

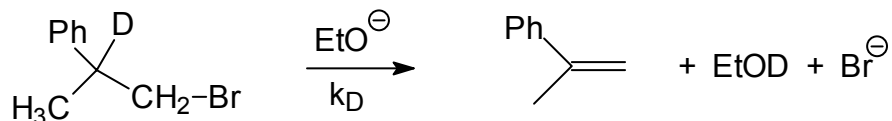
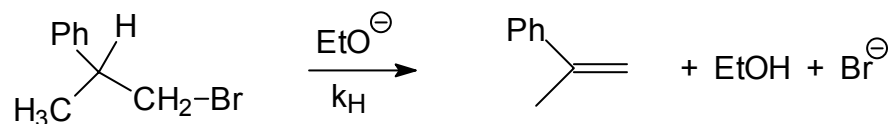
Kinetic isotope effects

Replacement of one or more atoms in a molecule by an isotope of that atom can affect the chemistry.

e.g. CH_4 , CH_3D , CH_2D_2 , CHD_3 , CD_4 ; All the same molecule except for the isotope of hydrogen; these are isotopomers, as also are $^{12}\text{CH}_4$, $^{13}\text{CH}_4$, $^{14}\text{CH}_4$.

The mass of one or more atoms has changed, but the electronic environment is unchanged, and the steric effects are very similar.

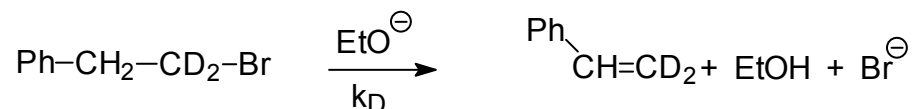
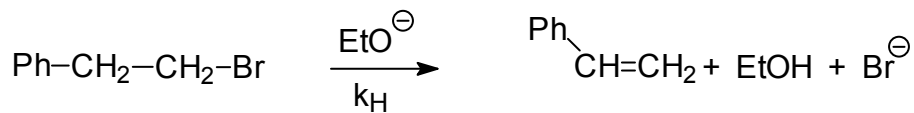
Example of a Kinetic Isotope Effect (KIE)



$$k_{\text{H}}/k_{\text{D}} = 7.82 \text{ at } 25^{\circ}\text{C}$$

In this example the C-H or C-D bond is broken during the reaction
PRIMARY Kinetic Isotope Effect (Primary KIE or 1° KIE)

Contrast with:



$$k_{\text{H}}/k_{\text{D}} = 1.09 \text{ at } 25^{\circ}\text{C}$$

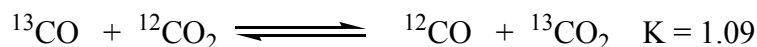
In this example the bonds to CH or CD are not broken during the reaction (but there is a change in hybridization at carbon, and thus a change in IR frequency for the CH bonds)

SECONDARY Kinetic Isotope Effect (Secondary KIE, 2° KIE)

Secondary KIE are usually small

KIE refer to rate constant ratios, $k_{\text{H}}/k_{\text{D}}$

There are also equilibrium isotope effects (EIE) which refer to equilibria $K_{\text{H}}/K_{\text{D}}$

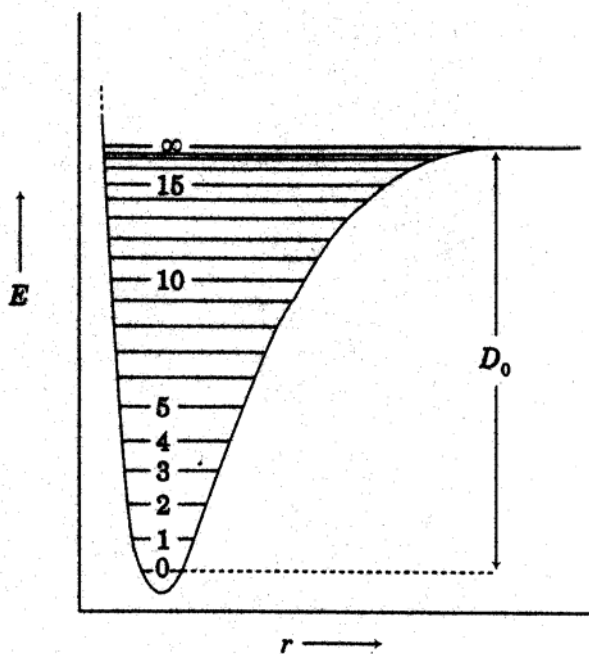


The hydrogen isotopes have special atomic symbols and names

^1H	Protium	H
^2H	Deuterium	D
^3H	Tritium	T

Some theory

The Morse curve for a hypothetical diatomic molecule X-H



Bond dissociation energy = $D_0 = \text{BDE} = E_\infty - E_0$. Note that BDE is relative to E_0 and not to the bottom of the energy well. Quantum mechanics (Heisenberg uncertainty principle) does not allow the position of a particle to be specified exactly

$$E_v = (n + \frac{1}{2})h\nu = (n + \frac{1}{2})hc\bar{\nu}$$

$$E_1 - E_0 = \Delta E = h\nu = hc\bar{\nu}$$

$\bar{\nu}$ is the wavenumber (cm^{-1})

c is the velocity of light ($3 \times 10^{10} \text{ cm s}^{-1}$)

For isotopomers, say C-H vs C-D, the C-H and C-D stretching frequencies differ because of the difference in mass.

