The effects of isotopic substitution on equilibria and reaction rates are described. In particular, the mechanistic details which can be obtained by quantifying the primary kinetic 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 focus in such studies is primarily the location and distribution of the label in the product(s). There is a more subtle effect of isotopes which when studied quantitatively can give even greater details of chemical processes. Isotopic substitution can influence an equilibrium, sometimes dramatically. For example, the equilibria are shifted significantly to the right for the two cases given below:

\[
HT + H_2O \rightleftharpoons H_2 + HTO \quad K_{eq} = 6.3 \quad (1)
\]

\[
2D_3O^+ + 3 H_2O \rightleftharpoons 2H_3O^+ + 3 D_2O \quad K_{eq} = 8.2 \quad (2)
\]

Isotopes also affect reaction rates. The magnitude of this kinetic isotope effect (KIE) would depend on the location of the isotope with respect to the ‘scene of action’. Therefore the following types of effects are commonly encountered: (a) primary KIE, (b) secondary KIE (\(\alpha\) and \(\beta\) types) and (c) steric KIE.

In this article we shall give examples of reactions which exhibit interesting primary kinetic isotope effects. We will see how such studies can help us understand the nature of the transition
state in each case. The concepts needed for interpreting the KIE will also be developed.

**Primary Kinetic Isotope Effect**

Primary kinetic isotope effect arises when the bond to the isotopic substitution is 'broken' at the transition state.

Let us consider a reaction in which a C-H bond is broken. If the rate constant $k_H$ becomes $k_D$ on deuterium labelling, the magnitude of KIE is given by $k_H/k_D$. The existence of primary KIE can be easily seen from the following equations for the electrophilic substitution of benzene, and for the oxidation of a secondary alcohol.

\[
\begin{align*}
C_6H(D)_6 + HNO_3 & \rightarrow C_6H(D)_5^–NO_2 \quad k_H/k_D = 1.0 \quad (3) \\
C_6H(D)_6 + Hg(ClO_4)_2 & \rightarrow C_6H(D)_5-Hg^+ \quad k_H/k_D = 6.7 \quad (4) \\
Me_2CH(D)-OH + CrO_3 & \rightarrow Me_2C=O \quad k_H/k_D = 7.7 \quad (5)
\end{align*}
\]

It is intriguing that both (3) and (4) represent electrophilic aromatic substitutions, but there is KIE in one, and not in the other. Equally puzzling is the reaction of toluene with chlorine or bromine, in which toluene(d₆) shows a KIE of 1.5 with Cl⁻, but 4.6 with Br⁻. How can one explain these variations?

**Theory**

In this section, we will look at a very elementary theory of primary KIE, and see how it helps us understand the reactions described above. We will find that this theory also allows us to calculate the equilibrium isotope effects shown in (1) and (2).

Let us consider the potential energy diagram for a typical system such as a C-H bond. The function is described by the well-known Morse curve (Figure 1). On either side of the minimum, the energy increases sharply. The value becomes constant at large internuclear distance, corresponding to dissociation.
very good approximation, the curve is unchanged on going to a C-D bond\(^1\). However, the energetics is altered. This is because the system does not stay at the minimum, but oscillates about it, even at 0K. This vibrational energy is known as the zero-point energy, and is different for the C-H and C-D bonds.

The zero point energy can be estimated by assuming the bond to be a simple harmonic oscillator (a spring which obeys Hooke's law). The energy is given by \(0.5hc\frac{1}{\nu}k\sqrt{\frac{k}{m}}\), where \(h\) is Planck's constant, \(c\) is the velocity of light, and \(\nu\) is the vibrational frequency (in cm\(^{-1}\)) given by (6).

\[
\nu = \frac{1}{2\pi c} \sqrt{\frac{k}{m}}
\]

In the above equation, \(k\) is the force constant of the bond (second derivative or the curvature at the minimum), and \(m\) is the reduced mass of the system.

Since the potential energy diagram is unaltered on going from H to D, \(k\) remains constant. However, the reduced mass is different. As a good approximation, on going from C-H to C-D, the reduced mass increases by a factor of approximately 2 (see Box 1). Therefore, the frequency for a C-D bond should be approximately \(1/\sqrt{2}\) or 0.71 times that of the corresponding C-H bond (\(\nu_{\text{H}}\)). In practice, however, this ratio is found to be closer to 0.74. What this means is that the zero-point-energy for a C-D system is lower than that of a C-H bond. Since the energy is the same at the dissociation limit, the bond energy is effectively higher for the C-D bond. In other words, the C-D bond is stronger. Therefore, any reaction in which the C-H bond is broken during or before the rate determining step will be slower if the hydrogen is replaced by a deuterium. The relative rates, \(k_{\text{H}}/k_{\text{D}}\) should be greater than 1. This is known as the normal primary kinetic isotope effect.

But what should be the value of this ratio? That part is easy to calculate. Let us consider a situation in which the C-H or the

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\(^1\)This is a consequence of Born-Oppenheimer approximation.

