

Isotope Effects

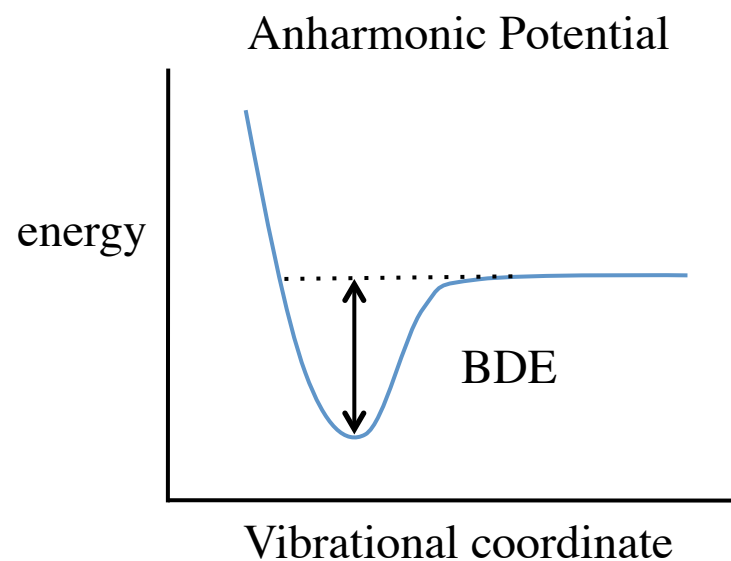
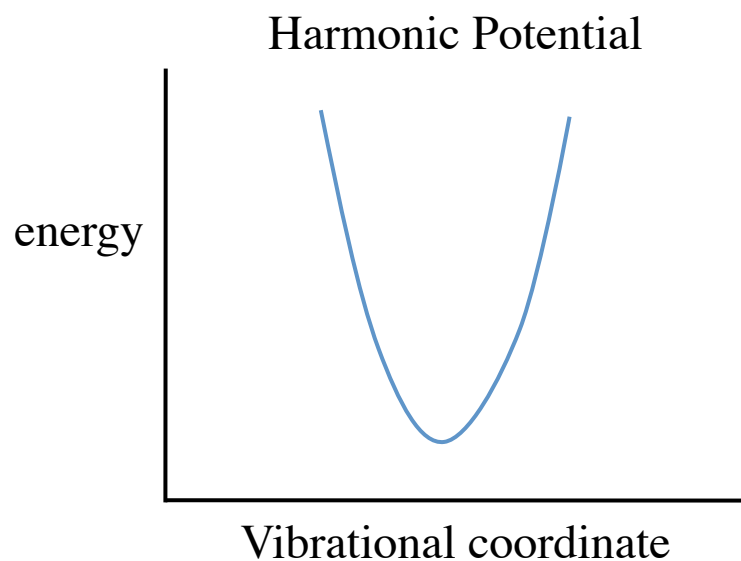
Kinetic Isotope Effects (K.I.E.):
the rate of a reaction changes with an isotopic substitution

At first glance, this might seem counterintuitive because an isotopic substitution does not influence the potential energy surface

How does it therefore affect the rate of a reaction?

What an isotopic substitution does affect is the vibrational energy of a bond

Consider a vibrational coordinate for a single bond



Isotope Effects

Due to uncertainty principle, the lowest vibrational energy is not at bottom of energy well
(and thus the bond dissociation energy does not occur from bottom of well)

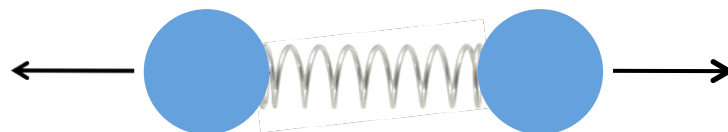
In addition, the vibrational energy levels are quantized

$$E_n = (n + 1/2) h\nu_o \quad \text{Where } n = 0, 1, 2, \text{ etc.}$$

The lowest energy level is thus $E_o = 1/2 h\nu_o$

To determine the frequency (ν_o) of the bond vibration:

For simplicity assume a simple two body vibration attached by a spring



According to Hooke's law, the force required to stretch a spring
is proportional to the amount of stretch

$$F = k X$$

Where k = force constant
 X = amount of stretch

Isotope Effects

The frequency of vibration is related to this force constant by a simple harmonic approximation

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \quad \text{Where } m = \text{mass of object}$$

If the two objects connected by the spring are of comparable mass, then need to use reduced mass in the equation

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

Therefore with a change in mass of a given substituent
(for example an isotopic substitution!)
the lowest energy vibrational state will change

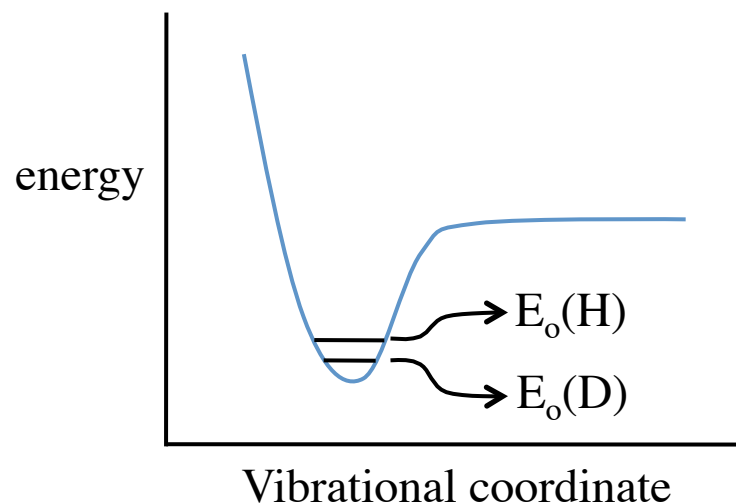
Which in turn means the bond dissociation energy will be different with isotopic substitution

Isotope Effects

$$E_0 = \frac{1}{2} h\nu$$

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

* The greater the mass, the lower will be the E_0 value



Heavier isotope *always* has a lower energy E_0 value

The magnitude of the isotope effect will inherently depend upon the difference in mass for the isotopic substitution

H(D) substitution is most widely studied (2 versus 1 in mass),
 $^{13}\text{C}/^{12}\text{C}$ has less of an effect (13 versus 12 in mass)

Isotope Effects

Kinetic isotope effects are further delineated according to what change is occurring in a given reaction mechanism *at the isotopic substitution*

Primary isotope effect (1° KIE)

Occurs whenever the bond to the isotopic substituent is broken in the rate determining step

Consider a radical halogenation mechanism which generates a carbon radical in the rate determining step



