

# Path-integral evaluation of the kinetic isotope effects based on the quantum-instanton approximation

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A general method for computing kinetic isotope effects is described. The method uses the quantum-instanton approximation and is based on the thermodynamic integration with respect to the mass of the isotopes and on the path-integral Monte-Carlo evaluation of relevant thermodynamic quantities. The central ingredients of the method are the Monte-Carlo estimators for the logarithmic derivatives of the partition function and the delta–delta correlation function. Several alternative estimators for these quantities are described here and their merits are compared on the benchmark hydrogen-exchange reaction,  $\text{H}+\text{H}_2 \rightarrow \text{H}_2+\text{H}$  on the Truhlar–Kuppermann potential energy surface. Finally, a qualitative discussion of issues arising in many-dimensional systems is provided.

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## 1 Introduction

Measurement and theoretical predictions of kinetic isotope effects belong among the main tools of chemical kinetics. Kinetic isotope effect (KIE) is defined as the ratio  $k_A/k_B$  of rate constants for two isotopomers  $A$  and  $B$ . Isotopomers  $A$  and  $B$  are two chemical species differing only by replacing a group of atoms in chemical species  $A$  by their isotopes in species  $B$ . Recently, observation of anomalously large KIEs has helped prove importance of quantum effects in enzymatic reactions at physiological (i.e. surprisingly high) temperatures [1]. This and similar results have changed our understanding of enzymatic catalysis and spurred an active experimental and theoretical research in the last several years.

Since the early days of chemical kinetics, KIEs have been predominantly described from the perspective of the transition-state theory (TST) [2,3]. This theory is intrinsically classical, although various quantum “corrections” have been incorporated in it over time. These include corrections due to the zero-point-energy effects, high-temperature Wigner tunneling correction [2,3], and various semiclassical approximations for treating the tunneling at low temperatures [4–6]. On the other end of the spectrum are exact quantum-mechanical methods for computing rate constants and KIEs [7], but in general these are not feasible for systems with many degrees of freedom. One therefore resorts to various approximations that make a computation practicable but are less severe than the TST. Among these belongs a variety of quantum transition-state theories [8–10], the most recent of which is the quantum instanton (QI) approximation [11], motivated by an earlier semiclassical instanton model [4]. In this contribution, we describe a method [12],

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based on the QI approximation, for computing KIEs directly, rather than via computing the rate constants for the two isotopomers first. Because of the ultimate goal of applying a similar method to enzymatic reactions, the method is implemented using a general path-integral approach that scales favorably with the number of degrees of freedom. Several alternative estimators for relevant quantities have been developed [12, 13] and their relative merits are compared in this contribution on the benchmark hydrogen atom–diatom exchange reaction.

## 2 Quantum-instanton approximation for the kinetic isotope effects

The quantum-instanton approximation for the rate constant was introduced in Ref. [11]. A simpler alternative derivation [14] described in detail in Ref. [12], starts with the Miller–Schwartz–Tromp formula [15] for the thermal rate constant  $k$ ,

$$k Q_r = \int_0^\infty dt C_{\text{ff}}(t). \quad (1)$$

Here  $Q_r$  is the reactant partition function (per unit volume for bimolecular reactions) and  $C_{\text{ff}}(t)$  is the symmetrized flux–flux correlation function,

$$C_{\text{ff}}(t) = \text{tr} \left( e^{-\beta \hat{H}/2} \hat{F}_a e^{-\beta \hat{H}/2} e^{i \hat{H} t / \hbar} \hat{F}_b e^{-i \hat{H} t / \hbar} \right) \quad (2)$$

with Hamiltonian operator  $\hat{H}$  and flux operator  $\hat{F}_\gamma$  denoting the flux through the dividing surface  $\gamma = a, b$ . Quantum-instanton expression follows by multiplying and dividing the integrand of Eq.(1) by the “delta–delta” correlation function  $C_{\text{dd}}(t)$  defined below in Eq. (5), assuming that  $C_{\text{ff}}(t)/C_{\text{dd}}(t)$  varies slowly compared with  $C_{\text{dd}}(t)$ , and applying the steepest-descent approximation to the resulting integral. Assuming further that the stationary-phase point is at  $t = 0$ , we obtain the QI thermal rate constant,

$$k_{\text{QI}} = \frac{1}{Q_r} C_{\text{ff}}(0) \frac{\sqrt{\pi}}{2} \frac{\hbar}{\Delta H}. \quad (3)$$

