

Kinetic Isotope Effects in Organic Chemistry

Rob Knowles
MacMillan Group Meeting
Sept. 14, 2005

Key References

Wiberg, K.B. *Chem. Rev.* **1955**, *55*, 713

Westheimer, F.H. *Chem. Rev.* **1961**, *61*, 295

Saunders, W.H., Melander, L. *Reaction Rates of Isotopic Molecules*, Wiley, New York, 1981

Dougherty, D.A., Anslyn, E.V. *Modern Physical Organic Chemistry*, University, Sausalito, 2005

Lowry, T.H., Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, Harper and Row, New York, 1987

Entering the Deuterated Age

1929 Giauque and Johnston discover heavy oxygen isotopes ^{17}O and ^{18}O . Based upon the accurately measured molecular mass of water this result leads to speculation that hydrogen must also have a heavy isotope.

1932 Urey and coworkers reported the first spectroscopic evidence for a heavy isotope of hydrogen. Shortly thereafter Urey reported the enrichment of heavy hydrogen in water upon electrolysis.

1933 Gilbert Lewis and coworkers isolated a pure sample of heavy water

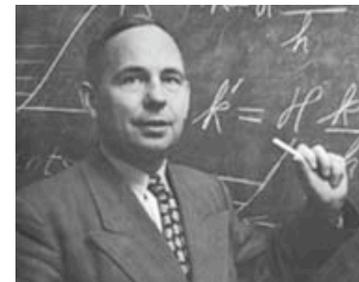
1933 Eyring and Polanyi independently and correctly postulate that protonated and deuterated compounds should react at different rates based upon differences in zero-point energies.

1934 Interest and the availability of deuterated compounds lead to an explosion of research into isotopically labelled molecules. More than 200 papers dealing with the preparation and uses of deuterated compounds were published. Urey is awarded the Nobel Prize for his work on deuterium.



Urey

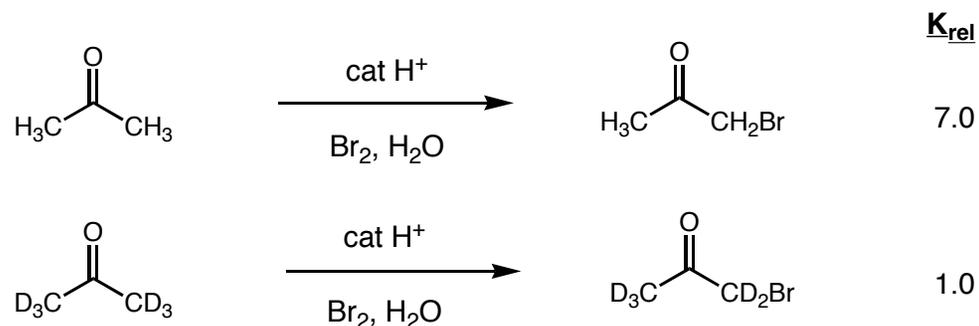
<u>isotope</u>	<u>natural abundance</u>
^2H	0.0015%
^3H	0.0001%
^{13}C	1.108%
^{15}N	0.365%
^{17}O	0.037%



Eyring

What Are Kinetic Isotope Effects?

- A kinetic isotope effect is a mechanistic phenomenon wherein isotopically substituted molecules react at different rates.



Key Assumptions

- Isotopic substitution does not affect the potential energy surface of the reaction or the energies of the electronic states.
- Only mass dependent properties are affected, most importantly vibrational frequencies.

- Interpretation of the rate differences provides information on the nature of the rate-determining step.



- There are several different classifications for KIE's

Primary isotope effect: Occurs when labelled bond is made or broken in the rate determining step

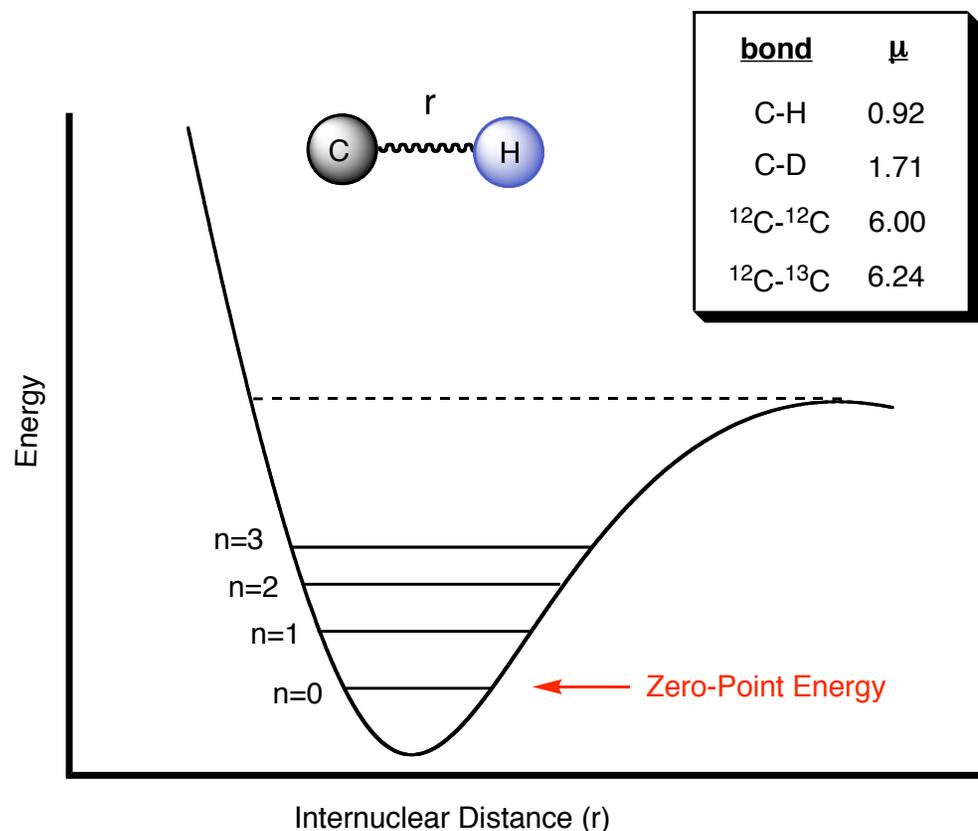
Secondary isotope effect: Occurs when labelled bond is not made or broken in the rate determining step

Normal isotope effect: Occurs when K_H/K_D is greater than 1

Inverse isotope effect: Occurs when K_H/K_D is less than 1

Quick Review of Vibrational Spectroscopy

- All bonds have quantized vibrational energy levels
- The vibrational energies (E_n) are dependent on the frequency of the bond stretch (ν), which is in turn dependent on the reduced mass of the two connected atoms (μ).



Three Key Equations

$$\nu = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

$$\mu = \frac{m_1 \cdot m_2}{m_1 + m_2}$$

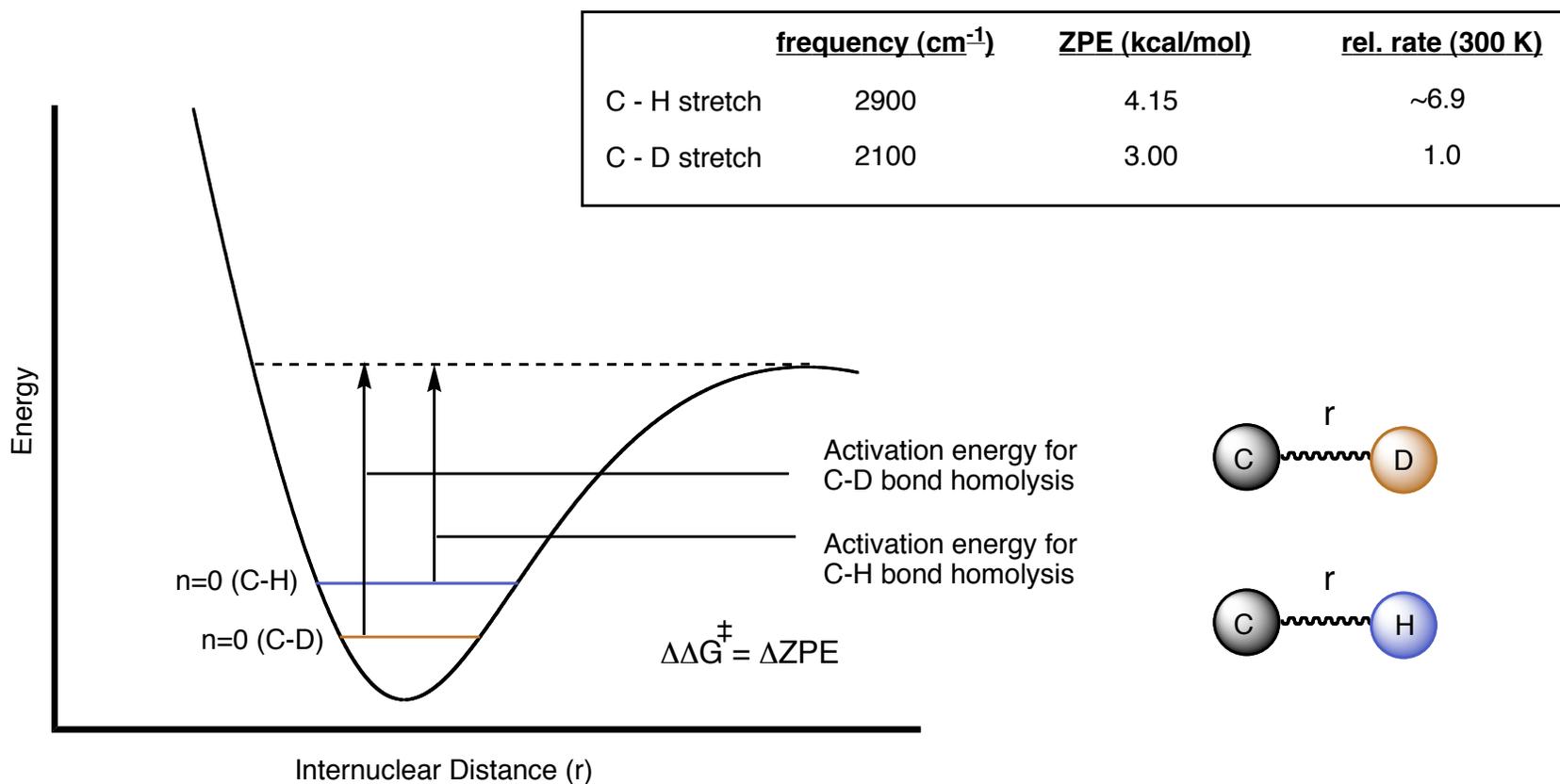
$$E_n = (n + 1) h\nu$$

99.9 % of C-H bonds are in the ground vibrational state ($n=0$) at room temperature

- The energy the molecule possesses in the ground vibrational state is known as the zero-point energy, and it forms the basis for the reactivity differences between isotomers.