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k_F}{\mu}} \quad \text{where } k_F \text{ is the force constant, corresponding to the "stiffness" of a spring, determined by electrons and charges - not changed by isotopic substitution}$$

$$\mu = \frac{m_1 m_2}{m_1 + m_2} \quad \mu \text{ is the "reduced mass"} \quad 1/\mu = 1/m_1 + 1/m_2$$

for C-H, $\mu = 12 \times 1 / (12 + 1) = 12/13 = 0.923$

for C-D, $\mu = 12 \times 2 / (12 + 2) = 24/14 = 1.714$

For CD and CH k_F 's are the same, so $\nu_D < \nu_H$, specifically

$$\frac{\nu_H}{\nu_D} = \frac{\frac{1}{2\pi} \sqrt{\frac{k_F}{\mu_H}}}{\frac{1}{2\pi} \sqrt{\frac{k_F}{\mu_D}}} = \sqrt{\frac{k_F \mu_D}{k_F \mu_H}} = \sqrt{\frac{\mu_D}{\mu_H}} = \sqrt{\frac{1.714}{0.923}} = 1.363$$

and so $\nu_D = \nu_H / 1.363 = 3000 / 1.363 = 2201 \text{ cm}^{-1}$

E_0 , the zero point energy

$$(E_0)_{CH} = \frac{1}{2} h \nu = \frac{1}{2} h c \bar{\nu} \quad \text{per molecule}$$

$$= \frac{1}{2} h c \bar{\nu}_{CH} N_A \quad \text{per mole}$$

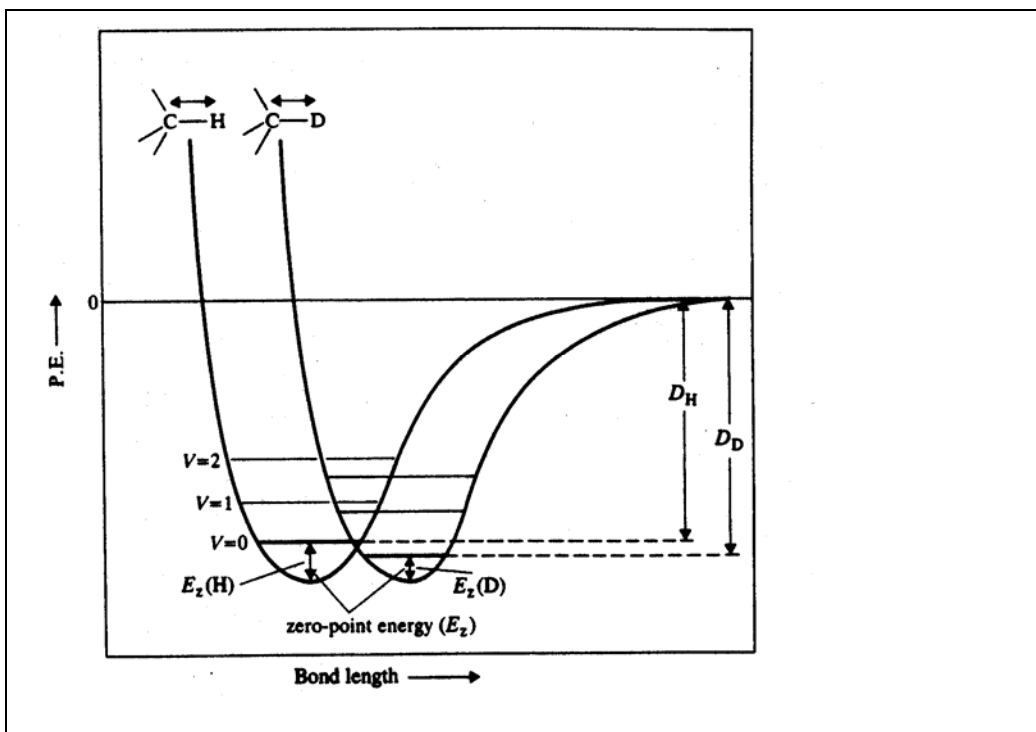
$$(E_0)_{CD} = \frac{1}{2} h c \bar{\nu}_{CD} N_A$$

$$\Delta E_0 = (E_0)_{CH} - (E_0)_{CD} = \frac{1}{2} h c (\Delta \bar{\nu}) N_A$$

$$= h c N_A \frac{800}{2}$$

$$= 6.626 \times 10^{-34} (\text{J}^1 \text{s}^1) \times 3.00 \times 10^{10} (\text{cm}^1 \text{s}^{-1}) \times 6.02 \times 10^{23} (\text{mol}^{-1}) \times 400 (\text{cm}^{-1})$$

$$= 4785 (\text{J}^1 \text{mol}^{-1}) = 4.785 (\text{kJ}^1 \text{mol}^{-1}) = 1.14 (\text{kcal}^1 \text{mol}^{-1})$$



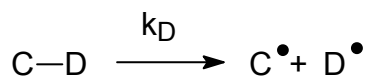
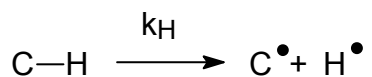
(These curves should be on top of each other but have been shifted sideways so you can see more clearly where the energy levels belong.)

$$\text{BDE} = E_{\infty} - E_0$$

For dissociation of the C-H (or C-D) bond

$$\text{BDE}_{\text{CD}} \text{ (for C-D bond)} = \text{BDE}_{\text{CH}} + 4.8 \text{ kJ mol}^{-1}$$