Here  $\Delta H$  is a specific type of energy variance [16],

$$\Delta H = \hbar \left[ \frac{-\ddot{C}_{\text{dd}}(0)}{2C_{\text{dd}}(0)} \right]^{1/2}, \quad (4)$$

and the delta–delta correlation function  $C_{\text{dd}}(t)$  is defined [12, 16] as

$$C_{\text{dd}}(t) = \text{tr} \left( e^{-\beta \hat{H}/2} \hat{\Delta}_a e^{-\beta \hat{H}/2} e^{i \hat{H} t / \hbar} \hat{\Delta}_b e^{-i \hat{H} t / \hbar} \right). \quad (5)$$

The generalized delta operator  $\hat{\Delta}$  will be defined below in Eq. (22).

In applying the QI approximation to the KIEs, it is useful to consider a continuous change of the isotope mass. If the two isotopomers are  $A$  and  $B$ , a real parameter  $\lambda \in [0, 1]$  can be defined such that

$$m_i(\lambda) = m_{A,i}(1 - \lambda) + m_{B,i}\lambda,$$

where  $m_{A,i}$  and  $m_{B,i}$  are the masses of the  $i$ th atom in the isotopomers  $A$  and  $B$ , respectively. Within the QI approximation (3), the KIE can be expressed as

$$\text{KIE}_{\text{QI}} = \frac{k_{\text{QI}}(0)}{k_{\text{QI}}(1)} = \frac{Q_r(1)}{Q_r(0)} \times \frac{\Delta H(1)}{\Delta H(0)} \times \frac{C_{\text{dd}}(0)}{C_{\text{dd}}(1)} \times \frac{C_{\text{ff}}(0)/C_{\text{dd}}(0)}{C_{\text{ff}}(1)/C_{\text{dd}}(1)}, \quad (6)$$

where the argument denotes the value of  $\lambda$  and for simplicity the time argument of the correlation functions has been omitted since it is always  $t = 0$  in the QI approximation. Also, for convenience, both numerator and denominator have been divided by  $C_{\text{dd}}(\lambda)$ .

Four types of quantities must be evaluated in order to compute the KIEs from Eq. (6): the ratio of the partition functions  $Q_r(1)/Q_r(0)$ , the ratio of the delta correlation functions  $C_{\text{dd}}(1)/C_{\text{dd}}(0)$ , and the energy variance  $\Delta H(\lambda)$  and the “velocity” factor  $C_{\text{ff}}(\lambda)/C_{\text{dd}}(\lambda)$  for  $\lambda = 0$  and 1. The last two quantities are in the form of thermodynamic averages (for a given  $\lambda$ ) and therefore can be directly computed by Metropolis Monte-Carlo techniques; the relevant estimators have been derived in Refs. [16, 17]. The most general forms are listed in Ref. [12]. The first two quantities cannot be evaluated directly since they are ratios of quantities for two different values of  $\lambda$ .

An elegant solution exists, however. Here is where considering a continuous isotope change (using a parameter  $\lambda$ ) becomes useful: instead of computing the ratios directly, we use the *thermodynamic integration* idea [18], applied to the parameter  $\lambda$  (i.e., to the masses of the isotopes instead to the usual inverse temperature  $\beta$ ). We can express the two ratios as an exponential of the integrals of logarithmic derivatives,

$$\frac{Q_r(1)}{Q_r(0)} = \exp \left[ \int_0^1 d\lambda \frac{d \log Q_r(\lambda)}{d\lambda} \right], \quad (7)$$

$$\frac{C_{\text{dd}}(1)}{C_{\text{dd}}(0)} = \exp \left[ \int_0^1 d\lambda \frac{d \log C_{\text{dd}}(\lambda)}{d\lambda} \right]. \quad (8)$$

Since the logarithmic derivatives can be expanded as

$$\frac{d \log \rho(\lambda)}{d\lambda} = \frac{d\rho(\lambda)/d\lambda}{\rho(\lambda)},$$

they are normalized quantities (thermodynamic averages) which can be directly computed by the Metropolis algorithm. We can compute ratios of both the reactant partition functions and the delta–delta correlation functions at  $\lambda = 0$  and 1, by computing the values of the corresponding logarithmic derivatives for enough values  $\lambda$  between 0 and 1, and then by integrating over  $\lambda$  and exponentiating, according to Eqs. (7) and (8).

