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Chapter 5: Direct *Ab Initio* Dynamics Methodology for Modeling Kinetics of Biological Systems

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1. Introduction

Modeling kinetic properties of reactions in biological systems has been a challenge in computational biology. The challenge has been for activated controlled reactions that involve bond breaking and forming. Most progress to date has relied on the empirical valence bond method to provide potential energy information for dynamical simulations [Warshel (1991)]. This method involves a difficult force-field fitting procedure for a given specific reaction and its accuracy is often questionable. For this reason, its use has been limited to a very small number of experts. Nevertheless, this method in combination with molecular dynamics (MD) simulations has been shown to be quite useful. The combined quantum mechanical/molecular mechanics (QM/MM) method [Gao (1996)] provides a more practical

approach where a small region of the active site can be treated by a quantum mechanical electronic structure theory while interactions in the remaining portion of the system are represented by a MM force field. However, in order to predict kinetic properties one must employ a rather sophisticated level of electronic structure theory such as correlated molecular orbital (MO) or hybrid non-local density functional theory (DFT) or their combinations to provide sufficiently accurate potential energy surface information. Such electronic structure calculations are often computationally expensive due to the typical size of biological systems. To calculate rate constants, a promising cost effective method is the variational transition state theory (VTST) augmented with multidimensional semi-classical tunneling approximations [Garrett and Truhlar (1979), Truhlar and Garrett (1984), Truhlar et al. (1985), Truhlar et al. (1982)]. In this method, information on the geometry, energy, gradient and Hessian at the stationary points and along the reaction path is needed. This information can be obtained directly from electronic structure calculations in what is known as "direct ab initio dynamics" methodology [Truhlar (1995), Truhlar and Gordon (1990), Truong et al. (1996)] rather than from some fitted potential force fields. The VTST method has been well established for calculating kinetics of small gas-phase combustion reactions; its application for detailed kinetic study of biological systems is only beginning.

There are two different approaches in direct ab initio dynamics methodology. Both have the same objective of reducing the computational demand for obtaining the necessary potential energy information. One known as "dual level dynamics" [Chuang and Truhlar (1997), Corchado et al. (1995)] relies on the use of a semi-empirical MO Hamiltonian as a fitting potential functional form (known as Specific Reaction Parameter (SRP)

methodology) to give coarse grain potential energy information. More accurate energetic properties are obtained from a higher level of ab initio electronic structure theory. The other employs an accurate level of ab initio electronic structure theory directly, however, reducing the computational demand by either using an interpolation [Corchado et al. (1998), Nguyen et al. (1995)] or a focusing method [Bell and Truong (1994), Duncan et al. (1998), Truong et al. (1996)] to minimize the number of electronic structure calculations. Both approaches are equally effective and accurate though there are some minor differences in their advantages and disadvantages regarding applications to biological systems. For instance, the main advantage of the dual level dynamics over the focusing approach is that it provides a cost effective methodology for exploring regions far from the minimum energy path where large curvature tunneling effects can be significant. However, the accuracy of the reaction path curvature resulting from Specific Reaction Parameters (SRP) is always questionable. Such information does have direct effects on the magnitude of the calculated tunneling probability.

This chapter provides a more detailed look at the direct ab initio dynamics methodology that we have been developing in our laboratory in the last few years. This method utilizes an advanced focusing technique and energy interpolation procedure to optimize the cost per performance ratio, i.e., minimizing the number of electronic structure calculations while maintaining the desired level of accuracy. An application of this method to a biological system is provided, in particular, proton transfer in free-base porphyrin. This system has significant biological interest for the reasons given below. This chapter is organized as follows. Section 2 provides a theoretical background with some overview on the choice of a particular

level of electronic structure theory. Section 3 gives a detailed discussion on the proton transfer in free-base porphyrin. Viewpoints for prospective applications to biological systems are given in Section 4. Finally, the conclusions are given in Section 5.

2. Theory

2.1   *Variational Transition State Theory*

Most activated-control reactions in biological systems can be modeled as unimolecular reactions in solution. The variational transition state theory (VTST) for reactions in solution within the direct ab initio dynamics methodology has recently been developed [Chuang et al. (1998)]. It is still in the early stage and thus is not yet widely employed. For many biological systems where solvent effects are small, it is still possible to use the gas-phase VTST method that is well developed and tested [Truhlar et al. (1996)]. In such a formalism, thermal rate constants for a gas phase unimolecular reaction are determined by varying the location of the dividing surface along a reference path to minimize the rate so as to minimize the recrossing effects [Truhlar and Garrett (1984), Truhlar et al. (1985)]. In the present study, the reference path is the minimum energy path (MEP), which is defined as the steepest descent path from the saddle point to both the reactant and product sides in the mass-weighted Cartesian coordinate system. The reaction coordinate, s, is defined as the distance along the MEP with the origin located at the saddle point and is positive on the product side and negative on the reactant side. For canonical ensemble

at a given temperature T, the canonical variational theory (CVT) thermal rate constant is given by

$$k^{CVT}(T,s) = \min_{s}\left\{k^{GT}(T,s)\right\} \tag{1}$$

where

$$k^{GT}(T,s) = \left\{\sigma \frac{k_B T}{h} \frac{Q^{GT}(T,s)}{\Phi^R(T)} e^{-V_{MEP}(s)/k_b T}\right\} \tag{2}$$

In these equations, $k^{GT}(T,s)$ is the generalized transition state theory rate constant at the dividing surface which intersects the MEP at s and is orthogonal to the MEP at the intersection point. Q^{GT} is the internal partition function of the generalized transition state with the local zero of energy at $V_{MEP}(s)$, which is the classical potential energy along the minimum energy path s with its zero of energy at the reactants; Φ^R is the reactant partition function; σ is the symmetry factor accounting for the possibility of more than one symmetry related reaction path; k_B is Boltzman's constant and h is Plank's constant. Both Q^{GT} and Φ^R are approximated as products of electronic, rotational and vibrational partition functions. The vibrational and rotational partition functions were calculated quantum mechanically within the harmonic and rigid rotor approximations, respectively. To include the quantum mechanical effects for motion along the reaction coordinate, CVT rate constants (k^{CVT}) are multiplied by a temperature dependent transmission coefficient, $\kappa(T)$. This coefficient accounts for both the non-classical reflection when the total energy of the system is above the barrier and the tunneling effects when the energy is below the threshold barrier. The final rate constant is given by

