

Testing a Mechanism: Kinetic Isotope Effects

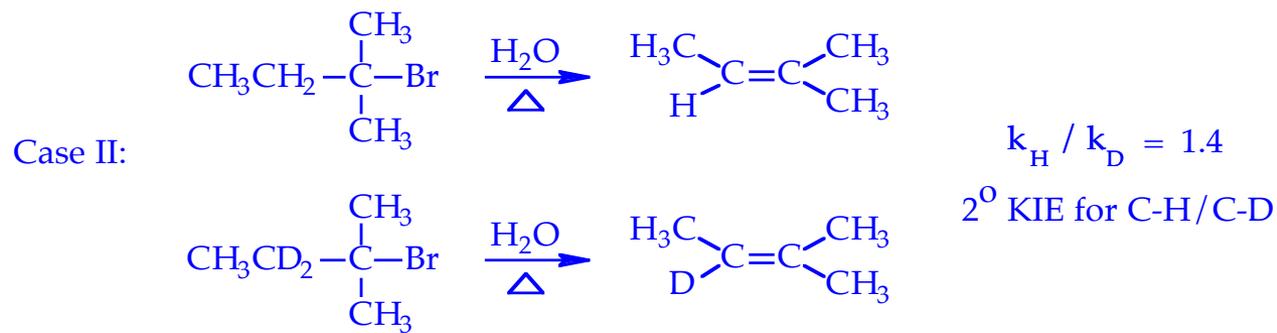
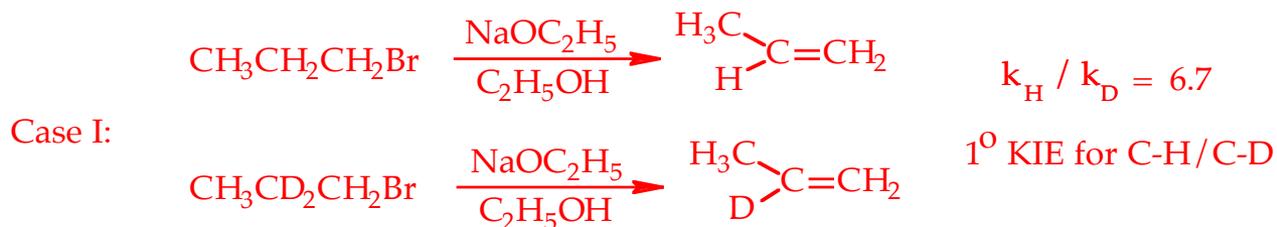
- ★ **Primary Isotope Effect** - rate change due to isotopic substitution at a site of bond breaking or bond making in the rate determining step of a mechanism.
- ★ **Secondary Isotope Effect** - rate change due to isotopic substitution at other than a site of bond breaking or bond making in the rate determining step of a mechanism.

Primary Kinetic Isotope Effect: Typical Values

<u>Nuclide</u>	<u>$k_{\text{light}} / k_{\text{heavy}}$ (at 25^o C)</u>
C-H/C-D	6 - 8
C-H/C-T	15 - 16
¹² C / ¹³ C	1.04
¹² C / ¹⁴ C	1.07
¹⁴ N / ¹⁵ N	1.03
¹⁶ O / ¹⁸ O	1.02
³² S / ³⁴ S	1.01
³⁵ Cl / ³⁷ Cl	1.01

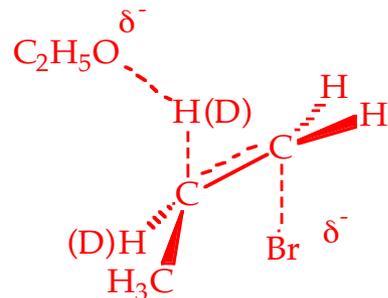
EXAMPLES OF KINETIC ISOTOPE EFFECTS

Consider the following dehydrohalogenation reactions:

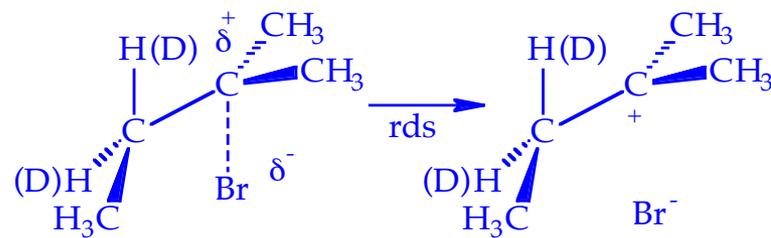


Rationale:

Transition State for Case I (E-2)



Transition State for Case II (E-1)



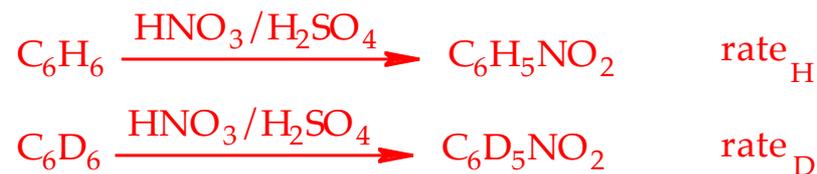
More Examples of Kinetic Isotope Effects

Consider the following decomposition of an azo compound:



Rationale: Although the above rate enhancement is small in absolute terms, for the nitrogen nuclides indicated, the enhancement is indicative of a primary kinetic isotope effect.