In fact, in a cruder version of the QI method, called the simplest quantum-instanton (SQI) approximation [11], the ratios of the partition and delta–delta correlation functions are all we need, since within that approximation, the kinetic isotope effect is just

$$\text{KIE}_{\text{SQI}} = \frac{Q_r(1)}{Q_r(0)} \times \frac{C_{\text{dd}}(0)}{C_{\text{dd}}(1)}. \quad (9)$$

The relevant estimators for the logarithmic derivatives have been derived in Refs. [12, 13]. In Ref. [12], *thermodynamic* estimators have been derived that differentiate the kinetic part of the action; in Ref. [13], *virial* estimators have been derived that differentiate the potential part of the action. In both cases, the derivations have been done for general systems with  $N$  atoms in  $d$  dimensions, even for cases with unbound degrees of freedom (such as the center-of-mass motion). In the next section, we present a simplified derivation of these estimators for a single particle in a one-dimensional external potential. This choice significantly simplifies notation, but preserves the main ingredients of the many-dimensional derivation.

### 3 Estimators for the logarithmic derivatives of $Q_r$ and $C_{dd}$

Below we derive three types of estimators for the logarithmic derivatives of both  $Q_r$  and  $C_{dd}$ . We refer to the three types of estimators as thermodynamic, virial, and generalized virial because of their resemblance to corresponding thermodynamic [19], virial [20], and generalized virial [21] estimators for the kinetic energy.

#### 3.1 Partition function

Let us consider a single particle of mass  $m$  in a one-dimensional potential  $V(r)$ . Since we have only one mass  $m$ , we do not need to define an additional parameter  $\lambda$ : we can just take  $m$  itself to be the parameter for the thermodynamic integration. The PI representation of the partition function is

$$Q_r \simeq \left( \frac{Pm}{2\pi\hbar^2\beta} \right)^{P/2} \int dr^{(1)} \dots \int dr^{(P)} \rho_r(\{r^{(s)}\}), \quad (10)$$

$$\rho_r(\{r^{(s)}\}) = \exp[-\beta\Phi(\{r^{(s)}\})], \quad (11)$$

$$\Phi = \frac{Pm}{2\pi\hbar^2\beta^2} \sum_{s=1}^P (r^{(s)} - r^{(s-1)})^2 + \frac{1}{P} \sum_{s=1}^P V(r^{(s)}).$$

Here  $s = 1, \dots, P$ , denotes the beads of the discretized paths ( $s = 0$  is identical to  $s = P$ ). In general, we will obtain the estimators for the logarithmic derivative directly, by computing the logarithmic derivative  $\frac{d \log Q_r}{dm} = \frac{1}{Q_r} \frac{dQ_r}{dm}$  of the particular form of the discretized PI. Applying this approach to the PI (10), we obtain the *thermodynamic* estimator

$$\frac{d \log Q_r}{dm} = \frac{P}{2m} - \beta \left\langle \frac{\partial \Phi}{\partial m} \right\rangle_{\rho_r}, \quad (12)$$

$$\frac{\partial \Phi}{\partial m} = \frac{P}{2\pi\hbar^2\beta^2} \sum_{s=1}^P (r^{(s)} - r^{(s-1)})^2.$$

Above,  $\langle A(\{r^{(s)}\}) \rangle_\rho$  denotes the average over paths weighted with the weight  $\rho$ ,

$$\langle A(\{r^{(s)}\}) \rangle_\rho \equiv \frac{\int dr^{(1)} \dots \int dr^{(P)} A(\{r^{(s)}\}) \rho(\{r^{(s)}\})}{\int dr^{(1)} \dots \int dr^{(P)} \rho(\{r^{(s)}\})}.$$

Alternatively, we can define new, mass-scaled coordinates as

$$x \equiv m^{1/2} r. \quad (13)$$

In these new coordinates, the partition function becomes

$$Q_r \simeq \left( \frac{P}{2\pi\hbar^2\beta} \right)^{P/2} \int dx^{(1)} \dots \int dx^{(P)} e^{-\beta\Phi}, \quad (14)$$

$$\Phi = \frac{P}{2\pi\hbar^2\beta^2} \sum_{s=1}^P (x^{(s)} - x^{(s-1)})^2 + \frac{1}{P} \sum_{s=1}^P V(m^{-1/2}x^{(s)}).$$

