# Use of Isotopes for Studying Reaction Mechanisms

## 3. Secondary Kinetic Isotope Effect

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The previous articles of this series were:
1. Isotopes as markers, May 1997.
2. Primary kinetic isotope effect, June 1997.

**The effects of isotopic substitution on equilibrium constants and reaction rates in processes which do not directly involve the isotopic atom are described. In particular, the mechanistic details which can be obtained by quantifying the secondary kinetic isotope effect and steric isotope effect are illustrated.**

### Introduction

In the first part of this series, we discussed how isotopes can be used as markers to determine the nature of intermediates in chemical reactions. The second part covered the effect of isotopes on equilibria and reactions, in processes where the bond to the isotopic atom is broken. We showed with specific examples how quantitative studies of such primary isotope effects provide information about transition states. Interestingly, isotopes located on atoms remote from the 'scene of action' can also affect reaction rates! In this article we shall discuss the factors determining the magnitude of long range isotope effects on equilibria and rates.

### Secondary Kinetic Isotope Effects

Secondary kinetic isotope effect ($2^{\circ}$-KIE) is defined as the isotope effect when the bond to the isotopically substituted atom does not cleave during the course of a reaction. The secondary KIE can be classified as $\alpha$ or $\beta$, depending upon whether the isotopic substitution is made on the $\alpha$ or $\beta$ center relative to the atom undergoing the chemical change. Typical examples are rate changes produced by deuterium labelling in solvolysis reactions. Depending on whether the label is placed on the carbon undergoing substitution or the next adjacent carbon, the isotope effect is α or β. In the next sections we shall consider these cases individually.

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## α -Secondary KIE

This type of isotope effect is significant (i.e. the ratio of the equilibrium constants or rates of the parent and labelled substrates deviates from unity) when the atom to which the isotopic atom is bonded undergoes a hybridization change. For example, $sp^3 \rightarrow sp^2$ or $sp^2 \rightarrow sp^3$ change of a carbon atom leads to a large equilibrium IE. A similar change in the hybridization during the formation of the transition state would lead to considerable KIE on the corresponding reaction rate. Depending upon the direction of hybridization change, the α-2°-KIE can be normal (>1) or inverse (<1). A systematic trend can be seen from the examples given in *Figure 1*. In the equilibrium process shown, the hybridization changes from $sp^2$ to $sp^3$. This process has an inverse isotope effect. On the other hand, the formation of the transition state in the $S_N1$ reaction shown next involves an $sp^3 \rightarrow sp^2$ conversion. This results in a normal isotope effect. The third reaction shows a similar effect, but the magnitude is dependent on the solvent. Interestingly, $S_N2$ reactions do not show significant 2°-KIE.

An explanation for many of the above trends was first provided by Andrew Streitweiser based on the zero point energy

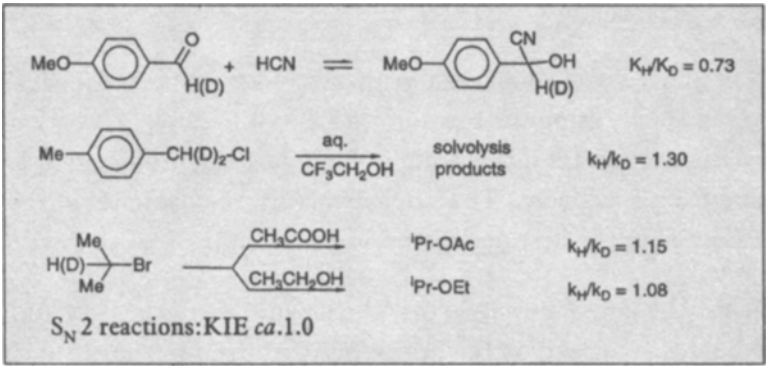
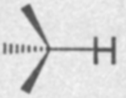
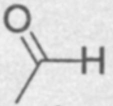


**Figure 1 Examples of α secondary isotope effects.**

***Table 1** List of vibrational frequencies of a C-H bond at sp$^3$ and sp$^2$ carbon centres.*

| | Frequency (cm$^{-1}$) for | |
|---|---|---|
| |  |  |
| Mode | sp$^3$ | sp$^2$ |
| Stretching | 2900 | 2800 |
| *In-plane* bending | 1350 | 1350 |
| *Out-of-plane* bending | 1350 | 800 |

differences of the two hybridized states. In solvolysis reactions, the sp$^3$ center becomes sp$^2$ at the transition state which behaves more like a carbenium ion. Since the infrared frequencies of a carbocation were difficult to obtain in those days, an aldehyde was taken as a model to represent the state of hybridization.

