Kinetic Isotope Effect

Chapter 8, sections 8.1.1-8.1.3

Isotope Effects

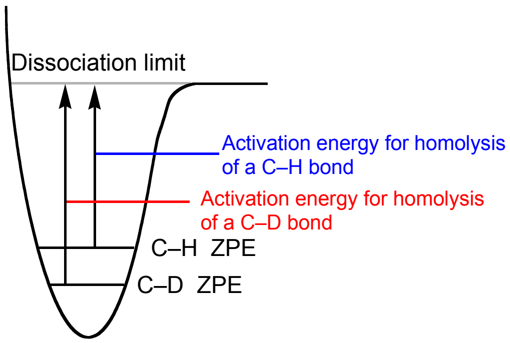
- Traditional kinetics studies do not provide information as to what bonds are broken/formed and changes in hybridization that occur during the rate-limiting step of a reaction.
- Isotope effects can provide this information.
- Substituting one iosotope for another at or near an atom at which bonds are breaking or rehybridizing typically leads to a change in the rate of the reaction.
- The effect of replacing H with D often is relatively large when the bonds being broken or formed involve H. This effect can be measured routinely.
- The effects of isotope replacement for other elements have been studied, but the effects are typically small and sometimes difficult to quantify.

Isotope Effects: Experimental

- An isotope effect is measured to determine if the bond at which the isotopic substitution has been made changes in some manner during the rate-limiting step.
- The isotope effect is expressed as a ratio of rate constants: the rate constant for the reaction with the natural abundance isotope over the rate constant for the reaction with the altered isotope. [for H/D substitutions: k_H/k_D]
- For a hydrogen isotope effect, typically a first order (or pseudo-first order) rate constant for the reaction of interest is determined. The natural abundance of deuterium (D) and tritium (T) [0.015% and 1×10^{-4}% respectively] is so low that their contribution to the observed rate is negligible.
- The magnitude of the isotope effect (deviation of k_H/k_D from unity) provides information about the reaction mechanism.
  - If $k_H/k_D = 1$ then the bond involving the substitution is not changing during the rate-limiting step or the isotope effect is too small to be detected.
  - If $k_H/k_D > 1$ then the effect is said to be **normal**.
  - If $k_H/k_D < 1$ then the effect is said to be **inverse**.
- **Primary isotope effect:** isotope effect attributed to a bond breaking event at X–H/X–D bond.
- **Secondary isotope effect:** isotope effect attributed to to rehybridization or substitution remote from bonds undergoing reaction in the transition state.

Origin of Primary Kinetic Isotope Effects

- The origins of all isotope effects is the difference in the frequencies of various vibrational modes of a molecule, arising when one isotope is substituted for another.
- At ambient temperature, the vibrational modes for bond stretches are dominated by $n=0$, with $e_0=1/2hv$ [referred to as the zero-point energy (ZPE)].
- For a bond breaking event, the stretching vibration of that bond is defined as the reaction coordinate.
- The frequency of the stretching is directly proportional to the square root of the force constant of the bond. (expressed as cm^{-1} in IR)
- The reduced mass for a bond between a heavy atom (i.e. C, N, or O) and a light atom such as H is significantly impacted when the H atom is replaced with D.

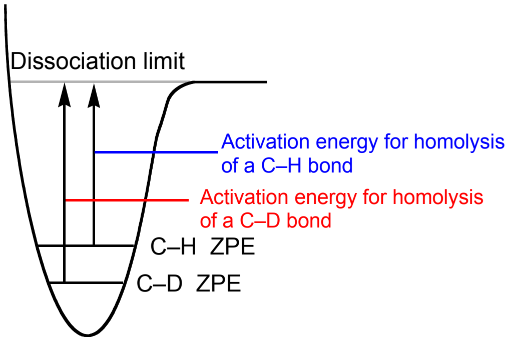


- The stretching frequency of a bond with D is lower due to the heavier mass.... the ZPE for the bond is thus lower as well.