$$k(T) = \kappa(T)\, k^{CVT}(T) \tag{3}$$

2.2 *Multidimensional Semiclassical Tunneling Methods*

The effective potential for tunneling is approximated as the vibrationally adiabatic ground-state potential, which has the form

$$V_a^G(s) = V_{MEP}(s) + \sum_{i=1}^{3N-7} \frac{1}{2} h\omega_i(s) \tag{4}$$

At TST level of rate calculation, where the potential energy surface information is used only at the stationary points, the Wigner [Wigner (1937)] and zero-curvature tunneling at zero-th order interpolation, denoted as ZCT-0 [Gonzalezlafont et al. (1991)], can be applied to calculate the transmission coefficients. The ZCT-0 approximation is commonly known as the Eckart tunneling model. In this model, $V_a^G(s)$ and $V_{MEP}(s)$ are represented by Eckart functions whose parameters are obtained from fitting to energetic information at the stationary points. More accurate treatments of tunneling effects require potential energy information along the tunneling path. Within the CVT framework, the transmission coefficients can be calculated with multidimensional semiclassical zero and small curvature tunneling methods [Lu et al. (1992), Truhlar et al. (1982)], denoted as ZCT and SCT, respectively. The SCT transmission coefficients, that include the reaction path curvature effect on the transmission probability, are based on the centrifugal-dominant small-curvature semiclassical adiabatic ground-

state approximation [Lu et al. (1992)]. In particular, the transmission probability at energy E, P(E) is given by

$$P(E) = \frac{1}{\{1 + e^{2\theta(E)}\}}$$

(5)

where $\theta(E)$ is the imaginary action integral evaluated along the tunneling path,

$$\theta(E) = \frac{2\pi}{h} \int_{s_l}^{s_r} \sqrt{2\mu_{eff}(s)|E - V_a(s)|}\, ds$$

(6)

and where the integration limits, s_l and s_r, are the reaction coordinate turning points. The reaction-path curvature (i.e., corner cutting) effect on the tunneling probability is included in the effective reduced mass, μ_{eff}. Thus, the ZCT transmission coefficients are obtained by setting μ_{eff} equal to μ in the above equation. The detailed descriptions on the VTST and tunneling methods are presented elsewhere [Lu et al. (1992), Truhlar and Garrett (1984), Truhlar et al. (1985), Truhlar et al. (1982)].

2.3 *Electronic structure calculations*

As described above, VTST rate calculations require geometries, energies, gradients and Hessians at the stationary points and along the MEP. It is known that geometry and frequency converge with respect to the level of electronic structure theory faster than the energy. Thus, it is possible to calculate geometry and frequency at a lower level of theory and then correct the potential energy with a small number of single-point

calculations at a higher level of theory. For relatively large biological systems, single-point energy calculations at a sufficiently accurate level of theory such as the CCSD level would be computationally unfeasible. In such a case, one can employ the QM/MM approach, where a small region of the active site can be treated at an accurate level of electronic structure theory. Another promising method is the recent integrated molecular orbital + molecular orbital (IMOMO) method or its generalized ONIOM approach [Dapprich et al. (1999), Humbel et al. (1996), Maseras and Morokuma (1995), Svensson et al. (1996)]. In such an approach only a small region containing the reactive moiety is treated at a high level of electronic structure theory while the remaining part of the system can be treated at a lower level of theory. It has the same spirit as the QM/MM method. The key difference is in the treatment of interactions between two different regions. It is much simpler in the ONIOM approach. Our recent study [Truong and Truong (1999)] showed that this approach has considerable promise for the kinetic study of large systems. We will illustrate its application in studying the proton transfer in free-base porphyrin below.

3. Applications: Kinetics of Proton Transfer in free-base porphyrin

Free base porphyrin has two hydrogen atoms in the inner part of the skeleton. It is well known that the inner hydrogen atoms migrate in a framework of four nitrogen sites known as double hydrogen atom transfer. Double hydrogen atoms transfer in free-base porphyrin is also known as NH

tautomerism and is significantly important in photosynthesis and metal coordination chemistry. Since porphyrins possess large extended Π-electron systems and have high stability, they are finding use in advanced materials as components in organic metals, molecular wires and other devices. Because of their photodynamic therapeutic behavior, porphyrins are also being used in medicine for the treatment of cancer and dermatological diseases. Due to these potential practical applications, the mechanism of the inner-hydrogen tautomerization in free-base porphyrin has been of considerable experimental [Abraham et al. (1974), Braun et al. (1996), Braun et al. (1994), Butenhoff et al. (1988), Butenhoff and Moore (1988), Chen and Tulinsky (1972), Crossley et al. (1986), Eaton and Eaton (1977), Hennig and Limbach (1979), Hennig and Limbach (1984), Hennig and Limbach (1982), Limbach et al. (1982), Limbach et al. (1984), Limbach et al. (1983), Radziszewski et al. (1990), Radziszewski et al. (1989), Schlabach et al. (1991), Schlabach et al. (1986), Spiro (1988), Spiro (1985), Stilbs (1984), Stilbs and Moseley (1980), Yu (1986)] and theoretical [Almlöf (1974), Almlöf et al. (1993, Baker et al. (1997), Ghosh (1994), Ghosh and Almlöf (1995), Ghosh and Almlöf (1993), Kozlowski et al. (1996), Kozlowski et al. (1995), Kuzmitsky and Solovyov (1980), Li and Zgierski (1991), Limbach and Hennig (1979), Maity et al. (2000), Merchàn et al. (1994), Merz and Reynolds (1988), Reimers et al. (1995), Sarai (1981), Sarai (1982), Sarai (1984), Smedarchina et al. (1988), Wu et al. (1997)] interest. There are two proposed mechanisms for this tautomerization namely stepwise [Abraham et al. (1974), Braun et al. (1996), Limbach et al. (1983), Maity et al. (2000), Sarai (1982), Schlabach et al. (1991)] and concerted [Eaton and Eaton (1977), Hennig and Limbach (1979), Limbach and Hennig (1979), Merz and Reynolds (1988), Smedarchina et al. (1988)]. The stepwise mechanism is