Box 1
The reduced mass \(m\) of a system containing two masses \(M\) and \(m\) is given by:

\[
\frac{1}{m} = \frac{1}{M} + \frac{1}{m}, \quad m = \frac{Mm}{M+m}
\]

We can see that typical values of reduced masses are 1/2 for H\(_2\), 2/3 for H-D and 3/4 for H-T. If the masses of the two atoms differ significantly, the reduced mass will be closer to that of the lighter atom. For example, the reduced mass for the C-H bond is close to 1 (0.92), while that for C-D is 1.7.
A spectacularly large primary kinetic isotope effect is found in the intramolecular hydrogen abstraction reaction shown here. The low temperature measurement contributes only partially to this large magnitude. A quantum mechanical process known as tunneling is primarily responsible for this unusual effect. Tunneling usually involves light particles (electron, hydrogen atom). The barrier should be low, and the width of the potential well should be small. Tunneling probability is highly sensitive to the mass. Hence the rate drops dramatically on substitution of the hydrogen atom by deuterium. Extremely large KIE values are used to prove the occurrence of tunneling.

Using a typical C-H vibration frequency of ca. 3000 cm\(^{-1}\) in (7) we get a value of primary KIE of about 6.5 at room temperature. It can be seen from (7) that KIE will be higher at lower temperatures (Box 2). It is gratifying to see that even this simple theoretical approach gives us a value which compares well with the results shown in (4) and (5). This validates the conclusion that in these reactions the key C-H bond is nearly broken at the transition state.

What about the KIE value of unity shown in (3)? The likely mechanism of nitration of benzene is shown in Figure 2. The reaction involves two steps. First a \(\tau\)-complex is generated, which then undergoes C-H(C-D) bond cleavage to regenerate

\[ \frac{k_H}{k_D} = \exp \left( \frac{0.13 \ h \ c \gamma_H}{kT} \right) \]
aromaticity. If the second step had been the rate determining step (Figure 2a), a normal KIE of close to 7 should have been observed. The absence of any isotope effect in the reaction implies that the first step is rate determining (Figure 2b). In other words, the bond to the isotopic atom is broken after the rate determining step.

This discussion still leaves one question unanswered. Why, for example, are the KIE for chlorination and bromination of toluene so different? Remember, in our simple derivation for the estimation of the primary KIE, we have assumed that both isotopically substituted transition states have the same zero point energy. In reality, this is not true. While the C-H(C-D) bond may cleave completely at the transition state, the H(D) must get attached to some other atom! For example, for chlorination of toluene, the Cl attacks the C-H(C-D) bond, and forms a benzyl radical and H(D)-Cl. Clearly, the energies of HCl and DCl (or for that matter HBr and DBr) are different! Hence, the transition state for the two isotopomers will necessarily have different zero point energy. The only question is how different
are they. It is clear from our discussion that if the H or the D atom is completely transferred to the X (halogen) atom the zero point energy difference at the transition state will be maximum. This will lead to a small KIE. The same result is also true in the opposite extreme case in which the H or D atom is hardly transferred at the transition state. On the other hand, if the H(D) atom is 'half-transferred' to X at the transition state, it will be 'equally' bonded to both atoms. This will lower the force constant, and therefore reduce the vibrational frequency. Hence the zero point energy difference at the transition state will be rather small, and, as a result, KIE will be high.

The extent to which an atom is transferred at the transition state can be guessed by qualitative considerations. For a highly exothermic reaction, the transition state resembles the reactants.\(^3\) Since the hydrogen abstraction reaction with Cl\(_2\) is more exothermic, the C-H bond cleavage in this case will be minimal. Therefore, the observed KIE of only 1.5 with chlorination of toluene is clearly consistent with the above analysis. The value for the reaction with bromine is closer to what one would expect for a greater degree of bond cleavage. In general, if the KIE is greater than 2, it usually implies that there is considerable C-H bond cleavage at the transition state.

**Origin of Equilibrium Isotope Effects**

Let us now see if we can explain the equilibrium isotope effects shown earlier in (1) and (2). Substitution by a heavier isotope always lowers the zero point energy. The magnitude of change is greater in systems with higher intrinsic vibrational frequency. For example, the stretching vibrational frequencies for H\(_2\) and H\(_2\)O are 4370 and 3440 cm\(^{-1}\), respectively. Introduction of tritium (\(^3\)H) produces a large decrease in the frequencies. The values for HT and HOT (O-T bond) are approximately 3570 and 2100 cm\(^{-1}\), respectively. Therefore, one can see that the combination of HT and H\(_2\)O will have higher ZPE than the combination of H\(_2\) and HOT, resulting in the equilibrium

\(^3\) This is known as Hammond postulate.
isotope effect which is greater than unity. The precise numerical value will depend on the temperature. For quantitative prediction, all the vibrational modes (including bending modes) of the species involved should be taken into account. Similarly, the equilibrium isotope effect for (2) can be calculated if all the vibrational frequencies are known.

Concluding Remarks

We have shown how the magnitudes of primary KIE can be used to derive information about transition states of reactions. We have exclusively discussed examples of isotope effects resulting from the replacement of hydrogen by its isotopes. Isotope effects should also exist with heavier atoms, such as C, N, S, Cl etc. However, since the ratio of reduced masses approaches unity as the atomic weight increases, the KIE values become smaller for heavier atoms. Typically, such isotope effects are between 1 and 1.1. Since the rate variations are very small, special efforts are needed to measure them with high precision.

The next part of this series will focus on other types of kinetic isotope effects, in which bonds to the isotopically substituted atom are not broken in the transition state.

Suggested Reading


Address for Correspondence
Uday Maitra and J Chandrasekhar
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012 India

Mathematics is the queen of science, and arithmetic the queen of mathematics.

Gauss