

Variation of kinetic isotope effect in multiple proton transfer reactions[#]

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Abstract. Recently, we had suggested that the motion along the promoter mode in the first part of the IRC of proton transfer reaction enhances the delocalization of n_σ electrons on the acceptor atom into the σ^* orbital of the donor-hydrogen covalent bond, and as a consequence weakens it. This leads to a reduction of the barrier to the proton transfer as well as the stretching frequency of donor-hydrogen bond. An extension of this to the concerted multiple proton transfer reactions implies that the kinetic isotope effect in such reaction depends exponentially on the number of protons that are being transferred. Computational evidence on three systems, $(\text{HF})_3$, formic acid dimer, and $(\text{H}_2\text{O})_n$ clusters is provided to support this assertion.

Keywords. Proton transfer; promoter modes; kinetic isotope effect.

1. Introduction

Kinetic isotope effect (KIE) is the dependence of the rate constant on the mass of the isotope of the atom in a chemical reaction. The primary kinetic isotope effect is the KIE when the bonds connecting that atom to the rest of the molecular frame are broken and reformed. If the isotope substitution is made away from the reaction centre, the resulting KIE is called the secondary kinetic isotope effect. In both cases, the KIE arises from the increase in the activation energy when a lighter isotope is replaced by a heavier isotope. This is primarily due to the changes in the zero point energies of the reactant and the transition state due to isotope substitution.

Consider the primary KIE in a reaction involving the breaking of an X–H bond. The reaction co-ordinate corresponds to the stretching mode of the X–H bond. The frequency associated with the stretching motion becomes imaginary at the transition state. From the transition state theory perspective, the rate constant of this reaction is given by

$$k = \frac{k_B T Q_{\ddagger}}{h Q_r} \exp \left[- \left(E_{el} - \frac{h\nu}{2} \right) / k_B T \right]. \quad (1)$$

Here, E_{el} is the electronic energy difference between the reactant and transition state structures, ν is the vibrational frequency of the X–H stretching mode in the reactant configuration, k_B is the Boltzman constant,

and the T is the temperature at which rate constant is measured and Q_r and Q_{\ddagger} are the partition functions of the reactant and the transition state respectively. When hydrogen atom is replaced by deuterium, ν decreases by nearly a factor of $\sqrt{2}$. Consequently, the ratio of the two rate constants can be written as

$$\frac{k_H}{k_D} \propto e^{-\frac{h(\nu_H - \nu_D)}{2k_B T}}. \quad (2)$$

More generally, in a polyatomic system one can write

$$\frac{k_H}{k_D} \propto e^{-\frac{(\Delta ZPE_H - \Delta ZPE_D)}{k_B T}}. \quad (3)$$

Here, ΔZPE is the difference between the zero point energies at the transition state and the reactant

$$\Delta ZPE = ZPE_{\ddagger} - ZPE^R. \quad (4)$$

For a typical X–H bond, the X–H stretch frequency is about 3000 cm^{-1} . From this, it follows that the k_H/k_D is about 7 at room temperature. Deviations from this number are indicative of the influence of other mechanisms. In particular, quantum mechanical tunneling has been invoked by several authors to explain such deviations.^{1–4} Several indices have been proposed to estimate the influence of tunneling such as the Swain–Schaad exponential relation.^{5,6}

KIE is large in proton transfer reactions due to the small mass of the proton and large change in its mass when it is replaced by deuterium. Several studies have been undertaken over the past few years to understand the dynamics of these reactions.⁷ The potential energy surfaces of this class of reactions have a characteristic feature. The transition state of these reactions is displaced along a line orthogonal to the straight line