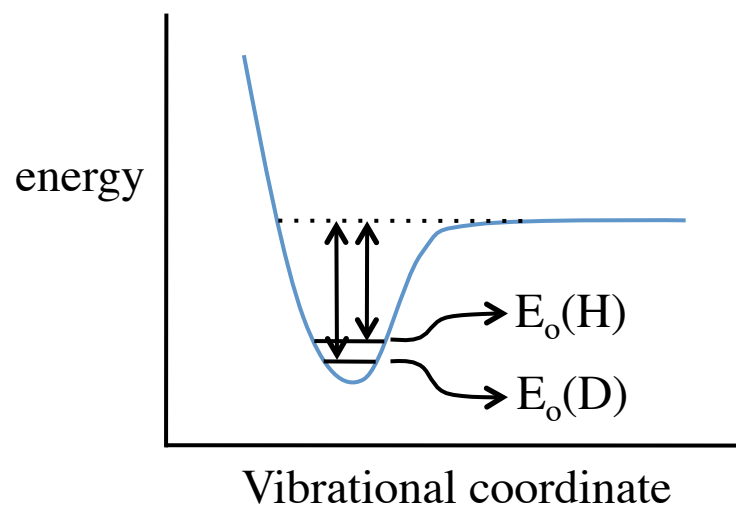
The C-H bond is broken homolytically in the rate determining step

Therefore, rate should be affected if use CH_3 or CD_3 substitution

* Force constant generally does not change with isotopic substitution

How to predict what would be the rate difference between toluene and deuterated toluene?

Primary Kinetic Isotope Effect



Energy difference makes breaking C-H bond easier than C-D bond

Energy difference for dissociation:

$$E = \frac{1}{2} h\nu_0$$

$$\Delta E = -\frac{1}{2} h(\nu_{\text{H}} - \nu_{\text{D}})$$

$$\nu = c / \lambda$$

$$\bar{\nu} = 1 / \lambda$$

Where $\bar{\nu}$ = wavenumber

$$\Delta E = -\frac{1}{2} hc(\bar{\nu}_{\text{H}} - \bar{\nu}_{\text{D}})$$

Primary Kinetic Isotope Effect

$$\Delta E = -\frac{1}{2} hc(\bar{u}_H - \bar{u}_D)$$

All terms are identical
except for the mass

$$\frac{\nu_D}{\nu_H} = \frac{\frac{1/(2\pi) \sqrt{\frac{k}{m}}}{1/(2\pi) \sqrt{\frac{k}{m}}}}{1/(2\pi) \sqrt{\frac{k}{m}}} = \sqrt{\frac{1}{2}}$$

Divide and multiply both
terms by \bar{u}_H

$$\Delta E = -\frac{1}{2} hc(\bar{u}_H - \bar{u}_D)$$

$$\Delta E = -\frac{1}{2} hc[1 - \sqrt{\frac{1}{2}}]\bar{u}_H$$

$$\Delta E \sim \Delta\Delta G^\ddagger$$

Energy doesn't change with
isotopic substitution

$$\Delta G^\ddagger = -RT \ln k$$

$$\ln k_H/k_D = -\Delta\Delta G^\ddagger / RT$$

$$k_H/k_D = e^{\frac{\frac{1}{2} hc (1 - \sqrt{\frac{1}{2}})\bar{u}_H}{K T}}$$

Primary Kinetic Isotope Effect

$$k_H/k_D = e^{-\frac{1/2 hc (1 - \sqrt{1/2}) \bar{\nu}_H}{K(T)}}$$

All these terms are known except:

1) Temperature

(as experiment is run at lower temperature the KIE increases)

2) Wavenumber for a C-H bond stretch

$$k_H/k_D = e^{-\frac{1/2 (6.626 \times 10^{-34} \text{ J}\cdot\text{s})(2.99 \times 10^8 \text{ m/s})(100 \text{ cm/m})(1 - \sqrt{1/2})(3000 \text{ cm}^{-1})}{(1.381 \times 10^{-23} \text{ J/K})(298 \text{ K})}}$$

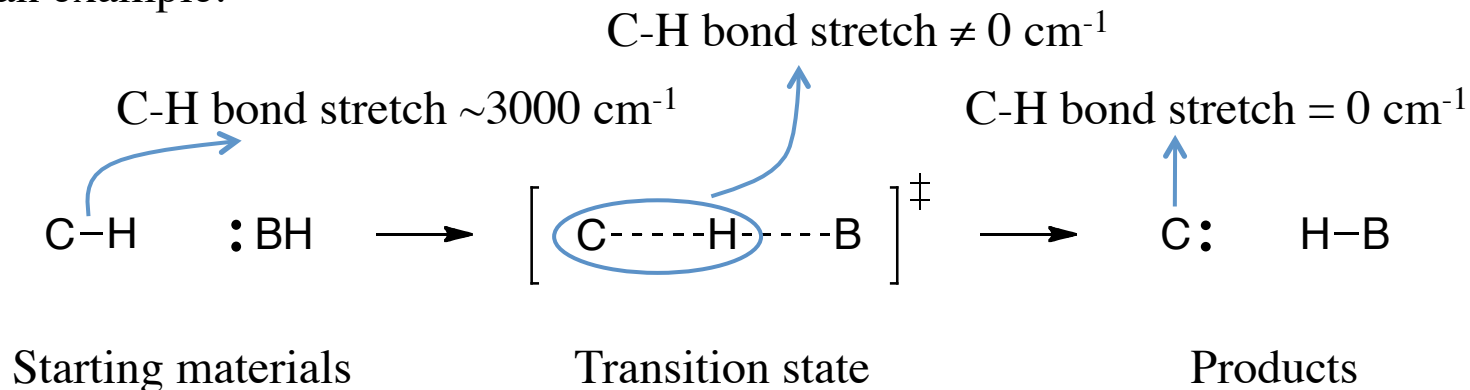
Therefore at room temperature (298 K) the primary KIE is predicted to be ~8

This value corresponds to a C-H bond versus a C-D bond freely dissociating

Primary Kinetic Isotope Effect

In a reaction, however, rarely is a C-H bond freely dissociating,
but rather another reagent is involved

As an example:



Always need to compare the starting material to the transition state structure when
considering a rate question for a reaction

The value of 8 determined previously assumed that the bond was freely dissociated
(thus went from a bond to no bond), but this is the structure of product not transition state

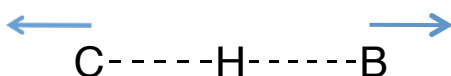
We need to consider vibrational differences between H and D
in three body transition state to predict the primary kinetic isotope value

Primary Kinetic Isotope Effect

In order to know how much the vibrational energy changes for isotopic substitution, the placement of the transition state structure is important

In a symmetrical transition state:

Hydrogen is mid-way
between C and base

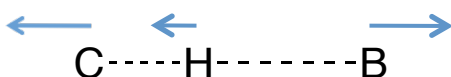


When C and base are stretched,
the hydrogen does not move

Because the hydrogen does not move, the vibrational energy for a C-H and C-D bond will be identical in the transition state and the rate difference is dependent only on the difference in vibrational energy for the starting material, therefore expect $k_H/k_D \approx 8$

In an early transition state:

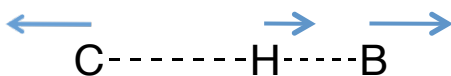
Hydrogen is closer to
carbon than base



When C and base are stretched,
the hydrogen moves toward C

In a late transition state:

Hydrogen is closer to
base than carbon



When C and base are stretched,
the hydrogen moves toward base

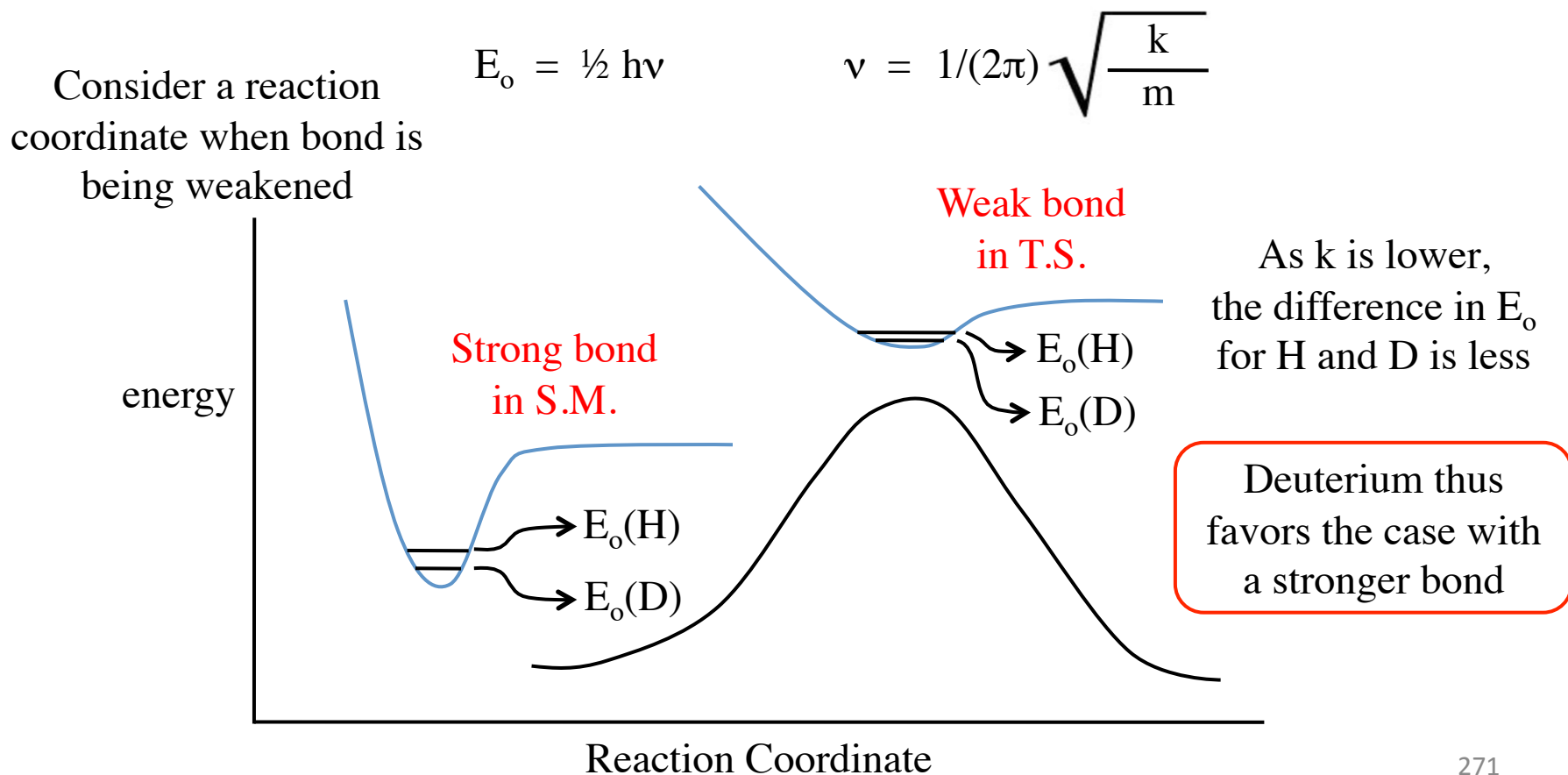
In either the early or late transition state, the hydrogen and deuterium will have different vibrational energies and thus the overall $k_H/k_D < 8$

Primary Kinetic Isotope Effect

Another way to visualize the difference is to consider the change to the force constant for the C-H bond

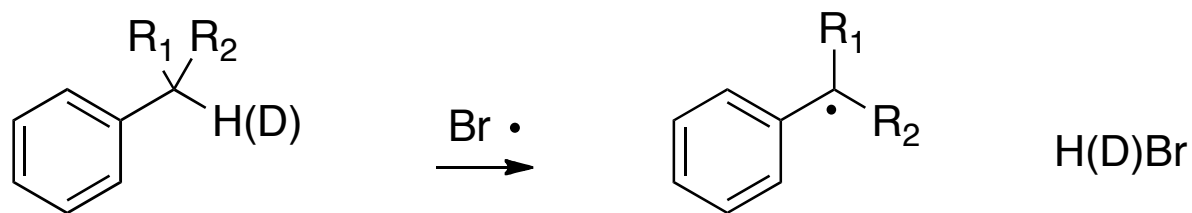
As a bond is being broken, the force constant for the bond is being weakened

As force constant is weakened, the frequency of bond stretch is less and E_0 is less



