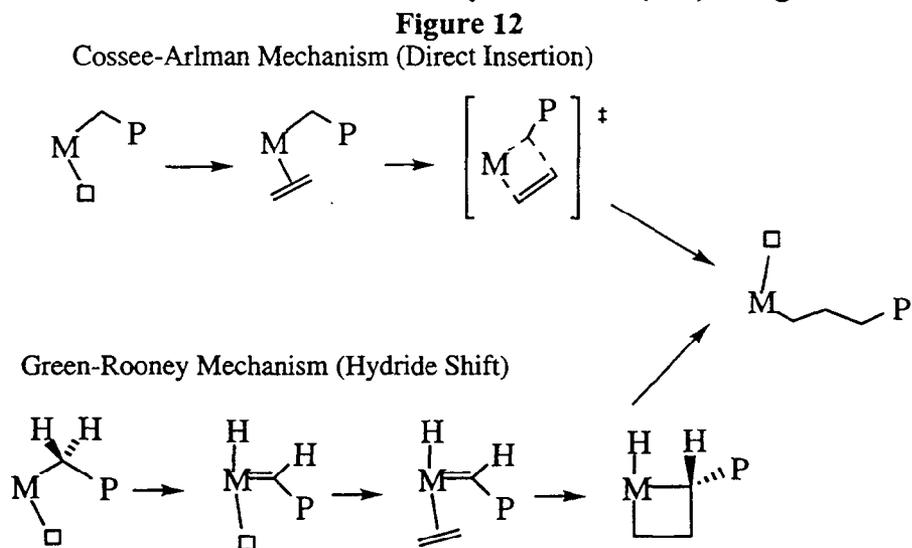
A detailed analysis of the calculated EIE (assuming a one-to-one symmetry correlation between vibrational modes for free and bound ethylenes) revealed that the major source of the inverse EIE was the zero-point energy from the binding of the ethylene rotational mode

symmetry. However that mode, like the out-plane-bending mode so often used as an indicator of secondary isotope effects, also fails to predict the relative ordering of EIEs.

Interestingly, the secondary EIE does *not* correlate with the extent of perturbation of the alkene carbons by the metal: while the inverse EIEs increase continuously down the triad, the extent of olefin rehybridization is discontinuous down the triad, e.g., the extent of olefin rehybridization is least for the silver, a trend also reflected in the *measured* binding enthalpies.(168)

**Olefin Polymerization.** The overall transformation of olefin monomers into polymer requires two carbon hybridization changes per monomer, and for this reason alone secondary isotope effects might seem a useful tool *a priori* for probing the nature of the transition state for monomer enchainment. Interestingly, analyses of the two leading mechanistic proposals of chain propagation in  $d^0$ -metallocene polymerization have largely ignored such secondary effects and have instead focussed on agostic CH-bonding ( $\alpha$  and  $\beta$  and even  $\gamma$ ) to metal centers. Grubbs and Coates have summarized many of the important experimental results,(169) and Rappé, Skiff, and Casewit have discussed theoretical model studies of metal-catalyzed olefin polymerizations.(170)

The original Cossee-Arman mechanism(171) for Ziegler-Natta polymerization is shown together with the olefin metathesis-like Green-Rooney mechanism(172) in Figure 12.

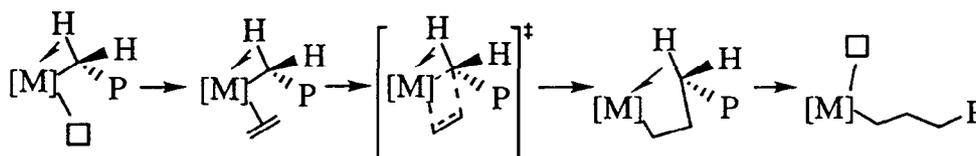


An early study which compared rate data for Ziegler-Natta polymerization of  $C_2H_4$  vs.  $C_2D_4$  had concluded that the *rates* were essentially the same,(173) however, as later pointed out by Grubbs,(174) the experimental error in that study was large enough to encompass 0.7 to 1.4, the range of healthy normal or inverse secondary effects. Because the Green-Rooney mechanism invokes the intermediacy of alkylidene hydrides, Grubbs and coworkers reasoned that a significant *primary* kinetic isotope effect for H(D) migration might distinguish the two mechanisms for the chain propagation step. They tested their hypothesis using  $Cp_2Ti(C_2H_5)Cl/Al(C_2H_5)Cl_2$  as catalyst in toluene solution. They copolymerized a mixture (an intermolecular competition) of  $H_2C=CH_2$  and  $D_2C=CD_2$  and analyzed the deuterium content of the polymer

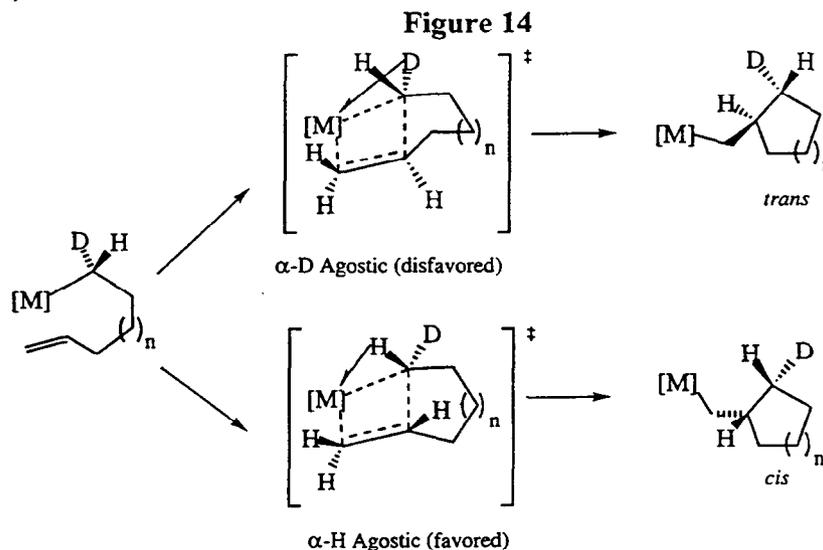
chains produced. The authors found a propagation *rate* ratio ( $k_H/k_D$ ) of  $1.04 \pm 0.03$  at ambient temperature and concluded that there was little isotope effect on chain propagation.

The alkyl to alkylidene hydride transformation in the original Green-Rooney mechanism requires formal oxidation addition and is difficult to reconcile with many 14-electron, formally  $d^0$ -transition metal systems. For this reason and others, Green and Rooney modified their original mechanism but included  $\alpha$ -agostic interactions as proposed by Brookhart and Green.(34) In the “modified Green-Rooney mechanism” (Figure 12)  $\alpha$ -CH-bonds of the growing alkyl chain interact with the metal center. Such  $\alpha$ -agostic (and related  $\beta$ -agostic bonding) have subsequently proven important for understanding polymerization catalysts and ultimately for controlling their selectivity.(169, 170)

**Figure 13**  
Modified Green-Rooney Mechanism



Grubbs and coworkers devised an ingenious intramolecular competition experiment to test for the presence or absence of significant  $\alpha$ -hydrogen interactions in the key olefin insertion step.(175) The experiment has been dubbed isotopic perturbation of stereochemistry,(176) and is outlined in Figure 14. An intermolecular version of the experiment has been devised by Brintzinger.(177)



In the upper pathway of Figure 14, the transition state is stabilized by an  $\alpha$ -D agostic interaction, while in the lower pathway, the transition state is stabilized by an  $\alpha$ -H agostic interaction. Because a CH(D) stretching force constant is weakened in the transition state, the pathway via the  $\alpha$ -H agostic should be slightly faster, leading to a normal effect, if changes in that force constant determine the isotope effect. Grubbs and Coates proposed that the transition state  $\alpha$ -agostic interaction is closely related to the  $\beta$ -secondary isotope effect, well-known in physical organic chemistry. Stille has used the method to detect and distinguish  $\alpha$ - and  $\beta$ -agostic

effects and has also discovered unusual counterion-dependent KIEs.(178) Isotopically chiral olefins have been used to probe the absolute stereochemistry of addition to an  $\alpha$ -olefin – this exquisite experiment relies only on observed vicinal H-H coupling constants.(179)

A variety of systems, corresponding to different metal-ligand combinations, “M” in the Figure 13 have been tested using the perturbation method and some systems appear to show a KIE while others do not. Wisler and Rappé have suggested that the reason some systems show agostic KIE while others do not is because the systems have different rate-limiting steps.(180) Grubbs and Coates discussed this apparent discrepancy in detail in their review(169) and have identified two factors which they believe account for the variability of the observed isotope effects: If olefin binding is rate-limiting, transition state  $\alpha$ -agostic interactions may be present but will not significantly affect either the rate or stereochemistry of the subsequent olefin insertion. The second key factor is the nature of the transition state itself: the magnitude of charge buildup and  $\alpha$ -C-H bond geometry will determine the magnitude of the isotope effect when an agostic interaction is present. It was noted(169) that systems with high reaction rates typically do not exhibit  $\alpha$ -isotope effects. In such systems, the barriers to both olefin coordination and olefin insertion must be relatively small and both of these factors contribute to low isotope effects. If coordination is rate-limiting and there are no  $\alpha$ -agostic interactions in the ground state, and no KIE is expected. If insertion is rate-limiting, the transition state will be early, resulting in a small amount of charge buildup, poor overlap with the  $\alpha$ -CH bonds and hence a small KIE. On the other hand, systems with lower reaction rates typically exhibit significant  $\alpha$ -isotope effects and there is strong evidence that olefin insertion is rate-limiting in these reactions.

