Kinetic isotope effect in malonaldehyde determined from path integral Monte Carlo simulations

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The primary H/D kinetic isotope effect on the intramolecular proton transfer in malonaldehyde is determined from quantum instanton path integral Monte Carlo simulations on a fully dimensional and validated potential energy surface for temperatures between 250 and 1500 K. Our calculations, based on thermodynamic integration with respect to the mass of the transferring particle, are significantly accelerated by the direct evaluation of the kinetic isotope effect instead of computing it as a ratio of two rate constants. At room temperature, the KIE from the present simulations is $5.2^{\pm0.4}$. The KIE is found to vary considerably as a function of temperature and the low-$T$ behaviour is dominated by the fact that the free energy derivative in the reactant state increases more rapidly than in the transition state. Detailed analysis of the various contributions to the quantum rate constant together with estimates for rates from conventional transition state theory and from periodic orbit theory suggest that the KIE in malonaldehyde is dominated by zero point energy effects and that tunneling plays a minor role at room temperature.

1 Introduction

Determining the rate at which a chemical reaction proceeds remains a challenging computational problem, in particular for high-dimensional systems. Stated in the most general way, two ingredients are required: a suitable multidimensional potential energy surface (PES) which describes how the interaction energy changes as a function of the coordinates and a method to solve the quantum dynamical problem. For three- and four-atom systems, considerable progress has been made for both issues mentioned above. Nowadays, fully dimensional PESs can be computed and fitted to high-level ab initio calculations for systems containing 10 atoms or more.1−3 Despite their undisputed utility and the level of detail they provide, their routine use is, however, limited in various ways. First, from a practical perspective the analytical representation is highly non-trivial. This can be avoided by using ab initio molecular dynamics techniques, which, however, at a sufficiently high level of theory [MP2 or CCSD(T)] is extremely costly and usually not employed, except for the smallest systems.4 Second, due to the extensive parameterization (1633 parameters for typical PESs such as that for malonaldehyde5) the analytical PESs can be quite tedious in force evaluations which are needed in every scheme that computes rates from dynamics. Third, extending the validity of a fully dimensional PES from one compound to a chemically similar one is in general not possible. In other words, for every system, a new PES needs to be computed and fitted.

Malonaldehyde (MA, see Fig. 1) has long served as a typical hydrogen transfer system to test and validate various...
computational approaches. Experimentally, the ground state tunneling splitting was determined to be 21.58314 cm\(^{-1}\) by different experiments with very high accuracy.\(^4\) Infrared spectra of MA have also been recorded at high resolution.\(^7\)–\(^10\) Limbach et al. have studied the proton transfer rate in its di-imine derivative with nuclear magnetic resonance (NMR) spectroscopy.\(^11\) Using \textit{ab initio} path integral Monte Carlo simulations, Tuckerman and Marx have demonstrated the importance of quantizing even the heavy-atom skeleton.\(^4\) One of the relevant quantities requiring a quantum mechanical treatment is the kinetic isotope effect (KIE). It relates the rate constants for hydrogen and deuterium transfer via KIE = \(k_H/k_D\) and can be determined in different ways.\(^12,13\) So far, the KIE for the intramolecular hydrogen transfer in MA has not been determined experimentally and computed estimates for the KIE at 300 K range from 1.54 to 5.10\(^{12}\) and from 6.49 to 11.41.\(^13\) Typical KIEs for organic reactions at 300 K are between 1 and 8, where the precise value depends strongly on the temperature and on the shape and height of the activation barrier.\(^14,15\) Significantly larger KIEs have been observed recently for enzymatic reactions at physiological temperature,\(^16,17\) which has spurred suggestions that quantum effects may be relevant even in biological systems. Whether enzyme active sites can increase their catalytic activity by enhancing these quantum mechanical effects such as zero point energy or tunneling, including single and multiple tunneling paths as well as corner-cutting. Note that this approximation can be systematically improved by including higher-order derivatives of the flux-flux correlation function.\(^28\)

Within the QI approximation the KIE, defined here as the ratio of the hydrogen and deuterium transfer rate constants, can be computed as:\(^24\)

\[
\text{KIE} = \frac{k_H}{k_D} = \frac{C_{\text{H}}(0)/C_{\text{D}}(0) \Delta H(1) Q_{E}(1) C_{\text{D}}(0)}{C_{\text{H}}(0)/C_{\text{D}}(1) \Delta H(0) Q_{E}(0) C_{\text{D}}(1)}
\]