Simplest *virial* estimator for the logarithmic derivative can again be derived by direct differentiation of PI (14),

$$\begin{aligned} \frac{d \log Q_r}{dm} &= -\frac{\beta}{P} \left\langle \sum_{s=1}^P \frac{\partial V[m^{-1/2}x^{(s)}]}{\partial m} \right\rangle_{\rho_r} = \\ &= -\frac{\beta}{P} \left\langle \sum_{s=1}^P \frac{\partial V[(m + \Delta m)^{-1/2}m^{1/2}r^{(s)}]}{\partial \Delta m} \Big|_{\Delta m=0} \right\rangle_{\rho_r} = \\ &= \frac{\beta}{2P} \left\langle \sum_{s=1}^P r^{(s)} \frac{\partial V(r^{(s)})}{\partial r^{(s)}} \right\rangle_{\rho_r}. \end{aligned} \quad (15)$$

Above are three estimators for the logarithmic derivative: the first one suitable if the MC simulation is done in mass-scaled coordinates  $x$ , the other two for original Cartesian coordinates  $r$ . The first two suggest evaluation of the derivative numerically, by finite differences, which will be in fact, more efficient in many dimensional systems than the analytical third expression that requires the knowledge of the gradient of the potential. Only for systems with few degrees of freedom and available gradient of the potential, the third expression may be preferable. The trick of using numerical derivatives with respect to a single parameter was originally used by Predescu for computing heat capacities [22] and higher temporal derivatives of the flux-flux correlation function [23] where the parameters were the inverse temperature and the imaginary time, respectively.

The simplest virial estimators (15) have one shortcoming compared to the thermodynamic estimators, namely, they only work in bound systems. This can be immediately seen by considering a free particle with  $V(r) = 0$ . This shortcoming can be remedied if the rescaling is done only after subtracting an arbitrarily chosen

(but fixed) slice from the remaining  $P - 1$  slices. To be more explicit, let us define relative coordinates as

$$y^{(s)} \equiv r^{(s)} - r^{(P)} \quad \text{for } s = 1, \dots, P - 1.$$

Since the Jacobian of the transformation is unity, we have

$$\begin{aligned} Q_r &= \left( \frac{Pm}{2\pi\hbar^2\beta} \right)^{P/2} \int dy^{(1)} \dots \int dy^{(P-1)} \int dr^{(P)} e^{-\beta\Phi}, \\ \Phi &= \frac{Pm}{2\pi\hbar^2\beta^2} \left[ \left( y^{(1)} \right)^2 + \sum_{s=2}^{P-1} \left( y^{(s)} - y^{(s-1)} \right)^2 + \left( y^{(P-1)} \right)^2 \right] + \\ &\quad + \frac{1}{P} \left[ \sum_{s=1}^{P-1} V(r^{(P)} + y^{(s)}) + V(r^{(P)}) \right]. \end{aligned} \quad (16)$$

Now we define mass-scaled coordinates as

$$x^{(s)} \equiv m^{1/2}y^{(s)} = m^{1/2}(r^{(s)} - r^{(P)}) \quad \text{for } s = 1, \dots, P - 1. \quad (17)$$

In these coordinates, the partition function becomes

$$\begin{aligned} Q_r &= \left( \frac{P}{2\pi\hbar^2\beta} \right)^{P/2} m^{1/2} \int dx^{(1)} \dots \int dx^{(P-1)} \int dr^{(P)} e^{-\beta\Phi}, \\ \Phi &= \frac{P}{2\pi\hbar^2\beta^2} \left[ \left( x^{(1)} \right)^2 + \sum_{s=2}^{P-1} \left( x^{(s)} - x^{(s-1)} \right)^2 + \left( x^{(P-1)} \right)^2 \right] + \\ &\quad + \frac{1}{P} \left[ \sum_{s=1}^{P-1} V(r^{(P)} + m^{-1/2}x^{(s)}) + V(r^{(P)}) \right]. \end{aligned} \quad (18)$$