[#]Dedicated to Prof. N Sathyamurthy on his 60th birthday

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path (SLP) that connects the reactant and product in the configuration space. As a result of this orthogonal displacement of the TS from the SLP, the barrier to the proton transfer process decreases significantly. Consequently, the IRC is essentially the motion along the orthogonal co-ordinate in the vicinity of the reactant and product structures. The proton motion becomes the reaction co-ordinate only in the neighbourhood of the transition state. Because of the reduction in the activation barrier due to the motion along the orthogonal mode, overall rate of the reaction increases significantly compared to a decoupled system. Such modes have been termed the promoter modes in literature.⁸ The characteristic feature of such modes were analysed by Cui, Karplus⁸ and Schwartz.⁹ In general, these modes represent the low frequency skeletal vibrations, that bring the donor and acceptor atoms closer before the proton migrates from the donor to the acceptor. They are symmetrically coupled to the proton transfer co-ordinate.⁸

Recently, we explored the electronic origin of the promoter modes.¹⁰ We found that as the donor and acceptor atoms come closer because of the motion along the promoter mode, the lone pair of electrons on acceptor atom delocalize into the antibonding σ^* orbital of the donor hydrogen covalent bond. This results in the weakening of the donor hydrogen covalent bond, and as result, to the reduction in the barrier for proton migration. One of the consequences of this is that the donor-hydrogen bond stretch frequency goes down and ultimately becomes imaginary in the neighbourhood of the transition state. In the case of concerted multiple proton transfer reactions, not only does the reaction co-ordinate frequency become imaginary, the other hydrogen stretch frequencies also go down because of the reduced bond strengths of donor-hydrogen bonds. For example, we found that in the case of (HF)₃ and FAD this decrease is about 1300 – 1500 cm⁻¹. The hydrogen bend frequencies, on the other hand, increase slightly, by about 300 – 400 cm⁻¹. Consequently, the overall zero point energy goes down as one moves to the transition state from the reactant. In addition, it appears as if the fall in the zero point energy is almost linearly proportional to the number of protons that migrate in a concerted manner. This is because there would be n -lone pairs located on n acceptor atom that delocalize into corresponding $n\sigma^*$ orbitals, lowering bond strength of n covalent bonds that hold hydrogen atoms with the donor atoms. While one of the normal modes associated with the hydrogen stretches becomes the reaction co-ordinate, the remaining $n-1$ vibrations go down leading to the drop in the zero point energy at the transition state

proportional to n . If so, the KIE (k_H/k_D) should vary exponentially with the number of deuterium atoms that are substituted.

The goal of the present work is to test this hypothesis computationally. We study three systems, FAD, cyclic (HF)₃ and cyclic (H₂O) _{n} clusters. We substitute the hydrogen atoms with deuterium sequentially and calculate the changes in ΔZPE as the number of deuterium atoms in the system increases. According to the discussion above, the ΔZPE should increase almost linearly with the number of deuterium atoms. We verify this. The water clusters provide a class of systems in which the number of protons that undergo cyclic exchange can be systematically increased. We verify that the ΔZPE in these systems increases nearly linearly with the number of protons that are exchanged.

2. Computational methodology

We have used the Gaussian 03 package¹¹ for all our calculations. Density functional theory (DFT) with the hybrid, Becke three-parameter (B3) functional¹² along with Lee–Yang–Parr (LYP) correction¹³ was used in all cases with aug-cc-pVTZ¹⁴ basis set. Natural bond orbital (NBO) analysis,¹⁵ was carried out to analyse population transfer and the second order interaction energy ($E^{(2)}$) between the lone pairs and σ^* (DH) orbitals. Since the NBO analysis requires fully defined wave functions as input,¹⁶ we have carried out all the calculations by the DFT approach. Geometry optimization for (HF)₃, FAD, and water clusters were done to locate the equilibrium and transition state structures in the usual way. C_{2h} and D_{2h} point group restrictions were placed for the equilibrium and transition state structures respectively for FAD, and C_{3h} and D_{3h} point groups for (HF)₃ to reduce the CPU time. The frequency calculations were done at the optimized structure of the reactant and transition state of the (HF)₃, FAD, and water clusters. The IRC¹⁷ was constructed towards the reactant and product sides from the transition state and the population transfers and second order interaction energy ($E^{(2)}$) analysis was carried out along the IRC.