(4)

where the dependence on time is ignored. Instead, the new argument is a real parameter \(\lambda \in [0,1]\) which refers to the mass of the transferring atom,

\[
m(\lambda) = m_{H}(1-\lambda) + m_{D}\lambda.
\]

(5)

The intermediate values of \(\lambda\) facilitate calculation of the ratios \(Q_{E}(1)/Q_{E}(0)\) and \(C_{\text{D}}(0)/C_{\text{D}}(1)\) by thermodynamic integration (TI) with respect to mass,\(^24\)

\[
\frac{Q_{E}(1)}{Q_{E}(0)} = \exp \left[ -\beta \int_{0}^{1} d\lambda \frac{dF_{E}(\lambda)}{d\lambda} \right]
\]

\[
\frac{C_{\text{D}}(1)}{C_{\text{D}}(0)} = \exp \left[ -\beta \int_{0}^{1} d\lambda \frac{dF_{\lambda}(\lambda)}{d\lambda} \right]
\]

(6)

where the free energy derivatives \(dF_{E}(\lambda)/d\lambda\) and \(dF_{\lambda}(\lambda)/d\lambda\) are evaluated, respectively, by unconstrained and constrained path integral Monte Carlo simulations using efficient centroid virial estimators.\(^25\) Major and Gao proposed a related but somewhat different method for computing the KIE using TI,\(^29\) while Wang and Zhao computed the KIE with QI approximation but without TI.\(^30,34\)

Finally, transition-state related quantities \(C_{\text{H}}(\lambda)/C_{\text{D}}(\lambda)\) and \(\Delta H(\lambda)\) required for eqn (4) are computed by constrained PIMC simulations with \(\lambda = 0\) and 1.\(^12,13\) For the constrained simulations, a harmonic constraint \(\frac{1}{2}K(r_{O-H} - r_{O-D})^2\) with \(K = 20\) a.u. is used to keep two path integral beads close to the dividing surface passing through the transition state. The effect of this constraint is illustrated in Fig. 2, where the two O–H distances \(r_1\) and \(r_2\) during PIMC simulations at 375 K with and without the constraint are projected onto a reduced two-dimensional (2D) PES for the proton transfer reaction. At low temperature – for hydrogen transfer below about 250 K – the optimal dividing
surface bifurcates, and the two beads should be constrained separately to these two dividing surfaces. For simplicity, we neglect this effect.

2.2 Conventional transition state theory approximation for the kinetic isotope effect

Conventional Transition State Theory (CTST) within the rigid-rotor harmonic oscillator (RRHO) approximation without tunneling, overbarrier reflection and corner-cutting corrections was used to estimate the KIE in order to assess the importance of quantum effects in the investigated temperature range. According to CTST the rate coefficient is proportional to the ratio of the full translational–rovibronic partition functions in the transition state \( Q(T) \) and in the reactant \( Q(r) \) calculated from the same reference energy level:

\[
k_{\text{TST}}(T) = \frac{Q(T)}{\hbar P(r)}, \quad \text{KIE}(T) = \frac{k_{\text{TST}}(T)}{k_{\text{TST}}(T)} = \frac{Q'(0)/Q(0)}{Q'(1)/Q(1)}.
\] (7)

As above, values \( \lambda = 0 \) and 1 in the argument correspond to the H- and D-variants of MA, respectively. The ratio of transition state \( Q(T) \) and reactant \( Q(r) \) partition functions was estimated considering only the lowest lying electronic states \( E_n \) without rovibronic coupling. Note that the translational partition functions per unit volume \( Q_{\text{trans}} \) can be factored out exactly; moreover, since they are the same for the reactant and transition states, they cancel. The rovibrational partition \( Q_{\text{rovib}} \) function was approximated with the product of rigid-rotor \( Q_{\text{rot,rr}} \) and harmonic oscillator \( Q_{\text{vib,HO}} \) partition functions.

Using elementary statistical mechanics, the final explicit expression for the KIE is

\[
\text{KIE} \approx \sqrt{\frac{\det \mathbf{I}_{\text{D}} \det \mathbf{I}_{\text{H}}}{\det \mathbf{I}_{\text{D}} \det \mathbf{I}_{\text{H}}}} \times \frac{Q_{\text{vib,HO,ZPE}}^{H} Q_{\text{vib,HO,ZPE}}^{D}}{Q_{\Gamma,\text{vib,HO,ZPE}}^{H} Q_{\Gamma,\text{vib,HO,ZPE}}^{D}}.
\] (8)

where \( I_{\text{ZPE}}, Q_{\text{vib,HO,ZPE}} \) are the moment of inertia tensor, the zero-point energy (ZPE) and the vibrational partition function measured from the ZPE level for reactant \( r \) and transition state \( t \) geometries for the two isotopologues (H, D), respectively.