Physical Origins of Primary Kinetic Isotope Effects

- Simplest case to treat is the homolytic cleavage of C - H/D bond where the bond is considered to be fully broken at the transition state. Reaction progress followed by observing the C - H/D bond stretch.

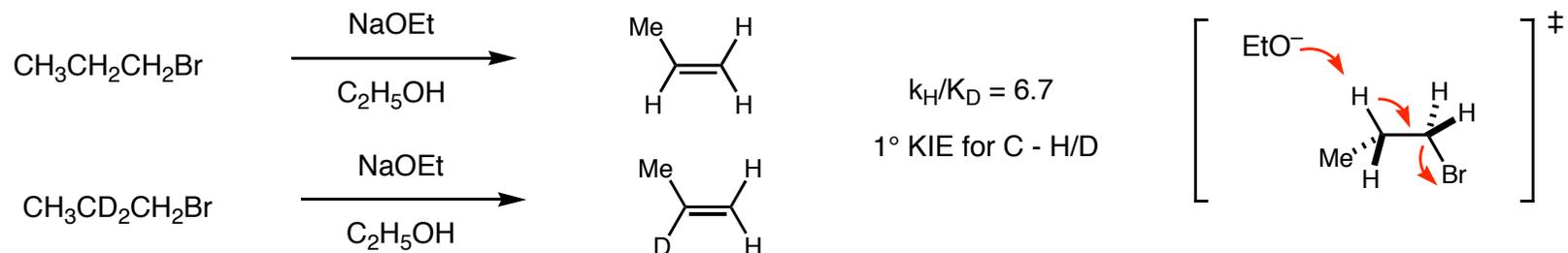


- As the C - H/D bond breaks at the transition state the stretch becomes a translation. As a result there is no new stretch in the TS that corresponds to the stretch of ground state bond. For this mechanism, the isotope effect is entirely controlled by the difference in the ground state ZPE's.

Using Primary KIE's to Distinguish Between Reaction Mechanisms

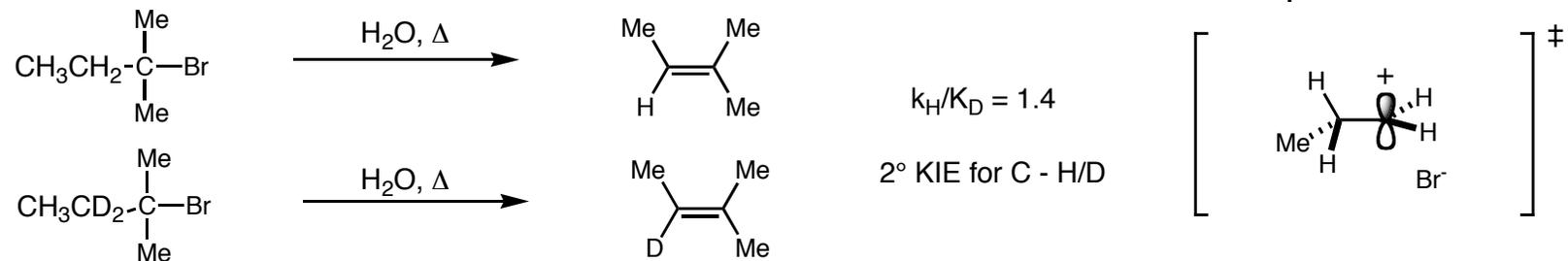
- KIE's give useful information about the rate determining step of the reaction mechanism

Case 1



- This KIE is consistent with an E₂ elimination in which the C - H/D bond is broken in the rate determining step.

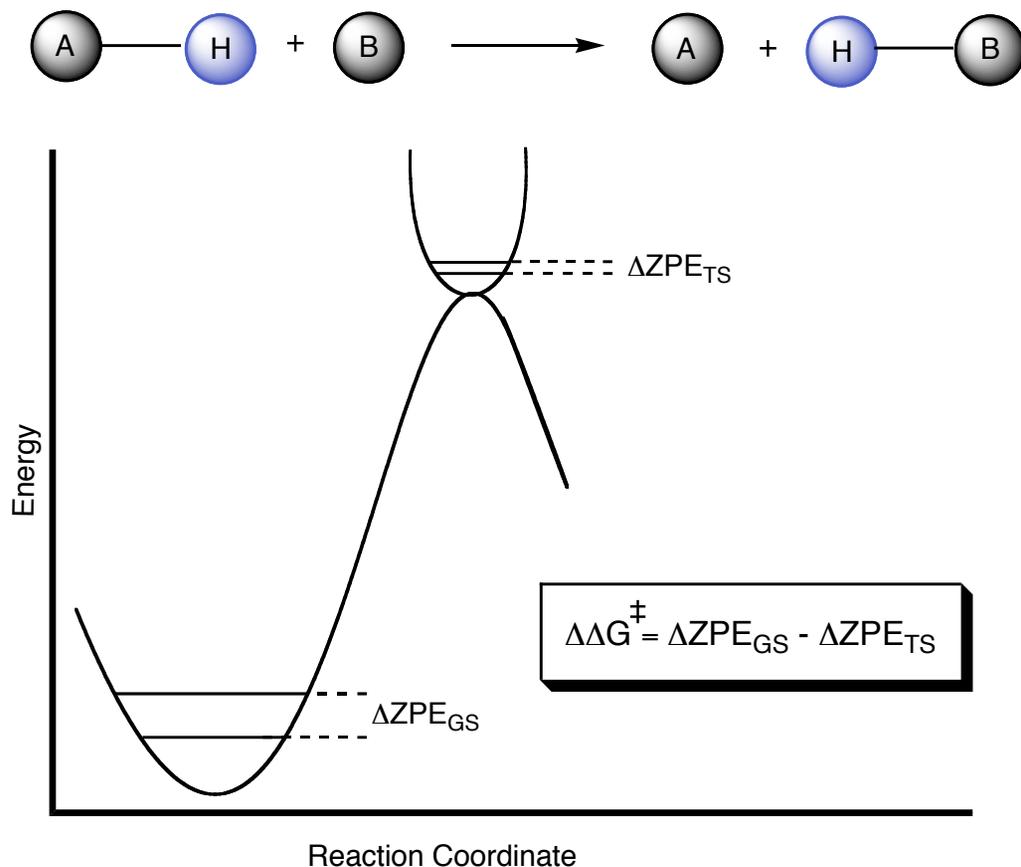
Case 2



- This KIE is consistent with an E₁ solvolysis in which the C - H/D bond is not broken in the rate determining step.

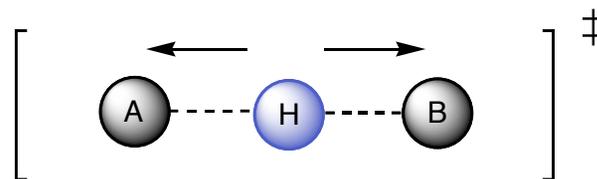
A More Realistic View of Primary Kinetic Isotope Effects

- In most reactions the bond of interest is not fully broken at the TS. Rather, it is only partially broken and thus the TS structure has its own ZPE's. Consider the deprotonation of A-H by B.



Important Considerations

- The A-H stretch in the SM defines the rxn coord. in the TS and does not contribute energetically to the primary KIE.
- Bending modes have much lower force constants than stretches and consequently contribute very little to the overall primary KIE.
- The proton is shared between A and B in the transition state, creating a new symmetric stretch that has no analogue in the SM.

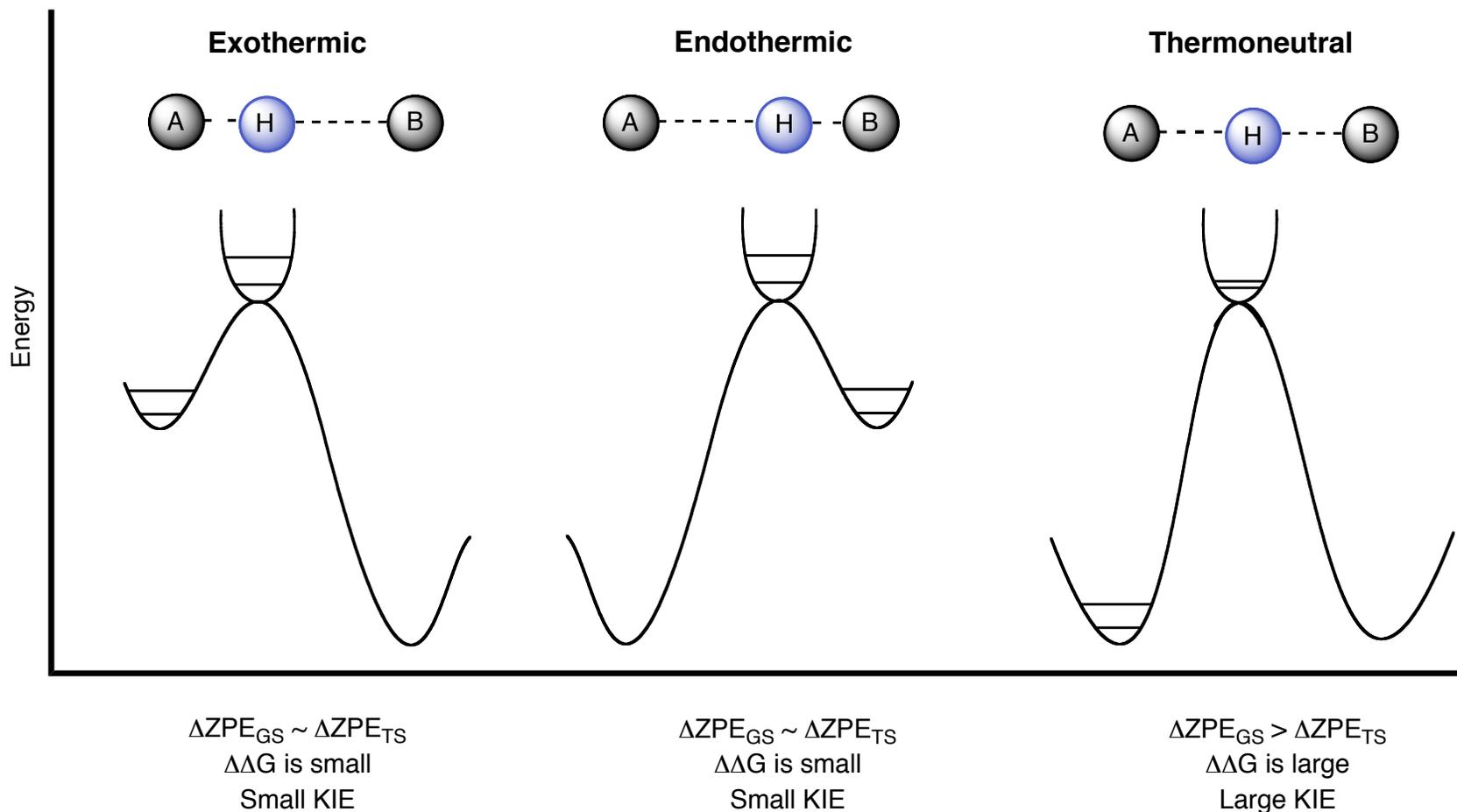


This new vibrational mode has a strong force constant and is the major energetic contributor to the KIE

- The ZPE changes between the ground state and the transition state because the force constant of the bond is changing. The difference in energy between the ΔZPE 's in the ground state and the transition state determine the magnitude of the kinetic isotope effect.