For dissociation



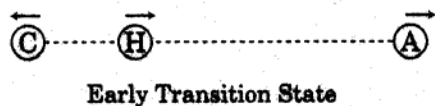
$$\frac{k_{\text{H}}}{k_{\text{D}}} = e^{(\Delta G_{\text{D}}^{\ddagger} - \Delta G_{\text{H}}^{\ddagger})/RT} = e^{\Delta \Delta G^{\ddagger}/RT} = e^{\frac{4785}{8.3145 \times 298}} = 6.9 \text{ at } 25^{\circ}\text{C}$$

larger at lower temperature, smaller at higher temperature

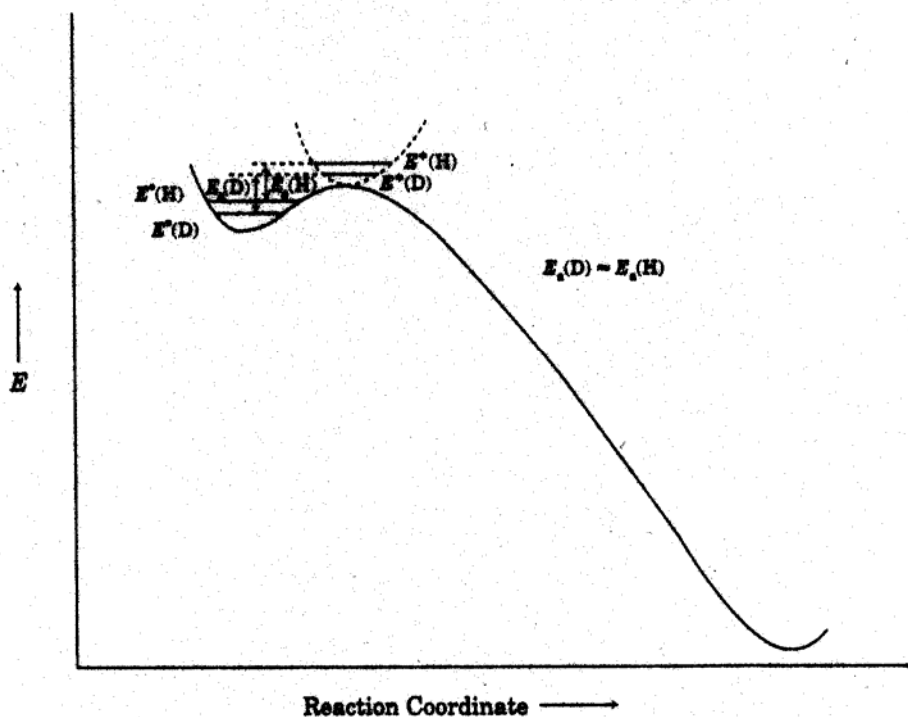
Most reactions are not bond dissociations. What about other types of reaction?

Note the treatment so far is oversimplified. One should consider bending vibrations as well. Inclusion of more terms gives a somewhat larger KIE.

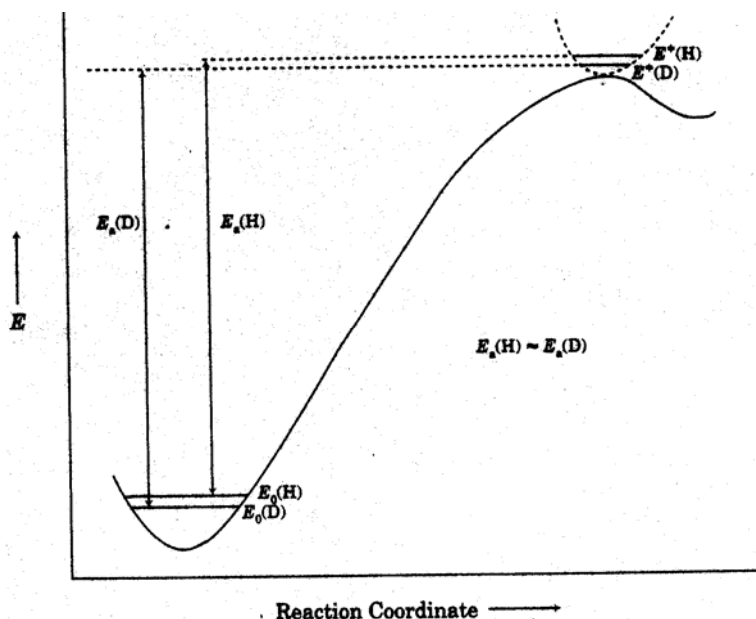
If the transition state occurs early, the C-H or C-D bond will be only slightly broken in the transition structure. The stretching vibrational mode shown below will be affected by the



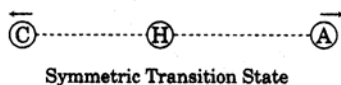
mass of the hydrogen (or deuterium) atom, so that the difference in transition state energy for the C-H or C-D species will be nearly the same in the transition structure as in the reactant. As shown on the hypothetical potential energy surface for the abstraction, there will be only a small difference in activation energies for the C-H or C-D reactions. Therefore, k_H/k_D will be close to unity for such a process.