Primary Kinetic Isotope Effect

Consider the KIE data for the following reaction



Will observe a
1° KIE as the C-H
or C-D bond is
broken in RDS

R ₁	R ₂	k _H /k _D
H	H	4.9
CH ₃	H	2.7
CH ₃	CH ₃	1.8

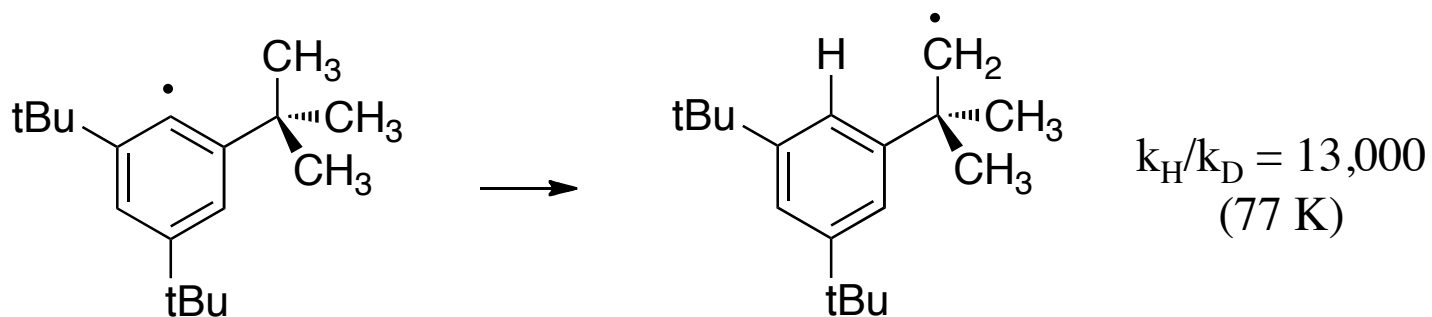
The stability of the transition state changes with more alkyl substituents, the primary KIE indicates the transition state is moving away from symmetrical with more alkyl substituents as seen by the lower values (further away from a predicted maximum value of ~8)

Primary Kinetic Isotope Effect

The magnitude of primary KIE thus could have a maximum value approaching 8,
but as the C-H bond is either broken less (earlier transition state)
or more (later transition state) in the transition state structure the KIE value decreases

Would expect that a primary KIE would have values between 1 and 8
(value could never be below 1, otherwise the C-D bond would break easier than a C-H)

There are many examples, however, where a primary KIE value is obtained
at room temperature that is greater than 8



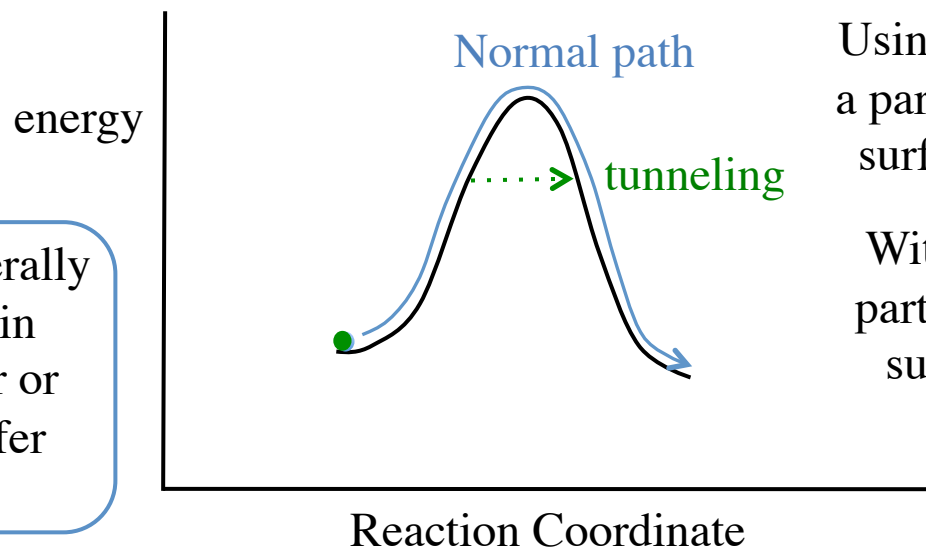
This implies that the rate for breaking a C-H bond is faster compared to the analogous C-D bond more than what is expected from the difference in zero point vibrational energies

Whenever such a scenario occurs, the mechanism probably involves
a process that is referred to as “*tunneling*”

Primary Kinetic Isotope Effect

Tunneling refers to a situation where a particle can exist in a region of space where the classical energy diagram says it shouldn't be able to occur

Tunneling is generally only observed in electron transfer or hydrogen transfer reactions



Using classical energy diagram, a particle would move along the surface of the energy diagram

With tunneling, however, the particle could “cut” across the surface to generate a lower energy of activation

The probability of tunneling occurring is dependent upon the mass of the particle

Because hydrogen is half the mass of deuterium, the probability for a hydrogen to tunnel is greater than a deuterium

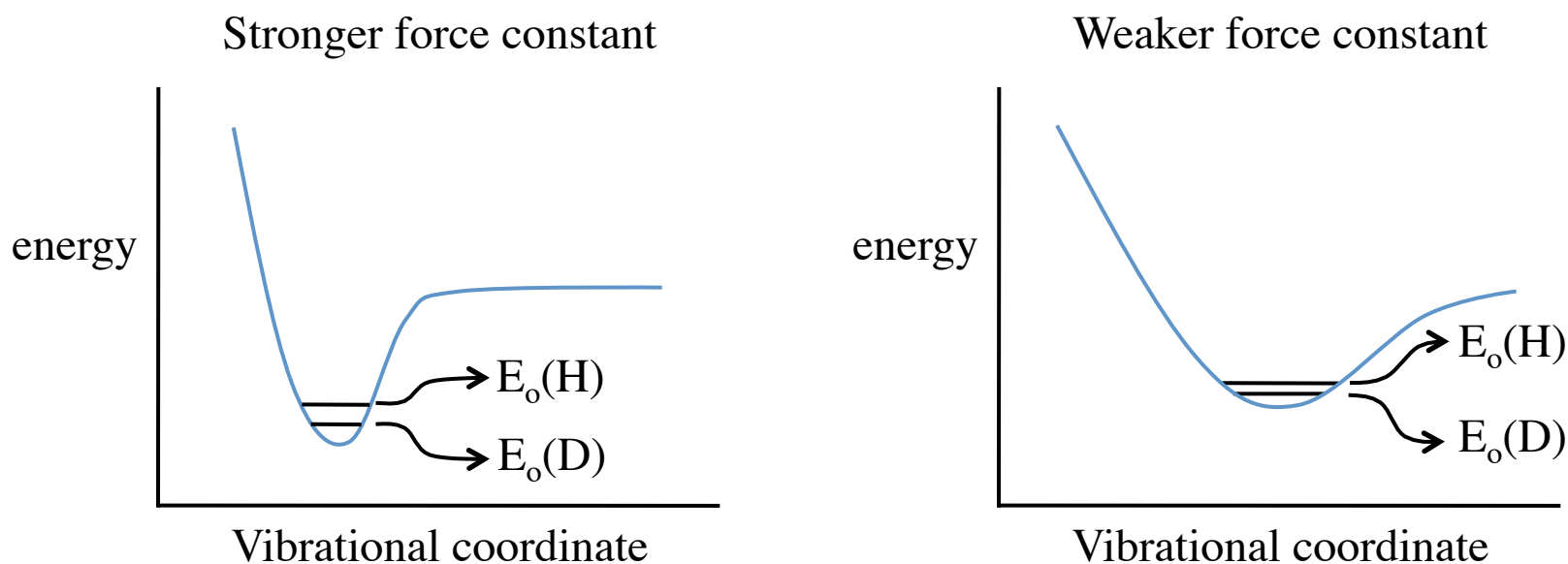
Therefore the $k_{\text{H}}/k_{\text{D}}$ value can increase due to tunneling since the rate of k_{H} can increase much larger than k_{D} then the classical energy diagram would predict