characterized by a trans-cis-trans conversion in which the two hydrogen atoms migrate one at a time as shown in path I of Figure 1. The concerted mechanism involves synchronous migration of both H atoms as shown in path II of Figure 1.
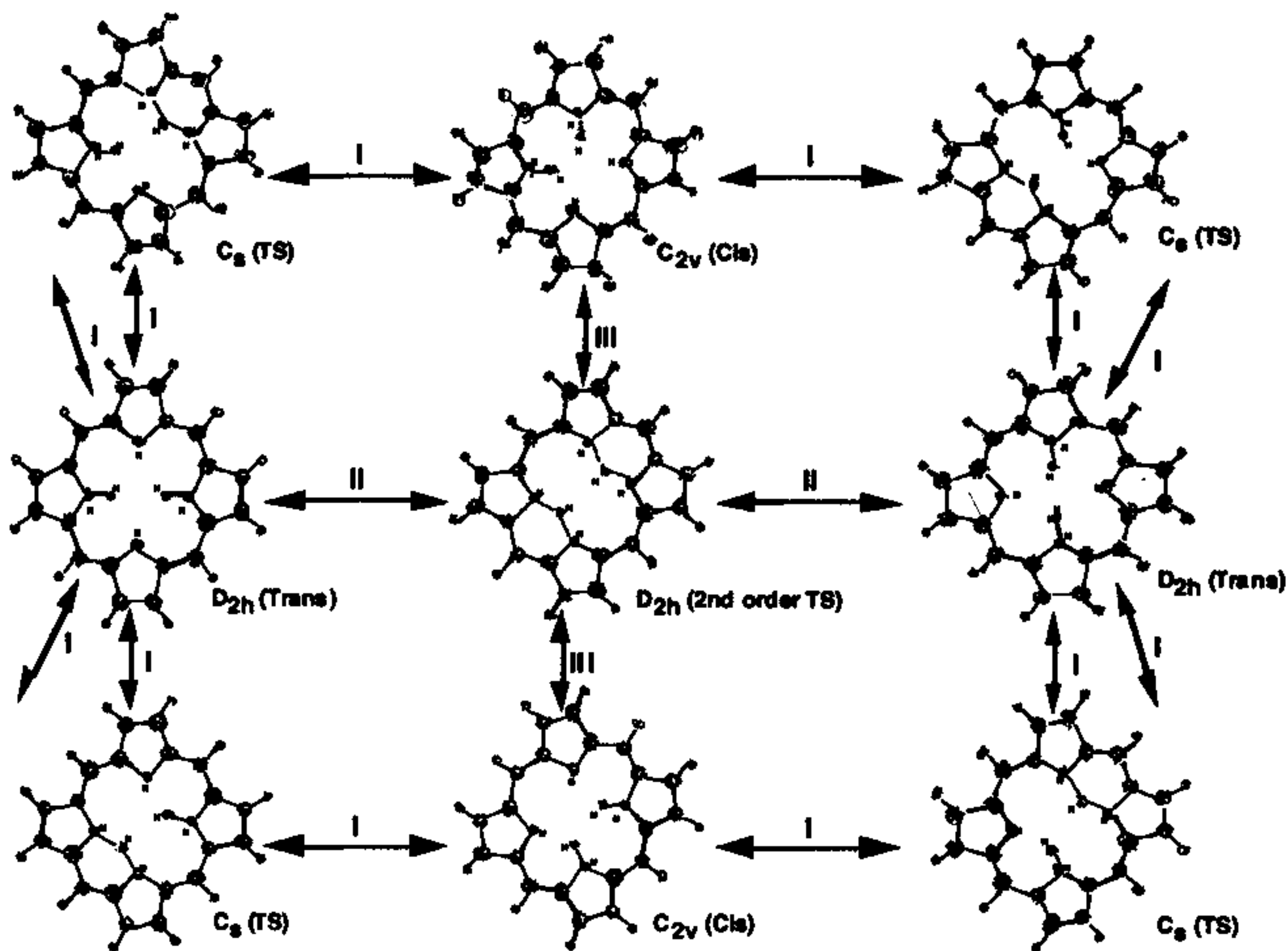

Figure 1. Schematic diagram for inner-hydrogen migration process of free-base porphyrin. The path for stepwise mechanism is labeled by I and that for concerted mechanism is labeled by II. Path III connects the second order saddle point geometry to the intermediate geometry.

Debate as to whether the mechanism is stepwise or concerted extends back many years for both experiment and theory. It is now generally accepted both theoretically and experimentally [Almlöf et al. (1993), Baker et al.