Hammond Postulate and Isotope Effects

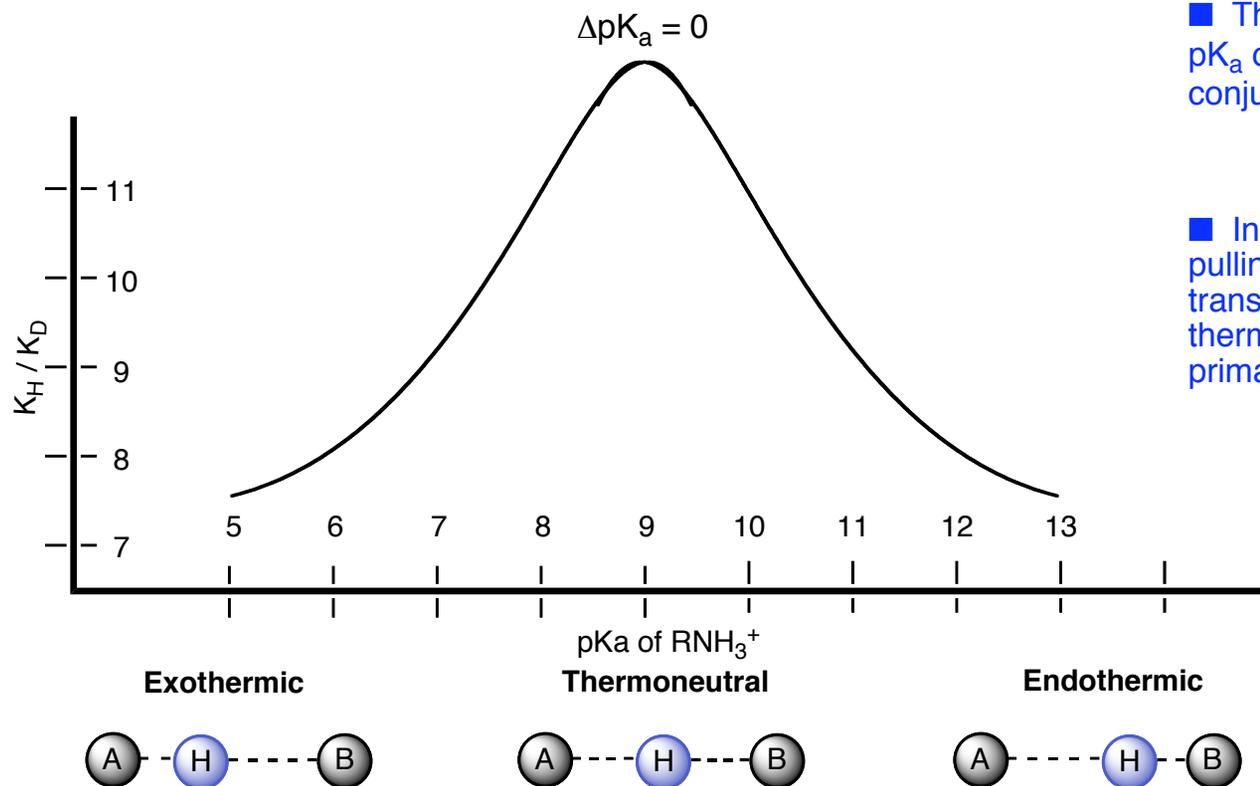
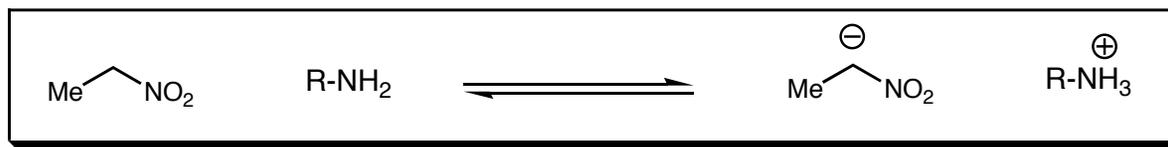
■ The Hammond postulate states the TS structure most resembles the molecule that it is closest in energy to. Therefore, the position of the TS on the reaction coordinate, and thus the KIE, will depend on the thermodynamic difference in energy between the starting material and the product.



■ In the exothermic and endothermic reactions, the TS is similar to the SM and product respectively. Thus ΔZPE_{TS} is very similar to ΔZPE_{GS} , yielding a small KIE. In the thermoneutral TS the symmetrical stretch is independent of the mass of the isotope, yielding very small values of ΔZPE_{TS} which in turn yield very large KIE's.

Kinetic Isotope Effects in Acid/Base Chemistry

■ This concept was nicely demonstrated by Bruice and coworkers in their work on the KIE's of nitroethane deprotonation by a variety of amine bases.



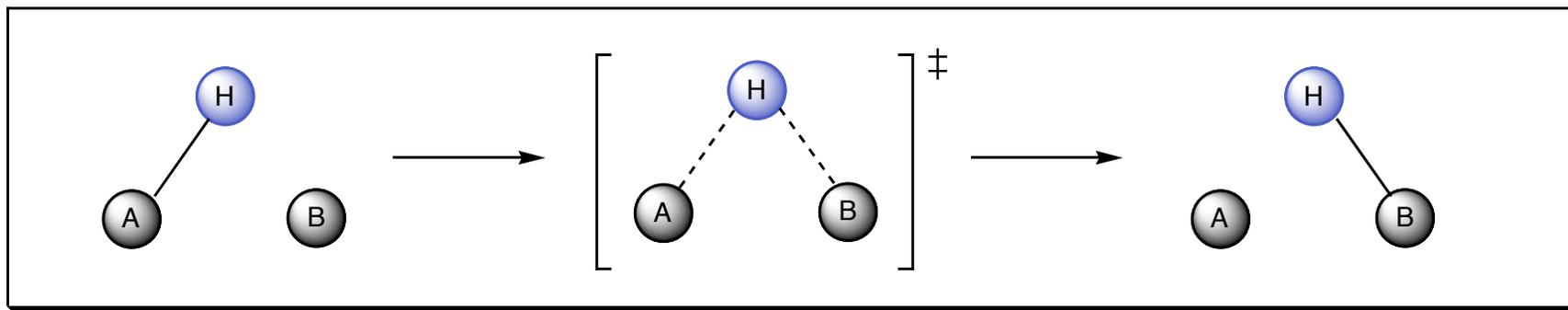
■ The greatest KIE is seen when the pK_a of the nitroethane equals that of the conjugate acid of the amine.

■ In this scenario, both reactants are pulling equally on the proton in the transition state, and the reaction is thermoneutral, giving a very large primary KIE.

KIE's reflect the symmetry of the TS structure, and how it varies with reaction conditions

Primary KIE's and Non-Linear Transition States

■ All the analysis so far has assumed that the TS is essentially linear, but very often rxns involving proton transfers do not have linear transition states.

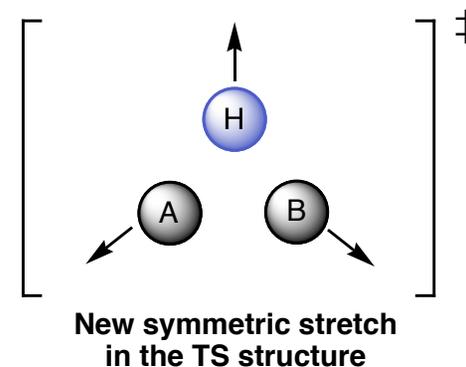
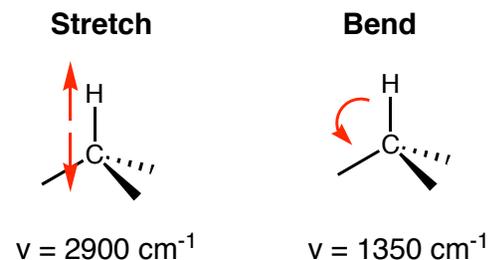


■ In general primary KIE's for nonlinear TS's are lower than those for more linear TS's for two reasons:

1. In going to a TS with bent bonds, the bending vibrational modes become more important. However, bending modes are much lower energy than stretching modes in linear TS's and thus the KIE's associated with bending are diminished.

2. There is a new symmetrical stretch in TS structure in which the hydrogen atom has a significant range of motion. This makes the frequency of this stretch highly mass dependent.

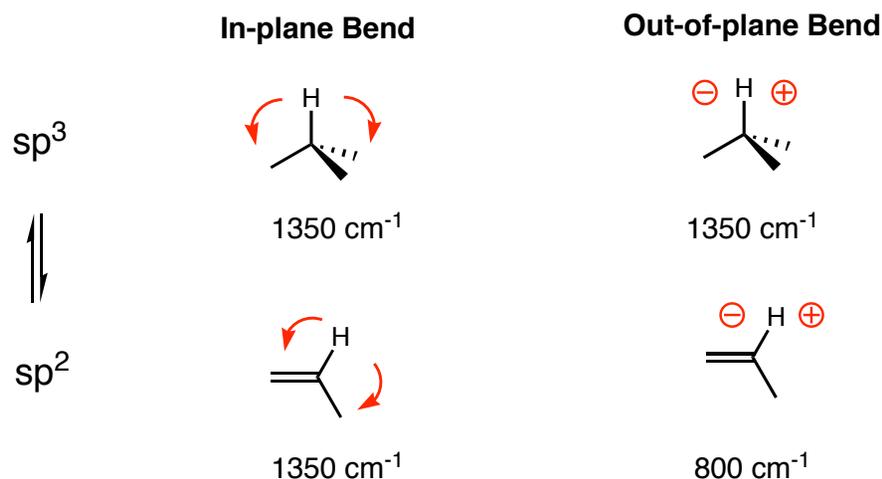
■ Generally primary KIE's for proton transfers occurring by non-linear TS's are on the order of 2.5 - 3.5.



Secondary Deuterium Kinetic Isotope Effects

- Secondary KIE arise from rate differences caused by isotopically labelled bonds that are not made or broken in the rate determining step. SDKIE can be normal or inverse.
- Generally, for deuterium these effects come from changes in hybridization and hyperconjugation.

