# Comparison of Transition State Theory rate constants for internal conformational motion with those obtained from Molecular Dynamics Simulations.

B.C. Hathorn,[a,*] B.G. Sumpter,[b] and D.W. Noid[b]

[a] Computer Science and Mathematics Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831

[b] Chemical and Analytical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831

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## Abstract

The results of molecular dynamics (MD) simulations are compared to transition state theory estimations for formation of conformational defects in a polymer crystal. The rates of conformational defect formation and destruction are obtained in terms of a distribution over possible conformational states. The rate constant obtained by this method, when normalized by the number of possible defect sites, is independent of the size of the system, in apparent contrast with the results MD simulations. The difference is interpreted in terms of the effective temperature of the molecular dynamics calculation.

## I. INTRODUCTION

The simulation of large molecular structures such as polymers and proteins with molecular dynamics (MD) modeling has become common. [1] Recently, however, serious questions have been raised as to whether a simulation based in classical mechanics can correctly describe a quantum system. [2,3]

In several recent calculations we have observed large amounts of conformational disorder in molecular dynamics simulations of crystalline polyethylene. [4–12] In particular, the amount of disorder, as measured by the fraction of bonds which undergo a gauche-trans isomerization, appears to increase nonlinearly with the size of the system. A detailed understanding of the conformational disorder of the crystals is fundamental to understanding such mesophase structures as liquid crystals, plastic crystals, conformationally disordered (CONDIS) crystals, which lie somewhere between the melt (liquid phase) and crystalline (solid phase) structures. [4]

In the present study, we present a model based on a statistical theory of the gauche-trans isomerization rate constant. Such a model can be considered independent of the more traditional molecular dynamics simulations which are used to treat such systems. In Sec. II we briefly describe the standard theories of unimolecular reactions in terms of Transition State Theory and relate the parameters involved to the properties of a polymer crystal. We obtain a rate constant for the total number of conformational defects *per bond* as an average over a distribution of canonical rate constants for polymers with different numbers of defects. In Section III we contrast the results to those obtained from direct MD simulations, and discuss the limitations of the later.

## II. THEORY

The gauche-trans isomerization of a polymer crystal is one example of a unimolecular reaction. There are two common approaches which give reliable estimates of unimolecular rate constants, Transition State Theory for canonical rate constants, and RRKM theory for microcanonical rate constants. [13–18] Both theories require similar parameters to be applied, mainly the energy of the barriers and the harmonic vibrational frequencies for the reactants and the transition state regions. These parameters allow for the calculation of the partition functions in the canonical case and the densities of states in the microcanonical case. We derive here rate constants for the canonical case for a system which has a variety of different initial conditions (the microcanonical case and its relation to the canonical case is described in the appendix). For the canonical case, we use the traditional grand canonical partition function, [19] where the additional variable is the number of conformational defects in the polymer chain.

In the present case, we make several simplifying approximations. We assume that introduction of a conformational defect is done at an energy cost of $V_0$, regardless of the location of the defect and its relative positions to any other defects present. Such a simplification is unnecessary in the event where detailed information on the energies and structure is known, but in the present case the simplification that defects are non-interacting allows an exact expression of the partition functions and rate constants. We also make the assumption that the vibrational frequencies of the polymer do not change with the introduction of a conformational twist. Again, this approximation would be unnecessary when detailed information about structures is known, but provides a convenient simplification for the present treatment. In essence, the two approximations indicate that the introduction of a conformational defect merely displaces the harmonic oscillator to a higher energy. We consider a system made up of a polymer which has $N$ possible locations for a conformational defect, or a position which has undergone a trans/gauche flip. In the non-interacting approximation, these defects could, in fact, be located in a number of different polymer strands making up a polymer crystal. In the case of a collection of $m$, $n$-mers we would have $N = m(n-1)$, with the corresponding number of possible transition states.

