Kinetic Isotope Effects: Interpretation and Prediction Using Degrees of Rate Control

Zhongtian Mao and Charles T. Campbell*

Department of Chemistry, University of Washington, Seattle, Washington 98195-1700, USA

* charliec@uw.edu

1. Proof of Eq 19

Here we show a proof for Eq 19 following a similar approach as shown in Eqs 2-6 in the Theory Section. Figure S1 schematically shows how this method works for a single elementary step.
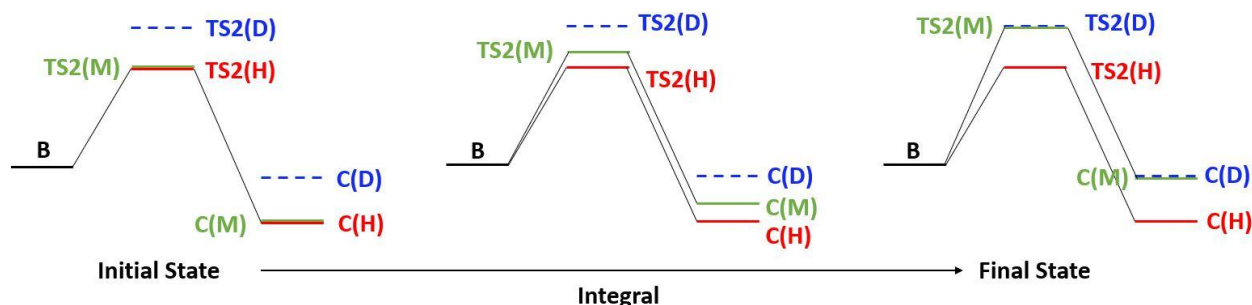

Figure S1. Schematic of the integral method we will use to derive Eq 19, using Step 2 in Figure 2 of the main paper as an example. The black solid lines denote the energies of species in the main reaction path, the red solid lines denote the energies of species in Branch H, the green solid lines denote the energies of species in Branch M (an imaginary isotope with standard-state free energies that will be varied continuously between those for H and D), and the blue dashed lines denote the energies of species in Branch D. In the initial state, the energies of species in Branch M equal their energies in Branch H. As the integral starts, the energies of species in Branch M start to move towards their energies in Branch D. In the final state, the energies of species in Branch M equal their energies in Branch D.

Let us assume that there is an arbitrary reaction's free-energy diagram for the reaction mechanism of interest but with energies appropriate for specific isotope masses, M. The standard-state Gibbs free energies of species i in this reaction path (we will call it "Branch M" below) are varied from M = H to M = D between the free energies of species i in Branch H and Branch D (as defined in the main paper), as shown by the green lines in Figure S1. Using the rate

in Branch H as a reference and keeping the standard-state Gibbs free energy of all species in Branch H constant, the DSRC of species in Branch M can be defined as

$$DSRC_{i(M)} = \left(\frac{\partial \ln\left(r_H/r_M\right)}{\partial\left(-G_{i(M)}^0\big/RT\right)} \right)_{G_{j\neq i}^0} \tag{S1}$$

In Figure S1, only Branch H and Branch M exist in the reaction system for a chosen value of the M, so it is a competition between Branch H and M. The energies of species in Branch D are given by blue dashed lines in Figure S1 because they do not exist in the reaction system for the competition until M = D at the final state of the integral. Since the species in the main reaction path (e.g., B) have constant energies and the species in Branch H (e.g., TS2(H) and intermediate C(H)) are anchored as the reference branch, the energies of species in Branch M (e.g., TS2(M) and C(M)) are the only variables in the system, and the total differential of $\ln\left(r_H/r_M\right)$ can be written as:

$$d\ln\left(\frac{r_H}{r_M}\right) = \sum_{i=\text{species in Branch M}} \left(\frac{\partial \ln\left(r_H/r_M\right)}{\partial\left(-G_{i(M)}^0\big/RT\right)} \right)_{G_{j\neq i}^0} d\left(-\frac{G_{i(M)}^0}{RT}\right) = \sum_{i=\text{species in Branch M}} DSRC_{i(M)} d\left(-\frac{G_{i(M)}^0}{RT}\right) \tag{S2}$$

Note that the summation in Eq S2 is over all species in Branch M. Taking integral on both sides of Eq S2 from some initial state to some final state gives:

$$\ln\left[\frac{\left(r_H/r_M\right)_{final}}{\left(r_H/r_M\right)_{initial}}\right] = \sum_{i=\text{species in Branch M}} \int_{M=initial}^{M=final} DSRC_{i(M)} d\left(-\frac{G_{i(M)}^0}{RT}\right) \tag{S3}$$

As shown in Figure S1, the initial state of the integral is M = H and the energies of species i in Branch M equal the energies of species i in Branch H. In this initial state, the probabilities for intermediate B to take Branch H and Branch M are 50%, so $r_H/r_M = r_H/r_H = 1$. As the integral starts, the energies of species i in Branch M move towards the energies of species i in Branch D, and finally a final state is achieved where the energies of species in Branch M equal their energies in Branch D. This final state is the same as the real reaction mechanism shown in Figure 2b in the main paper, and $r_H/r_M = r_H/r_D$ is the value for KIE. Taking the initial and final state shown in Figure S1, Eq S3 can be rewritten as:

$$\ln\left[\frac{(r_H/r_D)}{(r_H/r_H)}\right]=\ln\left[\frac{r_H}{r_D}\right]=\sum_{i=\text{species in Branch M}}\int_{M=H}^{M=D}DSRC_{i(M)}d\left(-\frac{G^0_{i(M)}}{RT}\right) \tag{S4}$$