Streitwieser's Rehybridization Model



1. The energy difference between the out-of-plane bending modes gives rise to secondary isotope effects.

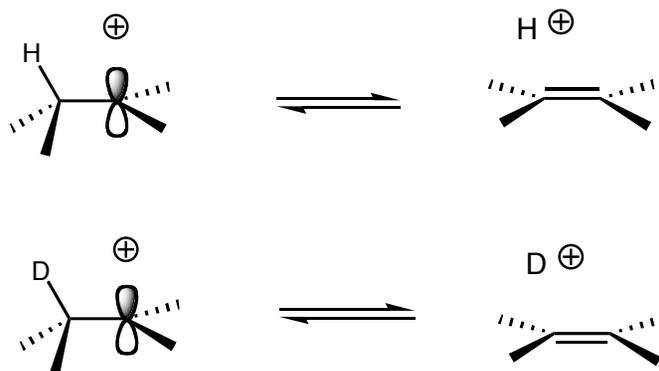
2. Since bending modes are relatively low-energy, the associated 2° KIE is small, with a theoretical maximum of ~1.4

Rule of Thumb		Expected SDKIE
sp ³ to sp ²	The out-of-plane bend weakens as the rxn approaches the TS, making ΔZPE_{TS} is less than ΔZPE_{GS} , giving a normal KIE	1.1 - 1.2
sp ² to sp ³	The out-of-plane bend strengthens as the rxn approaches the TS, making ΔZPE_{TS} greater than ΔZPE_{GS} , giving an inverse KIE	0.8 - 0.9

Hyperconjugation and Secondary Deuterium Kinetic Isotope Effects

- The ability of a β -hydrogen/deuterium to stabilize an adjacent carbocation can also effect the SDKIE
- Generally, these effects are normal and can be just as large as the KIE's arising from rehybridization.

Hyperconjugation

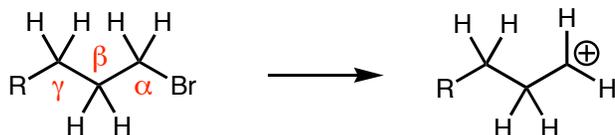


1. Hyperconjugation weakens the C - H/D bond and lowers its associated vibrational frequency

2. Since the deuterium labelled molecule has a stronger bond to carbon, it participates in the hyperconjugation to a lesser extent than the protonated molecule, giving a small normal KIE

Expected $K_H / K_D = \sim 1.1 - 1.2$

Systematic Investigation of SDKIE



isotopic substitution

α

K_H / K_D

1.1 - 1.2

β

1.15 - 1.25

γ

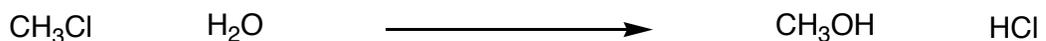
0.92 - 1.02

SDKIE can probe how sensitive reactions are to changes remote to actual bond making and bond breaking.

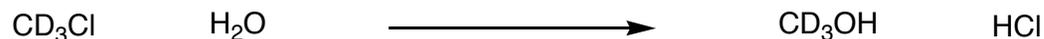
Secondary Considerations in Secondary Deuterium Kinetic Isotope Effects

- Differences in the steric demand of C - H/D bonds can influence rates

S_N2 Reactions

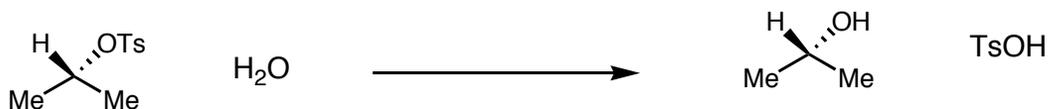


$$K_{\text{H}}/K_{\text{D}} = 0.97$$



- The C-D bond is shorter relative to the C-H bond, allowing the nucleophile a less hindered approach to the electrophile

S_N1 Reactions



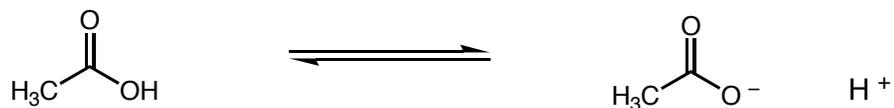
$$K_{\text{H}}/K_{\text{D}} = 1.13$$



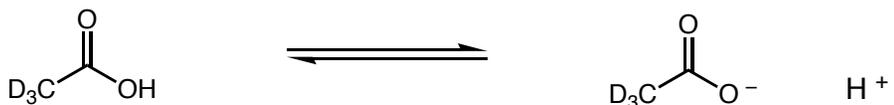
- The normal KIE found for this reaction implies that it is not going by an S_N2 mechanism. The KIE here mainly arises from changes in hybridization

- Inductive effects are also important to consider

Autoionization of carboxylic acids



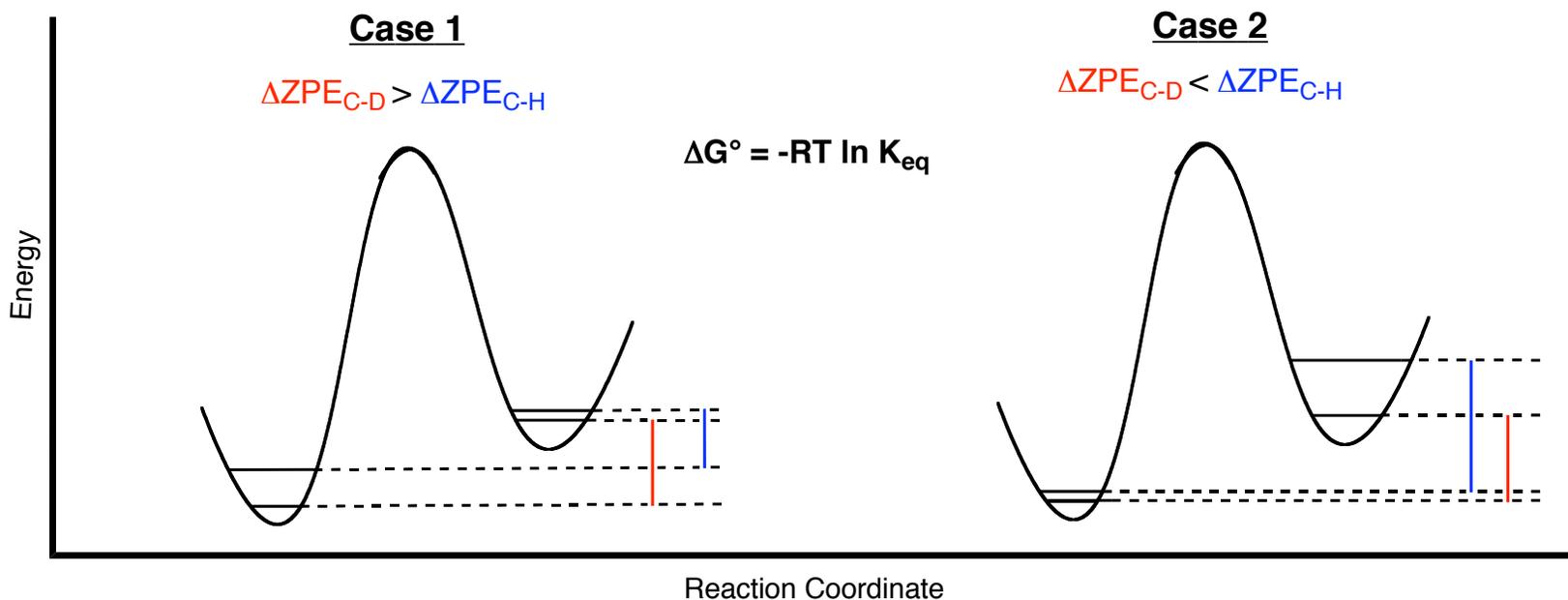
$$K_{\text{H}}/K_{\text{D}} = 1.06$$



- Hydrogen is slightly more electronegative than deuterium is, leading to an increase in acidity for the protonated isotopomer

Equilibrium Isotope Effects

- Isotopic substitution can also change the position of an equilibrium (thermodynamic isotope effect)
- Two cases to consider



Case 1

The difference in ZPE for the deuterated molecules is larger than that for the hydrogenated ones.

Equilibrium will lie further toward the product for the hydrogenated compounds than the deuterated ones.

Case 2

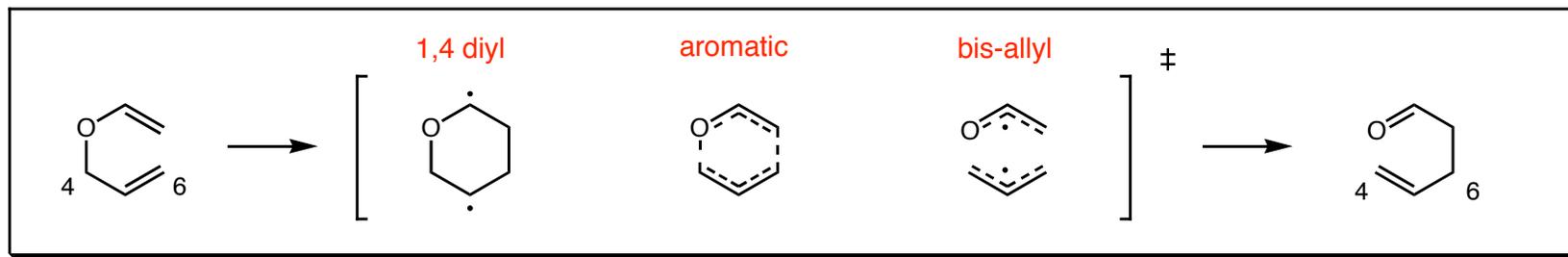
The difference in ZPE for the hydrogenated molecules is larger than that for the deuterated ones.

Equilibrium will lie further toward the product for the deuterated compounds than the hydrogenated ones.

Deuterium prefers the bond with the larger force constant

The Heart of the Beast

- The transition state structures for 3,3 sigmatropic rearrangements were debated for decades.
- For the aliphatic Claisen rearrangement, three limiting possibilities exist.