Consider the nitration of benzene shown below:



Observation: $\text{rate}_{\text{H}} \cong \text{rate}_{\text{D}}$

Conclusion to be drawn: A C-H (C-D) bond is not being broken in the rate determining step of electrophilic aromatic nitration.

Secondary Kinetic Isotope Effects

- ✦ ***Differences in steric demand***
- ✦ ***Hyperconjugative effects***
- ✦ ***Differences in inductive effect***

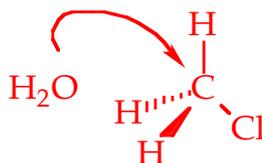
Examples of Secondary Kinetic Isotope Effects

Differences in Steric demand



Observation: $k_{\text{H}} / k_{\text{D}} = 0.97$

Rationale:



Example of an inverse α -isotope effect

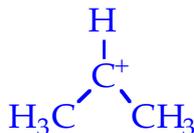
In order to initiate bond making, the incoming nucleophile must be able to approach the substrate from the rear.

The shorter C-D bonds (relative to C-H bonds) permit a closer approach by H_2O and bond making can begin sooner.



Observation: $k_{\text{H}} / k_{\text{D}} = 1.13$

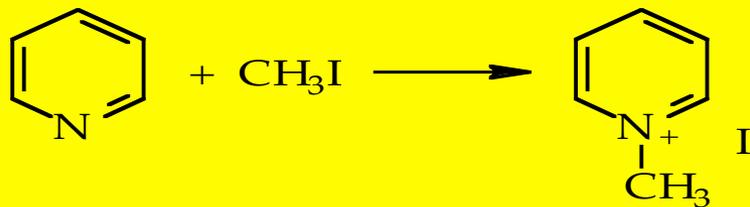
Rationale:



In the transition state leading to the isopropyl carbocation, there is a greater relief of strain for C-H relative to C-D.

Secondary Kinetic Isotope Effects

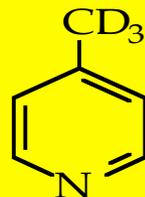
Example III:



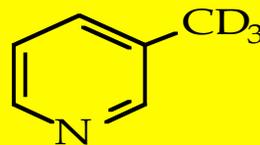
Observations:

Pyridine Substrate

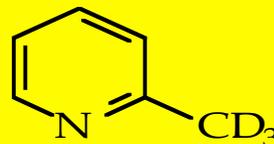
k_D / k_H



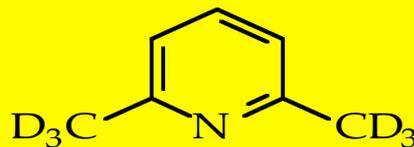
1.001



1.009



1.030

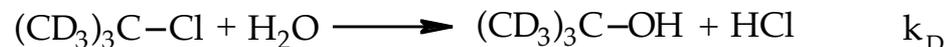
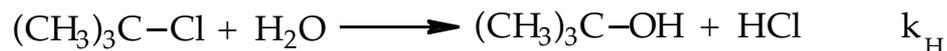


1.095

Secondary Kinetic Isotope Effects

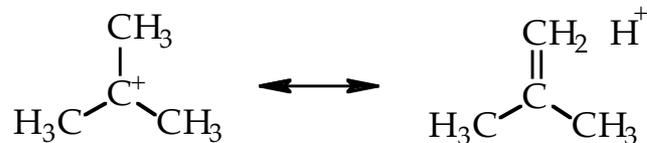
Hyperconjugative effects

Example: β -Isotope effect



Observation: $k_{\text{H}} / k_{\text{D}} = 1.21$

Rationale:



Whereas a C-D bond is slightly stronger than a C-H bond, hyperconjugation as shown above is not quite as effective at stabilizing the carbocationic intermediate for the reaction using deuterated reactant relative to that using unlabeled reactant.

Another view: Whereas C-H bonds at a given temperature are slightly longer than corresponding C-D bonds, formation of a carbocationic intermediate provides more relief from steric strain for unlabeled reactant compared with that experienced by deuterated reactant.

SECONDARY KINETIC ISOTOPE EFFECTS

Inductive effects



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

Rationale: Hydrogen is slightly more electronegative than deuterium.

Related Question: Which one of the following is more basic?