Beside CTST, the magnitude of tunneling rates was estimated from the experimentally determined tunneling splittings \( \Delta E \) (21.6 cm\(^{-1}\) for H and 2.9 cm\(^{-1}\) for D). Accurate theoretical estimates (21.2 cm\(^{-1}\) for H and 3.0 cm\(^{-1}\) for D) for the tunneling splittings were obtained from the instanton theory by Mil’nikov et al.,\(^{37}\) who found the instanton path between the two minima at the CCSD(T)/[aug]-cc-pVDZ level using the method in ref. 38. The excellent agreement of these results with experiments supports the validity of calculations at the CCSD(T) level (e.g. MMPT surface) for quantitative investigations of MA and justifies the consistency of experimental results in combination with numerical results obtained directly from the MMPT surface.

Miller\(^{19}\) derived expressions that relate tunneling energy splittings \( \Delta E \) to tunneling probabilities \( P_{\text{tun}} \) for a 1D symmetric double well potential based on periodic orbit theory,

\[
\sqrt{P_{\text{tun}}} = e^{-\theta} \approx \pi \Delta E n(E_0) \approx \pi \Delta E \frac{\omega_0}{2\pi}.
\] (9)

Here, \( \theta \) is the penetration integral (imaginary action integral) through the 1D potential barrier; \( n(E_0) \) is the derivative of the phase integral (semiclassical quantum number) in a single well with respect to \( E \) calculated at ground state energy \( E_0 \). The derivative within the HO approximation can be calculated from the frequency \( \omega_0 \). Furthermore, the tunneling rate \( k_{\text{tun}}^{\text{sym}} \) is also proportional to the oscillation frequency \( \nu_{\text{ooc}} \) within the well, for which an upper limit of \( \nu_{\text{ooc}} \leq \omega_0/2\pi \) can be given within the HO approximation to yield

\[
k_{\text{tun}}^{\text{sym}} \nu_{\text{ooc}} P_{\text{tun}} = \frac{\omega_0}{2\pi} \left( \pi \frac{\Delta E}{\omega_0} \right)^2 = \frac{\pi(\Delta E)^2}{2\hbar\omega_0}.
\] (10)

2.3 MMPT force field

The MMPT Force Field is used to compute the potential energies for MA during the PIMC simulations. A detailed account of the force field has been given in ref. 21 and 22. Briefly, MMPT uses parameterized three-dimensional potential energy surfaces fitted to MP2/6-311++G(d,p) ab initio calculations to describe the interactions within a general DH–A motif where D is the donor, H is the hydrogen, and A is the acceptor atom. Together with a standard force field—here CHARMM\(^{40}\) used—the bonded interactions on the donor and acceptor side are smoothly switched on and off depending on the position of the transferring H-atom (DH–A or D–HA). Recent work shows that the parameterized MMPT force field for MA leads to equilibrium structures, infrared spectra, tunneling splittings, and proton transfer rates that compare favorably with experimental and previous computational work.\(^{55}\) Fig. 2 shows the two-dimensional projection of the PES for the proton transfer in MA, and the corresponding proton transfer barrier height is
4.34 kcal mol\(^{-1}\), which is close to the \textit{ab initio} value of 4.1 kcal mol\(^{-1}\) at the CCSD(T) level.\(^2\)

## 3 Results and discussion

### 3.1 Simulation details

The PIMC simulations employed a combination of single-slice, multi-slice, and whole chain moves.\(^4,1\) The statistical errors of all the quantities were calculated by block averaging, which estimates statistical errors by removing inherent correlation in the Monte Carlo data.\(^2\) Test simulations were carried out to determine the required number \(P\) of imaginary time slices to converge the calculations. Fig. 3 shows the dependence of \(C_{\text{ff}}\) and \(dF(l)/dl\) on \(P\) for \(T = 375\) K. In general \(P = 64\) is sufficient for converging these quantities. The figure compares the thermodynamic estimator (TE)\(^24\) and centroid virial estimator (CVE)\(^25\) for the free-energy derivative \(dF(l)/dl\). While the two estimators yield similar average results, the statistical root mean square error (RMSE) of \(dF(l)/dl\) computed with TE grows with \(P\), whereas the RMSE of the CVE remains approximately constant up to \(P = 256\). The RMSEs of \(C_{\text{ff}}\) and \(\Delta H\) also increase significantly with \(P\), as shown in Fig. 3. In particular, \(\Delta H(0)\) and \(\Delta H(1)\) have the largest statistical errors (see Table 1), and much longer simulations are required to evaluate them, especially at lower temperatures where larger \(P\) values are needed. This could be remedied by using more efficient estimators for \(\Delta H\) and \(C_{\text{ff}}\).\(^4\)