Gajewski and Conrad devised a set of experiments to determine how isotopic substitution effects the rate of the Claisen

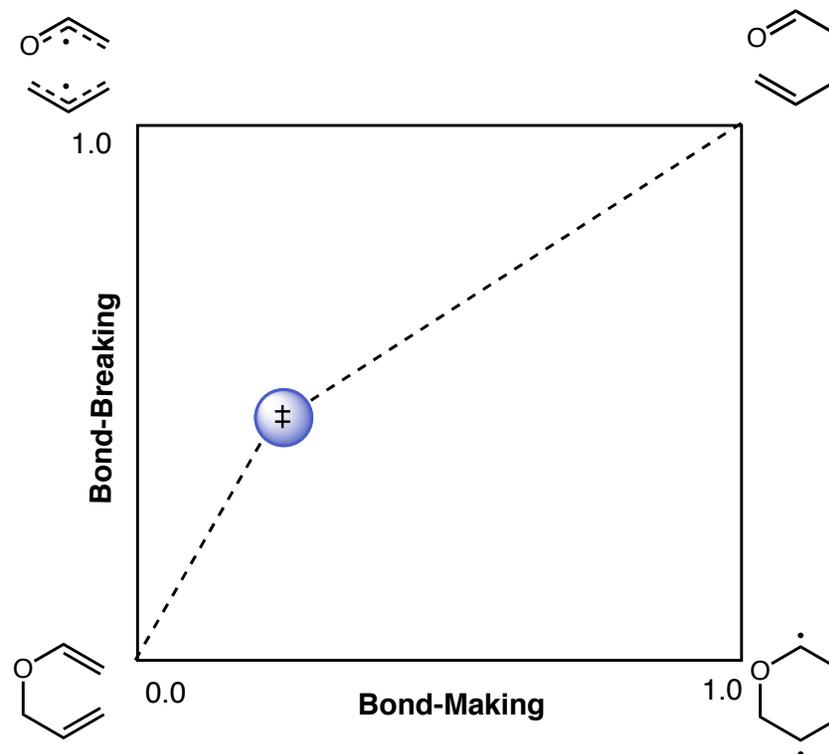
Key Assumptions

1. Substitution at C(4) will affect the rate of bond-breaking
2. Substitution at C(6) will affect the rate of bond-making
3. EIE's represent the largest possible 2° KIE

$$\text{BBKIE} = \frac{\text{KIE (C4)} - 1}{\text{EIE (C4)} - 1} = \frac{1.092 - 1.0}{1.27 - 1.0} = 0.33$$

$$\text{BMKIE} = \frac{\text{KIE (C6)} - 1}{\text{EIE (C6)} - 1} = \frac{0.976 - 1.0}{0.84 - 1.0} = 0.15$$

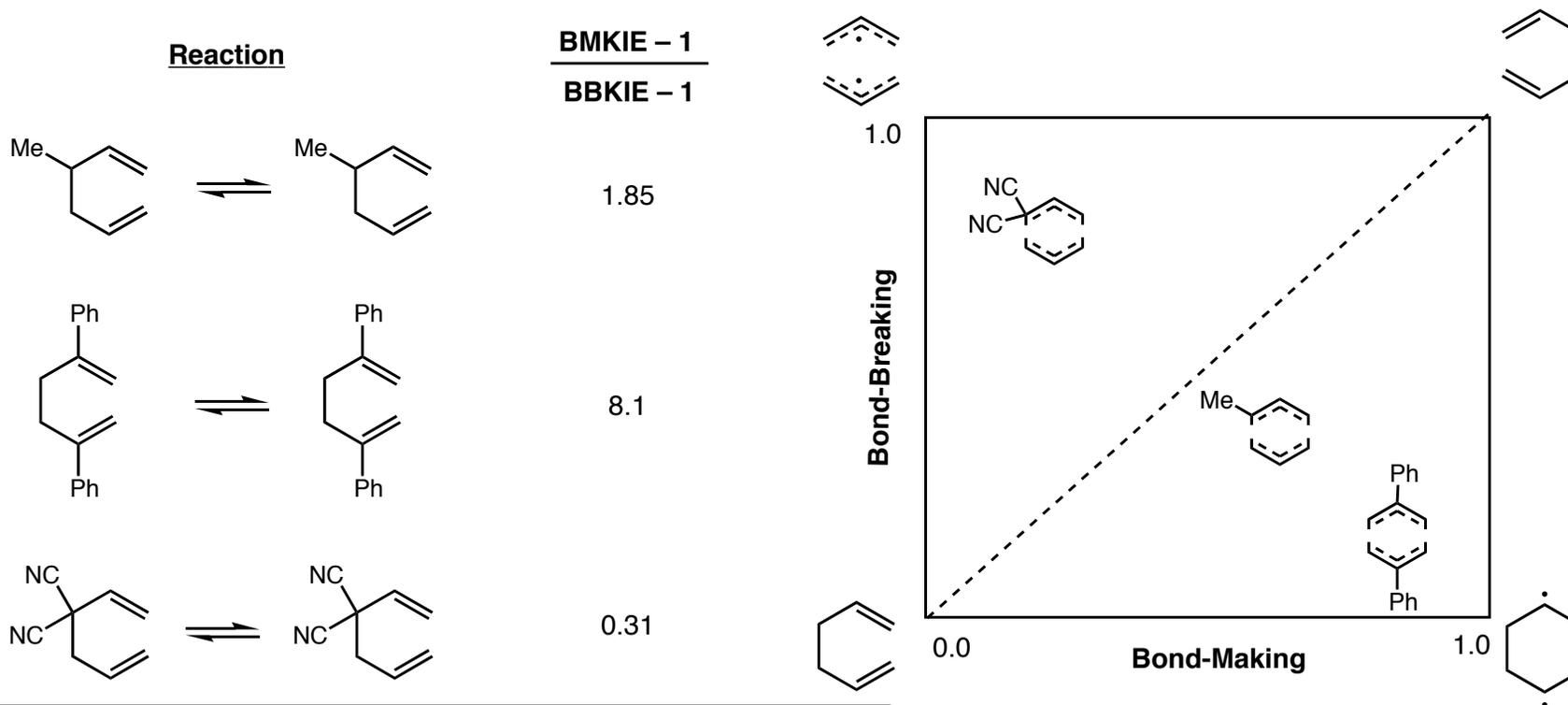
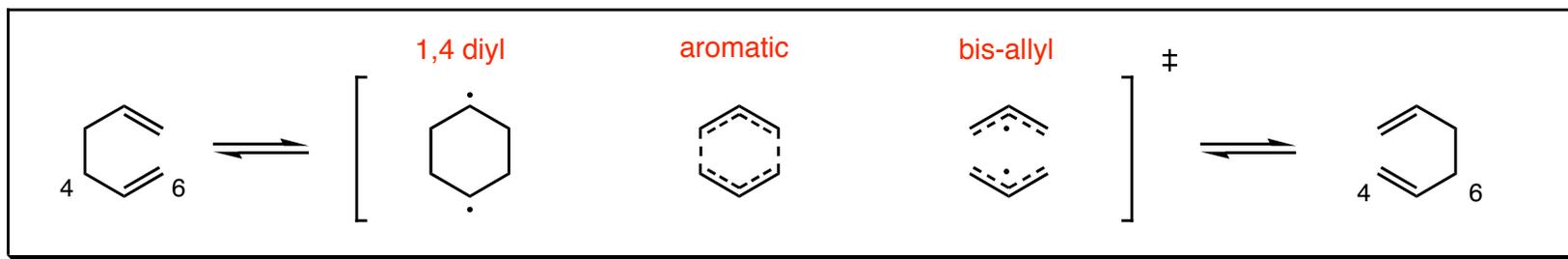
Bond breaking is more advanced at the TS than bond making



Gajewski, J, Conrad, N. *JACS* 1979, 101, 2747

Substituent Effects on Transition States

- Gajewski and coworkers also used this method to analyze a variety of Cope reactions
- Cope rearrangements of substituted hexadienes show drastic variation in rate. It is postulated that the substituents are able to change the nature of the TS.

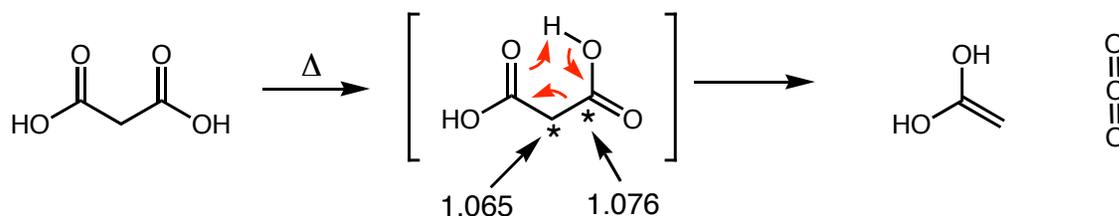


Different substitution can alter the nature of the TS structure

Heavy Atom Isotope Effects

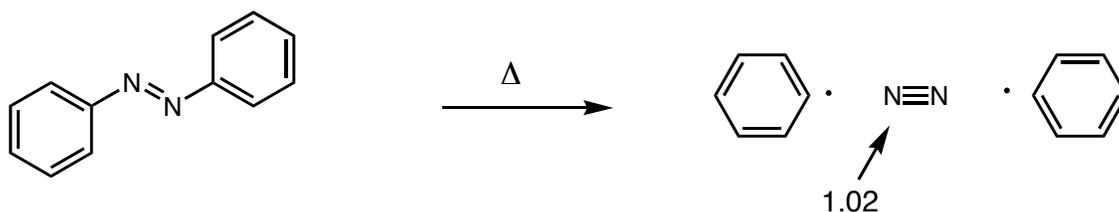
■ Kinetic isotope effects of heavy atoms can also give valuable information about reaction mechanisms, but often the effects are much smaller and more difficult to measure experimentally.

¹²Carbon - ¹⁴Carbon KIE



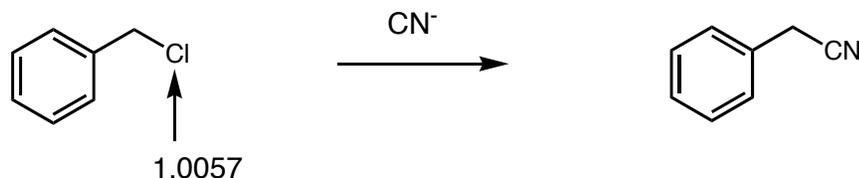
■ Similarity in KIE values at each carbon implies both are breaking in the RDS.

¹⁵Nitrogen KIE



■ Though very small in absolute terms, this value is indicative of a primary KIE

³⁷Chlorine KIE



■ Secondary isotope effects for heavy atoms are so small that they are generally ignored.

Nuclides	C-H/C-D	C-H/C-T	¹² C/ ¹³ C	¹² C/ ¹⁴ C	¹⁴ N/ ¹⁵ N	¹⁶ O/ ¹⁸ O	³² S/ ³⁴ S	³⁵ Cl/ ³⁷ Cl
1° KIE	6-8	15-16	1.04	1.07	1.03	1.02	1.01	1.01

The King of Kinetic Isotope Effects

- There are two major drawbacks to using KIE's to examine heavy atom isotope effects
 1. Prohibitive expense and difficulty in synthesizing isotopically labelled compounds
 2. Getting accurate kinetic data for reactions where even the largest KIE's are very small
- Singelton and coworkers have developed a clever method for precise measurement of ^{13}C and ^2H KIE at natural abundance's simultaneously for every atom in the molecule of interest using high field NMR.