Origin of Primary Kinetic Isotope Effects

- In a homolysis reaction that forms two radicals, the stretching vibration in the reactant is converted to a translational degree of freedom.
- Comparing C–H and C–D, the activation energy for C–D is larger.
- The magnitude of k_H/k_D for the reaction is >1.
- There are no vibrations for the bond that is breaking when the reaction is complete. Therefore, the force constant associated with this bond has gone to zero.
- Assuming that the bond of interest is 100% broken at the transition state (not usually the case), we can calculate the maximum possible isotope effect.
- Assuming 298K, k_H/k_D is calculated to be ~6.5
- Most isotope effects are attenuated from this value because reactions typically do not involve bonds that are completely broken in the transition state.
- For isotope effects we compare the ZPE of the various vibrations of the reactant and the activated complex.

Usually the bond is only partially broken or another is starting to form at the transition state. Both attenuate the isotope effect from that of total homolysis.

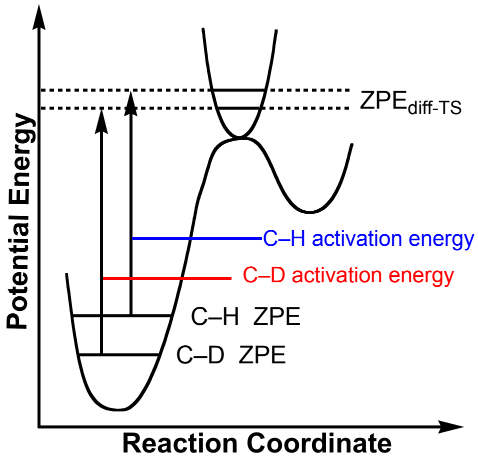


$$e_n = (n + 1/2)hv \quad n = 0, 1,2,\ldots$$

$$v = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}} \qquad m_r = \frac{m_1 m_2}{m_1+m_2}$$

Reaction Coordinate Diagrams and Isotope Effects

- Each point along a reaction coordinate is associated with a potential energy well that is perpendicular to the reaction coordinate. [relates to energy landscape]
- Each well has vibrational states associated with it.
- Activated complexes have vibrational modes with ZPE's just like any other molecular species.
- For every vibrational mode there is a ZPE difference between C–H and C–D:
  - Only those that are undergoing change along the reaction coordinate are relevant.
  - Give rise to energy differences between C–H and C–D activation energies, resulting in observed kinetic isotope effect.
- With primary kinetic isotope effects, the ZPE difference in the activated complex/transition state is smaller than in the reactants, resulting in a difference in activation energy between C–H and C–D.

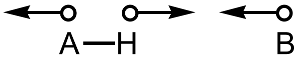


- The magnitude of a primary kinetic isotope effect depends on differences in the ZPE's in the reactant and the activated complex for all the vibrational modes of the reactant and activated complex.
- The changes in vibrations for the bonds undergoing transformations during the reaction dominate the isotope effect.

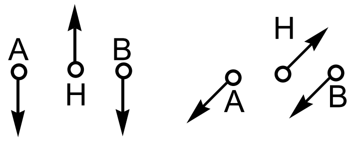
Primary Kinetic Isotope Effects for Linear Transition States

- Must have a reference point to compare to the transition state, and must identify the reaction coordinate.
- Hammond Postulate: the structure of the activate complex most resembles the structure of the molecules to which it is closest in energy.
- Based on Hammond Postulate, we can estimate the vibrational modes in the activated complex based on comparisons to the vibrational modes in the reactants and products (products may be reactive intermediates).
- Must also identify the vibrational mode that is the reaction coordinate because it will not contribute to the isotope effect at the transition state. [this vibration is not present in the transition state]
- Must pay attention to normal modes that are changing in the reactant and developing in the activated complex.