![Fig. 3 The dependence of \(C_{\text{ff}}\), \(\Delta H\), \(dF(l)/dl\) and \(dF(l)/dl\) on the number \(P\) of imaginary time slices for \(T = 375\) K and \(l = 0\).](image)

The free energy derivatives required for TI are evaluated for seven \(l\) values (see below) with both unconstrained and constrained simulations. Unconstrained simulations include \(2 \times 10^8\) steps, while constrained simulations are run for \(4 \times 10^8\) steps each except those for \(l = 0\) and 1 where \(8 \times 10^8\) steps are used to reduce the RMSE of \(\Delta H\). This results in 14 independent PIMC simulations and in a total number of \(5 \times 10^9\) Monte Carlo moves from which the KIE was estimated at each temperature.

The ratios of the partition functions and of the delta–delta correlation functions are computed by TI for \(l = j/6\) with \(j = 0, 1, \ldots, 6\). The free energy derivatives needed as an input for TI at different temperatures are shown in Fig. 4. With decreasing temperature, \(dF(l)/dl\) increases more rapidly than \(dF(l)/dl\), and this is the major cause for the temperature variation of the KIE in MA (see Table 1).

### 3.2 Kinetic isotope effect

The free energy derivatives shown in Table 1 were used to compute the KIE values shown in Table 1. The statistical errors are also listed, and the KIEs are determined to be within 10\% uncertainty. At very high temperature (\(\sim 1500\) K) the KIE is only slightly larger than 1, while at \(300\) K a KIE of 5.2 \pm 0.4 is found.

The temperature dependence of the KIE can be characterized in more detail by decomposing it into two factors, namely \(C_{\text{ff}}(0)/C_{\text{ff}}(1)\) and \(Q_{\text{ff}}(0)/Q_{\text{ff}}(1)\). As illustrated in Fig. 5, the ratio \(Q_{\text{ff}}(1)/Q_{\text{ff}}(0)\) grows exponentially with the inverse temperature. An exponential fit based on the six temperatures considered in the present work leads to \(Q_{\text{ff}}(1)/Q_{\text{ff}}(0) = 0.60513 \exp(568.86\text{ K}/T)\) with a correlation coefficient of 0.999. This implies that \(Q_{\text{ff}}(1)/Q_{\text{ff}}(0)\) is an Arrhenius component

![Fig. 4 Free energy derivatives for the reactant (left) and transition states (right) with respect to the mass parameter \(l\) used for thermodynamic integration.](image)

The table below shows the computed KIE values from PIMC simulations on the MMPT PES together with intermediate variables required for eqn (4). The statistical errors are also listed, and the KIEs are determined to be within 10\% uncertainty. At very high temperature (\(\sim 1500\) K) the KIE is only slightly larger than 1, while at 300 K a KIE of 5.2 \pm 0.4 is found.