Prof. Dan Singelton
(Texas A&M)

Kinetic Fractionation

$$R / R_0 = (1 - F)^{(1/\text{KIE} - 1)}$$

R / R_0 = ratio of isotope content in recovered reactant relative to the starting material

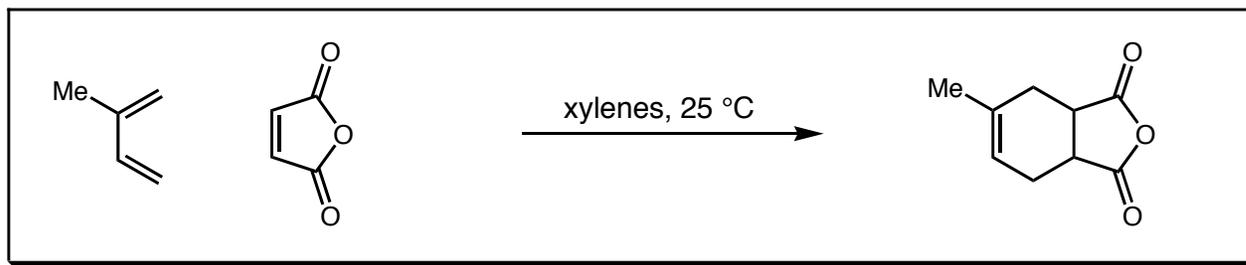
F = % conversion

- As the reaction progresses, the starting material becomes enriched in the slower reacting component. As the reaction approaches completion the ratio of R/R_0 becomes very sensitive to the value of the KIE.
- In the NMR it is possible to evaluate each ^{13}C and ^2H individually and simultaneously by using atoms on the the molecule of interest that will not have isotope effects as an "internal standard"

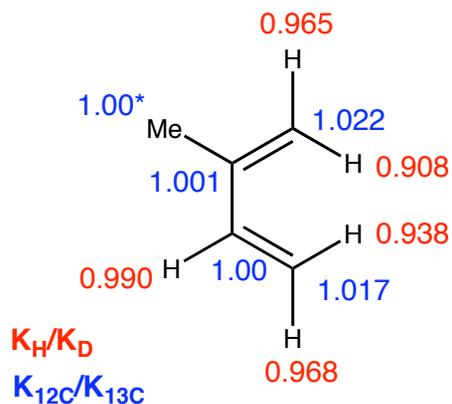
This method is general for nearly every type of reaction, making the study of KIE's a practical tool in elucidating even the most ambiguous mechanisms.

Teaching Old Isotopes New Tricks

- As proof of principle, Singleton studied the Diels–Alder reaction between isoprene and maleic anhydride



- Substitution on the diene methyl group was not expected to affect the rate. Thus it was used as the internal standard



The more pronounced ^2H KIE for C(1) relative to C(4) implies a concerted but asynchronous TS in which bond forming at C(1) is more complete at the transition state than the bond at C(4).

These results refute high level calculations and earlier experimental work on Diels–Alder reactions of isoprene with symmetrical dienophiles, which predicted a completely synchronous TS

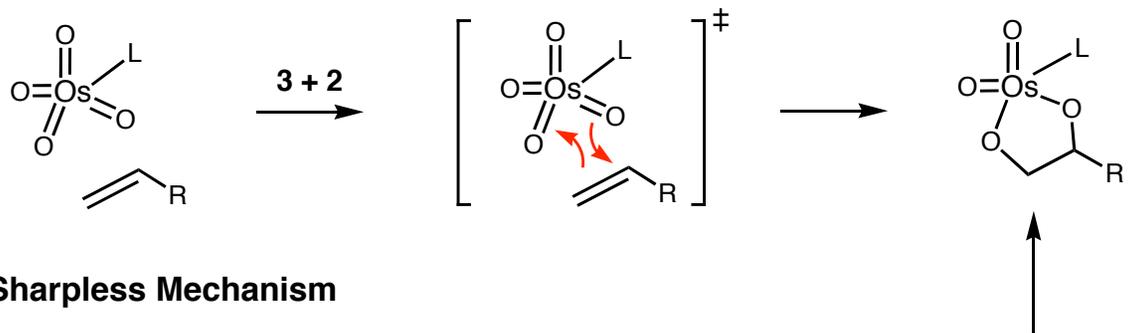
Requirements and Limitations

- Reaction must be scalable, irreversible, and the mechanism cannot change as the reaction progresses.
- For the error to be small, the reactions must go to high levels of completion and there can be no side reactions.

Clash of the Titans

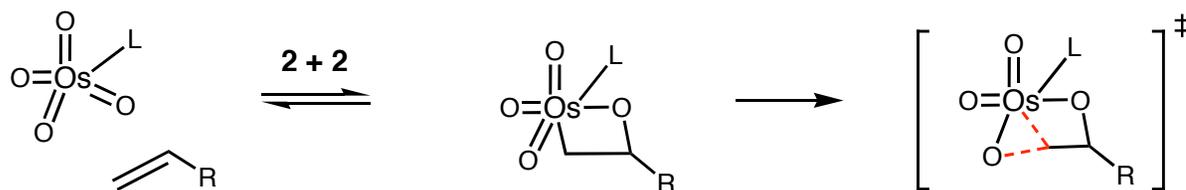
■ The exact nature of the mechanism of the OsO_4 catalyzed dihydroxylation of olefins was thought to occur by one of two distinct mechanisms.

Corey – Criegee Mechanism



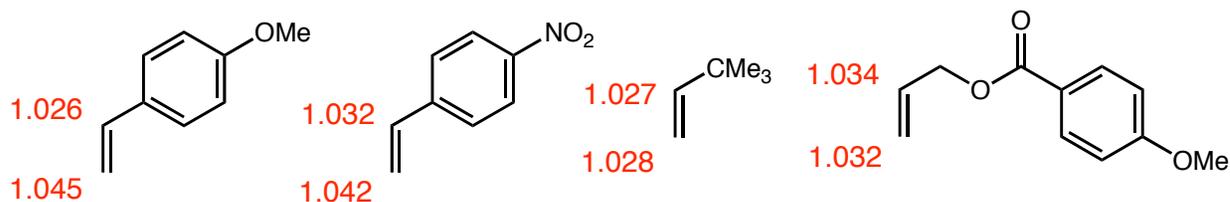
■ For a concerted mechanism, expect 2° KIE's on each carbon to be normal, large and nearly equivalent.

Sharpless Mechanism



■ For a rate determining ring expansion, only one carbon of the substrate should display a significant KIE, not both.

■ Singleton's method gives ^{13}C KIE's that are convincing evidence that the 3 + 2 pathway is likely operative.



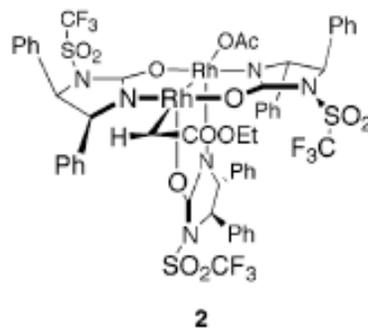
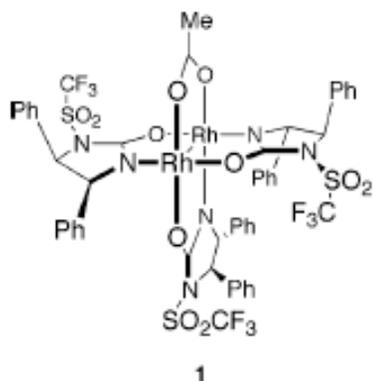
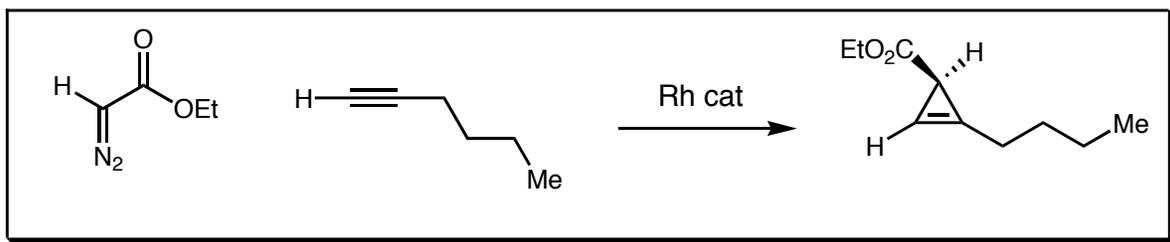
■ Large, normal KIE's are found for both carbons, inconsistent with the 2+2 mechanism

Houk, Sharpless, Singleton, *JACS* **1997**, *119*, 9907

Corey *Tet. Lett.* **1996**, *47*, 4899

Speak Truth to Power

■ Dirhodium(II) catalysts are generally thought to be tetrabridged, but in 2004 Corey proposed that they may react through a tribridged form **2** on the basis of ligand studies. Singleton takes a closer look.

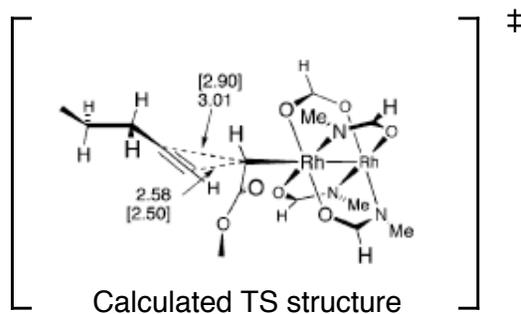
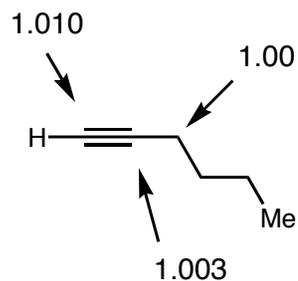


Key Points

■ Corey proposes that **2** is the active catalyst and that the mechanism proceeds by a 2+2 cycloaddition followed by reductive elimination

■ The Corey mechanism would predict large and comparable KIE's for both of the alkyne carbons.

■ Singleton demonstrates that KIE's point to an early asynchronous TS, inconsistent with 2+2 mechanism



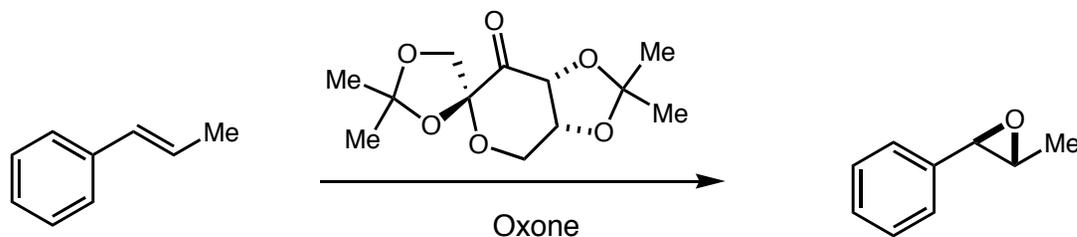
■ High level calculations showed that **2** is 21.5 kcal/mol uphill from tetrabridged **1**. Moreover, in simulations **2** proved resistant to affecting cyclopropanation at all.