Eq S4 gives a general equation for the evaluation of KIE defined as the selectivity ratio for a reaction mechanism shown in Figure 2 in the main paper. If we further assume, in the small range of interest from the initial state to the final state in the integral in Eq S4, the DSRC of species i can be treated as a constant, Eq S4 further simplifies to:

$$KIE=\ln\left[\frac{r_H}{r_D}\right]=\sum_{i=\text{species in Branch D}}\left[-DSRC_{i(D)}d\left(\frac{G^0_{i(D)}-G^0_{i(H)}}{RT}\right)\right] \tag{S5}$$

Eq S5 is the same as Eq 19 in the main paper. Note that Eq S5 (i.e., Eq 19) no longer relies on the arbitrary reaction's energy diagram Branch M. It is a summation over all species in Branch D and the DSRC used in the summation are for the species in Branch D.

To derive Eq S5 from Eq S4, we assumed that the DSRC of species i can be treated as a constant, independent of isotope M. This assumption is valid in most cases. For example, in the first case of Case Study IV in the main paper where Step 2 is the irreversible RDS, Eqs 22 and 23 still hold for Branch H and Branch M here, which can be written as:

$$X_{TS2(M),P(M)}=1 \text{ and} \tag{S6}$$

$$X_{TS2(M),P(H)}=0 . \tag{S7}$$

Note that the DRCs of the transition states TS2(M) for the two rates to generate P(M) and P(H) do not depend on $G^0_{TS2(M)}$. Thus, the DSRC of TS2(M) is truly a constant in the integral of Eq S4. In the second case of Case Study IV where Step 1 is the RDS and Step 2 is irreversible, Eqs 25 and 26 still hold for Branch H and Branch M here. They can be rewritten as:

$$X_{TS2(M),P(M)}=\frac{\exp(-G^0_{TS2(H)}/RT)}{\exp(-G^0_{TS2(H)}/RT)+\exp(-G^0_{TS2(M)}/RT)} \tag{S8}$$

$$X_{TS2(M),P(H)}=\frac{-\exp(-G^0_{TS2(M)}/RT)}{\exp(-G^0_{TS2(H)}/RT)+\exp(-G^0_{TS2(M)}/RT)} \tag{S9}$$

In this case the DRCs of the transition state TS2(M) for the two rates to the two products depend on $G_{TS2(M)}^0$, but the DSRC, which is the difference between these two DRCs, is constant:

$DSRC_{TS2(M)} = X_{TS2(M),P(H)} - X_{TS2(M),P(M)} = -1$. Thus, it does not change in the integral of Eq S4.

2. Proof of Eq 27

When Step 3 in Fig. 2 is the single RDS and intermediate C is equilibrated with intermediate B, the rate of Branch H can be calculated as:

$$r_H = k_{3,H} \left[C(H) \right] = k_{3,H} K_{2,H} \left[B \right] \tag{S10}$$

where $k_{3,H}$ is the forward rate constant of Step 3 in Branch H, $K_{2,H}$ is the equilibrium constant of Step 2 in Branch H, and [C(H)] is the concentration of intermediate C in the H branch. Similarly, the rate of Branch D can be calculated as:

$$r_D = k_{3,D} \left[C(D) \right] = k_{3,D} K_{2,D} \left[B \right] \tag{S11}$$

where $k_{3,D}$ is the forward rate constant of Step 3 in Branch D, and $K_{2,D}$ is the equilibrium constant of Step 2 in Branch D. The ratio r_H/r_D then equals:

$$
\begin{aligned}
\frac{r_H}{r_D} &= \frac{k_{3,H} K_{2,H}}{k_{3,D} K_{2,D}} \\
&= \frac{\exp\left[-\left(G_{TS3(H)}^0 - G_{C(H)}^0 \right) \middle/ RT \right] \exp\left[\left(G_{C(H)}^0 - G_B^0 \right) \middle/ RT \right]}{\exp\left[-\left(G_{TS3(D)}^0 - G_{C(D)}^0 \right) \middle/ RT \right] \exp\left[\left(G_{C(D)}^0 - G_B^0 \right) \middle/ RT \right]} \\
&= \frac{\exp\left[-\left(G_{TS3(H)}^0 \right) \middle/ RT \right]}{\exp\left[-\left(G_{TS3(D)}^0 \right) \middle/ RT \right]}
\end{aligned}
\tag{S12}
$$

Taking the logarithm of both sides of Eq S12 above gives:

$$\ln \frac{r_H}{r_D} = \frac{G_{TS3(D)}^0 - G_{TS3(H)}^0}{RT} \tag{S13}$$

Then the DSRC of TS3(D) can be calculated as:

$$DSRC_{TS3(D)} = \left(\frac{\partial \ln\left(r_H / r_D\right)}{\partial\left(-G_{TS3(D)}^0 / RT\right)} \right)_{G_{j \neq TS3(D)}} = -1 \qquad (S14)$$

This is the same as Eq 27 in the main text. One can also see from looking at Eq S13 that the DSRC is 0 for all of the other species in the mechanism (since they do not appear in Eq S13).