3. Results and discussion

We have taken the reactant and transition state structures of FAD and (HF)₃ and carried out frequency calculation after replacing the hydrogen atoms with deuterium. The resulting frequencies were used to calculate the various $\Delta ZPEs$. In the case of water clusters, there have been several reports in the recent past

to determine their structure and other equilibrium properties.^{18–26} We have taken the geometric parameters from reference¹⁸ as the starting point and optimized the structures once again with B3LYP/aug-cc-pVTZ level of theory for $n = 3–5$ clusters. The transition states were obtained by the usual procedure implemented in Gaussian suite of programs. Frequencies were obtained at the optimized geometries. The most stable structure for $n = 3–5$ clusters are cyclic-clusters. The most stable structure for $n = 6$ cluster is a prism structure.¹⁸ Since this will not support a concerted 6 proton transfer, we choose to study the chair form of a cyclic structure analysed by Xanthia's and Dunning.¹⁹ This supports a concerted six proton transfer. We now consider the effect of deuterium substitution on ΔZPE for the individual molecular systems.

3.1 (HF)₃

Four isotopomers of (HF)₃ are analysed, (HF)₃, (DF)(HF)₂, (DF)₂(HF) and (DF)₃. We begin our analysis with the description of the IRC of these systems. The promoter mode for (HF)₃ system and its isotopomers is the symmetric F–F stretch.¹⁰ We plot in figure 1, the distance between the donor and acceptor atoms of all the four isotopomers represented by

$$q_{DA} = R_{DA} - R_{DA}^{\ddagger}, \quad (5)$$

where R_{DA} is distance between donor and acceptor atoms at that point on the IRC. Similarly, R_{DA}^{\ddagger} is the distance between the donor and acceptor atoms at the transition state. The promoter mode goes through a characteristic U-shape path along the IRC, because

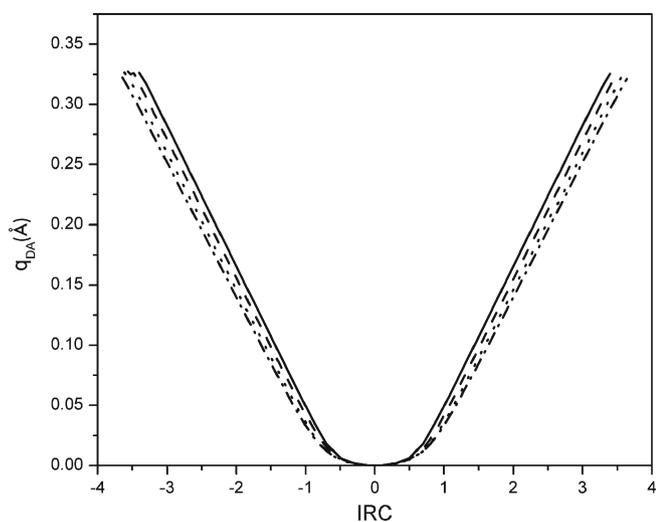


Figure 1. The average distance between donor and acceptor atoms along the IRC in (HF)₃(—), (DF)(HF)₂(- - -), (DF)₂(HF) (· · ·) and (DF)₃(- · -).