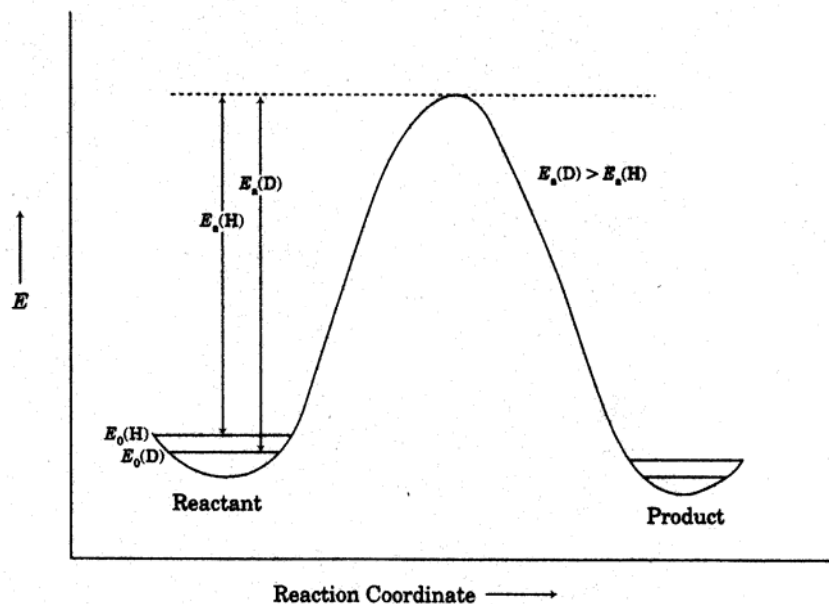
In a very endothermic reaction the transition structure closely resembles the product. Although the original C-H or C-D bond will be almost fully broken, the bond between H or D and the abstracting atom (A) will be nearly fully developed. In the transition structure there will be nearly the same difference in zero point energies for the developing A-H or A-D bond as there is in the C-H or C-D bond in the reactant. As a result, the activation energy for abstracting a deuterium will be very similar to that for abstracting a hydrogen atom, so there will be only a very small primary kinetic isotope effect. In the limit the KIE will become equal to the EIE which depends on the difference in vibrational frequencies between starting material and product.



In a thermoneutral reaction the transition state is symmetrically located along the reaction coordinate. Now the hydrogen atom does not move in the vibrational mode illustrated below, so the frequency of the vibration does not depend on its mass.

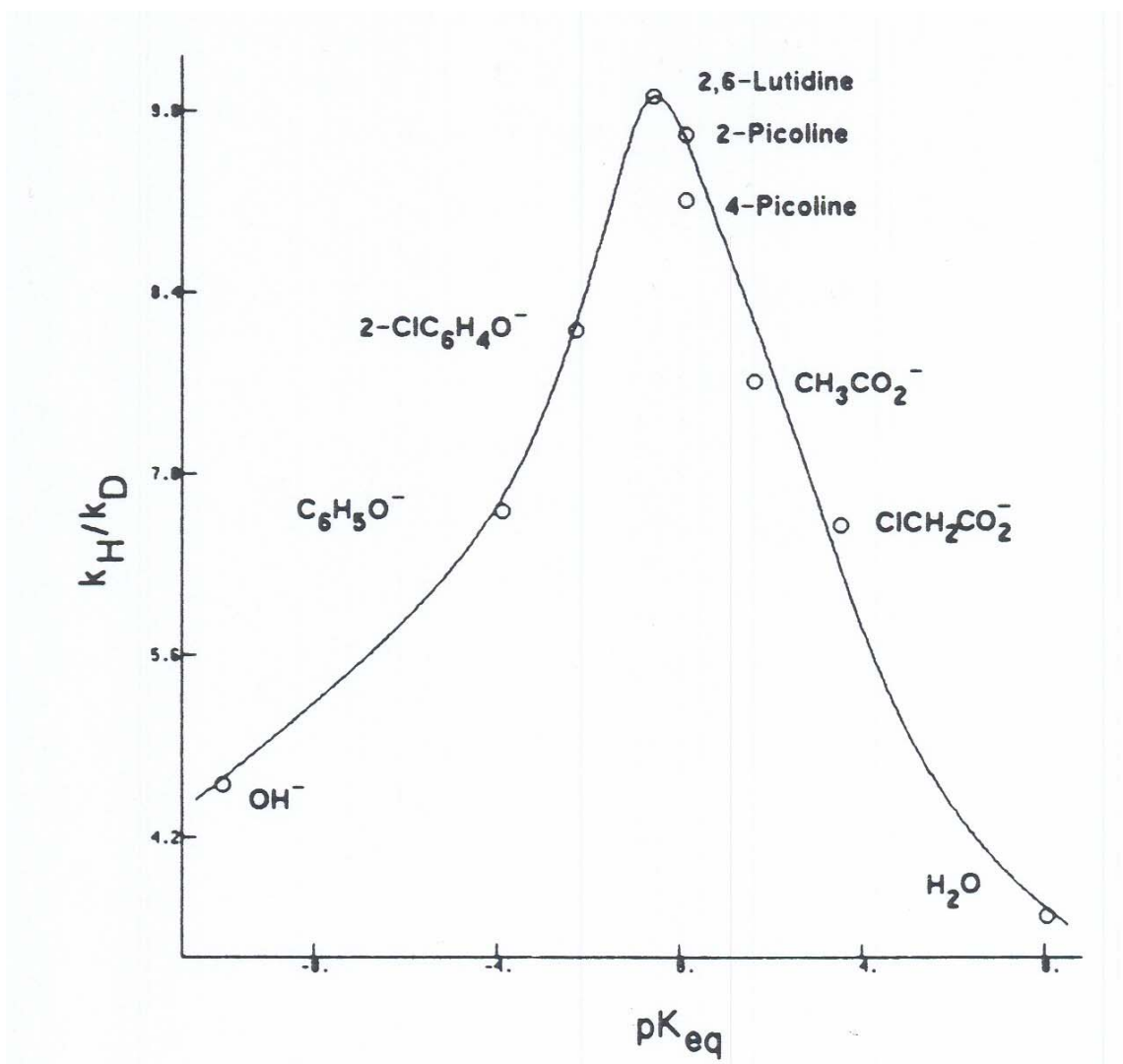


Therefore $E^\ddagger(D) = E^\ddagger(H)$; that is, the transition state energy is the same, whether it is a hydrogen or deuterium atom that is being abstracted. As shown below, the activation energies for the abstraction of H and D will differ by an amount equal to the difference in the C-H and C-D bond zero point energies, so there should be a significant kinetic isotope effect.