The *generalized virial* estimator for the logarithmic derivative follows by differentiating the PI expression (18),

$$\begin{aligned} \frac{d \log Q_r}{dm} &= \frac{1}{2m} - \frac{\beta}{P} \left\langle \sum_{s=1}^P \frac{\partial V [r^{(P)} + m^{-1/2}x^{(s)}]}{\partial m} \right\rangle_{\rho_r} = \\ &= \frac{1}{2m} - \frac{\beta}{P} \left\langle \sum_{s=1}^P \frac{\partial V [r^{(P)} + (m + \Delta m)^{-1/2}m^{1/2} (r^{(s)} - r^{(P)})]}{\partial \Delta m} \right\rangle_{\Delta m=0} \Big|_{\rho_r} = \\ &= \frac{1}{2m} + \frac{\beta}{2P} \left\langle \sum_{s=1}^P \frac{\partial V (r^{(s)})}{\partial r^{(s)}} (r^{(s)} - r^{(P)}) \right\rangle_{\rho_r}. \end{aligned} \quad (19)$$

Since we have chosen the slice  $s = P$  arbitrarily, we can do the same for any slice  $s$ , derive a corresponding estimator, and then take an average of these estimators.

The result is

$$\frac{d \log Q_r}{dm} = \frac{1}{2m} + \frac{\beta}{2P} \left\langle \sum_{s=1}^P \frac{\partial V(r^{(s)})}{\partial r^{(s)}} (r^{(s)} - r^c) \right\rangle_{\rho_r}, \quad (20)$$

$$r^c \equiv \frac{1}{P} \sum_{s=1}^P r^{(s)}.$$

and in general, we can replace  $r^{(P)}$  in all three forms (19) of the estimator by  $r^c$ .

Since the number of slices  $P$  appears explicitly only in the denominator of the generalized virial estimator (19) or (20), the statistical error should be independent of  $P$  for a fixed number of Monte-Carlo samples. On the other hand,  $P$  appears explicitly in the numerator of the thermodynamic estimator (12), so the error is expected to grow with  $P$ . This will be confirmed in the numerical example in Section 4.

### 3.2 Delta–delta correlation function

The derivation for  $C_{dd}$  is similar. However, due to the constraints to the two dividing surfaces, a new term appears in the estimator. The PI representation of  $C_{dd}$  is

$$C_{dd} \simeq \left( \frac{Pm}{2\pi\hbar^2\beta} \right)^{P/2} \int dr^{(1)} \dots \int dr^{(P)} \rho^\ddagger(\{r^{(s)}\}), \quad (21)$$

$$\rho^\ddagger(\{r^{(s)}\}) = \Delta[\xi_a(r^{(0)})] \Delta[\xi_b(r^{(P/2)})] e^{-\beta\Phi}.$$

The generalized delta function  $\Delta$  is defined [16] as

$$\Delta[\xi(r)] \equiv \left| \frac{m}{\partial_r \xi} \right|^{1/2} \delta[\xi(r)]. \quad (22)$$

For numerical purposes, it is convenient to replace the strict delta function by a Gaussian approximation [16],

$$\Delta[\xi(r^{(s)})] \approx \tilde{\Delta}[\xi(\bar{r}^{(s)})], \quad (23)$$

$$\bar{r}^{(s)} \equiv \frac{1}{2} (r^{(s)} + r^{(s+1)}),$$

$$\tilde{\Delta}[\xi(r)] \equiv \left( \frac{2P}{\pi\hbar^2\beta} \right)^{1/2} \exp \left\{ -\frac{2Pm}{\hbar^2\beta} \left[ \frac{\xi(r)}{\partial_r \xi(r)} \right]^2 \right\}.$$

We can define an effective action  $\Phi_{\text{eff}} = \Phi + V_{\text{constr}}$ , which includes the constraint potential

$$V_{\text{constr}} = \frac{2Pm}{\hbar^2\beta^2} \left[ \frac{\xi(r)}{\partial_r \xi(r)} \right]^2. \quad (24)$$

The logarithmic derivative will have one extra term due to this constraint potential,

$$\frac{d \log C_{\text{dd}}}{dm} = \frac{d \log Q_r}{dm} (\rho_r \rightarrow \rho^\ddagger) - \beta \left\langle \frac{\partial V_{\text{constr}}}{\partial m} \right\rangle_{\rho^\ddagger}, \quad (25)$$

where  $\frac{d \log Q_r}{dm} (\rho_r \rightarrow \rho^\ddagger)$  denotes that the corresponding estimator for  $Q_r$  given in Eq. (12), (15), or (19) should be used except that the sampling is done according to weight  $\rho^\ddagger$  instead of  $\rho_r$ . Using the PI representation (21) of  $C_{\text{dd}}$  in Cartesian coordinates, we find the additional term from Eq. (25) to the thermodynamic estimator (12) to be

$$\frac{\partial V_{\text{constr}}}{\partial m} = \frac{2P}{\hbar^2 \beta^2} \left[ \frac{\xi(r)}{\partial_r \xi(r)} \right]^2. \quad (26)$$

