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Implementation of the bisection sampling method in path integral simulations

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Dedicated to Professor Ian Hillier for his contributions to the understanding of enzymatic reaction mechanisms.

Abstract

A bisection sampling method is implemented in the framework of a quantized classical path algorithm to include nuclear quantum effects in path integral simulations. The present study examines the convergence of these calculations on two model systems with respect to the number of beads used in the polymer chain and the number of configurations both in free-particle sampling and in classical configuration sampling. The results will be useful for future studies of kinetic isotope effects in enzymatic reactions.

Keywords: Bisection sampling method; Path integral simulation; Polymer

1. Introduction

Proton and hydride transfer reactions play an important role in many chemical and enzymatic reactions, and numerous studies of these processes in the gas phase, solution phase, and enzymes have been carried out. In particular, the significant role of quantum mechanical (QM) dynamical effects in enzyme catalysis has received considerable attention, evidenced by the unusual experimental kinetic isotope effects in several enzyme systems including the hydride transfer reaction in liver alcohol dehydrogenase and the proton transfer reaction in methylamine dehydrogenase [1–6]. Furthermore, a number of theoretical studies have shown that quantization of bound vibrational motions, especially the inclusion of zero point energy, can significantly reduce the free energies of activation of enzyme reactions [7–9]. Although methods that incorporate quantum mechanical dynamical effects in gas phase reactions have been well-established, enzymatic and condensed phase reactions require a method that can be used to average quantum effects over a myriad of conformations [10,11]. This is most easily accomplished by computing the potential of mean force (PMF) along a reaction coordinate using classical Monte Carlo or molecular dynamics simulations [12–14], and then, the effects of quantized molecular vibrations and quantum mechanical tunneling are incorporated into the rate calculation by a transmission coefficient [8,9,11,14–16]. Thus,

$$k^{\mathrm{qu}} = \gamma k^{\mathrm{TST}} \tag{1}$$

where k^{qu} is the quantum mechanical rate constant and k^{TST} is the classical transition state theory (TST) rate constant. In general, the transmission coefficient in Eq. (1) is a product of the deviation from equilibrium behavior, the classical dynamic recrossing factor, Γ, and the quantum mechanical correction, κ [16]. The latter is defined as

$$\kappa = \mathrm{e}^{-\beta(G^{\neq}_{\mathrm{qm}} - G^{\neq}_{\mathrm{TST}})} \tag{2}$$

where $\beta = 1/k_{\mathrm{B}}T$, k_{B} is Boltzmann's constant, T is the temperature, and $G^{\neq}_{\mathrm{qm}}$ and $G^{\neq}_{\mathrm{TST}}$ are the quantum and classical free energy of activation, respectively.

Previously, we have adopted this strategy by using a semiclassical theory that incorporates multidimensional tunneling contributions, and we have successfully applied this ensemble-averaged variational transition state theory (EA-VTST) to several enzymatic reactions with excellent

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agreement between the calculated and experimental kinetic isotope effects [17]. An alternative approach is to use the path integral formulation of quantum mechanics, in which the isomorphism between the discretized path integral (DPI) and a classical system allows one to evaluate quantum effects using classical simulation techniques [18–20]. Here, a quantum particle is represented by a ring of classical beads with their effective interaction described by a harmonic potential that has a force constant proportional to the number of classical particles in the chain, P [19]. At the limit of infinitely large P, the correspondence of the equilibrium properties of a quantum system and the isomorphic classical system is exact. The DPI approach is particularly suited for systems with a large number of degrees of freedom, such as condensed phase solute/solvent systems or macromolecular biomolecules.