it is coupled symmetrically to the proton transfer coordinate. As evident from figure 1, the effect of deuterium substitution has a marginal effect on the donor – acceptor distance. This is due to the small mass of H/D compared to the mass of fluorine atoms. In figure 2, we present q_{DX} as a function of IRC of (DF)(HF)₂. Here, X is either H or D. q_{DX} is defined as¹⁰

$$q_{DX} = R_{DX} - R_{DX}^{\ddagger} - q_{DA}/2. \quad (6)$$

Here, R_{DX} is the distance between the donor and X, and R_{DX}^{\ddagger} is the distance between the donor and X atoms at the transition state. As can be seen from the figure 2 both proton and deuterium move almost identical distances from equilibrium at all points on the IRC. The number of electrons transferred into the antibonding σ^* orbital's of H–F bond and D–F bonds are presented in the upper panel of figure 3. These are identical to each other with in the drawing accuracy. The lower panel displays the second order estimate to the stabilization energy from this electron transfer. As can be seen the stabilization energy is also almost identical for both H–F and D–F bonds. From these three figures we can conclude that the isotope substitution has no noticeable effect on the IRC, the electronic wave function and the associated energies. Under these conditions, all the stretching vibrational frequencies should go down uniformly when sum of the hydrogen atoms are replaced with deuterium atoms. That would mean that the ΔZPE of (4) should increase.

The variation of the ΔZPE among these four isotopomers is presented in table 1. As can be seen from this data the ΔZPE increases almost linearly with

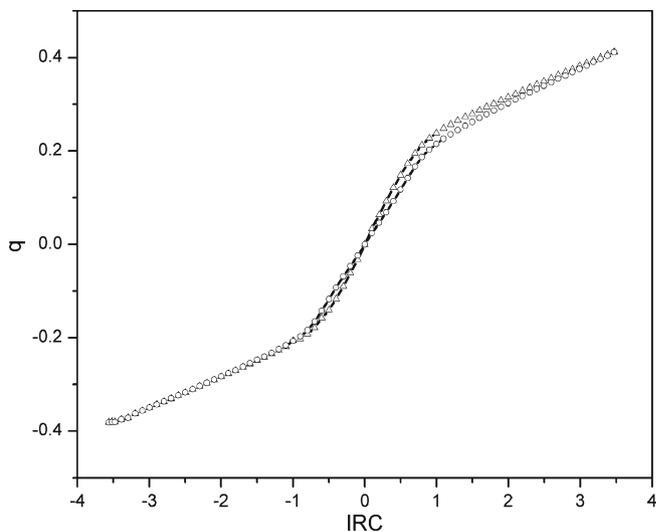


Figure 2. The average distance travelled by hydrogen atom from the donor atom (– Δ –) and the distance travelled by deuterium (– ○ –) from the donor atom in (DF)(HF)₂.

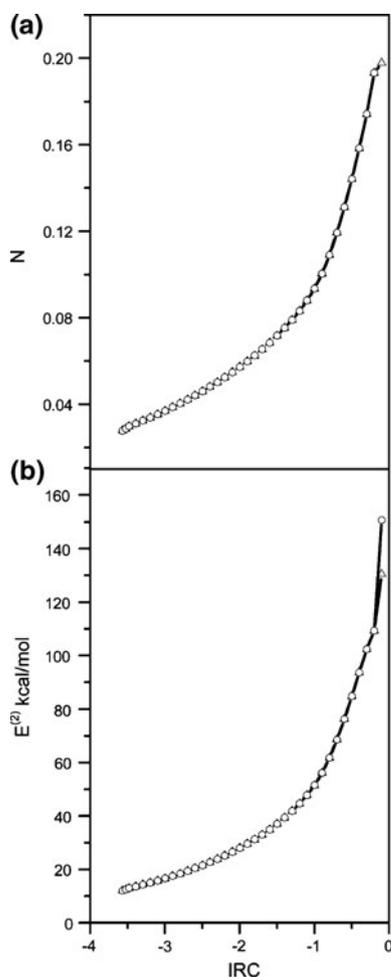


Figure 3. (a) The variation of population in $\sigma^*(\text{HF})$ (—) orbitals and $\sigma^*(\text{DF})$ (- o -) of $(\text{DF})(\text{HF})_2$ and (b) the associated second order stabilization energies.

each additional deuterium atom. The overall threshold energy for the reaction is given by

$$E_{th} = E_{el} + \Delta ZPE. \quad (7)$$

Here E_{el} is the difference between the electronic energy of the molecule at the transition state and reactant geometries. Since, it is independent of the isotope, the variation in E_{th} is controlled essentially by the ΔZPE . We present in figure 4, the variation of E_{th} for different isotopomers. As can be seen the threshold energy

Table 1. The difference in the zero point energies of the transition state and the reactant for different isotopomers of $(\text{HF})_3$.