### Table 1

<table>
<thead>
<tr>
<th>(T) [K]</th>
<th>(C_{\text{ff}}(0)/C_{\text{ff}}(1)) ([10^{-3}])</th>
<th>(C_{\text{ff}}(1)/C_{\text{ff}}(1)) ([10^{-3}])</th>
<th>(\Delta H(0)/[10^{-3}])</th>
<th>(\Delta H(1)/[10^{-3}])</th>
<th>(Q_{\text{ff}}(1)/Q_{\text{ff}}(0))</th>
<th>(Q_{\text{ff}}(1)/Q_{\text{ff}}(1))</th>
<th>(C_{\text{ff}}(0)/C_{\text{ff}}(0))</th>
<th>KIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500</td>
<td>5.004 \pm 0.039</td>
<td>4.769 \pm 0.052</td>
<td>7.469 \pm 0.242</td>
<td>8.776 \pm 0.579</td>
<td>3.503 \pm 0.001</td>
<td>4.054 \pm 0.012</td>
<td>1.07 \pm 0.08</td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>2.988 \pm 0.023</td>
<td>2.753 \pm 0.024</td>
<td>4.061 \pm 0.130</td>
<td>4.146 \pm 0.131</td>
<td>5.332 \pm 0.002</td>
<td>4.174 \pm 0.003</td>
<td>1.42 \pm 0.07</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>2.273 \pm 0.018</td>
<td>2.118 \pm 0.018</td>
<td>2.833 \pm 0.099</td>
<td>3.090 \pm 0.092</td>
<td>8.893 \pm 0.005</td>
<td>4.609 \pm 0.006</td>
<td>2.3 \pm 0.1</td>
<td></td>
</tr>
<tr>
<td>375</td>
<td>1.890 \pm 0.017</td>
<td>1.872 \pm 0.018</td>
<td>1.959 \pm 0.093</td>
<td>2.429 \pm 0.083</td>
<td>15.421 \pm 0.011</td>
<td>5.374 \pm 0.010</td>
<td>3.6 \pm 0.2</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>1.610 \pm 0.019</td>
<td>1.694 \pm 0.018</td>
<td>1.752 \pm 0.102</td>
<td>2.345 \pm 0.074</td>
<td>27.221 \pm 0.027</td>
<td>6.647 \pm 0.019</td>
<td>5.2 \pm 0.4</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>1.426 \pm 0.026</td>
<td>1.626 \pm 0.023</td>
<td>1.686 \pm 0.109</td>
<td>1.891 \pm 0.092</td>
<td>48.578 \pm 0.067</td>
<td>8.610 \pm 0.035</td>
<td>5.5 \pm 0.5</td>
<td></td>
</tr>
</tbody>
</table>
and the tedious TI calculations can be reasonably replaced by the fitted formula. As for the pre-factor $C_{\text{tr}}(0)C_{\text{ad}}(1)\Delta H(1)$, its temperature dependence is more involved, partially because of the large uncertainties in $\Delta H(1)$ and $\Delta H(0)$. However, this factor is relatively temperature-insensitive and close to 1.17 over a large temperature range. With these observations an empirical formula of $\text{KIE} = 0.708 \exp(568.86 \frac{K}{T})$ is expected to provide an estimate of the KIE for the proton transfer in MA above 300 K, with this PES, the KIE computed as the ratio of the two rate constants ranges from 2.41 ± 0.86 to 4.05 ± 0.27 using quantum instanton and path integral-quantum transition state theory. Employing thermodynamic integration similar to that presented here, Wong et al. obtained a KIE of 4.27 ± 0.01 and 5.10 ± 1.81 with the two methods. Despite the fairly large differences among their four results, the last one agrees (within the statistical error) with our QI value of 5.2 ± 0.4.

Results for absolute rates and KIEs from CTST calculations are reported in Table 2 and compared with those from QI/MMPT. Calculations at the MP2/6-311+G(d,p) level of theory were carried out with Gaussian09. For validation, the CTST results are compared with absolute rates determined previously at 300 K. The classical, “over-the-barrier” hopping rate for H-transfer from MD simulations on the MMPT surface is 2.4 ns$^{-1}$. The factor of 540/2.4 = 225 difference between CTST and MD-based H-hopping rates on the MMPT surface is due to ZPE effects, for which classical MD does not account. Within the HO approximation, the ZPE difference between the reactant and the TS reduces the barrier height by 3.7 kcal mol$^{-1}$, and thereby contributes to a Boltzmann factor of 470 at 300 K, explaining the factor of $\approx 10^3$ difference. Independent classical MD calculations along the lines of previous work were carried out for estimating the “over-the-barrier” hopping rate in H and D isotopologues on the MMPT surface. This yields 5.3 ns$^{-1}$ and 0.42 ns$^{-1}$ at 300 K for H- and D-hopping, suggesting a KIE of $\approx 13$, which is about twice as large as 6.9, the value obtained from CTST calculations on the MMPT surface.

Ground-state tunneling rates were calculated based on periodic orbit theory using the experimental ground-state splittings (21.6 cm$^{-1}$ and 2.9 cm$^{-1}$) and harmonic frequencies of the normal modes corresponding to O–H/D stretching (as upper estimates) obtained from the MMPT force field.

The temperature dependence of different components of the KIE: the exponentially-dependent factor $Q_{\text{tr}}(1)Q_{\text{ad}}(0)$ (top) and the pre-factor $C_{\text{tr}}(0)C_{\text{ad}}(1)\Delta H(1)$ (bottom) are reported. See the text for details.