Rescaling coordinates according to Eq. (13) gives a constraint potential

$$V_{\text{constr}} = \frac{2Pm}{\hbar^2 \beta^2} \left[ \frac{\xi(m^{-1/2}x)}{\partial_r \xi(m^{-1/2}x)} \right]^2.$$

The additional term from Eq. (25) to the simple virial estimator (15) becomes

$$\frac{\partial V_{\text{constr}}}{\partial m} = \frac{2P}{\hbar^2 \beta^2} \frac{d}{d\Delta m} (m + \Delta m) \left[ \frac{\xi(r_{\text{resc}})}{\partial_{r_{\text{resc}}} \xi(r_{\text{resc}})} \right]^2 \Big|_{\Delta m=0}, \quad (27)$$

$$r_{\text{resc}} \equiv \left( \frac{m}{m + \Delta m} \right)^{1/2} r.$$

Finally, if we rescale coordinates according to Eq. (17), or better, as

$$x^{(s)} \equiv m^{1/2}(r^{(s)} - r^c) \quad \text{for } s = 1, \dots, P,$$

we obtain the same estimator as (27), only the rescaled coordinate is defined as

$$r_{\text{resc}}^{(s)} \equiv r^c + \left( \frac{m}{m + \Delta m} \right)^{1/2} (r^{(s)} - r^c). \quad (28)$$

The generalization to more-dimensional systems is fairly straightforward. Only in the case of the simple virial estimator (15) or (27), care must be taken to account for the unbound (free) degrees of freedom by appropriately rescaling the corresponding volume. For instance, for bimolecular reactions, the potential in the reactant region is independent of the center-of-mass coordinate and the relative coordinate of the two molecules. For details, see Ref. [13].

## 4 Numerical results

In Ref. [12], the QI procedure for evaluating KIEs was successfully tested on several problems of increasing complexity: the one-dimensional Eckart barrier and the



isotopic variants of both the collinear and the three-dimensional hydrogen-exchange reaction  $\text{H}+\text{H}_2 \rightarrow \text{H}_2+\text{H}$ . The results for the  $\text{KIE} = k(\text{H}+\text{H}_2)/k(\text{D}+\text{D}_2)$  as a function of the inverse temperature  $1/T$  for both collinear and three-dimensional versions of the reaction are also shown here in Fig. 1. The figure compares the exact quantum-mechanical result [12, 24] with the results of the QI, SQI, and TST approximations. The three-dimensional version also shows the result of the canonical variational TST with semiclassical tunneling correction (CVT) [25]. In general, the results of the QI approximation are very good: the error is smaller than 10% for temperatures 250 to 600 K. For lower temperatures, the larger error is due to using a single dividing surface: results can be improved by considering two separate dividing surfaces. At high temperatures, the error is due to classical recrossing and cannot be corrected within the QI approximation. For further details of the calculation see Ref. [12].

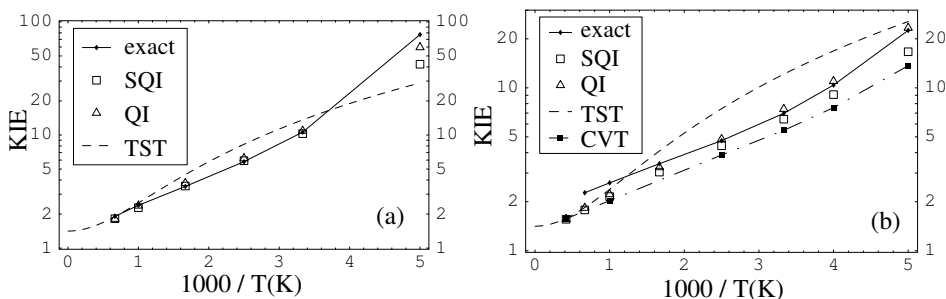


Fig. 1. Kinetic isotope effect  $k(\text{H}+\text{H}_2)/k(\text{D}+\text{D}_2)$  for the hydrogen exchange reaction: (a) the collinear version, (b) the three-dimensional version.