S. No	Molecule	$\Delta ZPE = (ZPE^\ddagger) - (ZPE^R)$ (kcal/mol)
1	$(\text{HF})_3$	-2.97
2	$(\text{HF})_2(\text{DF})$	-2.61
3	$(\text{HF})(\text{DF})_2$	-2.22
4	$(\text{DF})_3$	-1.81

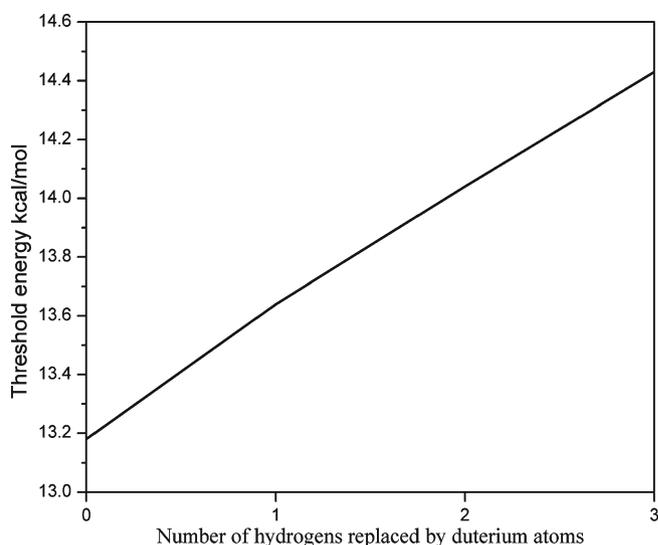


Figure 4. Threshold energy to proton transfer in $(\text{HF})_3$ with sequential deuterium substitution.

increases almost linearly with the number of deuterium atoms in the system. Consequently, the KIE depends on n exponentially due to (3).

3.2 FAD

There are two groups of hydrogen atoms in FAD, those that are attached to the oxygen atoms and undergo transfer reaction and those that are attached to the carbons and remain spectators to the proton exchange. As in the case of $(\text{HF})_3$, the IRC does not change much with deuterium substitution. We have calculated the variation of ΔZPE in four of the isotopomers of FAD. These results are collected in table 2. The ΔZPE of $(\text{HCOOH})_2$ and $(\text{DCOOH})_2$ are practically identical implying that the secondary KIE in this case is negligible. This is to be expected since, the C-H vibrational frequencies change little along the IRC. Replacing the O-H protons increases ΔZPE almost linearly with about 0.68 kcal/mol contribution for each hydrogen replacement. This number is to be contrasted with an increase of about 0.39 kcal/mol in the case of $(\text{HF})_3$.

Table 2. The zero point barrier of FAD and the each hydrogen replaced by deuterium.

S. No	Molecule	$\Delta ZPE = (ZPE^\ddagger) - (ZPE^R)$ (kcal/mol)
1	FAD	-4.04
2	$(\text{HCOOD})(\text{HCOOH})$	-3.38
3	$(\text{HCOOD})_2$	-2.69
4	$(\text{DCOOH})_2$	-4.05

Table 3. The zero point barrier of $(\text{H}_2\text{O})_n$ and the each hydrogen replaced by deuterium.