In principle, the quantum mechanical free energy of activation, $G^{\neq}_{\mathrm{qm}}$, can be obtained directly by using centroid path integral molecular dynamics simulations [21–24]. However, it is more convenient to evaluate the free energy difference, $G^{\neq}_{\mathrm{qm}} - G^{\neq}_{\mathrm{TST}}$, in Eq. (2), by making a quantum correction to the classical mechanical (CM) potential of mean force evaluated from molecular dynamics simulations [15,25–27]. This correction can be enumerated either by Monte Carlo or molecular dynamics simulations over the classical trajectories. To this end, Sprik et al. [25] described a procedure to obtain properties by averaging quantum corrections over classical configurations, through free-particle path integral sampling by constraining the center of mass (centroid) of the beads within a small cubic volume.

$$\langle A \rangle = \langle \langle A \rangle_{\mathrm{K}}^{\mathrm{FP}} \rangle \tag{3}$$

In Eq. (3), the inner average $\langle A \rangle_{\mathrm{K}}^{\mathrm{FP}}$ represents the quantum average of property A by free-particle path integral over a fixed configuration K obtained from a separate, classical Monte Carlo simulation. The outer average is over these Monte Carlo configurations. This double averaging strategy was further exploited by Warshel and coworkers [15], who constrained the centroid position of the quantized particle to that of the corresponding classical coordinates [26–28]. This procedure, termed the quantized classical path (QCP), utilizes the trajectory obtained from classical mechanics simulations to obtain the QM correction by performing free-particle path integral averaging with the centroid constrained to the classical position. The QCP method is well suited to treat nuclear QM effects of large macromolecular systems, and has been applied to several enzymatic systems and has been compared to experimental and exact theoretical results with good agreement [15,26,29,30].

However, the convergence in PI implementations in general and in the QCP method in particular is not a trivial matter. Although a number of techniques for free-particle path integral sampling have been proposed [31], it appears that a direct sampling procedure was used in previous QCP applications to enzymatic reactions. A detailed description of the method was presented by Aqvist and coworkers who applied the QCP approach to the calculation of the kinetic isotope effect in the proton transfer reaction catalyzed by Glyoxalase I [29]. In this study, 20 beads were employed to describe the quantized particles, and 1, 5, and 10 Monte Carlo Metropolis steps were used to obtain the quantum correction for each classical configuration. In another calculation, a total of 20,000 free-particle configurations were used for 18 beads along the entire reaction coordinate for an enzymatic reaction [30]. However, other studies suggest that extensive path integral sampling is needed even for a dilute hard-sphere system [25], and it appears that a detailed study of the convergence behavior of the QCP method is desirable.

In this study, we report an implementation of the quantum correction algorithm, employing an efficient bisection method [31] coupled with the QCP approach to perform path integral sampling (BQCP), and present a detailed analysis of the convergence of the method for model systems.

2. Theoretical background

The canonical QM partition function of the system is written as an integral over the trace of the density matrix:

$$Q^{\mathrm{qu}} = \int \mathrm{d}\mathbf{x}\rho(\mathbf{x},\mathbf{x};\beta) \tag{4}$$

where $\beta = 1/k_{\mathrm{B}}T$, and the coordinate representation of the density operator is $\rho(\mathbf{x},\mathbf{x};\beta) \equiv \langle \mathbf{x}|\mathrm{e}^{-\beta H}|\mathbf{x}\rangle$, in which H is the Hamiltonian operator of the system. For convenience of presentation, we limit our discussion to one dimension. In the path integral formulation, the density operator is written as integrals over all possible paths of the particles in the system:

$$\rho(\mathbf{x},\mathbf{x};\beta) = \int_{\mathbf{x}(0)=\mathbf{x}(\beta\hbar)} \mathrm{D}\mathbf{x}(\tau)\mathrm{e}^{-1/\hbar S[\mathbf{x}(\tau)]} \tag{5}$$

where $\hbar = h/2\pi$, h is Planck's constant, and the integral

$$\int_{\mathbf{x}(0)=\mathbf{x}(\beta\hbar)} \mathrm{D}\mathbf{x}(\tau)[\cdots] \tag{6}$$

denotes integration over all paths beginning at $\mathbf{x}(0)$ and ending at $\mathbf{x}(\beta\hbar)$. In Eq. (5), the imaginary time action functional for the path $\mathbf{x}(\tau)$ is given as

$$S[\mathbf{x}(\tau)] = \int_0^{\beta\hbar} H[\mathbf{x}(\tau)]\,\mathrm{d}\tau = \int_0^{\beta\hbar} \left\{ \frac{m}{2}\dot{\mathbf{x}}(\tau)^2 + U[\mathbf{x}(\tau)] \right\} \mathrm{d}\tau \tag{7}$$

where $U[\mathbf{x}(\tau)]$ is the potential energy function.