(1997), Ghosh and Almlöf (1995), Kozlowski et al. (1996), Kozlowski et al. (1995), Merchàn et al. (1994), Merz and Reynolds (1988), Reimers et al. (1995), Sarai (1981)] that the double proton transfer occurs via a stepwise mechanism involving a metastable cis intermediate rather than by a concert one-step path. The rate of tautomerization for the stepwise mechanism as a function of temperature has been measured using dynamic liquid-state ^{1}H NMR spectroscopy [Braun et al. (1996)] and can be used to compare with the calculated results. Most previous theoretical studies [Almlöf et al. (1993), Ghosh and Almlöf (1995), Kozlowski et al. (1995), Merchàn et al. (1994), Reimers et al. (1995)] of this tautormerization reaction focused on the structural aspect in comparison with experiments [Chen and Tulinsky (1972), Li and Zgierski (1991), Radziszewski et al. (1990), Radziszewski et al. (1989), Spiro (1988), Spiro (1985), Yu (1986)]. Recently, Bakers and coworkers [Baker et al. (1997)] reported for the first time the tautormerization rate constants calculated from the conventional transition state theory (TST) without any tunneling contribution. It is known that double hydrogen atom transfer with noticeable barrier such as this reaction would have significant tunneling effects even at room temperature. In this chapter, we illustrate how it can be accurately calculated using the multidimensional semiclassical SCT tunneling method within the full VTST formalism. In addition, the calculated potential energy information along the MEP provides a more detailed picture on the mechanism of the reaction.
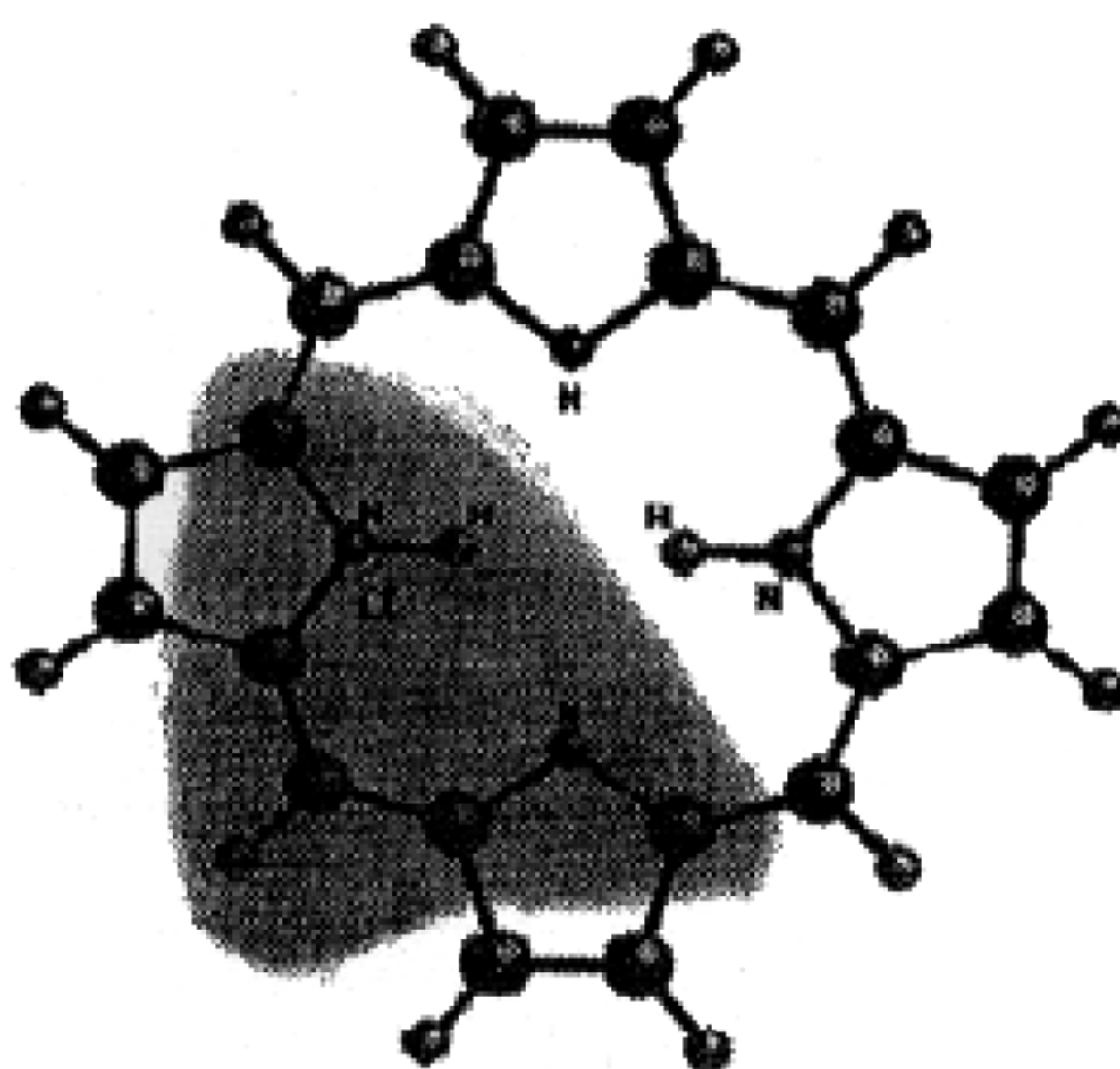
Figure 2: The model system for IMOMO calculations consists of atoms in the shaded area and capped hydrogen atoms.

In the results given below, the potential energy information, namely geometries, energies, gradients and Hessians at the stationary points and along the MEP, was calculated at the BH&HLYP/6-31G(d,p) level. To improve the energetic information along the preferred step-wise reaction path, single-point energy calculations were done using the IMOMO methodology. This method has been shown to yield rather accurate reaction barriers compared to full high-level calculations but at significantly less cost particularly for large systems such as porphyrin. In these calculations, the model system containing the reactive moiety of the stepwise mechanism and neighbor atoms to preserve aromaticity as shown in the shaded area in Figure 2 is treated at the CCSD(T)/cc-pvdz level of theory. The low level for the whole system is still at the BH&HLYP/6-31G(d,p) level. Thus, to

obtain IMOMO energies, additional calculations only for the model system are required.

3.1   *Energetics*

The calculated reaction energetic information along with previous theoretical and experimental results is listed in Table 1. IMOMO, B3LYP and MP2 predict the classical barrier height for the trans-cis tautomerization process in the stepwise mechanism to be between 16.2 to 16.9 kcal/mol. This is in good agreement with the upper limit of the experimental estimate range for the classical barrier height of 12.6-16.3 kcal/mol from a laser induced fluorescence spectroscopic measurement [Butenhoff and Moore (1988)]. The BH&HLYP barrier is about 2 kcal/mol too high compared to other theoretical results. The reverse classical barrier height for trans-cis tautomerization (the barrier height for the second step of tautomerization) process in the stepwise mechanism is calculated to be 9.9, 9.5 and 8.7 kcal/mol at the B3LYP, BH&HLYP, and IMOMO levels, respectively. For the concerted mechanism, MP2 gives the low limit of 19.3 kcal/mol while B3LYP yields the high limit of 24.4 kcal/mol for the classical barrier. In all cases, they are several kcal/mol higher than those for the step-wise mechanism. Zero-point energy corrections were found to lower the classical barriers in both mechanisms by about 3 kcal/mol and are significant.

To obtain an estimate for the solvent effects on the reaction energetics, we have performed single-point calculations of porphyrin in different solvents using the Polarizable Continuum Model (PCM) [Cossi et

al. (1996)]. In particular, heptane (dielectric constant, ε = 1.92), toluene (ε = 2.38) and ethanol (ε = 24.55) were chosen for such calculations as these

Table 1. Classical and Zero-Point Energy Corrected Barrier Heights (kcal/mol), $\Delta V^{\ddagger}$ and $\Delta V_a^{\ddagger}$, respectively.

	$\Delta V^{\ddagger}$	$\Delta V_a^{\ddagger}$
Stepwise Mechanism:		
trans → ts		
Butenhoff & Moore[a]	12.6-16.3	
MP2/DZP//RHF/DZP[b]	16.7	
B3LYP/TZ2P[c]	16.2	13.1
BH&HLYP/6-31G(d,p)	18.6	15.6
IMOMO(CCSD(T):BH&HLYP)	16.9	
cis → ts		
B3LYP/TZ2P[c]	9.9	5.0
BH&HLYP/6-31G(d,p)	9.5	6.8
IMOMO(CCSD(T):BH&HLYP)	8.7	
Concerted Mechanism:		
trans → ts		
MP2/DZP//RHF/DZP[b]	19.3	
B3LYP/TZ2P[c]	24.4	18.3
BH&HLYP/6-31G(d,p)	21.6	17.1

[a]Buttenhoff and Moore (1988), this is an experimental estimate.
[b]Reimers et al. (1995).
[c]Baker et al.(1997).

solvents were often used in the experimental studies. The calculated classical barrier heights for the step-wise mechanism are shown in Table 2.