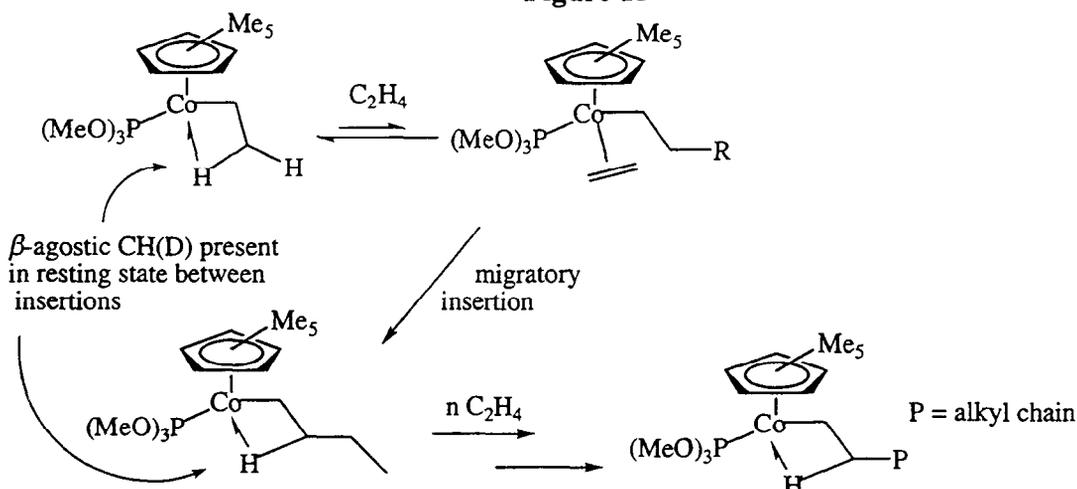
One aspect not discussed in the Grubbs and Coates analysis(169) is the possibility that the observed isotope partitioning occurs *after* the rate-limiting step. Because many (if not all) of the isotopic perturbation studies did not measure rates (but instead measured isotope distribution in stable products), it is possible that olefin binding is rate limiting (yet isotope insensitive or even inverse) and the observed “normal” isotope partitioning occurs in a subsequent isotope sensitive (but overall rate-*insensitive*) product forming step. Such rate-insensitive “product isotope effects” have long been known,(2g) and for an excellent discussion of such effects, the interested reader is directed to a recent paper by Singleton,(181) from which we quote one particularly lucid passage: “When a partially labelled molecule that is committed to react (having passed through the rate-limiting transition state) still has a stereochemical or regiochemical choice of reactive isotopes, the product distribution reflects the KIE for the product-determining step.”

In the context of  $\alpha$ -agostic effects and olefin polymerization, an isotope insensitive (but rate-limiting) olefin binding step could still show an agostic KIE, the isotope partitioning occurring *after* the olefin binding step. On the other hand, and particularly for intermolecular competition experiments, an *inverse* secondary olefin binding KIE may partially or completely compensate for the normal agostic effects-this subtlety has already been suggested by Brookhart in the case we consider next.

Isotope effects for the more recently discovered class of “late-metal” olefin polymerization catalysts(182) have been reported. Brookhart and coworkers measured both

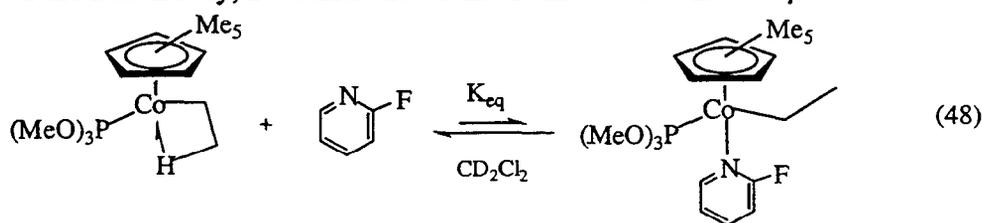
inter- and intramolecular kinetic isotope effects for polyethylene formation catalyzed by a Co(III)-system under mild conditions;(183) they demonstrated that *inverse* KIEs may arise for

Figure 15



olefin polymerization catalysts (Figure 15), in contrast to normal isotope effects sometimes observed in  $d^0$  systems. Brookhart and coworkers ascribed the inverse effect to changes in zero-point energies for an  $\beta$ -agostic CH bond in the ground state which becomes a stronger, “free” CH bond during or just prior to the insertion step.

Equilibrium isotope effect experiments support their interpretation: an inverse EIE of 0.59 was measured for eq. 48. Treatment of the agostic complex or its  $\text{Co}-\text{C}_2\text{D}_5$  analog with 2-fluoropyridine results in the partial conversion to the pyridine adduct with a “free” pendant alkyl. Integration of  $^{31}\text{P}$  signal for the  $\text{Co}-\text{C}_2\text{H}_5$  and  $\text{Co}-\text{C}_2\text{D}_5$  system gave an inverse EIE of ca 0.59, a value measurably different than the inverse KIE (ca 0.48) observed for ethylene polymerization KIEs. The authors noted that values of  $J_{\text{CH}}$  values for the agostic model complex are significantly different than the actual catalytic resting state, and the differing degree of agostic bonding between the model complex and “real” system may account for the difference between the KIE and the EIE. Lastly, Brookhart noted that normal  $\alpha$  and inverse  $\beta$  effects in the  $d^0$



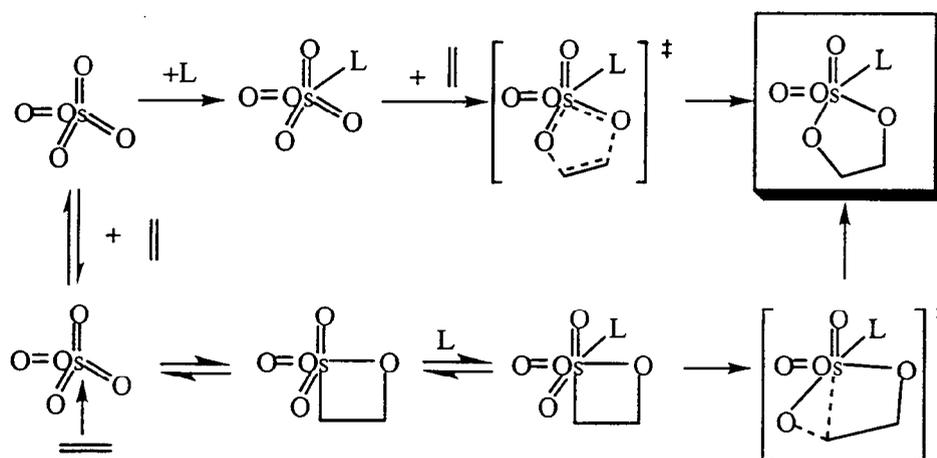
systems could offset each other, one another, leading to small or no observed isotope effect, and that this is a potential pitfall in measuring intermolecular competition effects.

**Olefin Oxidation.** Certain metal-oxo complexes are superb oxo transfer reagents, and when furnished with a terminal oxidant and a chiral auxiliary, they catalyze the enantioselective addition of one or two oxygen atoms to carbon-carbon double bonds. Perhaps the best known examples are Sharpless’ osmium-catalyzed asymmetric dihydroxylation,(184) Jacobsen’s manganese-catalyzed epoxidation.(185) A close runner-up (but one which doesn’t involve metal oxo multiple bonds) is the titanium-catalyzed asymmetric epoxidation of allylic

alcohols.(186) Other technologies are emerging rapidly, especially for the selective addition of other heteroatoms to olefins, for example, osmium-catalyzed asymmetric aminohydroxylation,(187) asymmetric aziridination,(188) and cyclopropanation.(189) Not surprisingly, isotope effect studies have begun to help us understand these important transformations.

**Asymmetric Dihydroxylation.** One controversial aspect of  $\text{OsO}_4$ -catalyzed dihydroxylation is whether the delivery of two metal-bound oxygen atoms to the olefin is concerted or occurs in a stepwise fashion, mediated by a metal-carbon bonded metallaoxetane (Fig 16). Both pathways lead to the same product, the Os(VI) glycolate ester (Fig. 16, upper right). In asymmetric dihydroxylation, L represents a nitrogenous base, typically a cinchona-derived alkaloid).

**Figure 16**  
**Concerted "3+2" Mechanism**



**Stepwise "2+2" Mechanism**

The essence of the mechanistic dispute is whether an olefin directly attacks at oxygen rather than the metal in  $\text{OsO}_4$ -mediated dihydroxylation of olefins. This controversy dates to a seminal paper by Sharpless,(190) who pointed out that if metal oxo bonds were polarized with negative charge on oxygen, then nucleophiles (including olefins) should attack the *metal* center by analogy to well-established carbonyl chemistry in organic chemistry. Isotope effects could help distinguish the two transition-states for the two pathways shown in Fig. 16, *if changes in force constants at the various atoms are sufficiently distinct*.