Secondary Kinetic Isotope Effect

A secondary kinetic isotope (2° KIE) involves a rate difference for isotopic substitution of a bond that is not broken in the rate determining step

Difference arises from vibrational change on the isotopic bond
(therefore the *force constant* for the bond changes)

Changing the force constant affects the shape of the vibrational coordinate



As force constant gets stronger, difference in energy between $E_0(D)$ and $E_0(H)$ is larger

Secondary Kinetic Isotope Effect

There are different types of secondary KIE depending upon where the isotopic substitution occurs relative to the site of reaction

An α -secondary KIE refers to when an isotopic substitution occurs α to reaction site

What is the magnitude of an α -2° KIE?

Need to use same analysis to predict magnitude of primary KIE, but now need to consider how the Δv changes going from one state to another (usually involves a change of hybridization for the atom attached to the isotopic bond)

$$\Delta E = -\frac{1}{2} h(\Delta v_H - \Delta v_D)$$

$$\Delta E = -\frac{1}{2} hc(\Delta \bar{u}_H - \Delta \bar{u}_D)$$

Change frequency to wavenumber

$$\Delta E = -\frac{1}{2} hc[1 - \sqrt{1/2}]\Delta \bar{u}_H$$

$$\Delta E = -\frac{1}{2} hc[1 - 1/1.35]\Delta \bar{u}_H$$

Empirical correction
(use 1/1.35 instead of $1/\sqrt{2}$)

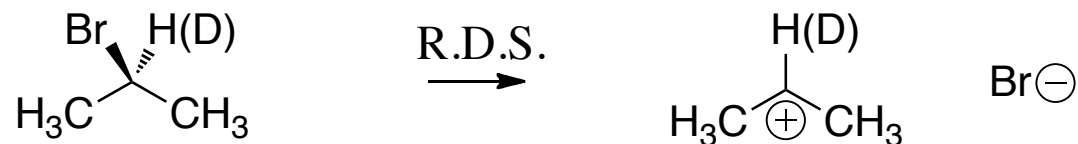
$$* \Delta \bar{u}_H = \bar{u}_H^\ddagger - \bar{u}_H$$

Secondary Kinetic Isotope Effect

$$k_{\text{H}}/k_{\text{D}} = e^{\frac{1/2 hc (1 - 1/1.35)\Delta\bar{\nu}_{\text{H}}}{K T}}$$

To determine the magnitude of α -2° KIE need to know the vibrational frequency (in wavenumbers) for a C-H bond attached to an atom going from sp^3 to sp^2 hybridization

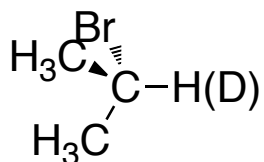
Streitweiser considered the acetolysis of 2-bromopropane



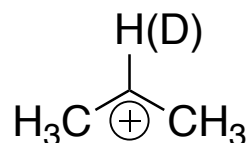
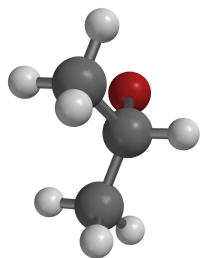
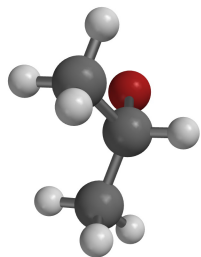
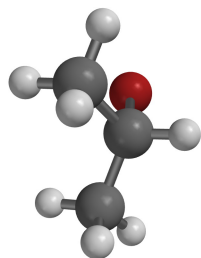
The wavenumber for the C-H bond in the starting material is relatively easy to obtain (just take an IR), the reason this reaction was studied is that the lifetime of the intermediate carbocation is long-lived enough to obtain an IR of the intermediate (this is thus not a “transition state”, but a carbocation intermediate)

Secondary Kinetic Isotope Effect

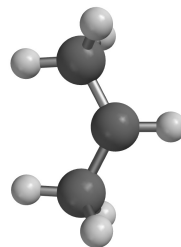
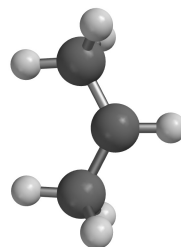
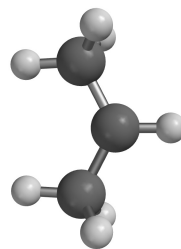
Need to analyze vibrations involving C-H bonded to atom undergoing hybridization change



sp^3 hybridized



sp^2 hybridized



* The biggest (energy) change occurs in the out-of-plane bending motion

Secondary Kinetic Isotope Effect

The difference in energy for this bending motion (540 cm^{-1}) can then be used to calculate the expected α - 2° KIE when going from a sp^3 to an sp^2 hybridized carbon

$$k_{\text{H}}/k_{\text{D}} = e^{\frac{1/2 hc (1 - 1/1.35)(540 \text{ cm}^{-1})}{K T}}$$

$$k_{\text{H}}/k_{\text{D}} = 1.41$$

Therefore a C-H bond where the carbon undergoes a hybridization change from sp^3 to sp^2 during the rate determining step, will react up to a maximum of 1.41 time faster than a C-D bond

As seen with 1° KIE, however, the magnitude will depend upon the structure of the transition state and how the vibrational energy changes with a different amount of bonding

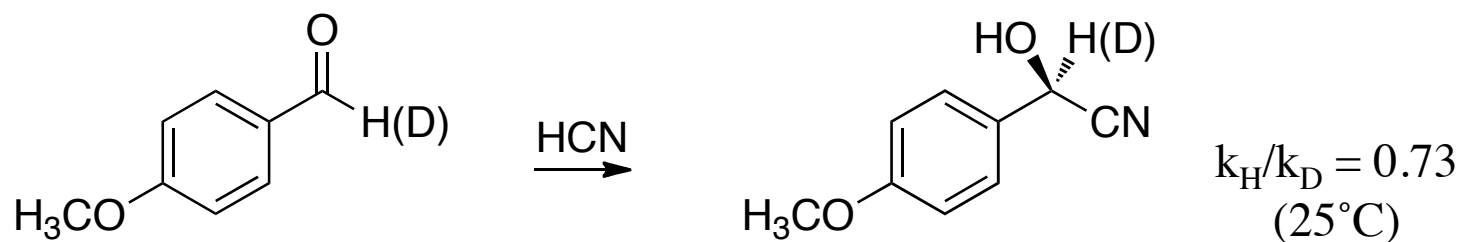
In practice the magnitude of the 2° KIE is usually in the 1.15 to 1.25 range