The vibrational frequencies of sp$^3$ and sp$^2$ hybridized carbon compounds are shown in *Table 1*. We find that the only major difference between the two hybridization states is in their *out-of-plane* bending frequencies. In the aldehyde, the *out-of-plane* bending frequency is much lower than the *in-plane* mode, while there is no such distinction in the sp$^3$ hybridized substrate. Higher the frequency, greater will be the reduction due to deuterium labelling. This would, therefore, mean that the change in zero point energy ($\Delta$ZPE) for an sp$^3$ system will be greater than the $\Delta$ZPE for an sp$^2$ counterpart. As a result, sp$^3 \rightarrow$ sp$^2$ transformation should be accompanied by a normal isotope effect, while the reverse transformation should show an inverse isotope effect.

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The above conclusions can be quantified from the frequencies given above, using the relation $\Delta \mathrm{ZPE} = 0.13\, hc\bar{v}_{\mathrm{H}}$. The calculated numbers for normal and inverse IE are approximately 1.4 and 0.7 respectively. The agreement with the data provided in *Figure 1* for the first two entries is quite good.

It may be noted, however, that the magnitude of the α-2° KIE would also depend on the degree of hybridization change at the transition state. For example, if we are carrying out a solvolysis reaction ($S_N1$), the rate determining step could be the formation of the contact ion-pair (CIP), the formation of the solvent separated ion-pair (SSIP), or the formation of the free ions. It can be intuitively inferred that the degree of $sp^2$ character increases as the rate determining step comes later in the process. In fact, it has been suggested that an $\alpha$-2°-KIE around 1.15 implies that the rate determining step is CIP formation, whereas if the dissociation of the SSIP is rate determining the isotope effect is higher, in the range 1.29-1.35.

The trigonal bipyramidal transition state puts two groups in the apical positions, resulting in a sterically crowded situation for the out-of-plane bending of the C-H(D) bond.

The above discussion, however, does not explain why the solvolysis of isopropyl bromide (shown in *Figure 1*) shows a solvent dependent KIE. This has to do with solvent participation in the solvolysis reaction. The $S_N1$ and $S_N2$ processes represent extreme cases of the solvolysis mechanism. In reality, there is a continuum of possibilities, in which the nucleophilic displacement has characters of both transition states. In a solvent assisted $S_N1$ process, the departure of the leaving group is accompanied by the solvent participation from the backside- particularly for substrates which do not form very stable cations. As a result, the transition state has some features of the $S_N2$ mechanism. The trigonal bipyramidal transition state puts two groups (the leaving group and the nucleophile/solvent) in the apical positions, resulting in a sterically crowded situation for the *out-of-plane* bending of the C-H(D) bond. This increases the force constant, thereby increasing the C-H(D) frequency. Hence the $\Delta$ZPE in the transition state may become only slightly smaller compared to the ground state. This effect reduces the magnitude of the KIE. Evidently, in the extreme case of a pure $S_N2$ process, the KIE will virtually be non-existent.

## β-Secondary KIE

This type of KIE is seen primarily when H(D) is present at a carbon β-to the site undergoing a solvolysis process. A few such examples are shown in *Figure 2*. It is interesting to see that the