Corey, *JACS* **2004**, *126*, 8916

Singleton, *JACS* **2005**, *127*, 6190

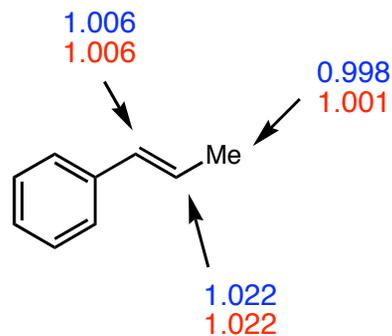
Experimental KIE's and High Level Calculations

■ Computational methods have largely taken over the role of traditional mechanistic investigation. However, often times computational models are unable to distinguish between two TS's that are of approximately the same energy. KIE's can often shed light on these situations



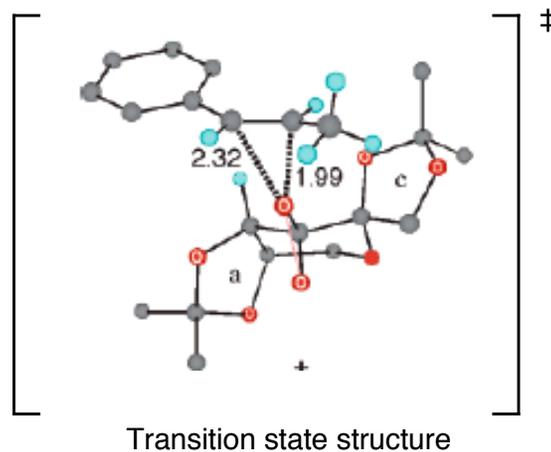
■ High level calculations found ~20 energetically similar TS's for this epoxidation, but was unable to postulate which was operative

■ Singleton compared the theoretical KIE's to the experimental KIE's and was able to show that one TS conformer was likely operative in the Shi epoxidations.



Theoretical KIE

Experimental KIE



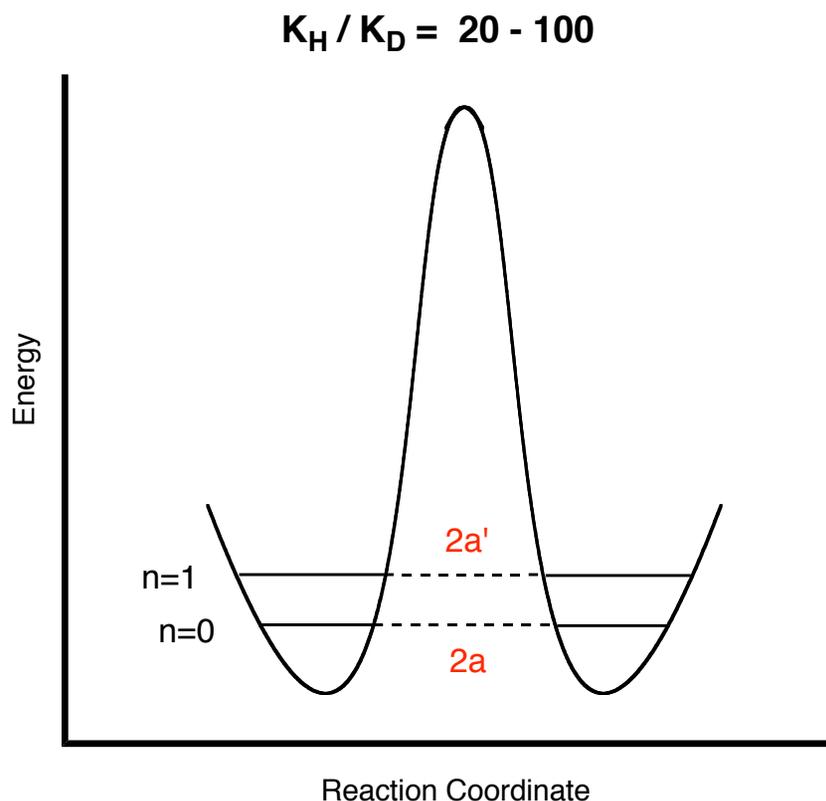
■ ^{13}C KIE show a large degree of asynchronous bond forming in the TS.

■ Singleton was able to examine the theoretical KIE's for each postulated TS and see which matched best

■ The experimental results agree well with the lowest energy TS overall.

Isotope Effects and Tunneling

■ Tunneling is a quantum mechanical phenomenon wherein particles pass directly through an energetic barrier rather than over it. Kinetic isotope effects are a classic way to identify mechanisms that proceed via tunneling



- Tunneling reaction can give enormous KIE values
- Tunneling contributes to the rate of many reactions involving proton transfers.
- Reactions in excited vibrational states experience narrower barriers, and undergo tunneling more readily.

$$k \propto \sqrt{m}$$
$$k \propto \frac{1}{2a}$$

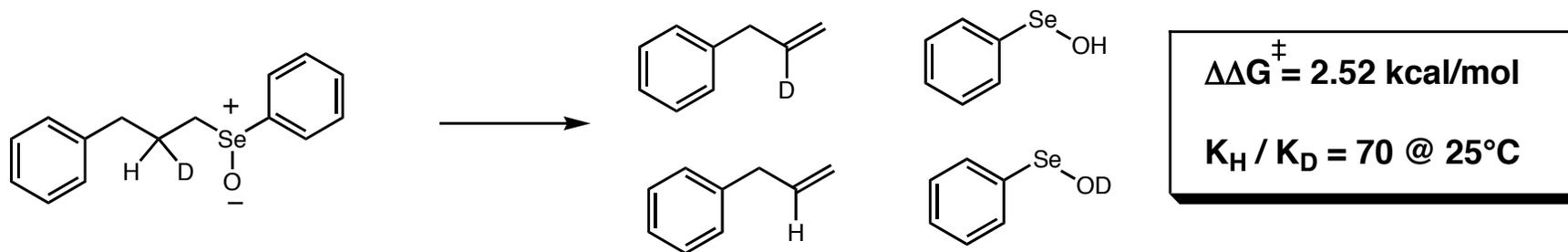
Tunneling is extremely sensitive to the width of the barrier and the mass of the particle tunneling through it

Hallmarks of a Tunneling Reaction

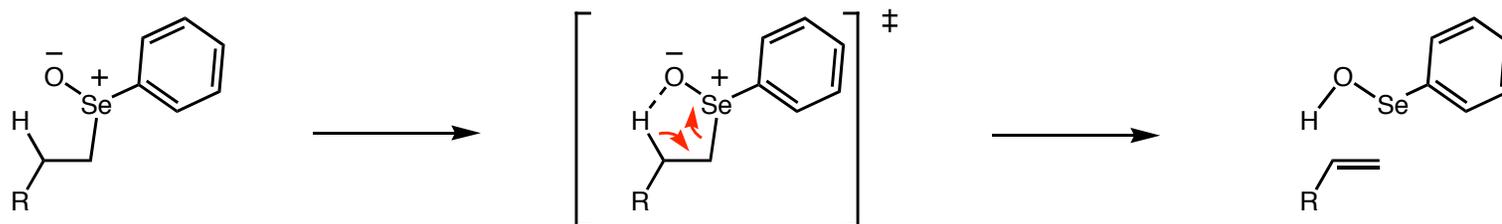
1. Difference in activation energies for H and D must be greater than the difference in their ZPE's
2. Tunneling reactions exhibit little effect of temperature on the rate and proceed rapidly even at temperatures approaching 0 K.
3. Large negative entropy of activation which implies that the TS structure is highly ordered.
4. The heavy atoms in the TS move very little and only the hydrogen is transferred. Analogously, very little nuclear movement can mean a very narrow barrier width.

Tunnel Vision

- Selenoxide eliminations to create double bonds is a commonly used organic reaction that proceeds via tunneling



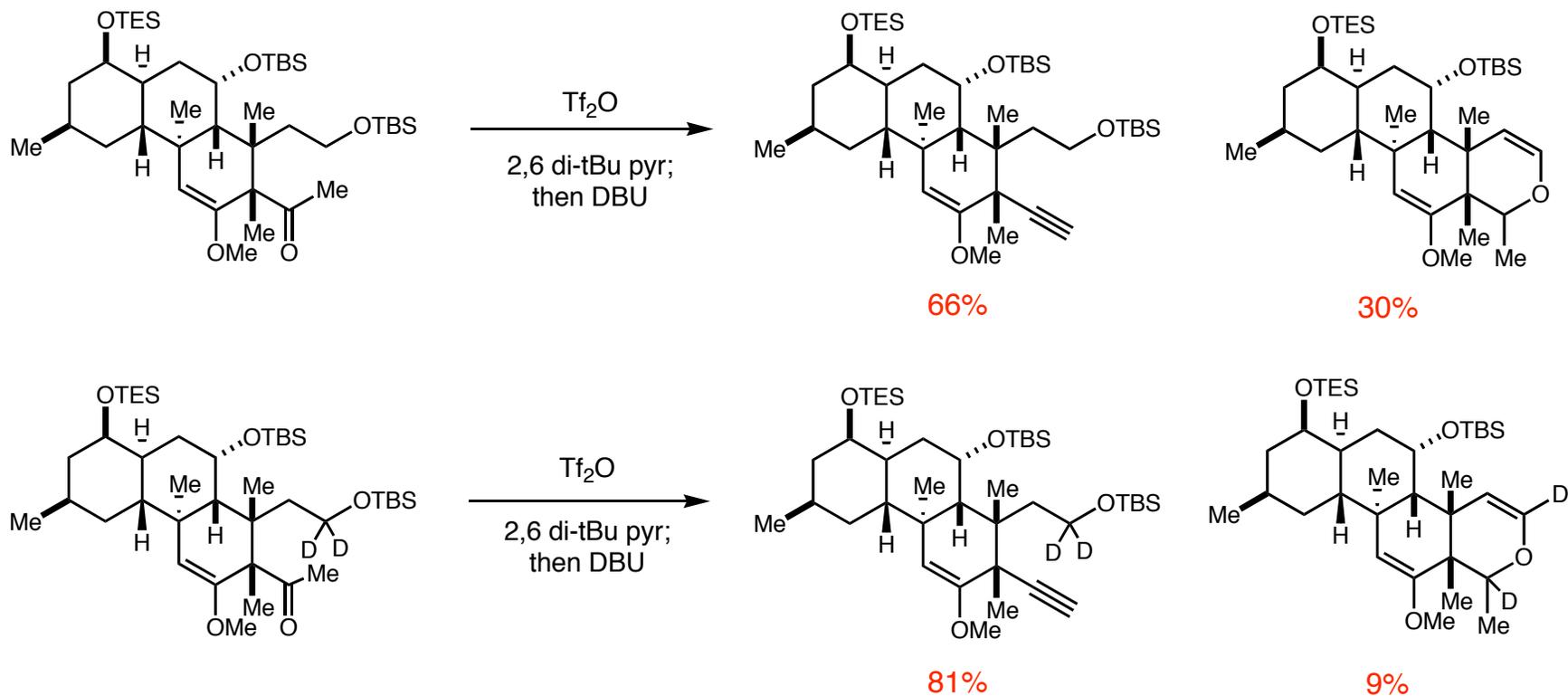
- Kwart and coworkers predicted a barrier width of 0.82 Å, implying that neither the oxygen or the carbon moved at all, only the proton was transferred. A typical C - H bond length is roughly 1.1 Å.