Corey and coworkers reported  $^{12}\text{C}/^{13}\text{C}$  KIEs(191) for the bis-cinchona- $\text{OsO}_4$  catalyzed dihydroxylation of three different olefin substrates using an NMR method developed by Singleton and Thomas which measures enrichment in slower reacting reactant molecules.(192) For two olefins, the  $^{12}\text{C}/^{13}\text{C}$  KIEs were substantial and similar at each carbon of the double bond; the latter result was argued to be indicative of a "symmetric" 3+2 transition state. For one case however, *p*-methoxystyrene, the  $^{13}\text{C}$  effects were dissimilar at the two carbons and this was rationalized in terms of a greater degree of bonding for the electron-rich terminal end of the olefin in the transition state.

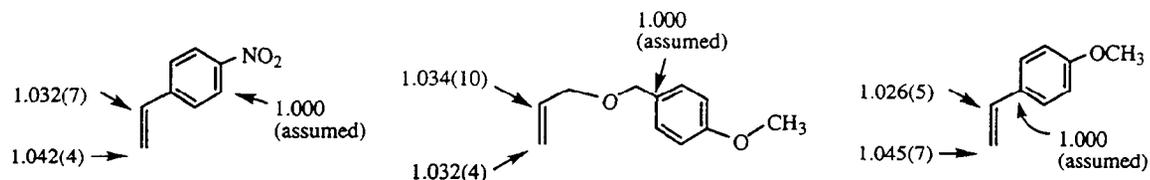


Figure 17

In a collaborative effort, Houk, Sharpless, and Singleton and co-workers reported(193) both measured *and* calculated  $^2\text{H}$  and  $^{13}\text{C}$  KIEs for the catalytic asymmetric dihydroxylation of *tert*-butylethylene using a chincona alkaloid/osmium tetroxide catalyst. Supporting DFT calculations used ammonia and propene to compute transition state frequencies and KIEs were calculated using the program QUIVER.(194) The results are summarized in Table 11.

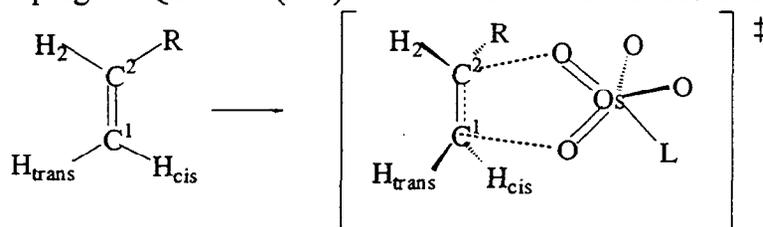


Figure 18

**Table 11. Experimental and Calculated “3+2” KIEs for Asymmetric Dihydroxylation**

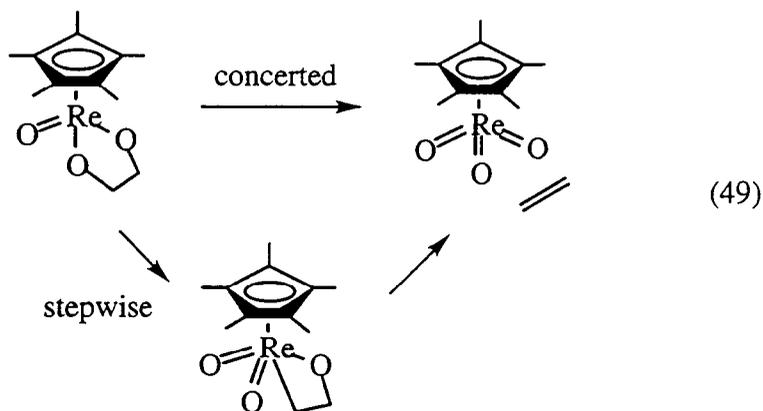
	H <sub>C2</sub>	H <sub>cis</sub>	H <sub>trans</sub>	C <sub>2</sub>	C <sub>1</sub>
R(exp) = C(CH <sub>3</sub> ) <sub>3</sub>	0.906(9)	0.919(5)	0.925(7)	1.027(1)	1.028(3)
L(exp) = (DHQD) <sub>2</sub> PYR	0.908(4)	0.917(8)	0.926(14)	1.026(3)	1.025(3)
R(calc) = CH <sub>3</sub>	0.908	0.913	0.921	1.025	1.025
L(calc) = NH <sub>3</sub>					

Remarkably precise agreement (considering the simplified model!) was obtained between experiment and theory for the concerted “3+2” transition state model. Several isomeric “2+2” transition state KIEs were also tested but all of them fit the data significantly worse (results not shown). Moreover, the DFT calculations from this and other(195) studies appeared to rule out an osmaoxetane *intermediate* because such intermediates appear to be energetically too costly. Yet despite these rather clear pronouncements by theory (as well as the isotope effect experiments), the mechanism of asymmetric dihydroxylation cannot be considered solved. Observed olefin substrate inhibition, indicating the presence and possible role of an olefin  $\pi$ -complex,(196) observed temperature breaks in modified Eyring plots of chemo-, regio-, and enantioselectivity,(197) and curved Hammett plots for substituted styrenes and stilbenes, as well as pyridine and quinuclidine bases,(198) support a more complex, stepwise mechanism. The incorporation of *all* these phenomenon into a single, unified mechanism for the osmium-catalyzed dihydroxylation of olefins remains an elusive goal.

Houk and Strassner(199) have calculated the deuterium KIE for the addition of ethylene and *trans*-2,4-pentadienoic acid to  $\text{MnO}_4^-$  and have compared the latter results with experimental

KIEs for the oxidation of *trans*-cinnamic acid. Both calculated and experimental “3+2” KIEs show that carbon-oxygen bond formation is asynchronous (is further advanced in the transition state for the nucleophilic end of the olefin). Nonetheless, they concluded that permanganate-mediated oxidations of olefins also proceed via a “3+2” transition state.

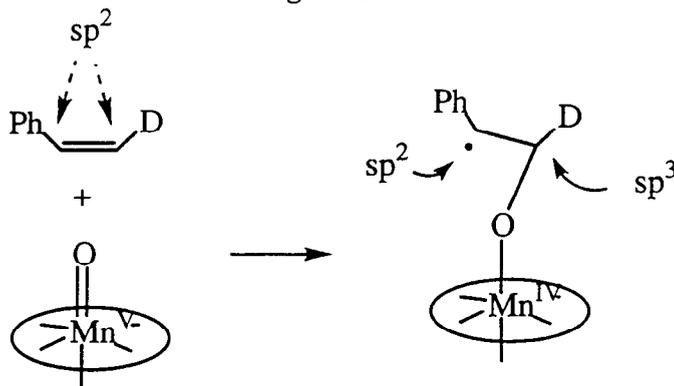
Gable and Phan measured(200) a significant deuterium KIE ( $1.25 \pm 0.05$  at 100 °C) for the elimination of  $C_2H_4$  vs  $C_2D_4$  from the Re(V) diolate complex shown in eq. 49, a reaction first reported by Herrmann and co-workers(201) and which resembles the microscopic reverse of olefin addition to  $OsO_4$ .



The KIE of 1.25, taken alone, is consistent with concerted olefin elimination.(202) However, Gable also noted the *absence* of significant ring-strain effects when the thermolyses of a series of strained olefins were compared: the barrier for the extrusion of a strained olefin should slow the rate of a concerted cycloreversion if significant release of strain (carbon rehybridization) occurs in the transition state. The authors concluded that only a stepwise mechanism of olefin extrusion was consistent with both observations. Gable and coworkers also developed a technique for the problematic quantification of  $C_2H_4/C_2D_4$  mixtures by mass spectrometry.(203)

**Olefin Epoxidation.** Jacobsen and coworkers studied secondary KIEs for the epoxidation *cis*- $\beta$ -deuterostyrene as part of a mechanistic study of electronic effects on enantioselectivity in (salen)Mn(III)-catalyzed epoxidation.(204) Interestingly, they found a direct correlation between the magnitude of the secondary KIE and the position of the transition state along the reaction coordinate. On transformation of olefin to the posited radical intermediate, the  $\beta$ -olefin carbon rehybridizes from  $sp^2$  to  $sp^3$ , while the  $\alpha$ -carbon remains  $sp^2$  hybridized. Observed KIEs were consistent with the mechanism in Figure 19: *cis*- $\beta$ -deuterostyrene shows an inverse KIE 0.86 at 22 °C, while  $\alpha$ -deuterostyrene shows no KIE. The *cis*- $\beta$ -deuterostyrene KIEs correlate (become more inverse) with electron donating substituents at the *para*-position of the phenyl ring.

Figure 19

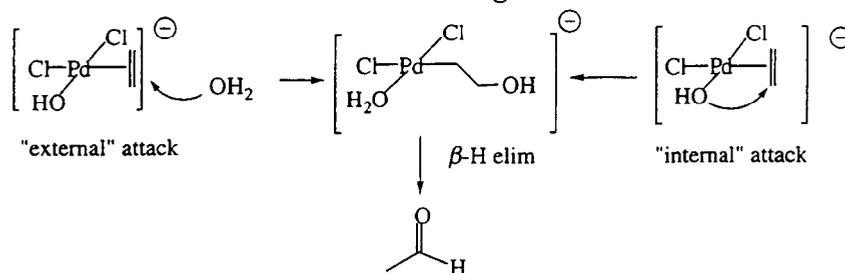


Finn and Sharpless reported inverse secondary KIEs for the epoxidation of 2-decen-1-ol as part of their definitive mechanistic study of titanium(IV)tartrate-catalyzed asymmetric epoxidation of olefins.(205) This study, which antedated that of Jacobsen and coworkers, also aimed to discern whether one C-O olefin bond forms faster than the other (thus probing the symmetry of the transition state). The results showed a slightly greater isotope effect at the carbon closer to the allylic OH, however the difference was not sufficiently different to conclude that the bond formation was significantly skewed.