The acetolysis reaction studied by Streitweiser shown previously, for example has an experimental value of $k_{\text{H}}/k_{\text{D}} = 1.15$

Secondary Kinetic Isotope Effect

When a C-H bond is attached to a carbon that undergoes a hybridization change from sp^3 to sp^2 during the rate determining step, when that bond is replaced with a C-D bond the rate change is called a *normal* α -2° KIE and the maximum value is expected to be 1.41 with the actual value many times between 1.15 and 1.25 depending upon the transition state structure

If the C-H bond is attached to a carbon undergoing a hybridization change from sp^2 to sp^3 , however, the rate change with a C-D isotopic change is called an *inverse* α -2° KIE



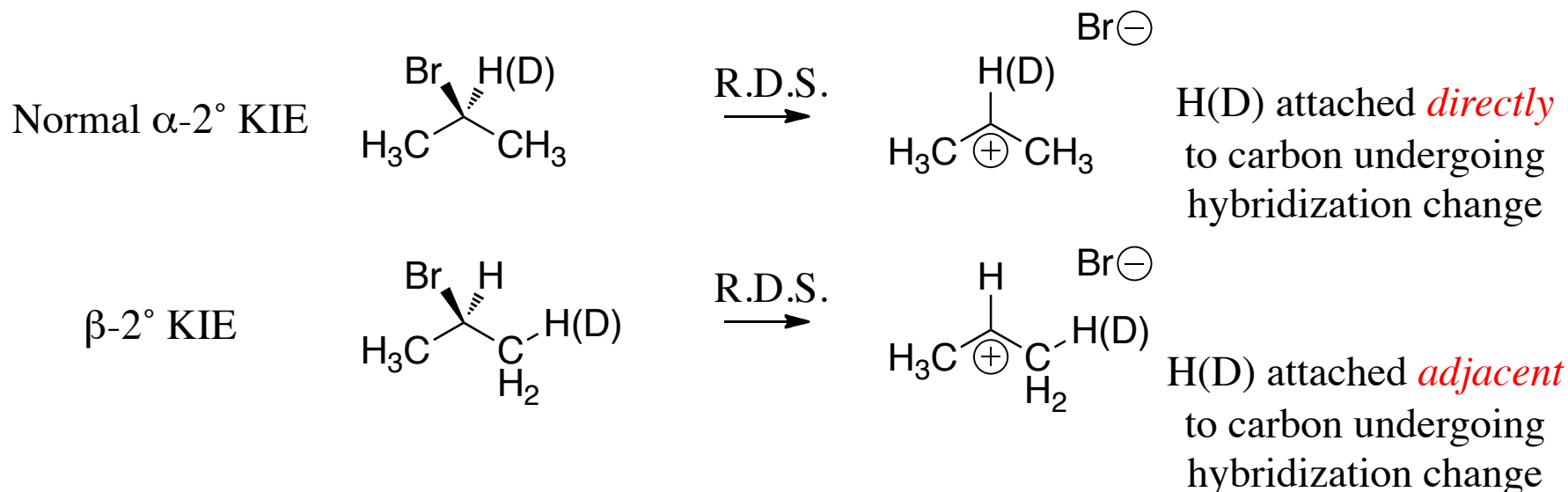
Called inverse α -2° KIE because value is below 1 (C-D bond reacts faster than C-H bond)

Magnitude is merely inverse of normal α -2° KIE
($k_{\text{H}}/k_{\text{D}} = 1/1.41 = 0.71$)

Just like normal α -2° KIE, the magnitude of inverse α -2° KIE is dependent upon transition state structure and usually see values between 0.8 – 0.9

Secondary Kinetic Isotope Effect

Another type of secondary isotope effect is when the C-H(D) bond is at the β position from reaction site, thus called a β -2° KIE



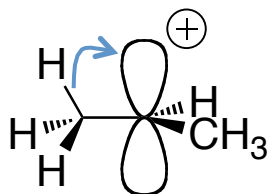
Might expect β -2° KIE to be even less than α -2° KIE since the isotopic bond is even further removed from the reaction site

Magnitude of β -2° KIE is often *larger* than α -2° KIE

β -2° KIE is a result of *hyperconjugation* effect on a neighboring carbocation

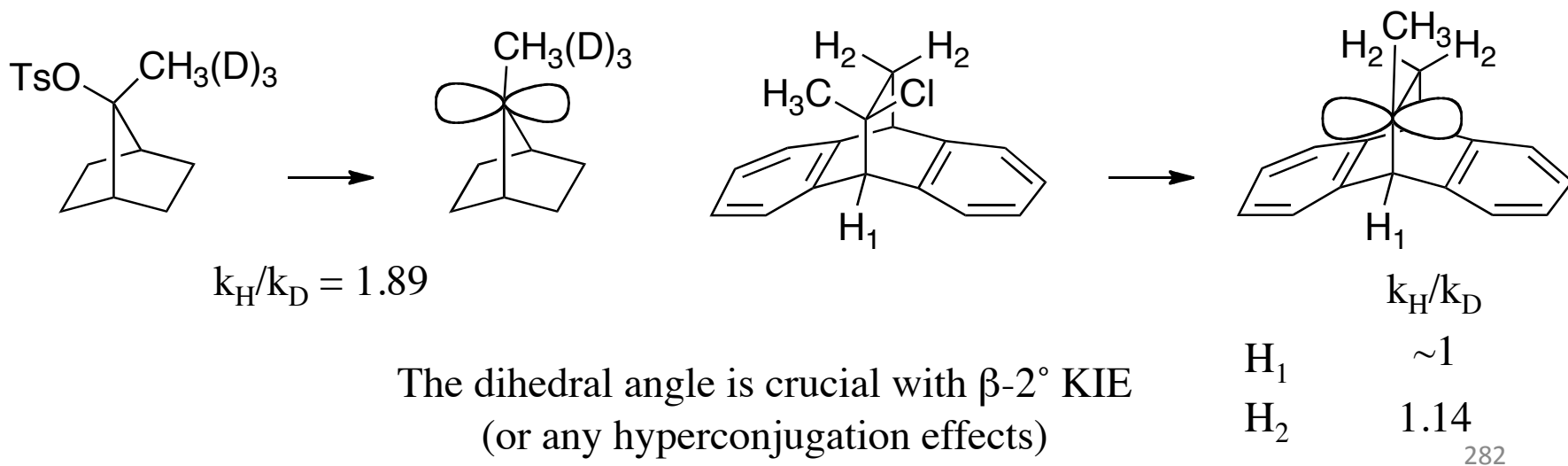
Secondary Kinetic Isotope Effect

Hyperconjugation is due to a neighboring C-H bond stabilizing a carbocation by donating electron density