For non-polar solvents such as heptane and toluene, solvent effects on the barrier height are negligible. The effect is slightly larger for polar solvents such as ethanol. Note that the barrier height is increased slightly by 1 kcal/mol in ethanol. These results support the earlier experimental report on small solvent effects on the rate of intra- molecular hydrogen atom transfer in free base porphyrin [Eaton and Eaton (1977)]. This also implies that gas phase calculations are sufficient to study the inner hydrogen transfer process in free base porphyrin system.

Table 2. Calculated BH&HLYP/6-31G(d,p) classical barrier heights for the step-wise mechanism, $\Delta V^{\ddagger}$ (kcal/mol) in gas phase and different solvents.

Solvent	$\Delta V^{\ddagger}$
Gas phase	18.6
Heptane	18.9
Toluene	18.8
Ethanol	19.7

3.2 Mechanism

Here we examine the structural changes of porphyrin as it proceeds from the reactant to the intermediate of the stepwise mechanism. The only significant change that are larger than 2% in the bond length is that of the transferring hydrogen atom. The N-H bond length of the transferring

hydrogen atom is lengthened by +32% to reach the transition state structure ($\approx$1.32 Å) from the reactant structure ($\approx$1.00 Å at -2.55 $amu^{1/2}$bohr of the MEP). The angle labeled by α in Figure2 was found to have the largest
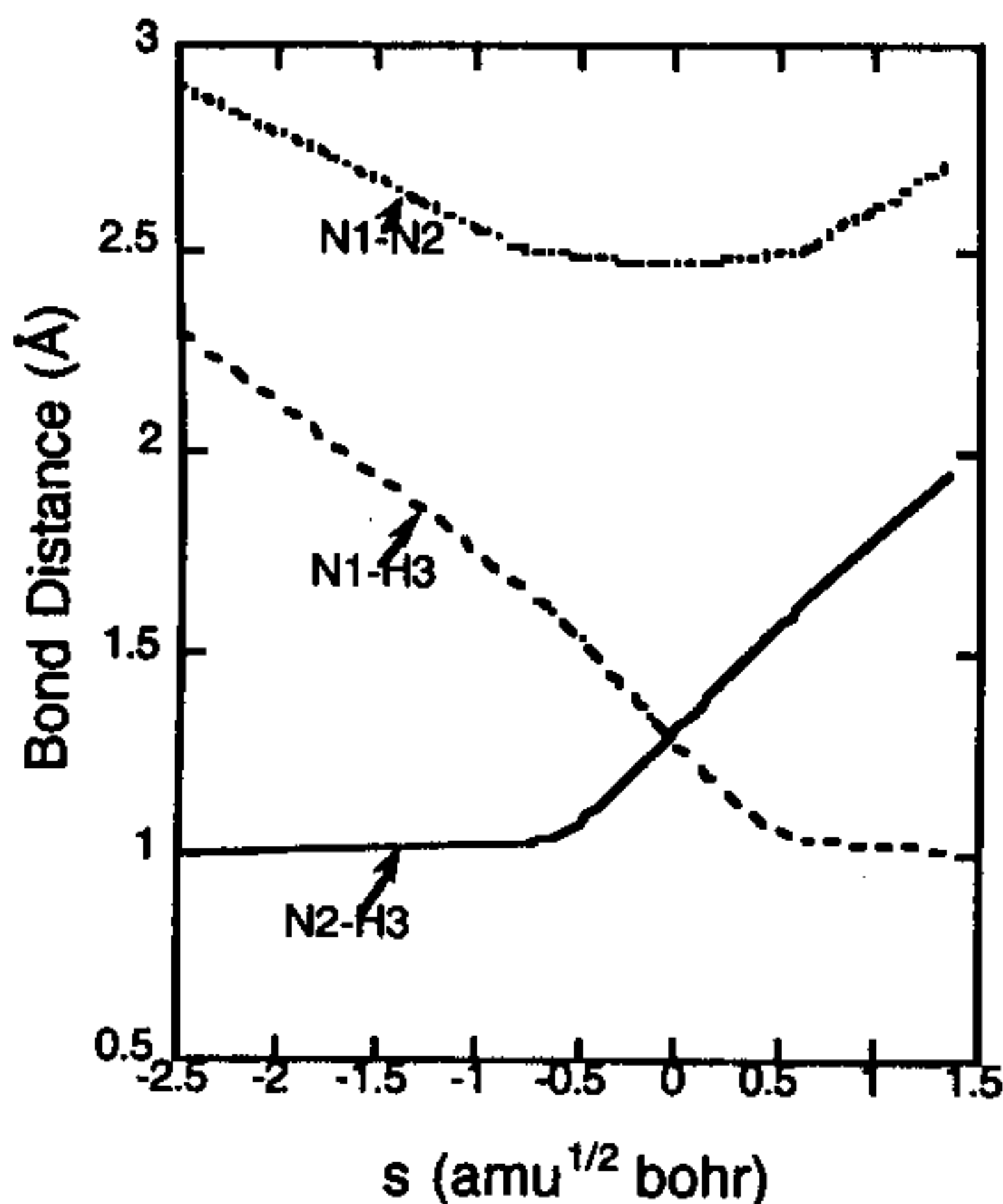

Figure 3: Selected bond distance profiles along the minimum energy path for NH tautomerization in free base porphyrin plotted vs. the reaction coordinate s in the mass-weighted Cartesian coordinate. N1 and N2 are the hydrogen atom donor and acceptor atoms, respectively. H3 is the transferring hydrogen.