**Cytochrome-P450.** Space constraints preclude a thorough review of these important olefin epoxidation (and alkane hydroxylation) enzymes *and model complexes*. Isotope effect studies on the enzyme systems have been reviewed (up to 1995);(206) more recent work has been reviewed by Shilov and Shul'pin(207), and other leading references have been cited elsewhere.(38) Significant *inverse* deuterium KIEs have been reported by Che for the epoxidation of styrene by Ru(IV)dioxoporphyrin complexes;(208) interestingly, the results closely parallel those observed by Jacobsen,(204) i.e., significant  $\beta$ -deuterium isotope effects are observed for deuterated styrene, while  $\alpha$ -deutero styrenes show no KIE, suggesting that C-O bond formation is more advanced at the  $\beta$ -carbon (nucleophilic end) than for the  $\alpha$ -carbon, consistent with a stepwise mechanism. Che has also reported(209) KIEs for the aziridination of styrene by a bis(tosylimido)Ru(IV) porphyrin; again the results show significant  $\beta$ -deuterium isotope effects are observed for deuterated styrene, while  $\alpha$ -deutero styrenes show no KIE, suggesting that C-O bond formation is more advanced at the  $\beta$ -carbon (nucleophilic end) and that these catalysts (which deliver an O-atom or N(Tosylate)) to an olefin operate by similar mechanisms.

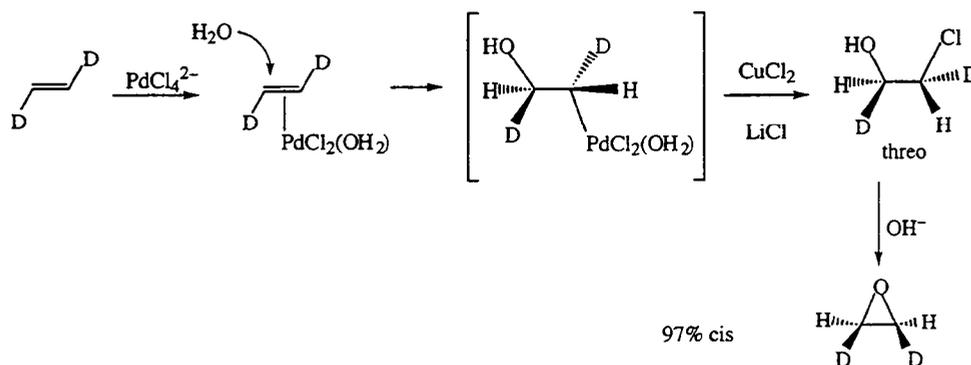
**Wacker Chemistry** Aqueous Pd(II) salts catalyze the oxidation of ethylene to yield acetaldehyde and oxidize  $\alpha$ -olefins to give mixtures of ketones and aldehydes. A mechanistic controversy has flourished around the mechanism of hydroxypalladation: whether solvent water attacks the activated double bond of the coordinated olefin or, instead, a metal-coordinated hydroxyl inserts internally into the same double bond (Fig. 20). Elegant isotopic stereochemical

Figure 20



studies by Bäckvall(210) convincingly showed that external water (or hydroxide) attacks the coordinated olefin. Thus *trans*-ethylene- $d_2$  is converted to *threo*-chlorohydrin, and *cis*-ethylene- $d_2$  is converted to *erythro*-chlorohydrin. The stereochemistry of the chlorohydrins was determined by conversion to their respective epoxides and analyzed by microwave spectroscopy (shown in Fig. 21). Whether these important results are relevant for the Wacker process under

Figure 21



*all* conditions has been questioned by Henry, and here the interested reader is referred to more detailed discussions for details.(211)

**Olefin Hydroformylation.** The hydroformylation reaction is one of the most important industrial uses of homogeneous catalysts. Alkenes are converted to aldehydes using Co- or Rh-catalyzed reactions under  $\text{H}_2$  and CO. Decades after its initial discovery, academic and industrial research continues to reveal details about the mechanism. A critical step involves insertion of a C=C bond into the M-H bond of a metal hydride, and isotope labeling experiments have played a key role in contributing to the understanding of this step. In the early 1970's Casey and Cyr(212) examined the hydroformylation of a mono-deuterated alkene (3-methyl-1-hexene-3- $d_1$ ) catalyzed by  $\text{Co}_2(\text{CO})_8$  and determined the location of the D label in the organic products. An overall 1,2 shift of the D label in some of the product provided evidence that the metal hydride added and eliminated the alkene prior to hydroformylation.

Use of  $\text{D}_2$  instead of  $\text{H}_2$  has also provided information about whether the insertion to give metal alkyl complexes is reversible or irreversible. Casey and Petrovich used Rh catalysts with chelating phosphines(213) to catalyze the deuterioformylation of 1-hexene. They found that the D label was in the  $\beta$ -carbon and the aldehyde carbon, with very little label in the recovered (unreacted) 1-hexene. This result indicated that the insertion of the alkene into the Rh-H bond to

give the metal alkyl is largely irreversible. Thus the regiochemistry of aldehyde formation (normal:iso ratio of aldehyde products) is set by conversion of the five-coordinate Rh(H)(alkene)(CO)(diphosphine) complex to the four-coordinate Rh(alkyl)(CO)(diphosphine) species. Lazzaroni and co-workers studied deuterioformylation of 1-hexene catalyzed by Rh<sub>4</sub>(CO)<sub>12</sub> and concluded that insertion into the Rh-H bond is irreversible at 20 °C, but was reversible when the catalysis was carried out at 100 °C.(214) Deuterioformylation of Ph<sub>2</sub>C=CH<sub>2</sub> catalyzed by Rh<sub>4</sub>(CO)<sub>12</sub> led mostly to the expected aldehyde product Ph<sub>2</sub>DCCH<sub>2</sub>CDO as the major product. The presence of Ph<sub>2</sub>C=CDH in this reaction provided evidence for the intermediacy of unusual tertiary alkyl rhodium complex which undergoes β-elimination under the reaction conditions.(215)

**Oxidations and Proton-Coupled Electron Transfer Reactions by Ru Complexes.** Roecker and Meyer studied the oxidation of alcohols by [(bipy)<sub>2</sub>(py)Ru=O]<sup>2+</sup>,(216) and they concluded that this reaction occurred by two-electron hydride transfer. A spectacular k<sub>H</sub>/k<sub>D</sub> = 50 (25 °C) was found for oxidation of PhCH<sub>2</sub>OH vs. PhCD<sub>2</sub>OH. The oxidation of H<sub>2</sub>O<sub>2</sub> by [(bipy)<sub>2</sub>(py)Ru<sup>IV</sup>=O]<sup>2+</sup> in aqueous solution gives O<sub>2</sub> and [(bipy)<sub>2</sub>(py)Ru<sup>II</sup>(OH<sub>2</sub>)]<sup>2+</sup>. These oxidations were found to exhibit large isotope effects when carried out in H<sub>2</sub>O vs. D<sub>2</sub>O (k<sub>H<sub>2</sub>O</sub>/k<sub>D<sub>2</sub>O</sub> = 22.0 ± 1.2 at 25 °C).(217) Kinetic and mechanistic considerations indicated that these reactions occurred by hydrogen atom transfer. Large isotope effects were also found in several reactions involving synchronous transfer of an electron and a proton (proton-coupled electron transfer). Oxidation of hydroquinone by [(bipy)<sub>2</sub>(py)Ru<sup>IV</sup>=O]<sup>2+</sup> gave k<sub>H<sub>2</sub>O</sub>/k<sub>D<sub>2</sub>O</sub> = 30.(218) Quantum mechanical tunneling must occur in these reactions to account for the magnitude of the observed KIEs.

**Outlook.** Despite having been born over 50 years ago and having matured somewhat alongside physical organic chemistry, isotope effects are an exciting and dynamic area of study and will continue to present new challenges to both theorists and experimentalists alike. For the theorist, the widespread availability of new calculational methods means that vibrational force fields (the *sine qua non* of isotope effects) for virtually any stable molecule or transition state can be generated with greater ease, more reliability and at lower cost than ever before. From this perspective, the days of interpreting KIEs and EIEs from one or two easily measured parameters may be numbered. For experimentalists, the challenge almost seems to be verification of increasingly precise and accurate glimpses at transition states which theory affords. But in the end, it is experiment which really convinces and so the challenge remains, as always, to conceive the next best experiment to test the ongoing evolution of ideas.