The neighboring C-H bond needs to be aligned with p orbital to allow hyperconjugation to occur

Hyperconjugation therefore weakens the C-H bond, C-H will thus react faster than C-D for same reasons a 1° KIE is faster with a C-H bond than C-D (and also why magnitude for β -2° KIE is larger than α -2° KIE)



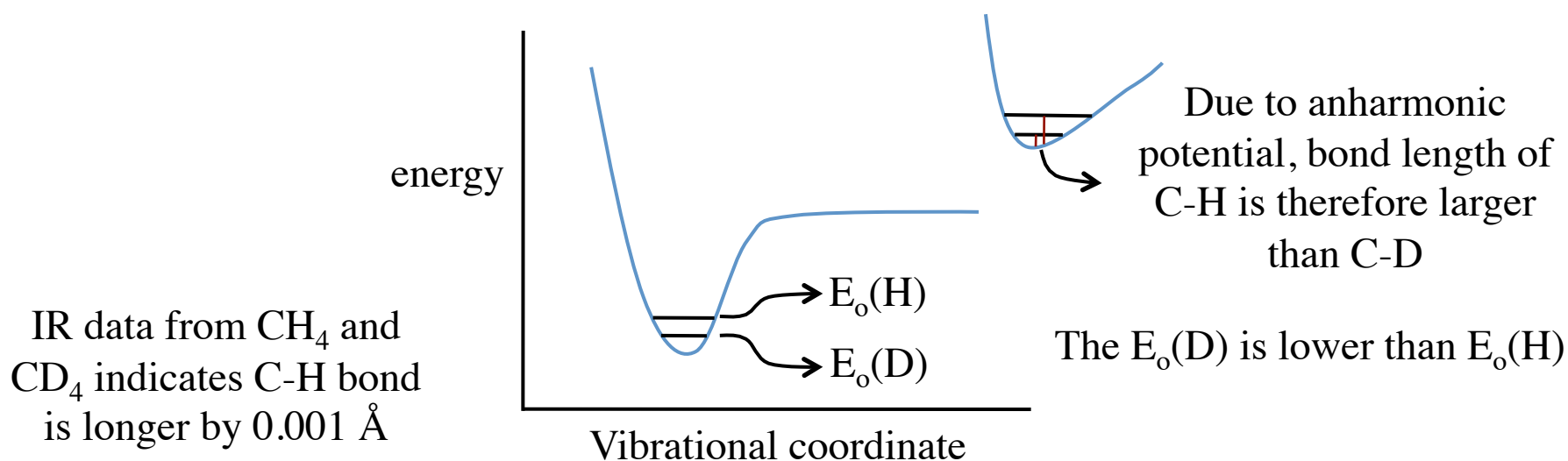
Secondary Kinetic Isotope Effect

If the isotopic substitution is further removed from the reaction site than the β position, then the rate difference is often too small to detect

There are some cases, however, where a large effect can be observed at these remote sites (γ or beyond) and are called *steric* isotope effect (or sometimes called *remote* isotope effect)

As the name suggests, the rate difference is due to a steric difference between the C-H and C-D bonds

Consider again an anharmonic vibrational coordinate for a C-H bond

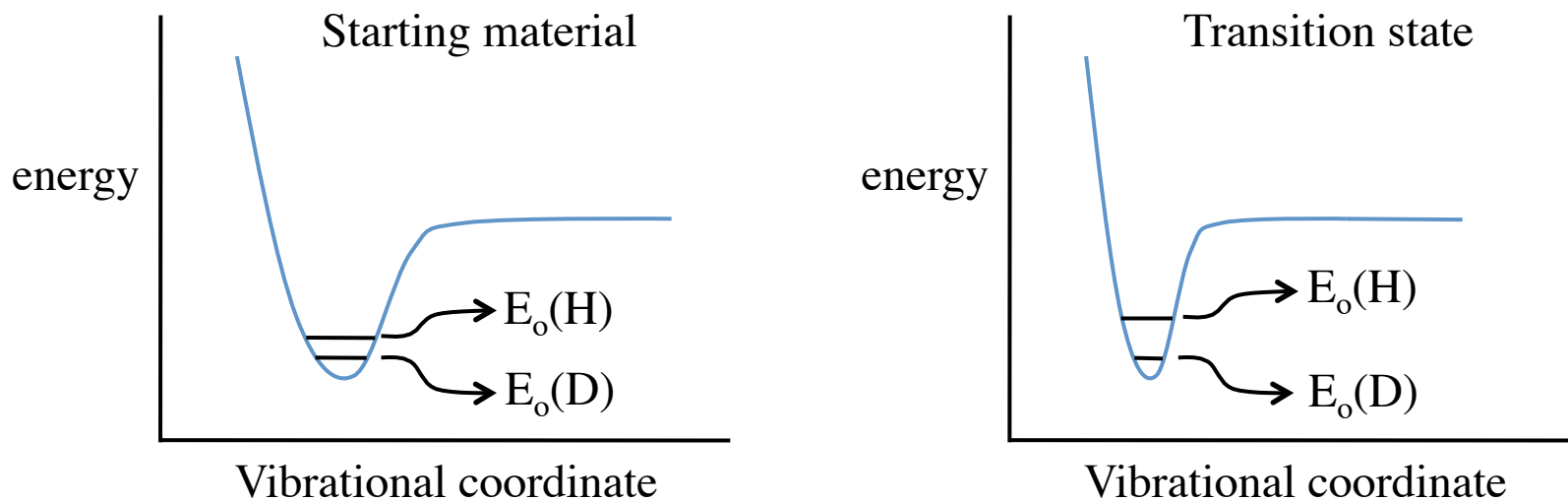


Secondary Kinetic Isotope Effect

These small differences in bond lengths can become important if the bond is located at a sterically demanding position in either the starting material or transition state structure

Another explanation for steric isotope effects is that as the structure enters a more sterically demanding position, the force constant to vibrate the bond becomes larger