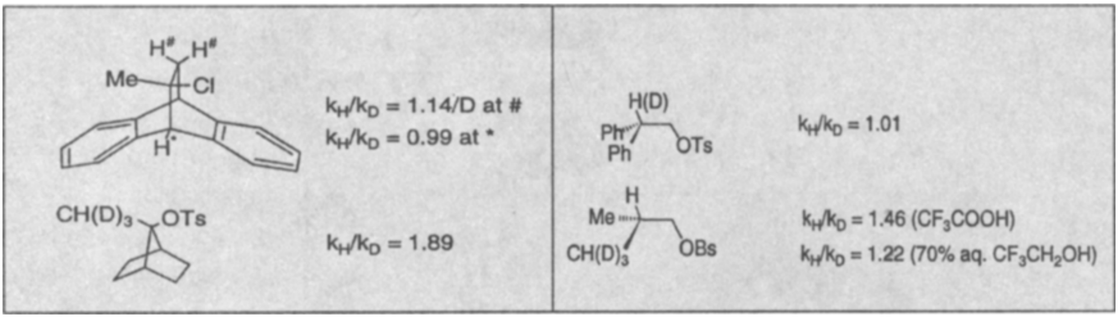

***Figure 2 Examples of β secondary isotope effects.***

β-secondary isotope effect is strongly dependent on geometric factors. This is clear from the first example shown in *Figure 2.* Isotopic substitution of the different β-hydrogen atoms do not lead to the same rate changes. It may also be somewhat surprising to see that the diphenylethyl derivative does not show much effect upon isotopic substitution.

The existence of β-secondary isotope effect can be readily explained by hyperconjugation. If a vacant p-orbital is formed in the substrate during the course of a reaction (as in a carbocation), and if a hydrogen atom is present at the β-position in a geometry in which the C-H σ bond can overlap with the p- (or the developing p) orbital, a stabilizing interaction, known as hyperconjugation, is possible. As an extreme description, hyperconjugation can be thought to be a partial cleavage of the β-C-H bond. Since a C-D bond is stronger (because of the lower zero-point energy), β-C-D bonds will clearly be less effective in stabilizing a carbonium ion like species. As a result, the solvolysis rate is lower in the deuterated derivative.

The β-secondary isotope effect is strongly dependent on geometric factors.

The above interpretation assumes that the C-H group is ideally oriented for hyperconjugation with the developing empty p-orbital. For this to be valid, the β-C-H bond must be as parallel as possible with the p-orbital, in order to overlap effectively. If they are orthogonal, there will be no overlap, and as a result isotopic substitution will not have any effect on the rate. This is exactly the reason why the '#' position in the bicyclo[2.2.2] system shows a normal isotope effect, whereas isotopic substitution at the '*' position shows practically no effect at all. It may be easily seen from a model that the C-H* bond and the p-orbital (after losing $Cl^-$) are orthogonal in the system shown.

The unusual β-KIE in the diphenylethyl derivative is a result of an interesting variation in its reaction mechanism. Since the carbenium ion formed after losing the tosylate is a primary cation, and since phenyl groups are present at the β-position, the departure of the tosylate group is assisted by phenyl participation. In other words, one of the phenyl groups migrates to form a bridged species. Due to participation of the phenyl group, the C-H bond remains almost orthogonal to the developing empty p-orbital on the adjacent center. Hence it is not surprising that there is practically no isotope effect.

We mentioned earlier that the magnitude of the α-2°-KIE for a solvolysis reaction provides a clue about the rate determining step. Similarly, the magnitude of the β-2°-KIE also tells us about the rate determining step. For instance, the example of the isobutyl brosylate shown in *Figure 2* has a high KIE of 1.46 when solvolyzed in trifluoroacetic acid (TFA), whereas the KIE drops to 1.22 in 70% aq. trifluoroethanol. It has been suggested that in TFA the dissociation of the CIP to the SSIP is the rate determining step, whereas in weaker aq. $CF_3CH_2OH$ formation of the CIP is rate determining.

The magnitudes of the α-2°-KIE and the β-2°-KIE for a solvolysis reaction provide a clue about the rate determining step.

## Steric Isotope Effect

In addition to the primary and secondary isotope effects discussed so far, remote substitutions also lead to large equilibrium and rate changes in some systems. An important such effect has a steric origin. But why should the sizes of hydrogen and deuterium be different?

In the previous part of the series, we pointed out that C-H and C-D bonds have the same potential energy diagram. However, inclusion of zero point vibrations makes the C-D bond effectively stronger than the C-H bond. In order to determine the effect of vibrations on the effective size of the atom, we have to incorporate an additional detail. The potential energy profile is not symmetrical about the minimum. While energy increases steeply on compressing the bond, stretching has a different effect. The energy levels off towards the dissociation limit. This results in an unsymmetrical energy curve. In effect, the vibrations are anharmonic. The most probable distance or the equilibrium bond length is slightly shifted away from the minimum energy distance. The deviation is larger for the C-H bond with its larger amplitude of vibration. Hence, the C-D bond is slightly shorter than the C-H bond (*Figure 3*)!