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## References

- (1) D. B. Northrop, *Biochemistry* **14**, 2644-2651 (1975)
- (2) L. Melander and W. H. Saunders, Jr. *Reaction Rates of Isotopic Molecules* (John Wiley and Sons, New York, 1980) (a) page 19 (b) page 29 (c) page 20 (d) page 36 (e) pages 189-199 (f) page 198 (g) page 91.
- (3) R. M. Bullock in *Transition Metal Hydrides*; ed. A. Dedieu; VCH, New York, 1992; pp 263-307 (Chapter 8).
- (4) J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.* **15**, 261-267 (1947)
- (5) M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.* **8**, 225-242 (1964)
- (6) M. Wolfsberg, *Acc. Chem. Res.* **5**, 225-233 (1972)
- (7) M. M. Kreevoy, *J. Chem. Educ.* **41**, 636 (1964)
- (8) M. Tilset and V. D. Parker, *J. Am. Chem. Soc.* **111**, 6711-6717 (1989), as modified in *J. Am. Chem. Soc.* **112**, 2843 (1990)
- (9) G. J. Kubas, R. R. Ryan, B. I. Swanson, P. J. Vergamini and H. J. Wasserman, *J. Am. Chem. Soc.* **106**, 451-451 (1984)
- (10) (a) D. M. Heinekey and W. J. Oldham, Jr., *Chem. Rev.* **93**, 913-926 (1993) (b) P. G. Jessop and R. H. Morris, *Coord. Chem. Rev.* **121**, 155-284 (1992)
- (11) T. Hascall, D. Rabinovich, V. J. Murphy, M. D. Beachy, R. A. Friesner and G. Parkin, *J. Am. Chem. Soc.* **121**, 11402-11417 (1999)
- (12) B. R. Bender, G. J. Kubas, L. H. Jones, B. I. Swanson, J. Eckert, K. B. Capps and C. D. Hoff, *J. Am. Chem. Soc.* **119**, 9179-9190 (1997)
- (13) F. Abu-Hasanayn, K. Krogh-Jespersen and A. S. Goldman, *J. Am. Chem. Soc.* **115**, 8019-8023 (1993)
- (14) D. G. Gusev, V. I. Bakhmutov, V. V. Grushin and M. E. Vol'pin, *Inorg. Chim. Acta* **177**, 115-120 (1990)
- (15) B. E. Hauger, D. Gusev and K. G. Caulton, *J. Am. Chem. Soc.* **116**, 208-214 (1994)
- (16) V. I. Bakhmutov, J. Bertrán, M. A. Esteruelas, A. Lledós, F. Maseras, J. Modrego, L. A. Oro and E. Sola, *Chem. Eur. J.* **2**, 815-825 (1996)
- (17) M. J. Hostetler and R. G. Bergman, *J. Am. Chem. Soc.* **114**, 7629-7636 (1992)
- (18) D. Rabinovich and G. Parkin, *J. Am. Chem. Soc.* **115**, 353-354 (1993)
- (19) P. B. Chock and J. Halpern, *J. Am. Chem. Soc.* **88**, 3511-3514 (1966)
- (20) P. Zhou, A. A. Vitale, J. San Filippo, Jr. and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **107**, 8049-8054 (1985)
- (21) F. Abu-Hasanayn, A. S. Goldman and K. Krogh-Jespersen, *J. Phys. Chem.* **97**, 5890-5896 (1993)
- (22) G. S. Hammond, *J. Am. Chem. Soc.* **77**, 334-338 (1955)
- (23) D. A. Wink and P. C. Ford, *J. Am. Chem. Soc.* **109**, 436-442 (1987)
- (24) S. P. Church, F.-W. Grevels, H. Hermann and K. Schaffner, *J. Chem. Soc., Chem. Commun.* 30-32 (1985)
- (25) W. Wang, A. A. Narducci, P. G. House and E. Weitz, *J. Am. Chem. Soc.* **118**, 8654-8657 (1996)
- (26) F. J. Safarowic, D. J. Bierdeman and J. B. Keister, *J. Am. Chem. Soc.* **118**, 11805-11812 (1996)

- (27) D. L. Packett and W. C. Trogler, *Inorg. Chem.* **27**, 1768-1775 (1988)
- (28) J. Halpern and M. Pribanic, *Inorg. Chem.* **9**, 2616-2618 (1970)
- (29) B. B. Wayland, S. Ba and A. E. Sherry, *Inorg. Chem.* **31**, 148-150 (1992)
- (30) K. B. Capps, A. Bauer, G. Kiss and C. D. Hoff, *J. Organomet. Chem.* **586**, 23-30 (1999)
- (31) P. A. McGovern and K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.* 1593-1594 (1996)
- (32) K. P. C. Vollhardt, J. K. Cammack, A. J. Matzger, A. Bauer, K. B. Capps and C. D. Hoff, *Inorg. Chem.* **38**, 2624-2631 (1999)
- (33) (a) R. B. Calvert, J. R. Shapley, A. J. Schultz, J. M. Williams, S. L. Suib and G. D. Stucky, *J. Am. Chem. Soc.* **100**, 6240-6241 (1978) (b) R. B. Calvert and J. R. Shapley, *J. Am. Chem. Soc.* **100**, 7726-7727 (1978)
- (34) (a) M. Brookhart and M. L. H. Green, *J. Organomet. Chem.* **250**, 395-408 (1983) (b) M. Brookhart, M. L. H. Green and L.-L. Wong, *Prog. Inorg. Chem.* **36**, 1-124 (1988)
- (35) (a) S. D. Ittel, F. A. Van-Catledge and J. P. Jesson *J. Am. Chem. Soc.* **101**, 6905-6911 (1979). (b) S. J. Holmes, D. N. Clark, H. W. Turner and R. R. Schrock, *J. Am. Chem. Soc.* **104**, 6322-6329 (1982) (c) C. P. Casey, P. J. Fagan and W. H. Miles, *J. Am. Chem. Soc.* **104**, 1134-1136 (1982) (d) G. M. Dawkins, M. Green, A. G. Orpen, and F. G. A. Stone, *J. Chem. Soc., Chem. Commun.* 41-43 (1982) (e) M. Cree-Uchiyama, J. R. Shapley and G. M. St. George, *J. Am. Chem. Soc.* **108**, 1316-1317 (1986). (f) T. K. Dutta, J. C. Vites, G. B. Jacobsen and T. P. Fehlner, *Organometallics* **6**, 842-847 (1987). (g) R. H. Crabtree, E. M. Holt, M. Lavin and S. M. Morehouse, *Inorg. Chem.* **24**, 1986-1992 (1985). (h) J. R. Blecke, J. J. Kotyk, D. A. Moore and D. J. Rauscher, *J. Am. Chem. Soc.* **109**, 417-423 (1987). (i) L. Carlucci, D. M. Proserpio and G. D'Alfonso, *Organometallics*, **18**, 2091-2098 (1999). (j) D. H. Hamilton and J. R. Shapley, *Organometallics* **19**, 761-769 (2000)
- (36) A. A. Gonzalez, K. Zhang and C. D. Hoff, *Inorg. Chem.* **28**, 4285-4290 (1989)
- (37) Reviews: (a) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.* **97**, 2879 (1997). Review of alkane complexes: C. Hall and R. N. Perutz, *Chem. Rev.*, **96**, 3125 (1996).
- (38) J. P. Collman, A. S. Chien, T. A. Eberspacher and J. I. Brauman, *J. Am. Chem. Soc.* **120**, 425-426 (1998)
- (39) (a) footnote 25b in D. F. Schafer II and P. T. Wolczanski, *J. Am. Chem. Soc.*, **120**, 4881 (1998). (b) P. E. M. Siegbahn, *J. Am. Chem. Soc.*, **118**, 1487 (1996)
- (40) T. J. Marks and J. R. Kolb, *Chem. Rev.* **77**, 263-293 (1977)
- (41) (a) R. H. Schultz, A. A. Bengali, M. J. Tauber, B. H. Weiller, E. P. Wasserman, K. R. Kyle, C. B. Moore and R. G. Bergman, *J. Am. Chem. Soc.* **116**, 7369-7377 (1994) (b) A. A. Bengali, R. H. Schultz, C. B. Moore and R. G. Bergman, *J. Am. Chem. Soc.* **116**, 9585-9589 (1994) (c) A. A. Bengali, B. A. Arndtsen, P. M. Burger, R. H. Schultz, B. H. Weiller, K. R. Kyle, C. B. Moore and R. G. Bergman, *R. G. Pure Appl. Chem.*, **67**, 281 (1995)
- (42) S. Geftakis and G. E. Ball, *J. Am. Chem. Soc.* **120**, 9953-9954 (1998)
- (43) R. Paur-Afshari, J. Lin and R. H. Schultz, *Organometallics* **19**, 1682 -1691 (2000)
- (44) Unpublished results; a portion of this work was summarized by Wolczanski(51)
- (45) V. I. Avdeev and G. M. Zhidomirov, *Catal. Today* **42**, 247 (1998)