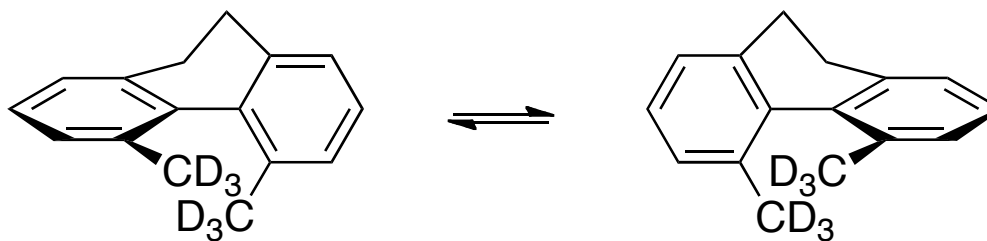
As the force constant becomes larger,
the difference in energy between $E_0(\text{H})$ and $E_0(\text{D})$ becomes larger



Either explanation, longer C-H bond or greater difference in E_0 values in sterically TS, predict that a C-H bond will react slower than a C-D with sterically demanding structures

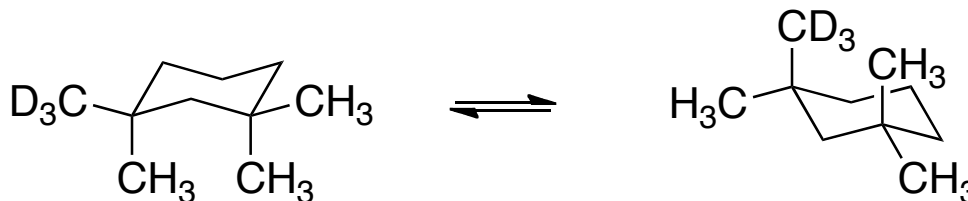
Secondary Kinetic Isotope Effect

When C-D bond goes through a sterically demanding transition state, the rate will be faster than when the isotopically related C-H is used instead



$$k_H/k_D = 0.86$$

Can also observe equilibrium differences



$$[CD_3]_{AX} / [CD_3]_{EQ} = 1.042 (-100^\circ C)$$

“smaller” CD₃ group prefers axial position at equilibrium
(not even a rate difference, but even see equilibrium differences)

Isotope Effects

The magnitude of kinetic isotope effects can therefore be used to distinguish mechanisms

Important to realize what range of values are possible for the different types of KIE

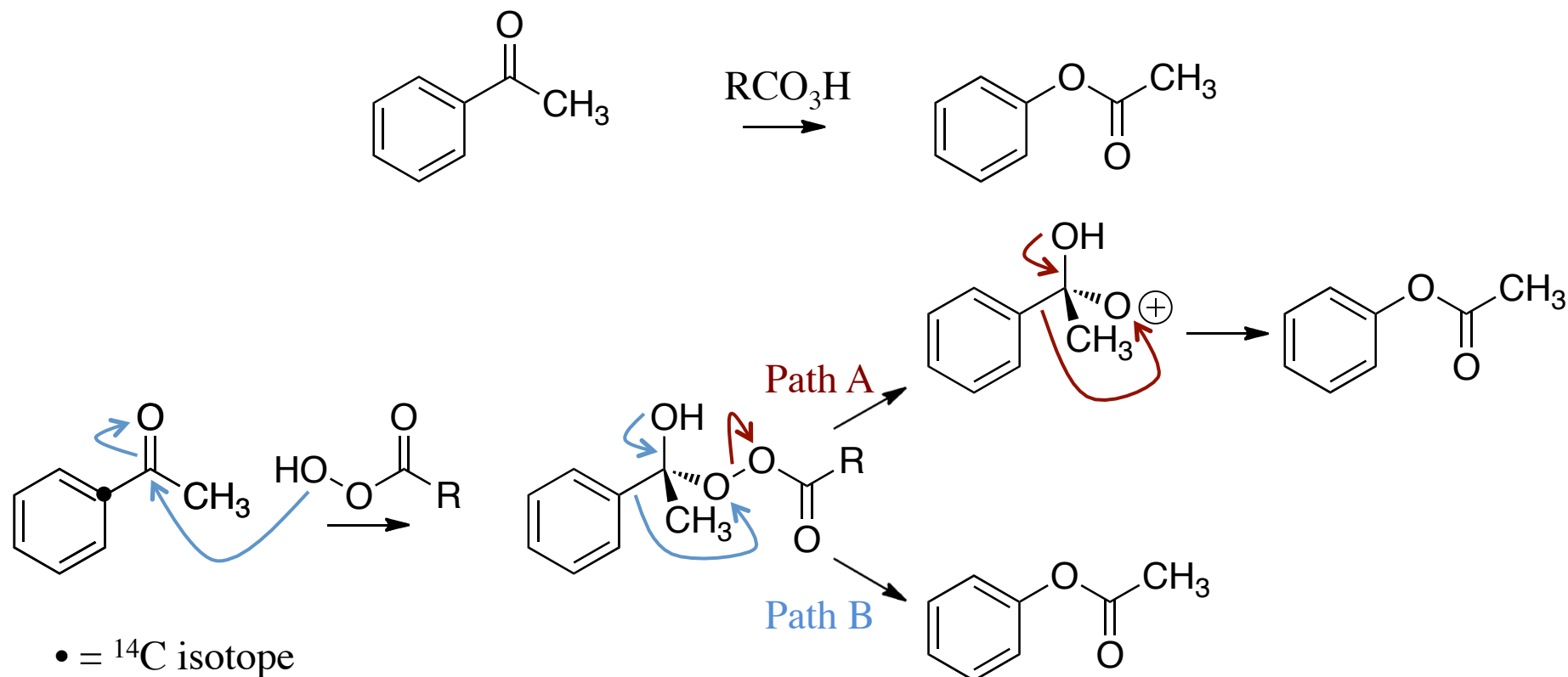
Type	Cause	Maximum* (at 25°C)	If lower	If higher
1° KIE	Breaking of C-H bond in R.D.S.	~8	Early or late TS structure	tunneling
Normal α -2°	Hybridization change of carbon in C-H from sp^3 to sp^2 (or sp^2 to sp)	1.41	Early or late TS structure	Cannot be much larger
Inverse α -2°	Hybridization change of carbon in C-H from sp^2 to sp^3 (or sp to sp^2)	0.71	Early or late TS structure	Cannot be much larger
β -2°	Hyperconjugation (C-H adjacent to cation)	$\sim < 2$ (up to a 1° KIE)	Dihedral alignment	Amount of hyperconjugation
Steric KIE	Sterically larger C-H	Depends on sterics	Depends on sterics	Depends on sterics

*(all entries assume a k_H/k_D KIE at 25°C)

Isotope Effects

Using KIE to distinguish possible mechanisms

Consider a Baeyer-Villiger oxidation



To distinguish possible pathway **A** or **B**, a ^{14}C isotope was placed at position indicated and a $k^{12}\text{C}/k^{14}\text{C}$ KIE of 1.048 was determined

Corresponds to a 1° KIE for $^{12}\text{C}/^{14}\text{C}$ (maximum would be 1.24), therefore must be path B