This situation appears to describe the oxidation of $\text{CH}_3\text{CDOHCH}_3$ by chromic acid, example 1 below. Westheimer and Nicolaidis found that the value of k_H/k_D for the reaction was approximately 6.6, thereby confirming that the H-C bond is broken in the rate-limiting step of the reaction sequence.

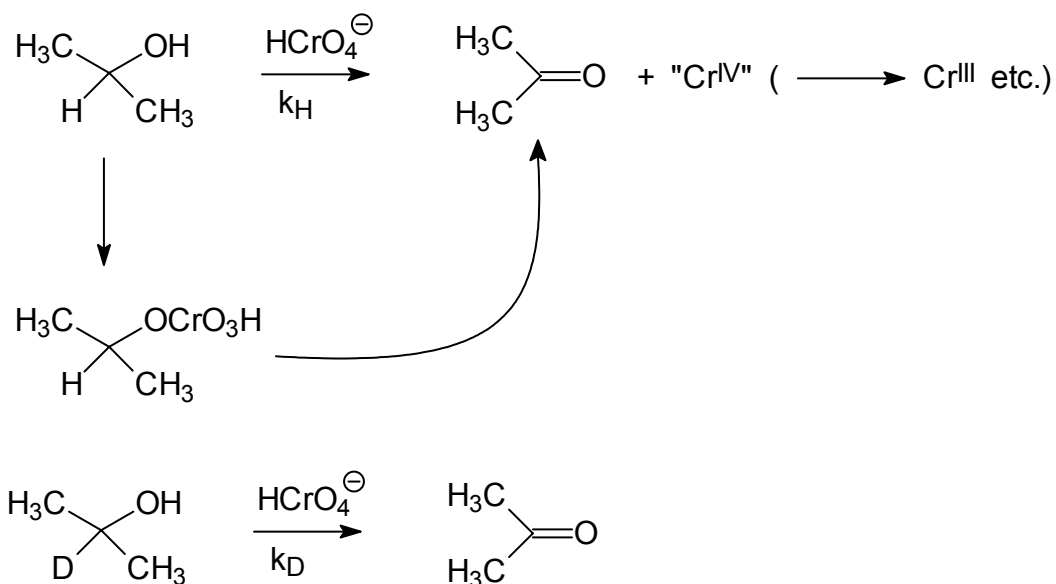
That there is a maximum in KIE has been confirmed for several systems



Kinetic Isotope Effects on the Reactions of Ethyl nitroacetate with Bases. pK_{eq} is the negative logarithm of the equilibrium constant for the proton transfer reaction. The curve drawn has no significance; it is meant only to guide the eye through the points. Data are from Bell, "The Proton in Chemistry"

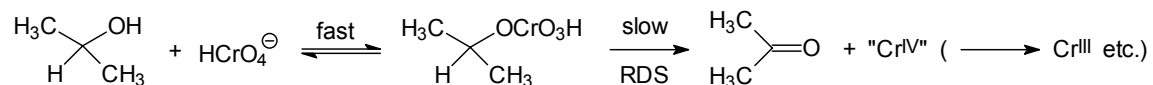
Applications of KIE's

1)



Found: $k_\text{H}/k_\text{D} = 6.6$ (under one set of conditions)

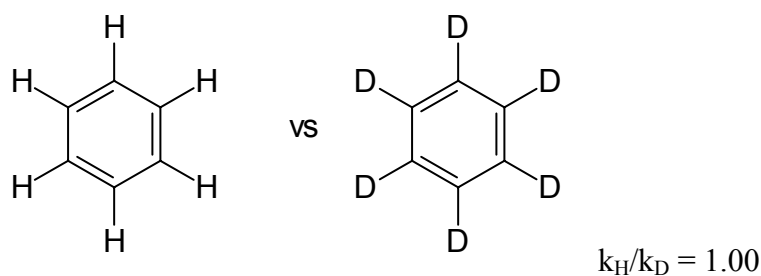
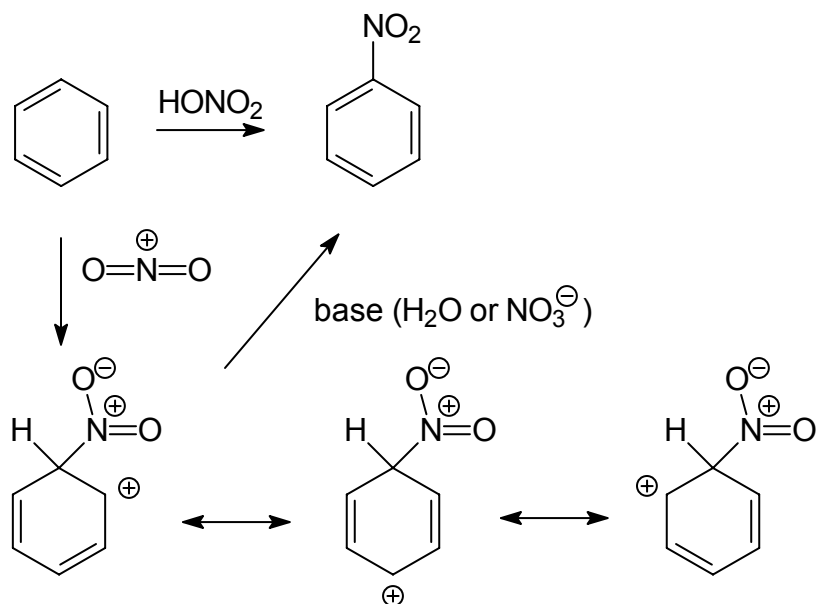
What does this result tell us? This size of the KIE says it is primary, therefore the C-H(D) bond is being broken in the RDS



The second step is RDS. Note that the esterification step might have been rate determining, because we do not know, *a priori*, how rapidly this sort of inorganic ester forms.

