Kinetic Isotope Effect (KIE):

The effect of isotopic substitution on a rate constant is referred to as a kinetic isotope effect, for example, in the reaction:

\[ A + B \rightarrow C \]

the effect of isotopic substitution in reactant A is expressed as the ratio of rate constants \( k_I/k_O \), where the superscripts l and h represent reactions in which the molecules A contain the light and heavy isotopes, respectively. Thus KIE is a mechanistic phenomenon wherein isotopically labelled molecules react at different rates. For example,

\[
\begin{align*}
\text{O} & \quad \text{H}_3\text{C}^-\text{C}^-\text{CH}_3 \quad \xrightarrow{\text{Br}_2, \text{H}_2\text{O}, \text{cat. H}^+} \quad \text{H}_3\text{C}^-\text{C}^-\text{Br}^- \\
\text{D}_3\text{C}^-\text{C}^-\text{CD}_3 \quad \xrightarrow{\text{Br}_2, \text{H}_2\text{O}, \text{cat. H}^+} \quad \text{D}_3\text{C}^-\text{C}^-\text{Br}^-
\end{align*}
\]

\[ k_{\text{rel.}} \quad k_{\text{H}} = 7.0 \quad k_{\text{D}} = 1.0 \]

The deuterated acetone (acetone-D6 / acetone-d6) reacts slower than acetone.

The kinetic isotope effect attributable to isotopic substitution of an atom to which a bond is made or broken in the rate determining step or in a pre-equilibrium step of a specified reaction is termed a primary kinetic isotope effect (PKIE).

**Key assumptions:**

1. Isotopic substitution does not affect the potential energy surface of the reaction or the energies of the electronic states.

2. Only mass dependent properties are affected, most importantly, vibrational frequencies.
   - Primary KIE: occurs when isotopically labelled bonds are made or broken in the RDS.
   - Secondary KIE: occurs when isotopically labelled bonds are not made or broken in the RDS.

**Quick review of vibrational spectroscopy:**

- All bonds have quantized vibrational energy levels.
- The vibrational energy levels \( \varepsilon_n \) are dependent on the frequency of the bond stretch (\( \nu \)), which in turn is dependent on the mass of the two connected atoms.

\[
\varepsilon_n = \left( n + \frac{1}{2} \right) h \nu \quad \text{where} \quad \nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}}
\]

where \( k \) is the force constant of the bond, and \( m \) is the reduced mass of the system:

![m1 -- m2](image)

and is given by

\[
\mu = \left( \frac{1}{m_1} + \frac{1}{m_2} \right)^{-1} = \frac{m_1 m_2}{m_1 + m_2}
\]
<table>
<thead>
<tr>
<th>Bond</th>
<th>Reduced mass ($\mu$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{12}$C-$^1$H</td>
<td>0.923</td>
</tr>
<tr>
<td>$^{12}$C-$^{2}$H</td>
<td>1.714</td>
</tr>
<tr>
<td>$^{12}$C-$^{13}$C</td>
<td>6.00</td>
</tr>
<tr>
<td>$^{12}$C-$^{15}$C</td>
<td>6.24</td>
</tr>
<tr>
<td>$^{15}$C-$^1$H</td>
<td>0.929</td>
</tr>
</tbody>
</table>

At room temperature, 99.9% of the C-H bonds are in the ground vibrational level ($n = 0$). The energy that the molecule possesses in the ground vibrational state is known as the zero-point energy (ZPE, $\frac{1}{2} \hbar \nu$) and this forms the basis of the reactivity difference in isotopomers.

**Physical origin of KIE:**

The simplest case is the homolysis of C-H/D bond where the bond is considered to be fully broken in the TS. The reaction progress is followed by observing the C-H/D bond stretch.

Point to note:

\[ \mu_{C-H} < \mu_{C-D} \]

We know that \[ \nu \propto \frac{1}{\sqrt{\mu}} \]

Therefore, \[ \nu_{C-H} > \nu_{C-D} \]

Calculation shows that,\[
\begin{array}{|c|c|c|c|}
\hline
 & \nu (\text{cm}^{-1}) & \text{ZPE (kcal.mol}^{-1}\text{)} & \text{Relative rate (300 K)} \\
\hline
\text{C-H stretch} & 2900 & 4.15 & \sim 6.9 \\
\text{C-D stretch} & 2100 & 3.00 & 1.0 \\
\hline
\end{array}
\]

Point to note that higher the ZPE, easier it is to break the bond (lesser energy has to be supplied to reach the continuum).

Therefore, it is easier to break a C-H bond than it is to break a C-D bond.

The following energy diagram is instructive.
As the C-H/C-D bond breaks at the TS the stretch becomes a translation. As a result, there is no new stretch in the TS that corresponds to the stretch of that bond in the GS. In other words, the TS for the protiated and the deuterated compounds are at the same energy level, but they start from different vibrational level in the respective reactants. For this mechanism, the difference of ZPEs control the isotope effect entirely.