A. *Vibration that defines the reaction coordinate.*



B. *Degenerate transition state bending vibrations.*

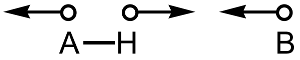


C. *Symmetric transition state stretch.*

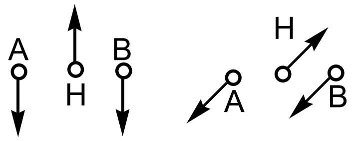
Primary Kinetic Isotope Effects for Linear Transition States

- Consider the deprotonation of an acid (H–A) by a base (B^-) that occurs with a linear transition state.
- The vibration that is the reaction coordinate leading to A–H bond cleavage and B–H bond formation is illustrated in figure **A.** to the right.
- The A–H bond stretching mode in the reactant is changing because this bond is breaking, but some binding remains in the transition state. Thus the observed isotope effect is diminished by other vibrational modes in the transition state.

A. *Vibration that defines the reaction coordinate.*



B. *Degenerate transition state bending vibrations.*



C. *Symmetric transition state stretch.*

- **B.** illustrates a pair of degenerate bending modes that occur in perpendicular planes. Bending modes are present in both reactants and transition state and have significantly lower force constants than stretches. Therefore, differences in bend modes do not typically contribute significantly to primary isotope effects.
- **C**. illustrates symmetric stretching vibration, which develops in the transition state that has not analogous mode in the reactants. This new vibration has a large force constant because it is a stretching vibration and thus will have a large effect on the magnitude of the isotope effect.

Primary Kinetic Isotope Effects for Linear Transition States

- If the deprotonation is very exothermic, then the transition state resembles the reactants, and little bond breaking has occurred at the acid and very little bond formation has occurred with the base.

  The bond holding the H to the complex closely resembles the bond in the reactant.

  The magnitude of the isotope effect is relatively small.

- If the reaction is very endothermic, the transition state resembles the products, and the bond between the proton and the base is almost completely formed.

  The symmetric stretch at the transition state greatly resembles the normal bond stretch in the product.

  When the B–H force constant is similar to that of A–H, the force constant for the transition state symmetric stretch will be similar to that of A–H, resulting in little difference between the ZPE's of the reactant and activated complex (small isotope effect).

- When the reaction is thermoneutral (or close to it), the bond that holds the H in the activated complex has it almost shared equally between A and B.

  The symmetric stretch is centered around the H with little or note movement of the H, and the frequency of this stretch does not depend strongly on the isotope.

  The ZPE difference between isotopes at the transition state very small.

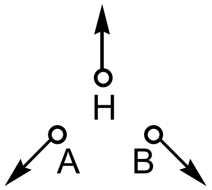
  The isotope effect is predicted to be large.

  Suggests that the isotope effect provides a rough measure of the position of the transition state along the reaction coordinate.

Isotope Effects for Linear vs. Non-linear Transition States

- To this point, we have focused on the analysis of the relative magnitude of isotope effects and changes in ZPE's for various vibrations that are transforming during a reaction.
- When the H/D transfer proceeds through an activated complex with bend bonds, bending modes become more significant.
- The force constants for scissoring and bending motions are significantly lower than for stretching motions.
- The changes in ZPE's between reactants and transition state are not as large for systems involving non-linear transition state as they are for reactions that involve linear transition states.
- The H in the analogous symmetric stretch still involves significant H movement.
- Expect lower magnitudes for primary kinetic isotope effects for systems involving non-linear (bent) transition states.

Symmetric transition state stretch.



Origins of Secondary Kinetic Isotope Effects

- Secondary kinetic isotope effect arises from isotopic substitution at a bond that is not being broken, and typically involve a change in bond hybridization or involvement of the bond in hyperconjugation.
- α or β secondary isotope effects: based on whether the isotope is on a position α or β to the bond that is changing.
- α effect occurs when the atom undergoing reaction has the associated isotope.
- β effect occurs when the associated isotope is on the atom neighboring that which is undergoing reaction.