- (46) J. M. Buchanan, J. M. Stryker and R. G. Bergman, *J. Am. Chem. Soc.* **108**, 1537-1550 (1986)
- (47) R. A. Periana and R. G. Bergman, *J. Am. Chem. Soc.* **108**, 7332-7346 (1986)
- (48) This situation is analogous to vapor/condensed phase equilibria for methane isotopes: J. Bigeleisen, C. B. Cragg and M. Jeevanandam, *J. Chem. Phys.*, **47**, 4335 (1967). For a general discussion of such effects see ref. 5.
- (49) B. R. Bender, *J. Am. Chem. Soc.* **117**, 11239-11246 (1995)
- (50)  $EIE(0.657) = MMI(3.244) \times \Pi EXC(0.823) \times \Pi ZPE(0.246)$
- (51) L. M. Slaughter, P. T. Wolczanski, T. R. Klinckman and T. R. Cundari, submitted to *J. Am. Chem. Soc.*
- (52) K. Yoshizawa, T. Ohta and T. Yamabe, *Bull. Chem. Soc. Jpn.* **71**, 1899-1909 (1998)
- (53) For the factor ZPE factor, the authors preferred the mathematically equivalent expression,  $\exp(\Delta\Delta ZPE/RT)$
- (54) D. M. Heinekey and W. J. Oldham, Jr., *J. Am. Chem. Soc.* **116**, 3137-3138 (1994)
- (55) N. F. Gol'dshleger, M. B. Tyabin, A. E. Shilov and A. A. Shteinmann, *Zh. Fiz. Khim.*, **43**, 2174 (1969). See ref 37a for a review of the important early work.
- (56) A. H. Janowicz and R. G. Bergman, *J. Am. Chem. Soc.* **105**, 3929-3939 (1983)
- (57) W. D. Jones and F. J. Feher, *J. Am. Chem. Soc.* **108**, 4814-4819 (1986)
- (58) M. J. Burk and R. H. Crabtree, *J. Am. Chem. Soc.* **109**, 8025-8032 (1987)
- (59) J. A. Maguire, W. T. Boese and A. S. Goldman, *J. Am. Chem. Soc.* **111**, 7088-7093 (1989)
- (60) P. J. Desrosiers, R. S. Shinomoto and T. C. Flood, *J. Am. Chem. Soc.* **108**, 7964-7970 (1986)
- (61) C. P. Schaller, J. B. Bonanno and P. T. Wolczanski, *J. Am. Chem. Soc.* **116**, 4133-4134 (1994)
- (62) E. Honegger, E. Heilbronner, A. Schmelzer and W. Jian-Qi, *Isr. J. Chem.* **22**, 3-10 (1982)
- (63) J. C. Nesheim and J. D. Lipscomb, *Biochemistry* **35**, 10240-10247 (1996)
- (64) A. M. Valentine, S. S. Stahl and S. J. Lippard, *J. Am. Chem. Soc.* **121**, 3876-3887 (1999)
- (65) (a) G. Brunton, D. Griller, L. R. C. Barclay and K. U. Ingold, *J. Am. Chem. Soc.* **98**, 6803-6811 (1976) (b) V. L. Vyazovkin and V. A. Tolkachev, *Chem. Phys.*, **195**, 313 (1995). (c) H. Tachikawa, N. Hokari, and H. Yoshida, *J. Phys. Chem.*, **97**, 10035 (1993). (d) T. Doba, K. U. Ingold, J. Luszytk,; W. Siebrand, and T. A. Wildman, *J. Chem. Phys.*, **98**, 2962 (1993). (e) T. Doba, K. U. Ingold, W. Siebrand and T. A. Wildman, *Faraday Discuss. Chem. Soc.*, **78**, 175 (1984). (f) A. Champion and F. Williams, *J. Am. Chem. Soc.*, **94**, 7633 (1972)
- (66) (a) A. Kohen and J. P. Klinman, *Acc. Chem. Res.* **31**, 397 (1998) (b) B. J. Bahnson,; J. P. Klinman, *Methods Enzym.*, **249**, 373 (1995)
- (67) Y. Kim and M. M. Kreevoy, *J. Am. Chem. Soc.* **114**, 7116-7123 (1992)
- (68) J. Espinosa-García, J. C. Corchado and D. G. Truhlar, *J. Am. Chem. Soc.* **119**, 9891-9896 (1997)
- (69) P. L. Watson, *J. Am. Chem. Soc.* **105**, 6491-6492 (1983)

- (70) (a) J. W. Bruno, G. M. Smith, T. J. Marks, C. K. Fair, A. J. Schultz and J. M. Williams, *J. Am. Chem. Soc.* **108**, 40-56 (1986) (b) C. M. Fendrick and T. J. Marks, *J. Am. Chem. Soc.* **108**, 425-437 (1986)
- (71) A. E. Sherry and B. B. Wayland, *J. Am. Chem. Soc.* **112**, 1259-1261 (1990)
- (72) (a) R. M. Bullock, C. E. L. Headford, K. M. Hennessy, S. E. Kegley and J. R. Norton, *J. Am. Chem. Soc.* **111**, 3897-3908 (1989) (b) R. M. Bullock, C. E. L. Headford, K. M. Hennessy, S. E. Kegley and J. R. Norton, *J. Am. Chem. Soc.* **111**, 3897-3908 (1989)
- (73) G. Parkin and J. E. Bercaw, *Organometallics* **8**, 1172-1179 (1989)
- (74) L. Abis, A. Sen and J. Halpern, *J. Am. Chem. Soc.* **100**, 2915-2916 (1978)
- (75) S. S. Stahl, J. A. Labinger and J. E. Bercaw, *J. Am. Chem. Soc.* **118**, 5961-5976 (1996)
- (76) R. A. Michelin, S. Faglia and P. Uguagliati, *Inorg. Chem.* **22**, 1831-1834 (1983)
- (77) M. Hackett, J. A. Ibers and G. M. Whitesides, *J. Am. Chem. Soc.* **110**, 1436-1448 (1988)
- (78) D. Milstein, *J. Am. Chem. Soc.* **104**, 5227-5228 (1982)
- (79) G. L. Gould and D. M. Heinekey, *J. Am. Chem. Soc.* **111**, 5502-5504 (1989)
- (80) C. Wang, J. W. Ziller and T. C. Flood, *J. Am. Chem. Soc.* **117**, 1647-1648 (1995)
- (81) D. D. Wick, K. A. Reynolds and W. D. Jones, *J. Am. Chem. Soc.* **121**, 3974-3983 (1999)
- (82) J. Evans, J. Schwartz and P. W. Urquhart, *J. Organomet. Chem.* **81**, C37-C39 (1974)
- (83) T. Ikariya and A. Yamamoto, *J. Organomet. Chem.* **120**, 257-284 (1976)
- (84) B. J. Burger, M. E. Thompson, W. D. Cotter and J. E. Bercaw, *J. Am. Chem. Soc.* **112**, 1566-1577 (1990)
- (85) T. J. McCarthy, R. G. Nuzzo and G. M. Whitesides, *J. Am. Chem. Soc.* **103**, 3396-3403 (1981)
- (86) (a) X.-L. Luo and R. H. Crabtree, *J. Am. Chem. Soc.* **112**, 4813-4821 (1990) (b) D. G. Hamilton, X.-L. Luo and R. H. Crabtree, *Inorg. Chem.* **28**, 3198-3203 (1989) (c) X.-L. Luo, G. K. Schulte, P. Demou and R. H. Crabtree, *Inorg. Chem.* **29**, 4268-4273 (1990) (d) X.-L. Luo, D. Michos and R. H. Crabtree, *Organometallics* **11**, 237-241 (1992) (e) X.-L. Luo, D. Baudry, P. Boydell, P. Charpin, M. Nierlich, M. Ephritikhine and R. H. Crabtree, *Inorg. Chem.* **29**, 1511-1517 (1990) (f) X.-L. Luo and R. H. Crabtree, *J. Chem. Soc., Dalton Trans.* 587-590 (1991)
- (87) R. H. Crabtree and A. Habib, *Inorg. Chem.* **25**, 3698-3699 (1986)
- (88) D. Michos, X.-L. Luo and R. H. Crabtree, *Inorg. Chem.* **31**, 4245-4250 (1992)
- (89) K. A. Earl, G. Jia, P. A. Maltby and R. H. Morris, *J. Am. Chem. Soc.* **113**, 3027-3039 (1991)
- (90) S. Sabo-Etienne and B. Chaudret, *Chem. Rev.* **98**, 2077-2091 (1998)
- (91) D. M. Heinekey, J. M. Millar, T. F. Koetzle, N. G. Payne and K. W. Zilm, *J. Am. Chem. Soc.* **112**, 909-919 (1990)
- (92) J. C. Peters, A. R. Johnson, A. L. Odom, P. W. Wanandi, W. M. Davis and C. C. Cummins, *J. Am. Chem. Soc.* **118**, 10175-10188 (1996)
- (93) D. M. Heinekey and M. van Roon, *J. Am. Chem. Soc.* **118**, 12134-12140 (1996)
- (94) K. Zhang, A. A. Gonzalez and C. D. Hoff, *J. Am. Chem. Soc.* **111**, 3627-3632 (1989)
- (95) W. J. Oldham, Jr., A. S. Hinkle and D. M. Heinekey, *J. Am. Chem. Soc.* **119**, 11028-11036 (1997)
- (96) R. A. Henderson and K. E. Oglieve, *J. Chem. Soc., Dalton Trans.* 3431-3439 (1993)