Table 2. CTST results for the KIE calculated on the MP2/6-311+G(d,p) and MMPT PESs. Absolute H- and D-transfer rates (in 100 ns$^{-1}$ units), the KIE, and contributions to the KIE from zero-point energy (KIE-ZPE) and vibrational excitations (KIE-VIB) are also reported. The temperature-independent contribution of rotation to the KIE amounts to less than 0.5% and is not reported. The last two columns report results from QI/MMPT (see also Table 1) and the percentage difference to the CTST/MMPT results.

<table>
<thead>
<tr>
<th>$T$ (K)</th>
<th>CTST/MP2</th>
<th>CTST/MMPT</th>
<th>QI/MMPT</th>
<th>MMPT</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$k_H$</td>
<td>$k_D$</td>
<td>KIE-ZPE</td>
<td>KIE-VIB</td>
</tr>
<tr>
<td>1500</td>
<td>22</td>
<td>15</td>
<td>1.31</td>
<td>1.15</td>
</tr>
<tr>
<td>750</td>
<td>13</td>
<td>6.7</td>
<td>1.71</td>
<td>1.12</td>
</tr>
<tr>
<td>500</td>
<td>8.4</td>
<td>3.4</td>
<td>2.24</td>
<td>1.10</td>
</tr>
<tr>
<td>375</td>
<td>5.7</td>
<td>1.8</td>
<td>2.93</td>
<td>1.08</td>
</tr>
<tr>
<td>300</td>
<td>3.8</td>
<td>0.90</td>
<td>3.84</td>
<td>1.06</td>
</tr>
<tr>
<td>250</td>
<td>2.6</td>
<td>0.50</td>
<td>5.02</td>
<td>1.04</td>
</tr>
</tbody>
</table>
dimer where it was also found that the maximum rate of transfer is slaved to the donor–acceptor vibrational frequency. Detailed investigations of such effects are, however, outside the scope of the present work.

The difference between QI and CTST at high and intermediate temperatures is mainly due to anharmonicity which is included in the QI but neglected in the CTST. However, it should be pointed out that high-temperature results of both QI and CTST for MA are somewhat academic since, at high temperature, the barrier is easily crossed and assumptions of classical or quantum transition state theories break down. Below 750 K, CTST estimates for the KIE are dominated by ZPE effects and vibrational excitation has little influence. CTST gives significantly different results for MMPT and MP2 at low temperature. This is probably related to the different harmonic frequencies in the MMPT and MP2 treatments. Another factor may be that during H-transfer the π-electron system of MA is rearranged and tautomerisation takes place. Such effects are included in MP2 calculations but are difficult to capture in a force field.

To explore the differences between QI theory and CTST and highlight the advantages of QI in the case of MA, the ZPE effects from QI calculations were estimated for both the reactant and transition states. According to Table 1, the two main factors contributing to the KIE when treated with the QI method are the ratios of $Q_r$ and $C_{dd}$, which are the Boltzmann factors of free energies of the isotopologues (see eqn (6)) for the reactant and the transition state, respectively. The asymptotic behaviour of the ratio of partition functions at low temperature is dominated by the Boltzmann factor of the ZPE differences, assuming a linear, Arrhenius-type behaviour [log vs. $1/T$]. An Arrhenius plot of these quantities (see Fig. 5) suggests a near-linear behaviour at low temperature. At 250 K $Q_r(1)/Q_r(0) = 48.578 \pm 0.067$ and $C_{dd}(1)/C_{dd}(0) = 8.610 \pm 0.035$ at the MMPT-QI level. This yields ZPE differences of $\Delta^{\text{PIMC}}_{\text{ZPE}} = 1.93 \text{ kcal mol}^{-1}$ and $\Delta^{\text{QI}}_{\text{ZPE}} = 1.07 \text{ kcal mol}^{-1}$ with a corresponding difference in ZPE-differences of $\Delta = 0.86 \text{ kcal mol}^{-1}$ ($\Delta = \Delta^{\text{PIMC}}_{\text{ZPE}} - \Delta^{\text{QI}}_{\text{ZPE}}$) which is the quantity that appears in the exponent of the KIE calculated with CTST in eqn (8). For an improved estimate as $T \to 0$ a general hyperbolic form of $\text{log} X = \frac{\Delta^{\text{PIMC}}_{\text{ZPE}}}{RT}(1 + \alpha T^\gamma)$ was fitted to the data at 500 K, 375 K, 300 K and 250 K, where $X$ denotes the ratios $Q_r(1)/Q_r(0)$ or $C_{dd}(1)/C_{dd}(0)$, and $\alpha$ and $\gamma$ are fitting parameters. This yields $\Delta^{\text{PIMC}}_{\text{ZPE}} = 1.805 \pm 0.002$ kcal mol$^{-1}$ and $\Delta^{\text{QI}}_{\text{ZPE}} = 0.929 \pm 0.016$ kcal mol$^{-1}$ for $T \to 0$.