Using KIE to distinguish between reaction mechanisms:

KIEs provide useful information regarding the RDS of a reaction mechanism. Consider the following:

Dehydrobromination: Loss of H and Br from adjacent (vinylal) carbons

This KIE result is consistent with an E2 elimination in which the C-H/D bond is broken in the RDS.

because the C-H bond is weaker than the C-D bond.
Again,

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Br} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

$\xrightarrow{\text{H}_2\text{O, heat}}$

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{D} & \quad \text{D}
\end{align*}$$

$\xrightarrow{\text{H}_2\text{O, heat}}$

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

value much smaller than PKIE

$$\frac{k_H}{k_D} = 1.4$$

SKIE for C-H/D

This KIE result is consistent with an E1 elimination in which the C-H/D bond is not broken in the RDS. Therefore, this mechanism cannot be E2. The formation of the carbocation is actually the rate determining step here:

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Br} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

$\xrightarrow{k_H \text{ slow}}$

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{H} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

RDS of E1

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Br} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

$\xrightarrow{k_D \text{ slow}}$

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{H} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

RDS of E1

because the C-H bond is weaker than the C-D bond

Considering hyperconjugation,

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

is more effective than

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

According to Hammond's postulate:

$$\begin{align*}
\text{TS leading to} \\
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

is more stable than the TS leading to

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

$$\begin{align*}
\text{E}_a \text{ for formation of} \\
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

is less than that for the formation of

$$\begin{align*}
\text{Me} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

$k_H > k_D \implies \text{KIE}$

But C-H / C-D does not break in the RDS, C-Br does. So this is not PKIE, it is SKIE.

This is an example of the secondary KIE. The deuterated compound ionizes a little bit slowly as the corresponding carbocation is less stable that its protium analogue. This is a result of the less efficient hyperconjugation involving C-Br bond, instead of the C-β-H bond. Because this involves a D/H at the β-carbon, it is called a β-SKIE. The less stable deuterated cation forms a little slowly than the protium analogue, rate differs for two compounds.

CEMA, CC-3
**Examples of PKIE:**

1. Bromination of acetone under acidic condition:

   $$\text{Me}^\text{C} = \text{C}\text{Me} \xrightarrow{\text{Br}_2, \text{cat. } H^+} \text{Me}^\text{C} = \text{C}\text{Me} \text{Br}$$

   Rate = $k [\text{acetone}][H^+]$, but independent of bromine concentration.

   This implies that the RDS is over before Br$_2$ gets involved. In other words, Br$_2$ is involved after RDS and subsequently does not show up in the rate equation.

   Proposed mechanism:

   $$\text{Me}^\text{C} = \text{C}\text{Me} \xrightarrow{\text{H}^+ \text{ fast}} \text{Me}^\text{C} = \text{C}\text{Me} \xrightarrow{-\text{H}^+ \text{ slow}} \text{Me}^\text{C} = \text{C}\text{Me} \text{Me} \xrightarrow{\text{Br}_2 \text{ fast}} \text{Me}^\text{C} = \text{C}\text{Me} \text{Me}$$

   i.e. the C$_\text{α}$-H bond breaks in the RDS. Thus, using (CD)$_3$CO, we get $k_8/k_{10} \approx 7$.

2. Oxidation of secondary alcohol by chromic acid in aqueous medium:

   **Step-1:** formation of chromate ester:

   $$\text{Me}^\text{C} = \text{C}\text{Me} \xrightarrow{\text{H,O}} \text{Me}^\text{C} = \text{C}\text{Me}$$

   **Step-2:** breakdown of chromate ester:

   $$\text{Me}^\text{C} = \text{C}\text{Me} \xrightarrow{-\text{H,O}} \text{Me}^\text{C} = \text{C}\text{Me} + \text{HCrO}_3^\text{−}$$

   If step-1 is fast and step-2 is slow, we can expect PKIE with (CH$_3$)$_2$C(OH)$_2$, and that is indeed the case.
3. Aromatic electrophilic substitution reactions like the following:

\[
\text{benzene} + \overset{+}{E} \rightarrow \overset{+}{\text{substituted benzene}} + \overset{+}{H}
\]

generally proceed via the following two-step mechanism:

**Step-1: Attack of the electrophile**

\[
\text{benzene} \rightarrow \overset{+}{\text{\sigma-complex}}
\]

**Step-2: Proton loss from \sigma-complex to regain aromaticity:**

\[
\overset{+}{\text{\sigma-complex}} \rightarrow \overset{+}{\text{substituted benzene}} - \overset{+}{H}
\]

The absence of PKIE in many \(S_{E}Ar\) (carried on isotopically labelled benzene, \(C_6D_6\)) implies that the attack of the electrophile onto the aromatic ring is the RDS, and not the proton loss. Thus the energy profile diagram for these reactions look like the following:

However, if a PKIE (\(k_{R} / k_{N} < 7\)) is observed with deuterated benzene (\(C_6D_6\)) then it implies that the second step is the RDS, and the energy profile diagram changes to:
And for some reactions, the PKIE is around 2-3. A case in point is the sulfonation of benzene. For these cases, the two TS are very close in energy. When C₆D₆ is used instead of C₆H₆, the TS-II rises ever so slightly, making the reaction slightly unfavourable for the deuterated substrate.

Suggested Reading:

CEMA, CC-3