For Ar-CH(CH₃)-OH the Hammett ρ is -0.4 to -1.0

2) Nitration of benzene

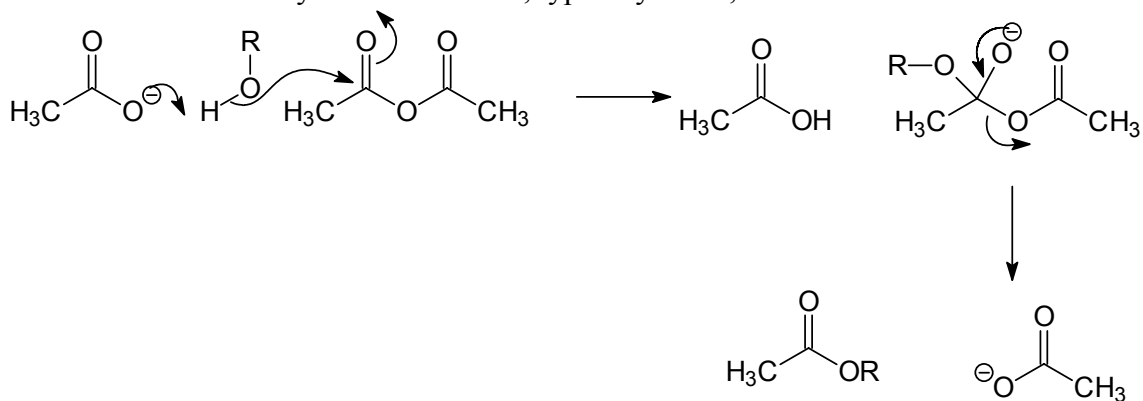


This means that H is lost after the RDS, so that there is no 1° KIE

Solvent Isotope Effects

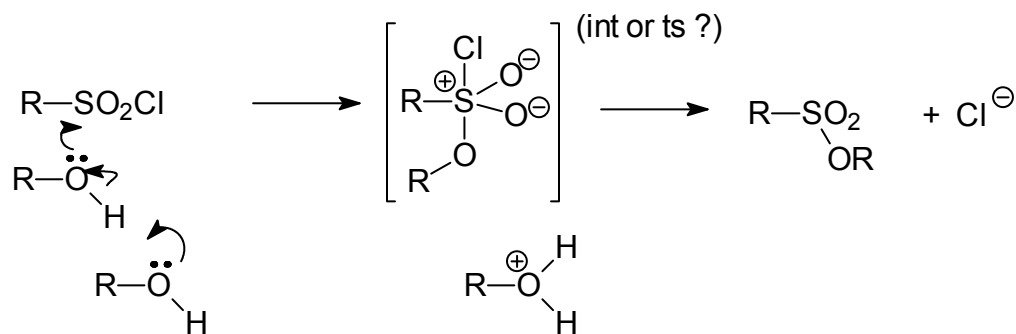
Reaction in H_2O vs D_2O or MeOH vs MeOD etc.

General acid/base catalysis: normal KIE, typically small, 1.0 - 3.0



Acetate ion acting as a general base (how do we know it is not acting as a nucleophile?)

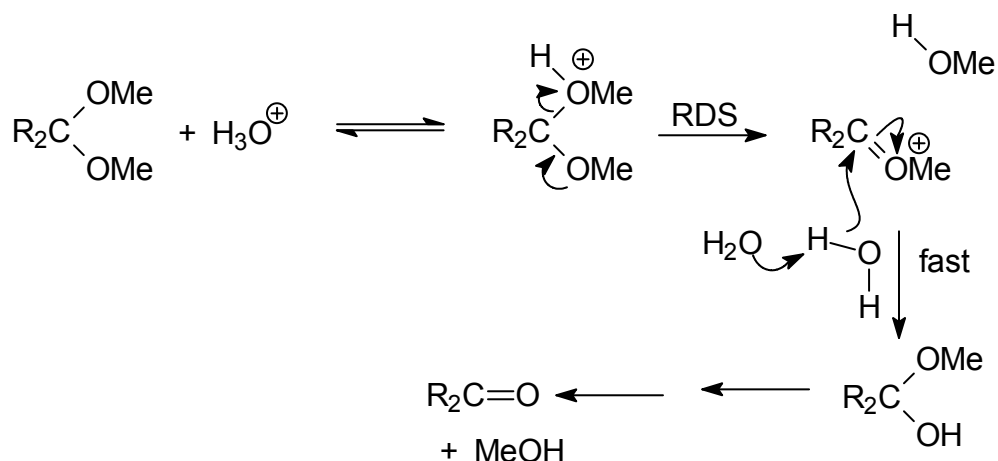
$k_{\text{H}}/k_{\text{D}} = 2.4$



$$k_H/k_D = 1.5$$

One would expect a primary KIE for the H being transferred from O to O. There is something going on here which is not well understood, and one generally does not see this expected primary KIE, and the observed KIE is from the secondary effects. A possible explanation is that the hydrogen bond involving the hydrogen which will be transferred at the rate determining step becomes shorter as the energy difference between the proton not transferred and proton transferred species becomes smaller. For transfer between oxygens (or other electronegative atoms) this can mean that the hydrogen never really has to cross a barrier, and thus that there is no primary isotope effect. For removal of a hydrogen from carbon, there is only a weak hydrogen bond, which never gets short, so there is always a barrier to be crossed, and thus a normal primary isotope effect.