change of -15.1% to reach the transition state (105.8 degrees) from the reactant structure (124.6 degrees). These active bond lengths and angle essentially relate to the N-H stretching and bending modes that were
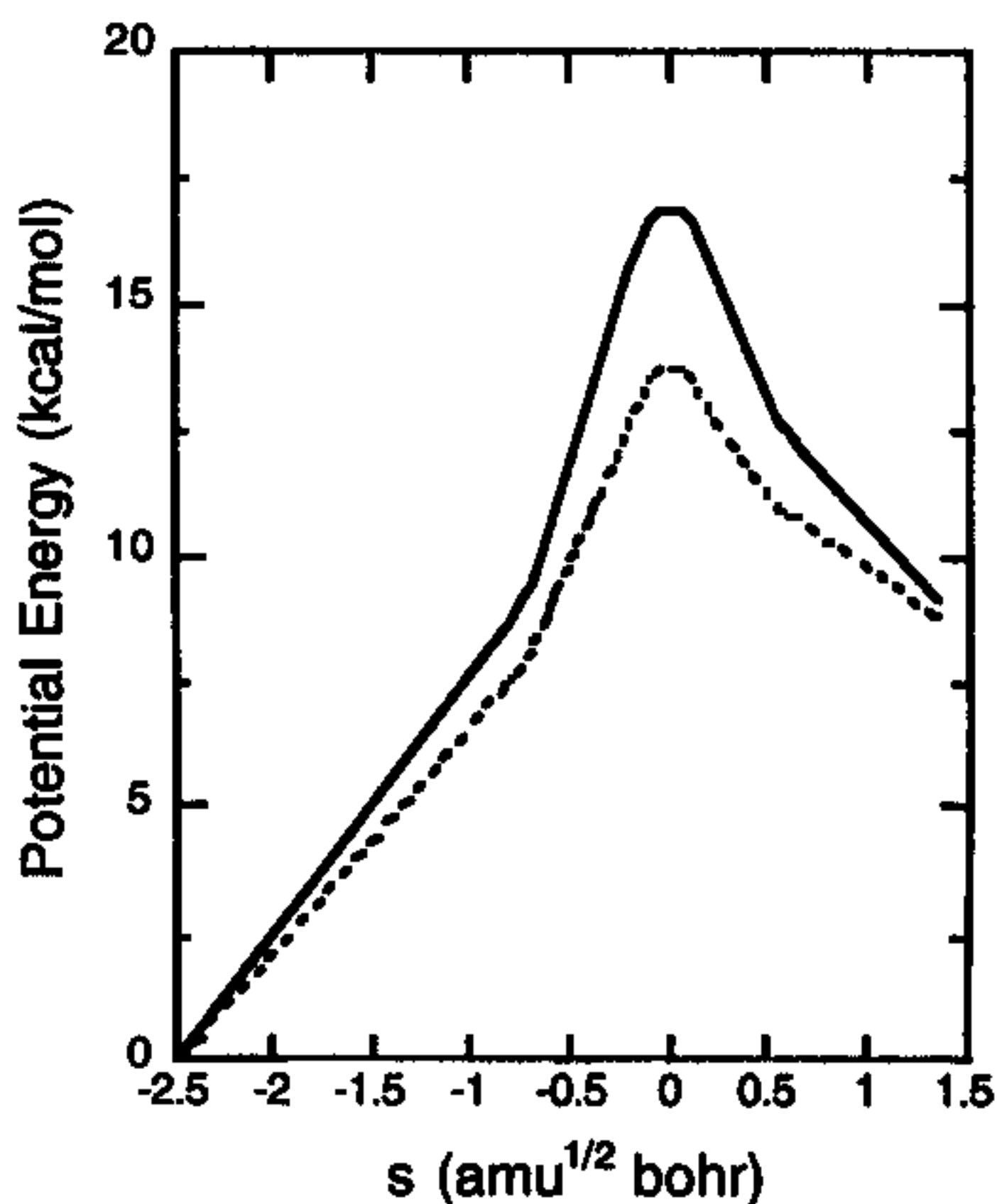
Figure 4: The classical potential energy $V_{MEP}(s)$ (solid line) and the vibrationally ground-state adiabatic potential energy $V_a^G(s)$ (dashed line) curves along the minimum energy path for NH tautomerism in free base porphyrin plotted vs. the reaction coordinate s in the mass-weighted Cartesian coordinate.

thought to be responsible for mode selective tautomerization in vibrational spectroscopic studies [Butenhoff et al. (1990)]. The structural changes vs. reaction coordinate can be viewed as the changes in N-N and N-H bond distances, respectively, as displayed in Figure 3. Examination of N-N and

N-H bond distance profiles as functions of the reaction coordinate reveals an interesting observation.

In particular, the first step of the stepwise tautomerization process can be viewed as a two-stage process in which the changes in the structure along the reaction path can be divided into two distinct parts, each involving different types of motions. It is to be noted that this is different from a two-step process that involves a stable intermediate. More specifically, the active N-N bond distance (N1-N2 bond as shown in Figure 3) first compressed approximately from 2.91 to 2.51 Å while the breaking N-H bond distance (N2-H3 bond as shown in Figure 3) remains relatively unchanged approximately up to s=-0.8 amu$^{1/2}$ bohr from the reactant. At this point, the N-N bond distance stays relatively constant while the hydrogen atom transfers from one N center to the other as its bond length is stretched from 1.0 to 1.32 Å to reach the saddle point. One can think of this two-stage process as the porphyrin first goes through a global structure compression to bring the donor and acceptor sites closer together so as to lower the barrier for hydrogen atom transfer. Such deformation will reach a point when further compression would outcost the hydrogen atom transfer process. At that point one observes the hydrogen atom starts to migrate with no further global structure compression. Figure 4 depicts the energy cost for global compression to be about 8.7 kcal/mol (the potential energy value at s= -0.8 amu$^{1/2}$ bohr along the MEP). The remaining energy cost of ~ 8.2 kcal/mol can be thought as the barrier to hydrogen atom transfer in the second stage [Maity et al. (2000)]. Such a two-stage process observed here is not unique to this tautomerization process. We have also observed the similar structural changes in the concerted double hydrogen atom transfers in formamidine-water and formamide-water complexes [Bell and Truong

(1994)]. This information could be very useful in designing new porphyrins for material science and biological applications.