Origins of Secondary Kinetic Isotope Effects: Hybridization Changes

- A difference in ZPE differences between the reactant and the transition state is necessary for the isotope effect to manifest.
- Consider the changes in vibrational modes that occur when an atom or atoms associated with a bond undergo rehybridization.
- Those vibrational modes that the largest force constants and those that undergo the largest changes will have the greatest impact on the isotope effect.
- A limited number of vibrational modes undergo large changes when a C–H bond involving an sp^3 hybridized C is changing to a bond involving an sp^2 hybridized C. [affected modes: stretching, and in-plane and out-of-plane bending bending motions].
- Similar vibrational mode changes arise when an sp^2 hybridized C is changing to a bond involving an *sp* hybridized C.
- C–H bond strengths: $sp^3 < sp^2 < sp$.... trend reflected in the bond stretching frequencies.
- A change in force constant occurs in the stretches of a bond undergoing rehybridization, but this change is small compared to when bond breaking is involved (primary kinetic isotope effect).
- The change in force constant due to rehybridization is too small to create significant isotope effects.

Origins of Secondary Kinetic Isotope Effects: Hybridization Changes

- In the case of *sp*^{3} and *sp*^{2} hybridized C, in-plane bending is essentially the same in both cases, indicating that there is little difference in the force constants of these motions.
- The in-plane and out-of-plane bends are degenerate for *sp*^{3} hybridized C, but the in-plane bend in *sp*^{2} C is much stiffer than the out-of-plane bend for *sp*^{2} C.
- The large difference in the force constants associated with out-of-plane bends for *sp*^{3} and *sp*^{2} hybridized C means that there will be a significant difference in the ZPE differences between C–H and C–D bonds in reactions that involve rhybridization between *sp*^{3} and *sp*^{2}.
- Therefore, it is this bending mode that gives rise to the measurable secondary isotope effect. [even at their largest, these effects are much smaller than those of typical primary kinetic isotope effects].
- In typical reaction coordinate diagrams, we plot potential energy wells for bending motions. Since the transition state is developing character at the C bearing the isotopic substitution, the force constant is weaker at the transition state than for the reactant.... The reaction is slower when the reaction has a D on the C undergoing rehybridization.

Origins of Secondary Kinetic Isotope Effects: Hybridization Changes

- In the case of going from *sp*^{2} and *sp*^{3} hybridization at C, the force constant for the bending motion gets larger at the transition state because the vibration is becoming stiffer.
- In this scenario, the ZPE difference at the transition state is larger than at the reactant, which means the reaction for the deuterated reactant proceeds faster. [<u>inverse kinetic isotope effect</u>]
- Isotope effects values of 0.8 to 0.9 are common in these cases.
- A secondary isotope effect can also arise form the involvement of C–H(D) bond through hyperconjugation in a rate-limiting step.
- For example S$_N$1 reaction a carbocation is created in the slow step, and C–H(D) bonds β to the cationic center stabilize the cation by hyperconjugation. This weakens the C–H (D) bonds, which will lead to a normal secondary kinetic isotope effect.

Steric Isotope Effects

- An alternative mechanism by which we can see isotope effects in cases that do not involve breaking or making C–H bonds.

- **Steric effect:** the differing effective steric sizes of H and D come into play.

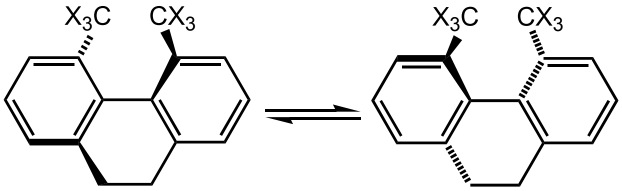
- C–H vs. C–D: not only is the ZPE less for D, but the vibrational amplitude for D should be less than H... and accordingly, D should appear smaller than H.

- Racemization of a chiral biphenyl compound provides a classic example of steric isotope effect:

  Rotation around the central bond racemizes the material and forces a sever steric class between the two methyl groups in the transition state.

  Compound with deuterated methyl groups racemizes faster than the analogous protio compound.... behavior consistent with notion that D is effectively smaller than H.

  The effect is not large (only a 15% difference between D and H methyl groups).



$$\frac{k\ (X=D)}{k\ (X=H)} = 1.5$$

- Steric isotope effects can be comparable to other secondary isotope effects and should be considered when evaluating experimental data.