Specific acid/base catalysis with INVERSE isotope effect



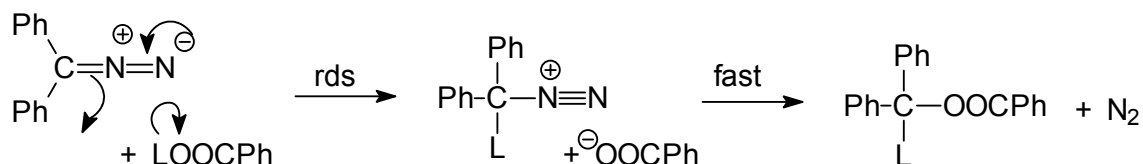
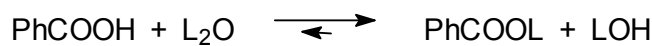
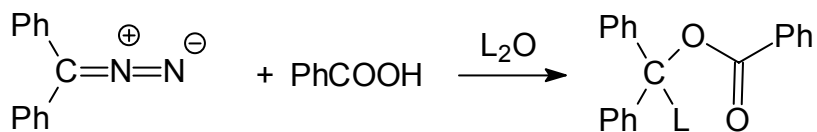
$$k_H/k_D = 0.33 \text{ to } 0.55 \text{ depending on R}$$

How so? Acids are stronger in H_2O than in D_2O by a factor of approximately 3 ($\Delta pK_a = 0.5$). The net KIE results from an inverse EIE for K_1 and a small normal KIE for k_2 .

$$\text{observed KIE} = (1/3)(1 \leftrightarrow 3) = 0.33 \leftrightarrow 1.0$$

With a more elaborate method we could do a better prediction, but this is enough to confirm that inverse KIE is expected for SAC.

Another example



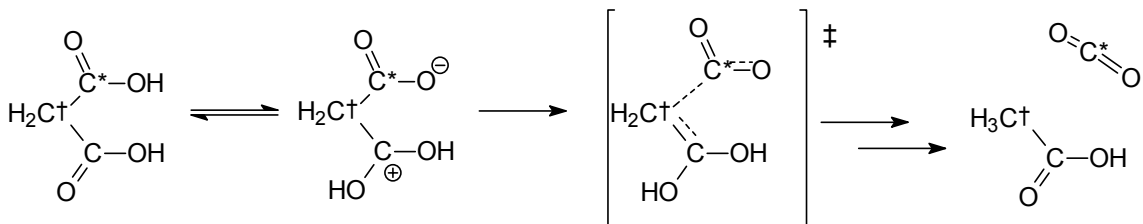
$k_H/k_D \sim 4$ to 5 .

This is a proton transfer from O to C and as such is an inherently slow process for which we see the normal sort of primary KIE

Heavy atom isotope effects

Possible and useful, but the effects are small: recall that the KIE depends on

$$\sqrt{\frac{\mu_{\text{heavy}}}{\mu_{\text{light}}}}$$



$$* \quad k_{12}/k_{14} = 1.065; \quad \ddagger \quad k_{12}/k_{14} = 1.076$$

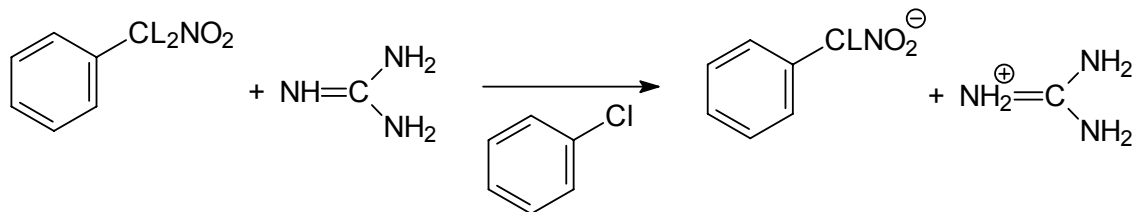
Usually measured by mass spectrometry; often with a specialized isotope ratio mass spectrometer.

	Typical value
Carbon isotope effects: k_{12}/k_{14} , k_{12}/k_{13}	1.07 1.04
Chlorine isotope effects: k_{35}/k_{37}	1.0106
Bromine isotope effects: k_{79}/k_{81}	1.002
Sulfur isotope effects: k_{32}/k_{34}	1.014
Oxygen isotope effects: k_{16}/k_{18}	1.06
Nitrogen isotope effects: k_{14}/k_{15}	1.04

Tunneling effects

Quantum mechanical tunneling - usual reason assigned for occasional observation of very large KIE's for hydrogen. Often accompanied by non linear Arrhenius plots of $\log k_H$ vs $1/T$