3.3 Kinetics

Transition state theory (TST) and canonical variational transition state theory rate calculations have been performed for the trans↔cis isomerization process in free base porphyrin in the temperature range of 200-1000 K. Figure 5 displays the Arrhenius plot of the calculated rate constants for the forward reaction of trans ↔ cis isomerization. Recrossing effect was found to be very small as expected due to the relatively large barrier height.   However, tunneling effects were found to be very significant, especially in the lower temperature range as indicated by the curvature of the CVT/SCT curve and its large deviation from the CVT results.   For example, at 200 K, tunneling enhances the transfer rate by a factor of about 410 [Maity et al. (2000)].   Previous TST calculation without incorporating any tunneling corrections done by Baker and co-workers [Baker et al. (1997)] yields rate constant lower by a factor of 60 compared to the experimental value from Braun et al. (1996) at 260 K.   Since the potential energy information used in our rate calculations is similar to that in Baker et al.'s study, our calculations confirm that this factor of 60 is mainly due to tunneling. The CVT/SCT calculated overall transfer rate is in excellent agreement with the experimental data as displayed in Figure 5.

Calculated activation energies (E_a) in the temperature range of 200-300 K for NH tautomerization along with available experimental data are listed in Table 3. Notice first the CVT/SCT calculated activation energy of
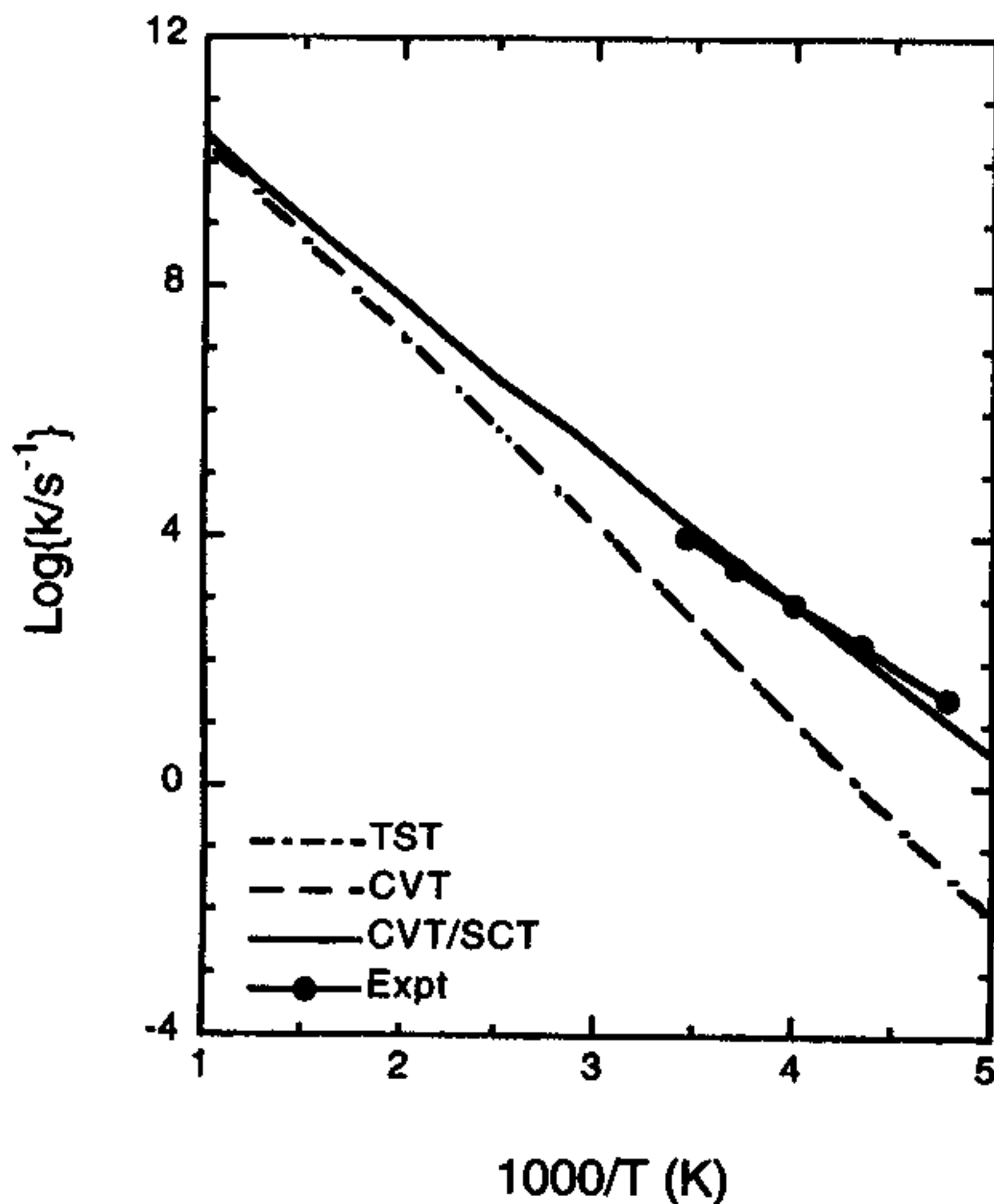
Figure 5: Comparison of experimental and calculated forward (trans-isomer → cis-isomer) rate constants vs. 1000/T at different levels of theory. The experimental data are generated from the Arrhenius equation suggested by Braun et al. (1994).

10.8 kcal/mol is within the range of experimental data provided by Eaton and Eaton (1977) and higher than that the experimental data provided by Braun et al. (1996) from their NMR line shapes and a modified Bell tunneling model. The experimental activation energy of 4.8-5.6 kcal/mol at 110 K provided by Butenhoff and Moore from their laser-induced

fluorescence spectroscopy and a one-dimensional Eckart tunneling model is much lower than the present calculated data as well as other experimental

Table 3. Comparison of experimental and calculated activation energies, E_a, (kcal/mol).

Method	E_a	
Experimental		
Abraham et al.[a]	9.2 (308K)	
Eaton & Eaton[b]	9.0-11.4 (298K)	
Braun et al.[c]	8.9 (209-290K)	
Butenhoff & Moore[d]	4.8-5.6 (110K)	
Theory		
TST	14.1	
TST/W	13.3	
TST/Eckart	11.1	
CVT	14.1	
CVT/ZCT	11.6	
CVT/SCT	10.8	

[a]Abraham et al. (1974).
[b]Eaton and Eaton (1977).
[c]Braun et al. (1994).
[d]Butenhoff and Moore (1988).

data. This indicates that at this low temperature range tunneling is the dominating process governing the transfer rate. The tunneling path in this case would exhibit large curvature character due to the H-L-H nature of the hydrogen transfer process; therefore the SCT method would greatly underestimate its contribution at very low temperatures. For this reason, we

have provided here the rate constants only above 200 K. The activation energy from the TST rate data reported by Baker and co-workers is 13.6 kcal/mol, which is consistent with that of 14.1kcal/mol from the present TST data. When tunneling corrections are included, the calculated E_a improves as more accurate tunneling methods were employed.