The traditional TST rate constant for a reaction with one possible transition state is given by [13]

$$k(T) = \frac{k_B T}{h}\frac{Q^\dagger}{Q}. \tag{1}$$

Here, $k_B$ is Boltzmann's constant, $T$ is the temperature, $h$ is Planck's constant, $Q$ is the canonical partition function of the reactant and $Q^\dagger$ is the canonical partition function of the transition state, and explicitly includes the exponential difference in energy for the lowest state and the threshold of reaction, $\exp(-V^\dagger/k_B T)$. The transition state partition function differs from that of the reactant by changes in the vibrational frequencies, but mainly in the absence of one degree of freedom, which corresponds to the motion along the reaction coordinate. As a result, the expression reduces to the form $k = \nu_{eff} \exp(-V^{\dagger}/k_B T)$ where $\nu_{eff}$ is the effective vibrational frequency for the omitted coordinate, which under the approximations introduced above is identical for all polymers, regardless of the number and location of conformational defects. An approximation which is frequently employed to estimate the rate constant is to assume that the rate constant is simply that of the case of only one transition state, multiplied by the number of identical transition states, with an appropriate scaling to obtain a *per bond* rate constant. [4] We see below that this is consistent with the present treatment, however, in the present treatment we also establish rate constants for the formation and destruction of conformational defects.

In the present case there is the possibility of slightly different rate constants for polymers with different numbers of conformational defects. In this case it is necessary to perform an average over the appropriate rate constants. As a result, we introduce a grand canonical partition function, $\Xi$,

$$\Xi = \sum_{j=0}^{N} \binom{N}{j} 2^j Q(j) e^{-jV_0/k_B T}. \tag{2}$$

In this case, $Q(j)$ is the partition function for the polymer system with $j$ conformational defects, evaluated at the zero-point energy of that particular conformational isomer. The binomial coefficient represents the number of possible ways of introducing the conformational defects into the system, and the factor of $2^j$ arises from the existence of both a gauche(+) and gauche(-) configuration for each conformational defect. Using the simplifications introduced above, we note that each of the conformational partition functions $Q(j)$ is equivalent, and the series can be evaluated exactly,

$$\Xi = Q(1 + 2e^{-V_0/k_B T})^N. \tag{3}$$

The function $\Xi$ gives the normalization of the probability distribution for finding $j$ conformational defects $P(j)$,

$$P(j) = (1 + e^{-V_0/k_BT})^{-N} \binom{N}{j} 2^j e^{-jV_0/k_BT}. \tag{4}$$

The thermal rate constant is the sum of the rate constant for each individual conformational isomer, times the probability of finding that conformational isomer,

$$k(T) = \sum_j P(j) k_j(T). \tag{5}$$

The individual rate constants for a particular conformational isomer are given by Eq. (1), multiplied by the number of identical transition states, which is $N - j$, leading to the overall rate constant

$$k(T) = (1 + 2e^{-V_0/k_BT})^{-N} \frac{k_BT}{h} \frac{Q^\dagger}{Q} \sum_{j=0}^{N} (N - j) \binom{N}{j} 2^j e^{-jV_0/k_BT} \tag{6}$$

The summation, after suitable rearrangement, is conveniently evaluated as the derivative of the sum of a binomial series, yielding the final expression for the *per bond* rate

$$k(T) = \frac{k_BT}{h} \frac{Q^\dagger}{Q} \left[ \frac{1 + 4\exp(-V_0/k_BT)}{1 + 2\exp(-V_0/k_BT)} \right] \tag{7}$$

A similar expression naturally exists for the rate constant for reverting to a state with fewer conformational defects. In this case, there distribution function $P(j)$ remains the same, however the thermal rate constants are slightly different, owing to a shift of $V_0$ in the barrier height for the reverse process, and the presence of $j$ identical transition states for the reverse process. The average rate corresponding to (6) is

$$k_{-1}(T) = (1 + 2e^{-V_0/k_BT})^{-N} \frac{k_BT}{h} \frac{Q^\dagger}{Q} e^{V_0/k_BT} \sum_{j=0}^{N} j \binom{N}{j} 2^j e^{-jV_0/k_BT}. \tag{8}$$

The *per bond* rate constant for the reverse process is now given by

$$k_{-1}(T) = \frac{k_BT}{h} \frac{Q^\dagger}{Q} \frac{1}{1 + 2e^{-V_0/k_BT}}. \tag{9}$$

The total *per bond* rate of transitions, given by the sum of the forward and backward rate constants, is indeed given by Eq. (1) subject to the constraint that it is recognized that it will be the sum of both the forward and backward reactions. If the reaction measured is that in only one direction, the required rate constants are given by Eqs. (6) and (9).