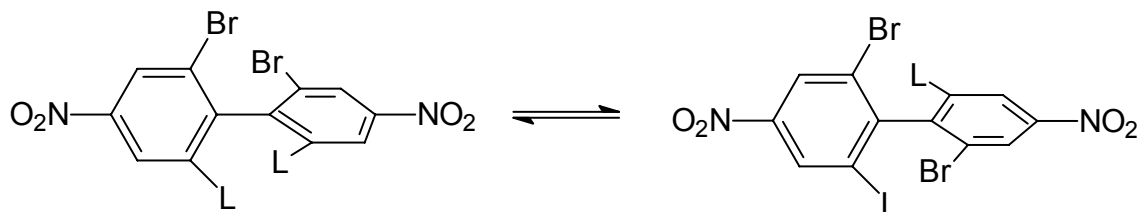
(very often seen only for reactions where the proton being transferred is "hidden" from solvent or in a non-hydrogen bonding solvent)



$$k_H/k_D = 50$$

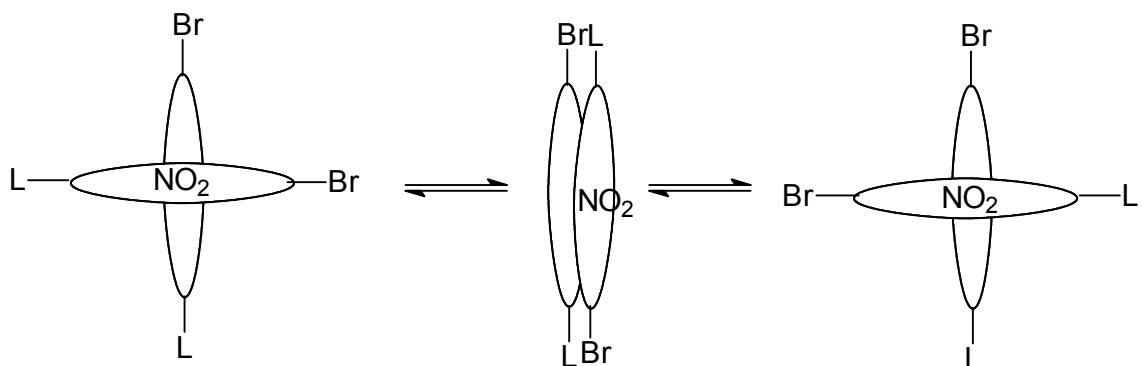
Tunneling effects are observed in a number of enzyme catalyzed redox reactions involving hydrogen transfer.

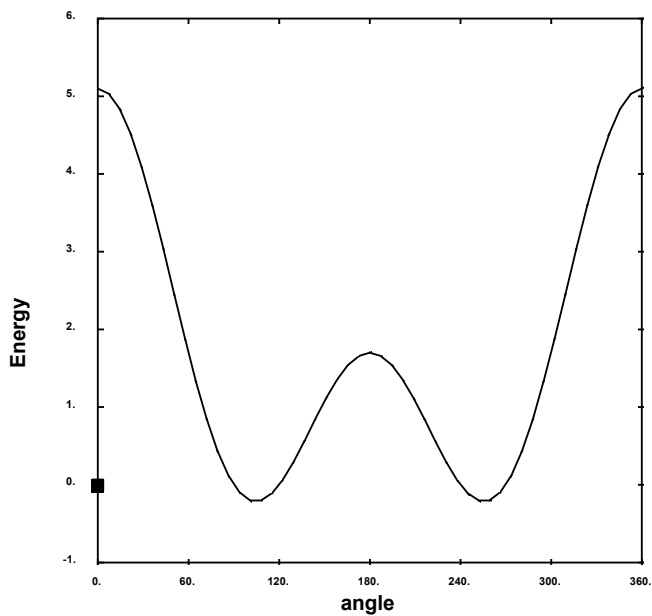
Steric isotope effects



Atropoisomers

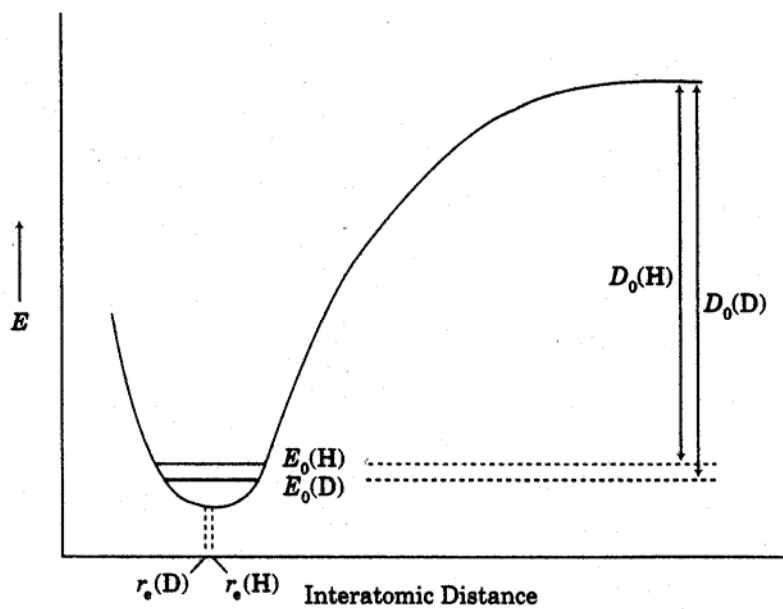
A pair of enantiomers differing only by rotation about a single bond. The bulk of the bromine makes this slow enough to follow





$k_H/k_D = 0.84$. Why is this?

Because of the lower zero point frequency for C-D the deuterium is effectively smaller than the hydrogen. The lower frequency leads to a smaller amplitude of vibration for C-D and thus C-D is effectively smaller, and thus imposes a smaller barrier to Br slipping past as the biphenyl rotates.



Summary

H/D isotope effects

Primary KIE

Maximum (central TS) 7 to 8

For unsymmetrical transition states

Early small to 1.0

Late limit is the EIE, so a limit of 1 to 2

Secondary KIE

Small, 0.71 to 1.41

Equilibrium isotope effect (EIE)

Typically 0.7 to 1.4

Solvent (H₂O/D₂O)

GAC or GBC: $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ is 1 to 3

SAC or SBC: $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ is 0.33 to 1.0