For low temperatures ($T < 300 \text{ K}$) the CTST and QI kinetic isotope effects do not agree particularly well. The HO approximation on the MMPT surface yields $\Delta^{\text{PIMC}}_{\text{ZPE}} = 2.04 \text{ kcal mol}^{-1}$ and $\Delta^{\text{QI}}_{\text{ZPE}} = 0.92 \text{ kcal mol}^{-1}$ with a corresponding $\Delta = 1.12 \text{ kcal mol}^{-1}$. Hence, for the TS excellent agreement is found between QI/PIMC-MMPT (0.92 kcal mol$^{-1}$) and CTST/HO-MMPT (0.93 kcal mol$^{-1}$), whereas for the reactant state the HO approximation is inadequate due to the large anharmonicity in the O–H stretching vibration. We conclude that the major contribution to the deviation between KIEs calculated by TST and QI at low temperature (see Table 2) is from ZPE differences in the reactant

(2310 cm$^{-1}$ and 3149 cm$^{-1}$). Periodic orbit theory suggests ground-state tunneling rates of 44 ns$^{-1}$ and 1.1 ns$^{-1}$ for H and D isotopes, respectively, which are significantly slower (10% for H and 1–2% for D) than the CTST estimates for the over-the-barrier rates (540 ns$^{-1}$ and 80 ns$^{-1}$ at 300 K). Despite the fact the MMPT force field has a 1 kcal mol$^{-1}$ higher barrier, CTST with electronic structure calculations at the MP2/6-311++G(d,p) ground-state tunneling rates of 44 ns$^{-1}$ and 1–2% for D) than the CTST estimates for the over-the-barrier rates (540 ns$^{-1}$ and 80 ns$^{-1}$ at 300 K). Despite the fact the MMPT force field has a 1 kcal mol$^{-1}$ higher barrier, CTST with electronic structure calculations at the MP2/6-311++G(d,p) level gives comparable rates of 380 ns$^{-1}$ and 90 ns$^{-1}$. This is due to differences in zero point energies between the MMPT and MP2 PESs. Our CTST results are comparable to hopping frequencies in the transition state for the two isotopes$^{24}$ – $\Delta^{\text{CTST}}_{\text{ZPE}} = 0.86 \text{ kcal mol}^{-1}$ and $\Delta^{\text{QI}}_{\text{ZPE}} = 0.87 \text{ kcal mol}^{-1}$ for H and D, respectively. Deviation from the Arrhenius-type behaviour is due to differences in zero point energies between the MMPT and MP2 PESs. Our CTST results are comparable to hopping frequencies in the transition state for the two isotopes$^{24}$ – $\Delta^{\text{CTST}}_{\text{ZPE}} = 0.86 \text{ kcal mol}^{-1}$ and $\Delta^{\text{QI}}_{\text{ZPE}} = 0.87 \text{ kcal mol}^{-1}$ for H and D, respectively.

Kinetic isotope effects from QI and CTST calculations are compared in Fig. 6. The PIMC/QI KIE shows Arrhenius type (linear) behavior in the temperature range of 300 to 750 K, whereas deviations from it can be observed both at lower and higher temperatures. The curvature appearing at low temperature is due to tunneling, whereas at high temperature it is mainly due to convergence to the classical limit and probably also due to neglecting recrossing effects, which are higher for H than for D. Deviation from the Arrhenius-type behaviour due to tunneling was observed, e.g., already in early experiments on CO rebinding in myoglobin. The classical high-temperature limit from CTST – given by the ratio of harmonic imaginary frequencies in the transition state for the two isotopes$^{24}$ – converges to a constant value of 1.398 at temperatures above 750 K, while its ZPE contribution (KIE-ZPE) tends to 1. On the other hand, classical MD simulations between 500 K and 2000 K also show that the rate for H- and D-transfers becomes $T$-independent above 1250 K. Such simulations include recrossing, which is neglected in CTST and QI, but classical MD on the PES neglects ZPE effects. The fact that at higher temperature the crossing rate from MD becomes constant was also observed in earlier simulations on H-transfer in a protonated ammonia...
state ($\Delta_{\text{HH}}^{\text{ZPE}}$), giving rise to a factor of 1.65 at 250 K. Another contribution to this difference may follow from the fact—mentioned in subsection 2.1—that at low temperature the optimal QI dividing surface bifurcates into two dividing surfaces.\textsuperscript{23,27} Our use of a single dividing surface determined by symmetry lowers the rate constant for hydrogen at and below about 250 K.\textsuperscript{23,27} Since the bifurcation occurs at even lower temperature for deuterium, the approximate QI rate probably slightly underestimates the KIE at 250 K. Nevertheless, our analysis above has shown that for significant vibrational anharmonicity (e.g. in the reactant state) due to the presence of low-lying barriers and of a neighboring well, the use of QI/PIMC becomes crucial, as it can capture these effects by exploring all relevant regions of the phase-space in contrast to the CTST/HO approximation, which uses only local information.