- (97) X.-L. Luo and R. H. Crabtree, *J. Am. Chem. Soc.* **112**, 6912-6918 (1990)
- (98) M. T. Haward, M. W. George, P. A. Hamley and M. Poliakoff, *J. Chem. Soc., Chem. Commun.* 1101-1103 (1991)
- (99) M. Bautista, K. A. Earl, R. H. Morris and A. Sella, *J. Am. Chem. Soc.* **109**, 3780-3782 (1987)
- (100) J. Halpern, *Science* **217**, 401-407 (1982)
- (101) C. R. Landis and J. Halpern, *J. Am. Chem. Soc.* **109**, 1746-1754 (1987)
- (102) (a) C. R. Landis and S. Feldgus, *Angew. Chem., Int. Ed. Engl.*, in press. (b) S. Feldgus and C. R. Landis, submitted for publication.
- (103) C. R. Landis and T. W. Brauch, *Inorg. Chim. Acta* **270**, 285-297 (1998)
- (104) J. M. Brown and D. Parker, *Organometallics* **1**, 950-956 (1982)
- (105) C. R. Landis, P. Hilfenhaus and S. Feldgus, *J. Am. Chem. Soc.* **121**, 8741-8754 (1999)
- (106) (a) M. J. Burk, *J. Am. Chem. Soc.* **113**, 8518-8519 (1991) (b) M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.* **115**, 10125-10138 (1993)
- (107) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.* **30**, 97-102 (1997)
- (108) W. Leitner, J. M. Brown and H. Brunner, *J. Am. Chem. Soc.* **115**, 152-159 (1993)
- (109) Z. Lin and T. J. Marks, *J. Am. Chem. Soc.* **109**, 7979-7985 (1987)
- (110) A. A. Vitale and J. San Filippo, Jr., *J. Am. Chem. Soc.* **104**, 7341-7343 (1982)
- (111) G. Parkin and J. E. Bercaw, *J. Chem. Soc., Chem. Commun.* 255-257 (1989)
- (112) J. Knight and M. J. Mays, *J. Chem. Soc. (A)* 711-714 (1970)
- (113) D. C. Pribich and E. Rosenberg, *Organometallics* **7**, 1741-1745 (1988)
- (114) C. P. Casey, K. P. Gable and D. M. Roddick, *Organometallics* **9**, 221-226 (1990)
- (115) T. H. Whitesides and J. P. Neilan, *J. Am. Chem. Soc.* **97**, 907-908 (1975)
- (116) S. N. Anderson, C. J. Cooksey, S. G. Holton and M. D. Johnson, *J. Am. Chem. Soc.* **102**, 2312-2318 (1980)
- (117) P. L. Motz, D. J. Sheeran and M. Orchin, *J. Organomet. Chem.* **383**, 201-212 (1990)
- (118) R. T. Edidin, J. M. Sullivan and J. R. Norton, *J. Am. Chem. Soc.* **109**, 3945-3953 (1987)
- (119) K.-T. Smith, M. Tilset, S. S. Kristjánssdóttir and J. R. Norton, *Inorg. Chem.* **34**, 6497-6504 (1995)
- (120) M. Y. Darensbourg and M. M. Ludvig, *Inorg. Chem.* **25**, 2894-2898 (1986)
- (121) R. L. Sweany and J. Halpern, *J. Am. Chem. Soc.* **99**, 8335-8337 (1977)
- (122) R. L. Sweany, D. S. Comberrel, M. F. Dombourian and N. A. Peters, *J. Organomet. Chem.* **216**, 57-63 (1981)
- (123) J. A. Roth, P. Wiseman and L. Ruzsala, *J. Organomet. Chem.* **240**, 271-275 (1983)
- (124) F. Ungváry and L. Markó, *Organometallics* **1**, 1120-1125 (1982)
- (125) R. M. Bullock, B. J. Rappoli, E. G. Samsel and A. L. Rheingold, *J. Chem. Soc., Chem. Commun.* 261-263 (1989)
- (126) R. M. Bullock and E. G. Samsel, *J. Am. Chem. Soc.* **112**, 6886-6898 (1990)
- (127) J. W. Connolly, *Organometallics* **3**, 1333-1337 (1984)
- (128) B. Wassink, M. J. Thomas, S. C. Wright, D. J. Gillis and M. C. Baird, *J. Am. Chem. Soc.* **109**, 1995-2002 (1987)
- (129) T. A. Shackleton and M. C. Baird, *Organometallics* **8**, 2225-2232 (1989)
- (130) J. Bigeleisen, *J. Chem. Phys.* **17**, 675-678 (1949)

- (131) L. Melander, *Acta Chem. Scand.* **25**, 3821-3826 (1971)
- (132) D. C. Eisenberg and J. R. Norton, *Isr. J. Chem.* **31**, 55-66 (1991)
- (133) E. N. Jacobsen and R. G. Bergman, *J. Am. Chem. Soc.* **107**, 2023-2032 (1985)
- (134) T. E. Nalesnik, J. H. Freudenberger and M. Orchin, *J. Mol. Catal.* **16**, 43-49 (1982)
- (135) M. A. Rodkin, G. P. Abramo, K. E. Darula, D. L. Ramage, B. P. Santora and J. R. Norton, *Organometallics* **18**, 1106-1109 (1999)
- (136) J. Bigeleisen, *Pure Appl. Chem.* **8**, 217-223 (1964)
- (137) A. Bakac and I. A. Guzei, *Inorg. Chem.* **39**, 736-740 (2000)
- (138) A. Bakac, *J. Am. Chem. Soc.* **119**, 10726-10731 (1997)
- (139) K. A. Gardner and J. M. Mayer, *Science* **269**, 1849-1851 (1995)
- (140) (a) A. A. Gridnev, S. D. Ittel, B. B. Wayland and M. Fryd, *Organometallics* **15**, 5116-5126 (1996) (b) A. A. Gridnev, S. D. Ittel, M. Fryd and B. B. Wayland, *Organometallics* **15**, 222-235 (1996)
- (141) K. B. Capps, A. Bauer, K. Sukcharoenphon and C. D. Hoff, *Inorg. Chem.* **38**, 6206-6211 (1999)
- (142) M. Y. Darensbourg and C. E. Ash, *Adv. Organomet. Chem.* **27**, 1-50 (1987)
- (143) S. C. Kao, C. T. Spillett, C. Ash, R. Lusk, Y. K. Park and M. Y. Darensbourg, *Organometallics* **4**, 83-91 (1985)
- (144) P. L. Gaus, S. C. Kao, M. Y. Darensbourg and L. W. Arndt, *J. Am. Chem. Soc.* **106**, 4752-4755 (1984)
- (145) T.-Y. Cheng, B. S. Brunschwig and R. M. Bullock, *J. Am. Chem. Soc.* **120**, 13121-13137 (1998)
- (146) T.-Y. Cheng and R. M. Bullock, *J. Am. Chem. Soc.* **121**, 3150-3155 (1999)
- (147) R. A. More O'Ferrall, *J. Chem. Soc. (B)* 785-790 (1970)
- (148) J. Halpern, T. Okamoto and A. Zakhariev, *J. Mol. Catal.* **2**, 65-68 (1976)
- (149) N. M. Doherty and J. E. Bercaw, *J. Am. Chem. Soc.* **107**, 2670-2682 (1985)
- (150) K. G. Moloy and T. J. Marks, *J. Am. Chem. Soc.* **106**, 7051-7064 (1984)
- (151) B. P. Sullivan and T. J. Meyer, *Organometallics* **5**, 1500-1502 (1986)
- (152) J. H. Merrifield and J. A. Gladysz, *Organometallics* **2**, 782-784 (1983)
- (153) E. V. Anslyn, M. Green, G. Nicola and E. Rosenberg, *Organometallics* **10**, 2600-2605 (1991)
- (154) E. Rosenberg, *Polyhedron* **8**, 383-405 (1989)
- (155) M. J. Hostetler and R. G. Bergman, *J. Am. Chem. Soc.* **112**, 8621-8623 (1990)
- (156) M. J. Hostetler, M. D. Butts and R. G. Bergman, *J. Am. Chem. Soc.* **115**, 2743-2752 (1993)
- (157) F. R. Hartley, *Chem. Rev.* **73**, 163-190 (1973)
- (158) (a) P. O. Stoutland and R. G. Bergman, *J. Am. Chem. Soc.*, **110**, 5732-5744 (1988). (b) V. Schurig, *Angew. Chem. Int. Ed. Engl.*, **15**, 304-305 (1976). (c) V. Schurig, *Chem-Zeitung*, **101**, 173 (1977)
- (159) A. Streitwieser, Jr., R. H. Jagow, R. C. Fehey and S. Suzuki, *J. Am. Chem. Soc.* **80**, 2326 (1958)
- (160) E. A. Halevi, *Prog. Phys. Org. Chem.* **1**, 109 (1963)