We note, however, that the sum of the *per bond* rate constant is, in fact independent of the size of the system, $N$, as our intuition from the physical behavior of macroscopic systems suggests.

## III. RESULTS AND DISCUSSION

We begin with a few comments on the limitations of the present theory. The present theory is kinetic in nature, not thermodynamic. As a result, it predicts the rate at which isomerizations in the crystal will occur, leading to crystal defects. The present theory does not speak to the thermodynamic stability of these systems where isomerizations have been introduced. The thermodynamic stability of the systems is best addressed in terms of the overall equilibrium constant of the transition. The equilibrium properties of the system can frequently be treated separately from the dynamic properties through the use of Monte Carlo and similar techniques. [3] The present treatment does, however, provide estimates of the time constants for interconversion between various isomers, and shows that as the size of the system gets larger in a thermal system, the rate constant should be largely unchanged, in the approximation that the defects introduced into the crystal are non-interacting.

We now seek to compare the results of the transition state theory model, Eqs. (6) and (9) to the rate constants predicted by Molecular Dynamics Simulations which are commonly employed. Although the Molecular Dynamics Simulation is formally accomplished by integrating the equations of motion of the system at a fixed energy, $E$, we note that this microcanonical approach is entirely equivalent to the canonical treatment, when the energy used is the average energy which would be expected for the temperature in Eq. (1). A demonstration of this is given in the Appendix by comparing the microcanonical reaction rate and the thermal reaction rate for an appropriate ensemble average.

In the present model, we find that the total rate of transitions from gauche to trans and *vice versa* on a *per site* basis, should be $k + k_{-1}$, which is independent of the size of the system, $N$. In a straightforward plot of the data from a set of molecular dynamics calculations [4] shown in Fig. 1, we find that for the molecular dynamics calculations there is a significant dependence of the calculated rate constant on the size of the system, and that this trend is consistent over a range of temperatures. In order to align the data for the different calculations, we must assume a translation to the left in the larger systems, corresponding to a reduction in the effective temperature. The enhancement of the scaled rate constant between the largest and smallest systems in these calculations amounts to a shift of approximately two orders of magnitude, well within the expected uncertainty of the molecular dynamics simulation.

The rate constant being a function of the size of the system leads to the conclusion that the use of molecular dynamics in this way must be utilized with caution. In the present case, there are several likely sources of the effect. We note that the effective temperature of the system in the MD simulation has been obtained by use of the relation [4]

$$\langle E_{kin} \rangle = \frac{3}{2} N k_B T = \sum_i \frac{1}{2m_i} \left( p_{xi}^2 + p_{yi}^2 + p_{zi}^2 \right), \tag{10}$$

where $i$ indexes each of the particles in the simulation and the $p_i$'s are the momenta and $m_i$ is the particle mass, and the system is composed of $N$ particles. In this case, all of the energy of the system is available to access the reaction coordinate, and also for supplying energy for producing configurational defects. In a true quantum mechanical system, however, a certain fraction of the energy, corresponding to the zero-point energy, must be unavailable for these purposes, and thus, the total energy available in the classical mechanical calculation tends to be too large, and thus, the effective temperature appears to be too high, producing a rate constant which is too large. The excess of energy is only increased by increasing the size of the system as the number of vibrational motions and their corresponding zero-point energies, is increased. A well-known example of this problem is evidenced in a very large molecule at low temperatures, where the zero-point energy alone is sufficient to overcome the activation energy for many reactions.

Another influence of the excess energy which contributes to the discrepancy between the transition state theory and MD reaction rate constants is the issue of the conformational disorder. The excess of available energy enhances the conformational disorder, since the higher "effective temperature" drives the populations to systems with more conformational defects in Eq. (4). The effect of this is to drive the system to a greater weighting of the reactions for the reverse process, which naturally have a faster rate, due to a smaller activation energy. The tendency of the system to relax to one with a large amount of conformational disorder is demonstrated in the MD simulations of large polymer crystals, where with increased size the system loses nearly all semblance of structure.

In the present result, the system is expected to equally populate all regions of the reactant and transition state phase space, whereas in the classical mechanical simulations the energy tends to concentrate in the lowest frequency modes. [2,8,23] In the real system, the zero-point energy must be conserved in each of the modes, preventing the concentration of energy in the low frequency modes. The so-called "adiabatic leak" [3,20–22] in the classical mechanical simulations allows the energy to flow into the low energy modes, in contrast with the principles of quantum mechanics.