S. No	Number of water clusters	ΔZPE with all hydrogens (kcal/mol)	ΔZPE with innerdeuterium (kcal/mol)	ΔZPE with all deuterium (kcal/mol)
1	$(\text{H}_2\text{O})_3$	-3.99	-2.33	-2.53
2	$(\text{H}_2\text{O})_4$	-6.16	-3.76	-3.97
3	$(\text{H}_2\text{O})_5$	-8.28	-5.22	-5.41
4	$(\text{H}_2\text{O})_6$	-10.92	-7.01	-7.22

3.3 $(\text{H}_2\text{O})_n$

Isotopomers of four water clusters were studied. Three classes of isotopomers were considered. The all hydrogen system, clusters with hydrogen bond forming hydrogens replaced by deuterium and finally clusters in which all the hydrogen atoms are replaced by deuterium. The results are presented in table 3. Since we have considered only cyclic clusters, each n cluster under goes a concerted n proton transfer. From the data in table 3 it is apparent that ΔZPE decreases almost linearly with the number of protons that migrate to the other side of the hydrogen bond. For example, in the all hydrogen clusters the ΔZPE decreases by about 2.3 kcal/mol for each molecule of water added to the cluster with a maximum deviation from this average by about 0.26 kcal/mol. Similar trends hold for other two isotopomers also.

Comparing the three classes of isotopomers, we note that ΔZPE values are practically identical for the all deuterium one and the one in which the inner hydrogens (that are part of the hydrogen bond) are replaced. They differ by about 0.2 kcal/mol in all the four clusters. This small difference must be due to secondary KIE.

Finally, comparing the protonated species and deuterated species, we note that the change in the zero point energy on deuteration closely follows the reaction

$$\Delta\Delta ZPE = -0.6n, \quad (8)$$

where n is the number of monomers in the cluster and $\Delta\Delta ZPE$ is defined as

$$\Delta\Delta ZPE = \Delta ZPE^H - \Delta ZPE^D. \quad (9)$$

This again falls in line with our hypothesis that the ΔZPE is almost linearly proportional to the number of protons/deuteria that are transferred in a concerted manner.

4. Conclusions

In this work, we have analysed the variation of ΔZPE on the number of protons that undergo a concerted transfer. Each of these n donor-hydrogen (D-H) covalent

bonds receive donations from the lone pairs on the associated acceptor atoms as a consequence of promoter mode motion. Out of the n D-H stretch modes, one turns imaginary at the transition state. This mode represents the concerted n -proton transfer co-ordinate. However, all the force constants associated with the D-H stretch modes go down more or less uniformly depending on the nature of the donor and acceptor atoms and the hydrogen bond between them. Consequently, the frequencies of all the *normal modes* associated with D-H stretch motion are scaled down as one travels along the IRC to the transition state. Note that the net charge transfer from the acceptor n_σ lone pairs of the acceptor atom to the σ^* (D-H) orbitals increases linearly with n to the leading order. As a result of the drastic fall in the stretch vibrational frequencies the overall zero point energy decreases significantly at the transition state. Since, this decrease in the transition state zero point energy is proportional to n , the ΔZPE also falls (approximately linearly) as n increases.

Since the ΔZPE affects the rate constant in an exponential manner, the KIE measured as k_H/k_D also depends on the number of protons being exchanged exponentially. Such exponential dependence was noted by earlier authors.²⁷ Venkatsubban and Silverman²⁷ measured the CO_2 hydration catalyzed by carbonic anhydrase enzyme in several mixtures of water and deuterium oxide. The rate constant for this reaction was calculated by Smedarchina *et al.*²⁸ Both of them noted that the KIE's have an exponential dependence on the deuterium concentration in the $\text{H}_2\text{O}/\text{D}_2\text{O}$ mixture and concluded that the reaction undergoes a concerted transfer through a bridge of two water molecules. Indeed, Smedarchina and co-workers²⁸ noted that the large KIE exhibited by this system is due to the accumulation of zero point energy differences. Obviously, this decrease in zero point energy is due to the donation of acceptor atom lone pair into the σ^* (D-H) orbitals.

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