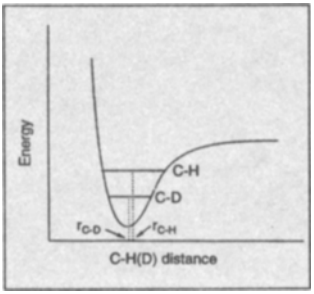

***Figure 3** The anharmonic potential energy curve for C-H(D) bond. The lowest vibrational levels of C-H and C-D bonds are shown as horizontal lines. The equilibrium bond lengths are marked as dotted lines.*

An important consequence of the difference in effective bond lengths is that a deuterium atom feels more 'comfortable' in a sterically congested environment than a hydrogen. This would lead to KIE depending on whether the transition state is less or more encumbered than the ground state. Two examples shown in *Figure 4* clearly demonstrate this concept. If the ground state is more crowded than the transition state (in other words, if strain is relieved upon going to the transition state), the observed KIE will be normal (i.e., > 1). This is indeed the case in the solvolysis of the t-butyl substituted adamantane derivative. On the other hand, if the transition state is more crowded, a deuterium can be accommodated more easily in it. The observed KIE will then be inverse (i.e., < 1). The racemization of the

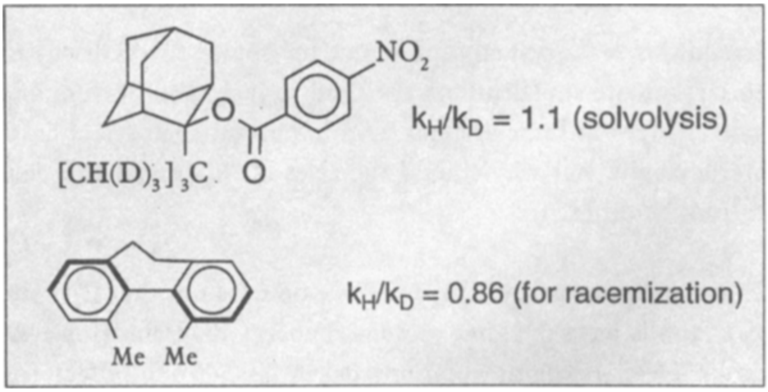

***Figure 4** Examples of 'steric' isotope effects.*

dihydrophenanthrene derivative in *Figure 4* serves as an excellent example. The molecule is twisted in the ground state to avoid steric repulsions between the methyl groups. It is therefore chiral. At the racemization transition state, the molecule is flat, bringing the two methyl groups very close to each other. Since the deuterated derivative has a lesser degree of steric repulsion, the observed KIE is less than unity.

The steric isotope effect is therefore an ideal way of estimating the steric crowding of the transition state relative to the ground state.

## Concluding Remarks

The α-2°-KIE is a clear indicator of the nature of hybridization change on going from the reactant to the transition state. If the reaction center changes from $sp^3$ to $sp^2$, the KIE is greater than unity. For a reverse change, an inverse KIE results. These trends can be used to make subtle distinctions between different mechanistic pathways in solvolysis reactions.

The β-2°-KIE in $S_N1$ reactions results primarily from the more effective hyperconjugative ability of a C-H bond relative to C-D bond. It is therefore highly sensitive to the orientation of the C-H(D) bond relative to the developing carbocation center.

The C-D bond is effectively shorter than a C-H bond due to the anharmonic nature of the potential energy surface. Hence, a deuterium can be placed more easily in a sterically congested structure. The steric isotope effect is therefore an ideal way of estimating the steric crowding of the transition state relative to the ground state.

In the last part of the series, we shall provide a few advanced applications of isotopic substitution for studying reaction mechanisms and dynamic structures.

## Suggested Reading

- **B K Carpenter. *Determination of Organic Reaction Mechanisms.* John Wiley. New York, 1984.**
- **F A Carey and R J Sundberg. *Advanced Organic Chemistry.* Part A. 3rd Ed. Plenum Press. New York, 1990.**

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