Typically, the reaction coordinate tends to be a low frequency mode, and thus, if the amount of energy in this mode is too large, the predicted reaction rate too fast. In addition to the failure to conserve the zero-point energy, the energy in the MD simulations appears to be overemphasized in the low frequency modes. [2,8,23] This effect has been attributed elsewhere to the onset of "too much classical chaos" in the large systems, where, even below the total zero-point energy of the system, large scale conformational motions can occur. [3]

An important consequence of this study is to call into question the rates predicted from MD simulations for large systems. Currently, modeling is done on proteins to describe the collective motions which lead to such phenomena as the formation and migration of conformational defects or protein folding. [1,6,7,9,11] The concentration of energy in low frequency modes and the effective temperature which is too large in the simulations will lead to rates of protein folding which are too large, can interfere with the interpretation of the results, and could potentially undermine the usefulness of the study. In particular, it is likely that the timescales for conformational motion determined from classical MD simulations may be too short. It may be possible to mitigate the effects of the "adiabatic leakage" by restricting the simulations to very short timescales when this effect is minimized, [3] however, in short timescales the sampling of the transition state region is likely to be too infrequent to provide meaningful estimates of the rate constants. It remains to be seen if successful modifications of the MD studies can be made to properly scale the effective temperature and to successfully overcome the errors introduced by allowing the energy to concentrate in the low frequency modes through the mechanisms of "adiabatic leak" and the onset of classical chaotic motion.

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## APPENDIX A: RELATION BETWEEN THE CANONICAL AND MICROCANONICAL RATE CONSTANTS

In present example, we compare the canonical rate constant obtained by Transition State Theory to one which is obtained from a classical mechanical simulation at fixed energy, e.g., a microcanonical reaction rate. It is possible to demonstrate that the two are, in fact, equivalent, when an appropriate distribution of states is employed. We demonstrate this here by the introduction of a microcanonical ensemble where there is an additional degree of freedom which corresponds to the number of conformational defects.

In this case, the necessary quantities are the density of states of the system in the case where there are $j$ conformational defects, for a fixed energy, $E$

$$\rho(j,E) = \binom{N}{j} 2^j \rho(E - jV_0) \tag{A1}$$

where $\rho(E - jV_0)$ is the density of states of a collection of harmonic oscillators with a minimum at the zero of energy for the lowest state, located at $E = jV_0$. In a practical calculation one could employ a classical count of the density of states and include the zero-point energy, [14–17] however the present treatment is independent of the nature of the density of states employed. The binomial coefficient arises from the different possible arrangements of a system with $j$ conformational defects. The microcanonical probability distribution of conformational states is now given by

$$p(j,E) = \rho(j,E)\Omega(E)^{-1} \tag{A2}$$

with

$$\Omega = \sum_{j=0}^{\infty} \rho(j,E). \tag{A3}$$

The microcanonical (RRKM) reaction rate, averaged over the ensemble of conformational states is now given by

$$k(E) = \sum_j p(j,E) k(j,E), \tag{A4}$$

with the rate constant given by

$$k(j,E) = \frac{N^{\dagger}(j,E)}{h\rho(E,j)}. \tag{A5}$$

Here $N^{\dagger}(E,j)$ is the sum of states at the transition state, given by

$$N^{\dagger}(E,j) = (N - j) N^{\dagger}(E - jV_0), \tag{A6}$$

where $N^{\dagger}(E)$ is the sum of states for a single transition state. We note that if a Boltzmann average is performed over the averaged reaction rate,

$$k(T) = \frac{\int \Omega(E) k(E) \exp(-E/k_B T) dE}{\int \Omega(E) \exp(-E/k_B T) dE} \tag{A7}$$

we arrive at exactly the transition state theory expression, Eq. (6), when we use the standard relations, $Q = \int \rho(E) \exp(-E/k_B T) dE$ and $k_B T Q^{\dagger} = \int N^{\dagger}(E) \exp(-E/k_B T) dE$. For a macroscopic sample, the distribution of energies represented by a Boltzmann distribution is very narrow, and corresponds to the average energy in Eq. (10).

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FIG. 1. Arrhenius plot of rate constants obtained from MD simulation (Ref. [4]). Lines are fitted to the 4 individual data sets.