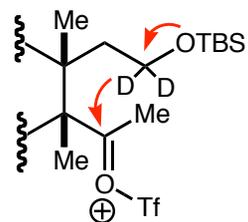
- This reaction is facilitated by the long bonds to selenium as compared to the sulfur variant of this reaction, which proceeds by a normal proton transfer and has a much smaller difference in activation energy (1.15 kcal/mol).

Isotope Effects in Synthesis

- Miyashita's recent synthesis of norzoanthamine made good use of kinetic isotope effects



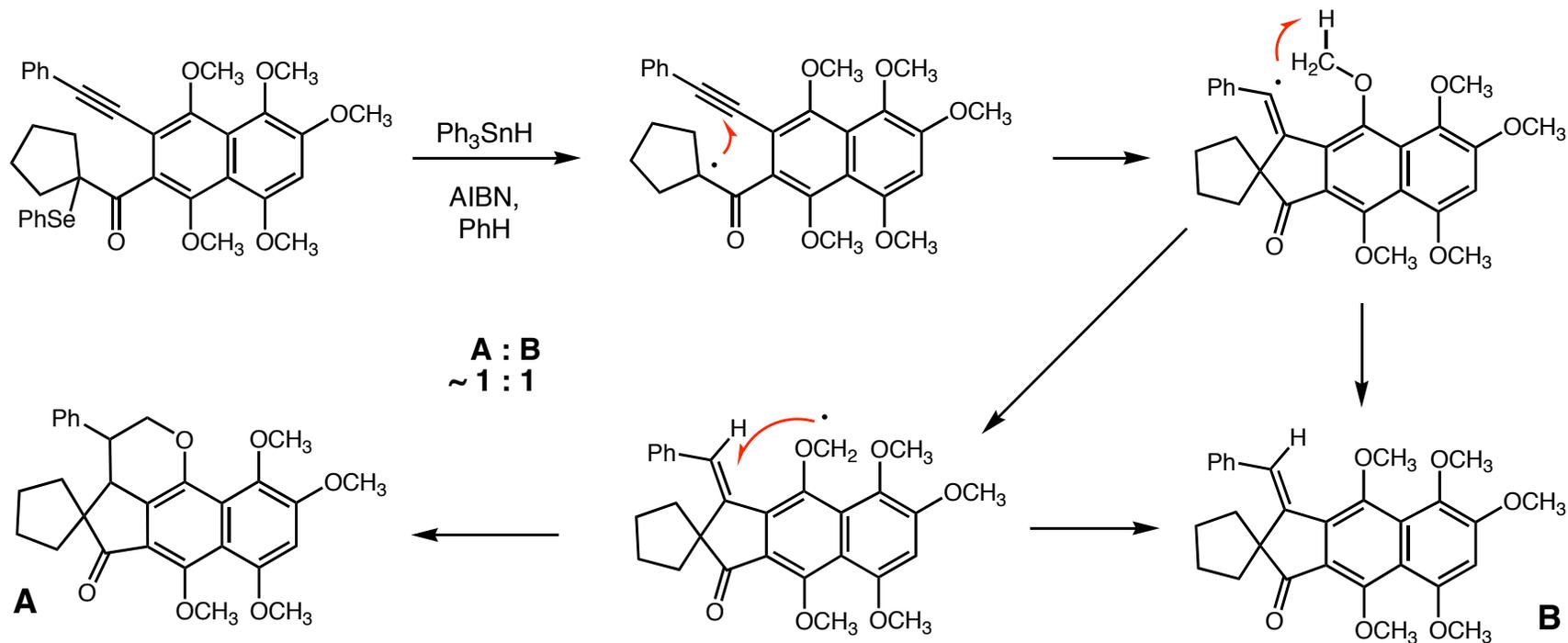
Mechanistic Rationale



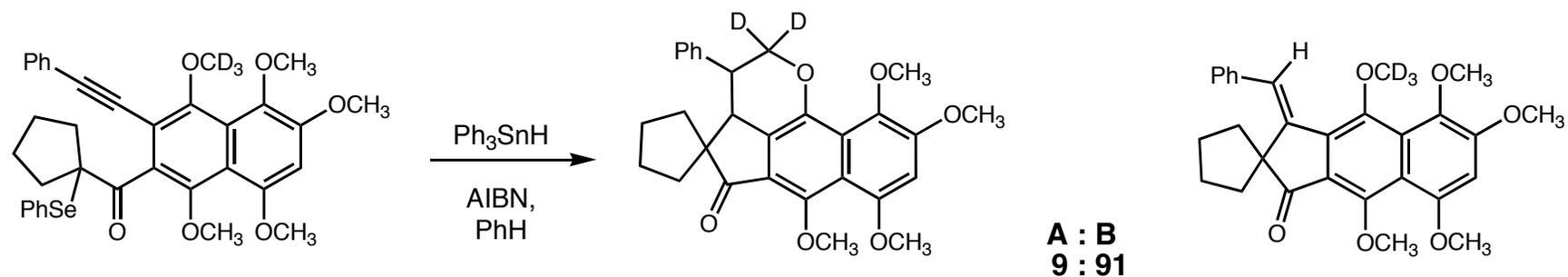
- 1,5 hydride shift gives rise to unwanted byproduct. Switching to deuterated version greatly increases the ratio of products, all based on the difference in zero-point energies between C-H and C-D.

More Isotope Effects in Synthesis

- Clive's synthesis toward fredericamycin used KIE's to partition a reaction away from an undesired side product

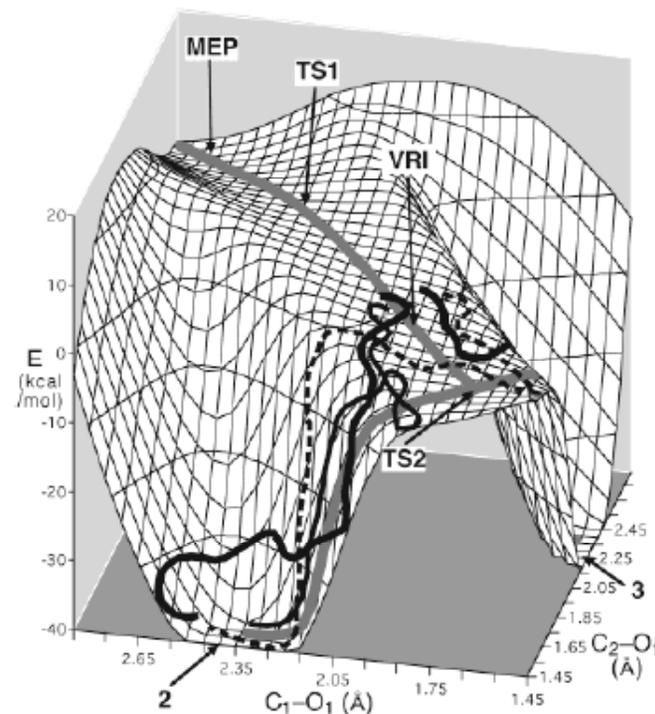
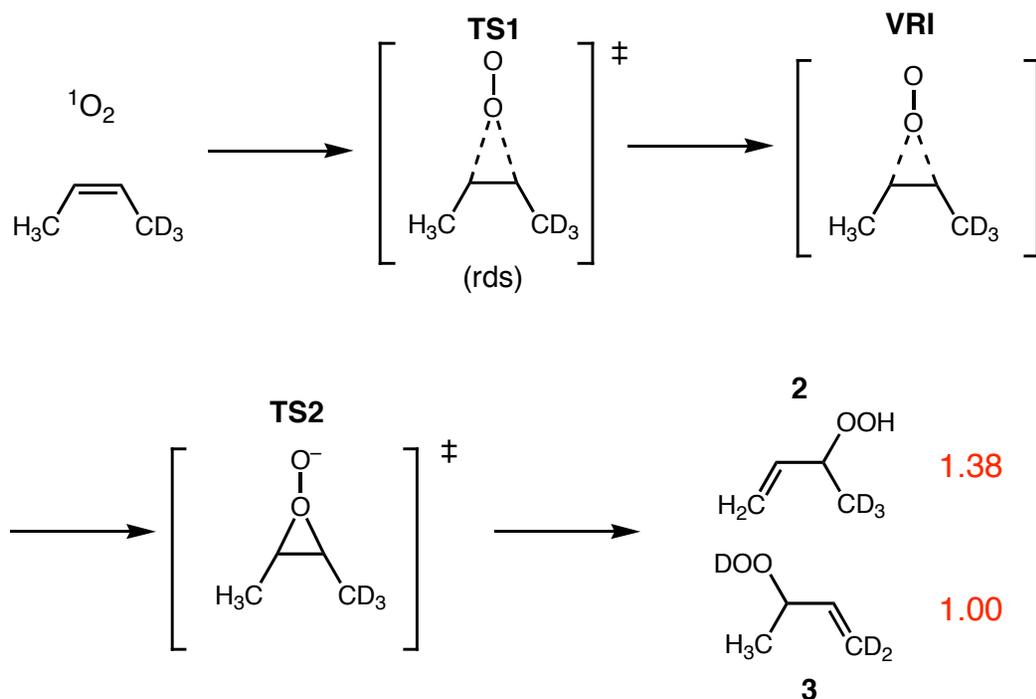


- Isotopic substitution on the methyl group gives a better result



Dynamic Dan Strikes Again

- Singleton found that even completely symmetrical potential energy surfaces can give mixtures of products. This an entirely new and unprecedented form of KIE that is dynamical in nature



- C-H bonds vibrate with greater frequency and with greater amplitude than do C-D bonds due to their higher ZPE. This asymmetry in the vibrational modes of each methyl group of the activated complex creates a perturbation that is sufficiently energetic as to alter the product distribution.

- The broader implication is that the long-held notion that any form of selectivity that is not manifested in the rate-determining step implies the formation of intermediate is not necessarily true

- This reiterates the point that reaction mechanisms are truly complex and that even the most minute perturbations can make truly large differences in reaction outcomes.

Conclusions

- Kinetic isotope effects arise from intrinsic differences in the physical properties of isotopes. This is mainly a manifestation of the difference in mass on the vibrational energy levels of the isotopomers.
- Primary kinetic isotope effects arise mainly from differences in zero-point energy
- Secondary deuterium isotope effects arise mainly from changes in hybridization and hyperconjugation
- Tunneling is an important contributor to the rate of many proton (or carbon) transfer reactions and often tunneling reactions exhibit abnormally large kinetic isotope effects
- KIE's provide a uniquely sensitive probe of transition state structures and provide valuable information about the rate determining step in reaction mechanisms
- Recent practical developments make obtaining detailed KIE profiles for reaction by running a single experiment which analyzed by NMR in a routine fashion
- KIE's can be used to partition product mixtures in the synthesis of complex molecules.