Due to the importance of tunneling in this process, it is worthwhile to examine the performance of different tunneling approximations considered here. Figure 6 displays the calculated transmission coefficient (κ) as functions of the temperature using different tunneling models. The SCT method is the most accurate approximation presented here and thus we used it as a reference point for comparison. First of all, the Wigner model as expected greatly underestimates the tunneling contribution since it assumes tunneling to occur at the top of the barrier and is reasonable only at moderate to high temperatures. Even though the Eckart model requires additional potential information at the intermediate beyond those needed for TST calculation, it predicts a much more accurate tunneling contribution than the Wigner model. Recall that in the Eckart model, the vibrationally ground-state adiabatic potential energy curve for tunneling is approximated by a one-dimensional Eckart function. In other words, it is an approximation to the ZCT method.

A remarkable agreement between the Eckart model and theZCT method indicates the potential curve along the MEP can be well represented by an Eckart function. Our results suggest that the Eckart tunneling model should be used in experimental analysis as done by Butenhoff and Moore. Finally, comparing the ZCT and SCT results, we found that the 'corner cutting' effect accounts for nearly an order of magnitude increase in the rate at the room temperature.
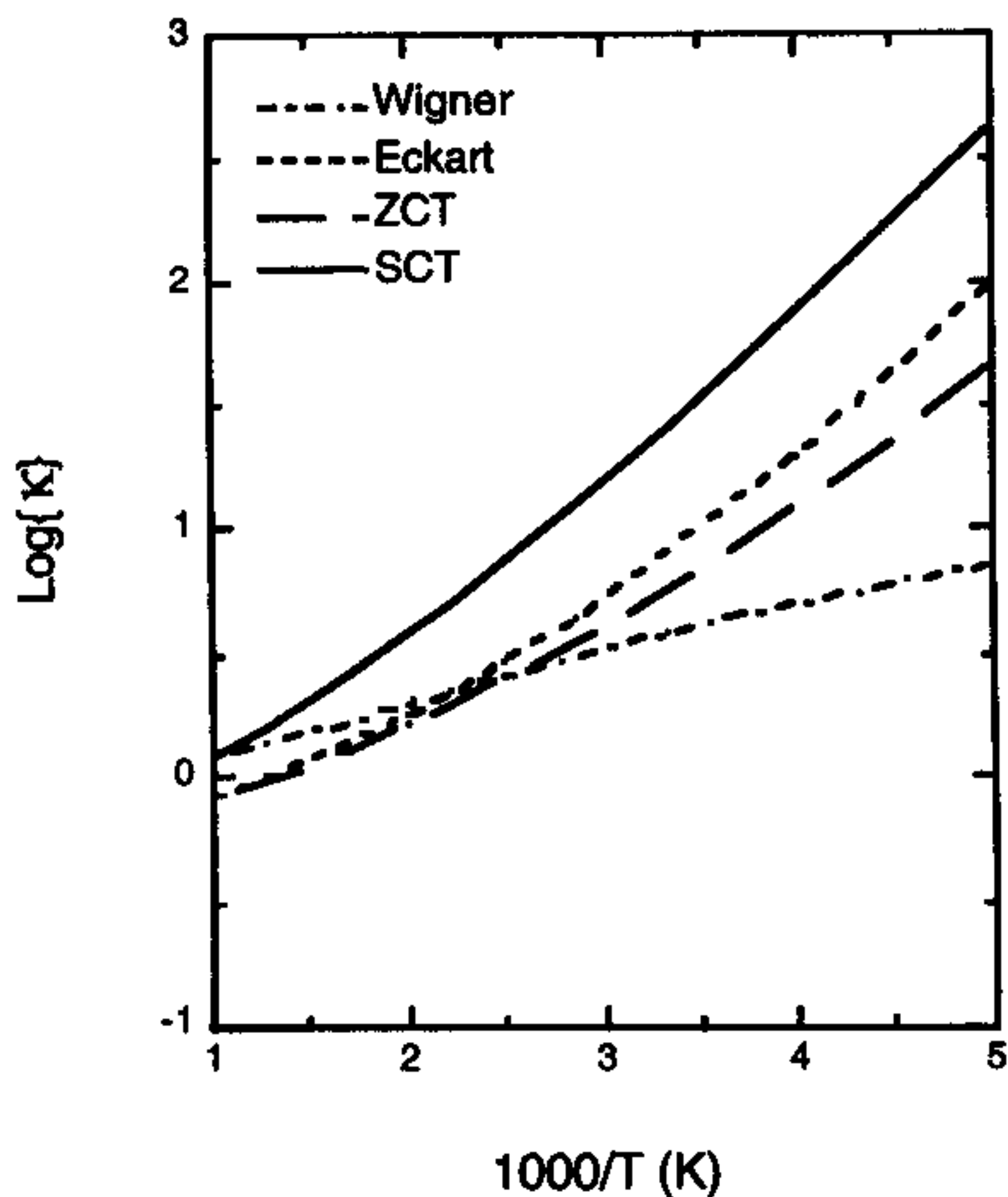
Figure 6: Log plot of transmission coefficient (κ) calculated using different tunneling models vs. 1000/T.

4.   Prospects for protein kinetics

The example above illustrates that it is now possible to predict quantitatively kinetics of reactions in reasonably large biological systems from first principles. However, theoretical studies of enzyme mechanisms and kinetics may take advantage of the combined quantum molecular/molecular mechanics (QM/MM) method to explore the potential

surface. Some initial efforts have already been devoted to this area [Alhambra et al. (1999)]. Furthermore, the recently proposed reaction class approach [Truong et al. (1999), Truong et al. (2000)] provides an efficient way to obtain necessary potential energy information of large chemical reaction for VTST rate calculations from a small model reaction. This will further improve the feasibility of the method presented here for protein kinetics.

5.   Conclusions

With advances in computer technology and direct dynamics methodology, it is now possible to model kinetics of chemical reactions of relatively large systems. Although it is only at the beginning stage, there are indications that in combination with the QM/MM or ONIOM methodology the VTST method provides a practical and robust framework for calculating thermal rate constants of reactions in biological systems. We will certainly see more biological applications of this method in the near future.

Acknowledgments

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