- (161) (a) R. J. Cvetanovic, F. J. Duncan and W. E. Falconer, *Can. J. Chem.* **41**, 2095-2097 (1963) (b) R. J. Cvetanovic, F. J. Duncan, W. E. Falconer and R. S. Irwin, *J. Am. Chem. Soc.* **87**, 1827-1832 (1965) (c) J. G. Atkinson, A. A. Russell and R. S. Stuart, *Can. J. Chem.* **45**, 1963-1969 (1967) (d) S. P. Wasic and W. Tsang, *J. Phys. Chem.* **74**, 2970 (1970)
- (162) K. B. Hong, K.-H. Jung and S. H. Kang, *Bull. Kor. Chem. Soc.* **3**, 79-81 (1982)
- (163) D. Y. Youn, K. B. Hong, K.-H. Jung and D. Kim, *J. Chromatography* **607**, 69-77 (1992)
- (164) (a) O. P. Strausz, I. Safarik, W. B. O'Callaghan and H. E. Gunning, *J. Am. Chem. Soc.* **94**, 1828-1834 (1972) (b) O. P. Strausz and I. Safarik, *J. Phys. Chem.* **76**, 3613 (1972)
- (165) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry, 3rd Ed.*; Harper and Row: New York, 1987; pp. 238-240. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Third Ed. Part A: Structure and Mechanism*; Plenum Press: New York; 1990; pp 216-220. (c) Gajewski, J. J. *Isotopes in Organic Chemistry, Vol. 7*; Buncl, E.; and Lee, E., Eds.; Elsevier: New York, 1987, Chapter 3, p. 121.
- (166) B. R. Bender, D. L. Ramage, J. R. Norton, D. C. Wiser and A. K. Rappé, *J. Am. Chem. Soc.* **119**, 5628-5637 (1997)
- (167) D. Schröder, R. Wesendrup, R. H. Hertwig, T. Dargel, H. Grauel, W. Koch, B. R. Bender and H. Schwarz, *Organometallics* **19**, 2608-2615 (2000)
- (168) R. H. Hertwig, W. Koch, D. Schröder, H. Schwarz, J. Hruák and P. Schwerdtfeger, *J. Phys. Chem.* **100**, 12253 -12260 (1996)
- (169) R. H. Grubbs and G. W. Coates, *Acc. Chem. Res.* **29**, 85-93 (1996)
- (170) A. K. Rappé, W. M. Skiff and C. J. Casewit, *Chem. Rev.* **100**, 1435-1456 (2000)
- (171) E. J. Arlman and P. Cossee, *J. Catal.* **3**, 99-104 (1964)
- (172) K. J. Ivin, J. J. Rooney, C. D. Stewart, M. L. H. Green and R. Mahtab, *J. Chem. Soc., Chem. Commun.* 604-606 (1978)
- (173) E. A. Grigoryan, F. S. Drachkovskii and A. Shilov, *Polym. Sci. USSR (Engl Trans)* **7**, 145 (1965)
- (174) J. Soto, M. L. Steigerwald and R. H. Grubbs, *J. Am. Chem. Soc.* **104**, 4479-4480 (1982)
- (175) L. Clawson, J. Soto, S. L. Buchwald, M. L. Steigerwald and R. H. Grubbs, *J. Am. Chem. Soc.* **107**, 3377-3378 (1985)
- (176) W. E. Piers and J. E. Bercaw, *J. Am. Chem. Soc.* **112**, 9406-9407 (1990)
- (177) (a) H. Krauledat and H.-H. Brintzinger, *Angew. Chem., Int. Ed. Engl.* **29**, 1412-1413 (1990) (b) M.-H. Prosenc, C. Janiak and H.-H. Brintzinger, *Organometallics* **11**, 4036-4041 (1992)
- (178) N. S. Barta, B. A. Kirk and J. R. Stille, *J. Am. Chem. Soc.* **116**, 8912-8919 (1994)
- (179) J. H. Gilchrist and J. E. Bercaw, *J. Am. Chem. Soc.* **118**, 12021-12028 (1996)
- (180) (a) Wiser, D. C. Ph. D. Dissertation, Colorado State University, 1990. (b) D. C. Wiser and A. K. Rappé, *Polym. Mater. Sci. Eng.* **74**, 423 (1996)
- (181) D. A. Singleton and M. J. Szymanski, *J. Am. Chem. Soc.* **121**, 9455-9456 (1999)
- (182) S. D. Ittel, L. K. Johnson and M. Brookhart, *Chem. Rev.* **100**, 1169-1203 (2000)
- (183) M. J. Tanner, M. Brookhart and J. M. DeSimone, *J. Am. Chem. Soc.* **119**, 7617-7618 (1997)

- (184) H. C. Kolb and K. B. Sharpless in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, Vol. 2*; Ed. M. Beller and C. Bolm; Wiley-VCH Publishers, Weinheim, 1998; pp 219-242, Chapter 2.5
- (185) E. N. Jacobsen in *Catalytic Asymmetric Synthesis*; ed. I. Ojima; VCH, New York, 1993; Chapter 4.2
- (186) R. A. Johnson and K. B. Sharpless in *Catalytic Asymmetric Synthesis*; ed. I. Ojima; VCH, New York, 1993; Chapter 4.1.
- (187) H. C. Kolb and K. B. Sharpless in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, Vol. 2*; Ed. M. Beller and C. Bolm; Wiley-VCH Publishers, Weinheim, 1998; pp 243-260, Chapter 2.6
- (188) (a) Z. Li, K. R. Conser and E. N. Jacobsen, *J. Am. Chem. Soc.* **115**, 5326-5327 (1993) (b) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson and D. M. Barnes, *J. Am. Chem. Soc.* **115**, 5328-5329 (1993)
- (189) M. P. Doyle in *Catalytic Asymmetric Synthesis*; ed. I. Ojima; VCH, New York, 1993; Chapter 3
- (190) K. B. Sharpless, A. Y. Teranishi and J.-E. Bäckvall, *J. Am. Chem. Soc.* **99**, 3120 (1977)
- (191) E. J. Corey, M. C. Noe and M. J. Grogan, *Tetrahedron Lett.* **37**, 4899-4902 (1996)
- (192) D. A. Singleton and A. A. Thomas, *J. Am. Chem. Soc.* **117**, 9357-9358 (1995)
- (193) A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner and A. A. Thomas, *J. Am. Chem. Soc.* **119**, 9907-9908 (1997)
- (194) M. Saunders, K. E. Laidig and M. Wolfsberg, *J. Am. Chem. Soc.* **111**, 8989-8994 (1989)
- (195) (a) U. Pidun, C. Boehme and G. Frenking, *Angew. Chem., Int. Ed. Engl.* **35**, 2817-2820 (1996) (b) S. Dapprich, G. Ujaque, F. Maserras, A. Lledos, D. G. Musaev and K. Morokuma, *J. Am. Chem. Soc.* **118**, 11660-11661 (1996) (c) M. Torrent, L. Deng, M. Duran, M. Sola and T. Ziegler, *Organometallics* **16**, 13-19 (1997)
- (196) E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.* **118**, 319-329 (1996)
- (197) T. Göbel and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.* **32**, 1329 (1993)
- (198) D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H.-L. Kwong, D. V. McGrath, A. E. Rubin, P.-O. Norrby, K. P. Gable and K. B. Sharpless, *J. Am. Chem. Soc.* **119**, 1840-1858 (1997)
- (199) K. N. Houk and T. Strassner, *J. Org. Chem.* **64**, 800-802 (1999)
- (200) K. P. Gable and T. N. Phan, *J. Am. Chem. Soc.* **116**, 833-839 (1994)
- (201) W. A. Herrmann, D. Marz, E. Herdtweck, A. Schaefer, W. Wagner and H.-J. Kneuper, *Angew. Chem., Int. Ed. Engl.* **26**, 462-464 (1987)
- (202) M. A. Pietsch, T. V. Russo, R. B. Murphy, R. L. Martin and A. K. Rappé, *Organometallics* **17**, 2716-2719 (1998)
- (203) K. P. Gable, T. N. Phan and D. Griffin, *Org. Mass Spectrom.* **28**, 397-399 (1993)
- (204) M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Gueler, T. Ishida and E. N. Jacobsen, *J. Am. Chem. Soc.* **120**, 948-954 (1998)
- (205) M. G. Finn and K. B. Sharpless, *J. Am. Chem. Soc.* **113**, 113-126 (1991)
- (206) K. R. Korzekwa, J. R. Gillette and W. F. Trager, *Drug Metabol. Rev.* **27**, 45-59 (1995)
- (207) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.* **97**, 2879-2932 (1997)

- (208) (a) C.-J. Liu, W.-Y. Yu, C.-M. Che and C.-H. Yeung, *J. Org. Chem.* **64**, 7365-7374 (1999) (b) W.-H. Fung, W.-Y. Yu and C.-M. Che, *J. Org. Chem.* **63**, 7715-7726 (1998)
- (209) S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung and C.-M. Che, *J. Am. Chem. Soc.* **121**, 9120-9132 (1999)
- (210) J. E. Bäckvall, B. Åkermark and S. O. Ljunggren, *J. Am. Chem. Soc.* **101**, 2411-2416 (1979)
- (211) O. Hamed, C. Thompson and P. M. Henry, *J. Org. Chem.* **62**, 7082-7083 (1997)
- (212) C. P. Casey and C. R. Cyr, *J. Am. Chem. Soc.* **95**, 2240-2247 (1973)
- (213) C. P. Casey and L. M. Petrovich, *J. Am. Chem. Soc.* **117**, 6007-6014 (1995)
- (214) R. Lazzaroni, G. Uccello-Barretta and M. Benetti, *Organometallics* **8**, 2323-2327 (1989)
- (215) R. Lazzaroni, G. Uccello-Barretta, S. Scamuzzi, R. Settambolo and A. Caiazzo, *Organometallics* **15**, 4657-4659 (1996)
- (216) L. Roecker and T. J. Meyer, *J. Am. Chem. Soc.* **109**, 746-754 (1987)
- (217) J. Gilbert, L. Roecker and T. J. Meyer, *Inorg. Chem.* **26**, 1126-1132 (1987)
- (218) R. A. Binstead, M. A. McGuire, A. Dovletoglou, W. K. Seok, L. Roecker and T. J. Meyer, *J. Am. Chem. Soc.* **114**, 173-186 (1992)