It is also possible to rationalize why, below 500 K, CTST-MP2 gives KIEs that are closer to the QI-MMPT values than the KIEs obtained with CTST-MMPT. The HO approximation on the MP2 surface gives $\Delta_{\text{HH}}^{\text{ZPE}} = 2.17 \text{ kcal mol}^{-1}$ and $\Delta_{\text{DD}}^{\text{ZPE}} = 1.36 \text{ kcal mol}^{-1}$ and a difference $\Delta = 0.81 \text{ kcal mol}^{-1}$, which explains that the “better agreement” of CTST-MP2 with QI-MMPT at low temperature is simply due to an accidental cancellation of errors.

While CTST theory within the RRHO approximation can only be considered to be qualitative, it appears to correctly capture the magnitude of the KIE, becoming 81% of the QI/MMPT values at 250 K. Nevertheless, our analysis above has shown that for significant vibrational anharmonicity (e.g. in the reactant state) due to the presence of low-lying barriers and of a neighboring well, the use of QI/PIMC becomes crucial, as it can capture these effects by exploring all relevant regions of the phase-space in contrast to the CTST/HO approximation, which uses only local information.

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We refer to rigorous quantum simulations utilizing a validated PES for H-transfer in MA, the KIE was found to be $5.2 \pm 0.4$ at room temperature. As required, the KIE tends to 1 for higher temperatures and a strong temperature dependence for low temperatures is found. The latter can be primarily linked to the variation of the free energy as a function of the progression coordinate $\lambda$ at the reactant and transition state, respectively. The working expression for the KIE (eqn (4)) allows the quantity of interest to be decomposed into a largely $\lambda$-independent prefactor and a part which follows an Arrhenius behaviour. Such an empirical relationship can be valuable for experimental studies. Periodic orbit theory based tunneling rate estimates and detailed comparisons with CTST at various levels suggest that the KIE in MA is largely determined by zero-point energy effects and that tunneling plays a minor role.

Our results suggest several ways to accelerate the PIMC calculations in future applications: the pre-factor in the KIE (consisting of $C_{\text{HH}}/C_{\text{DD}}$ and $\Delta H$) is determined from simulations for H- and D-transfer ($\lambda = 0,1$), while the computation of the free energy part [$Q(1)/Q(0)$ and $C_{\text{DD}}(1)/C_{\text{DD}}(0)$] involves TI at a series of intermediate $\lambda$ values. As shown in Table 1, the relative error of $Q(1)/Q(0)$ and $C_{\text{DD}}(1)/C_{\text{DD}}(0)$ are orders of magnitude smaller than those of $\Delta H(0)$ and $\Delta H(1)$, implying that much shorter PIMC simulations would be sufficient for TI in calculating the KIE. Fig. 3 also shows that in free energy calculations a smaller number of imaginary time slices such as $P = 32$ could be used to further speed up the simulation. Another acceleration would result from using different numbers of beads for different parts of the system.\textsuperscript{46} For example, $P = 64$ can be used for atoms that are directly related to hydrogen transfer, while a much smaller number of beads, such as $P = 4$, is possibly sufficient for the remaining particles in the system. In the future we will explore the possibilities of lowering the $P$ values by using higher order factorization of the path integral and of lowering the statistical errors of $C_{\text{HH}}/C_{\text{DD}}$ and $\Delta H$ by implementing the CVE for these quantities.

In summary, a combination of an experimentally validated and efficient force field with rigorous and numerically robust means to compute quantum correlation functions yields KIEs in MA with statistical errors below 10% even at the lowest studied temperature of 250 K. The favorable scaling of the force field evaluation with the number of atoms and the possibility to reduce the number of beads required to describe atoms far from the proton transfer motif suggests the possibility of applying the present approach to the calculation of KIEs even in larger, biologically relevant systems.

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