Three types of estimators for the logarithmic derivative of  $Q_r$ , given in Eqs. (12), (15), and (20), are compared in Fig. 2. This calculation is for the collinear version of the  $\text{KIE} = k(\text{H}+\text{H}_2)/k(\text{D}+\text{D}_2)$  at 300 K. The calculation was done with 10 walkers and a fixed number  $10^5$  Monte-Carlo moves for all  $P$ . The left part of the figure shows the convergence of the partition-function ratio  $Q_r(1)/Q_r(0)$  as a function of the number of slices  $P$ . The ratio was computed via the thermodynamic integration (7) in which the three different estimators (12), (15), and (20) for  $\frac{d \log Q_r}{d \lambda}$  were used. The right panel shows the  $P$ -dependence of the relative error of  $Q_r(1)/Q_r(0)$ . As expected, for large  $P$ , the error of the generalized virial estimator (20) is almost independent of  $P$ . On the other hand the error of the thermodynamic estimator (12) grows with  $P$ . Even for small  $P$ , the generalized virial estimator is superior. Finally, we can see the importance of subtracting the centroid motion before rescaling in Eq. (17) by comparing errors of the simple (15) and generalized (20) virial estimators. The difference is due to the fact that we have two free degrees of freedom in the reactant region of the collinear bimolecular reaction. Similar conclusions (not shown here) can be obtained for the ratio  $C_{\text{dd}}(1)/C_{\text{dd}}(0)$ , except that the error of the generalized virial estimator has a weak dependence on  $P$  arising from the additional

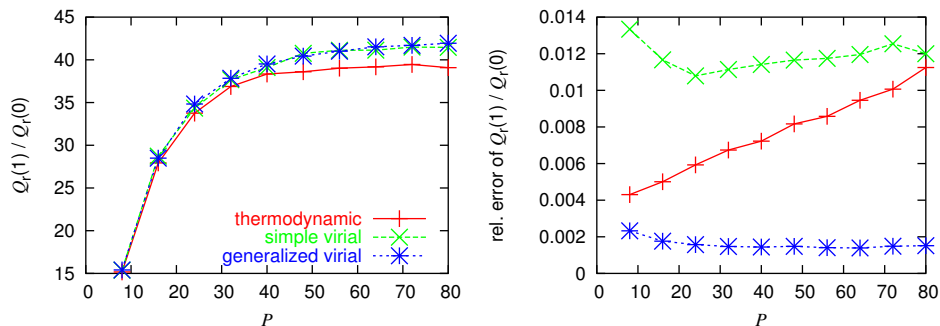


Fig. 2. Comparison of the thermodynamic, virial, and generalized virial estimators for the logarithmic derivative of  $Q_r$ . Left: ratio of the partition functions as a function of  $P$ , right: its relative error as a function of  $P$ .

term due to the constraint to the dividing surfaces.

## 5 Conclusion

Judging from the numerical results in the previous section, the QI approach for computing kinetic isotope effects is very promising. The procedure is quite general: multi-dimensional estimators for all relevant quantities are presented in Refs. [12, 13]. Although the path-integral approach has been chosen because of its favorable scaling with the number of degrees of freedom, the computations for many-dimensional systems are still difficult.

One obstacle is the difficulty of efficient sampling of a many-dimensional configuration space. With proper estimators, we may decrease statistical and systematic discretization errors, but it is difficult to avoid systematic errors due to long correlations. For this reason, it may be efficient to use a different number of imaginary time slices [26] for different degrees of freedom, which is a generalization of more crude mixed quantum-classical methods.

Another obstacle to obtaining a good match between theory and experiment is the potential energy surface for the reaction. While more accurate *ab initio* potentials are computationally very expensive, the much faster molecular-mechanics force fields are often too crude. In Ref. [13], in which the QI method is used to compute the KIE for the isomerization of *cis*-pentadiene, two approaches are taken: in one, an empirical valence bond (EVB) potential is formed from the equilibrium potentials for reactants and products; in the other, a more accurate but also a more expensive semi-empirical potential is used. Because of the computational expense already for this system with 39 degrees of freedom, it appears that due to their better accuracy such semi-empirical potentials will be the potentials of choice for intermediate-size systems, and the EVB potentials based on molecular-mechanical force fields the potentials of choice for truly many-dimensional systems.

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