CHAPTER 15

VIBRATIONAL ENERGY RELAXATION (VER) OF A CD STRETCHING MODE IN CYTOCHROME c

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CONTENTS

I. INTRODUCTION

Vibrational energy relaxation (VER) is fundamentally important to our understanding of chemical reaction dynamics as it influences reaction rates significantly [1]. In general, estimating VER rates for selected modes in large molecules is a challenging problem because large molecules involve many degrees of freedom and, furthermore, quantum effects cannot be ignored [2]. If we assume a weak interaction between the "system" and the surrounding "bath," however, we can derive an estimate of the VER rate through Fermi's golden rule [3–6]: A VER rate is written as a Fourier transformation of a force–force correlation function. Though it is not trivial to define and justify a separation of a system and a bath, such a formulation has been successfully applied to many VER processes in liquids [7] and in proteins [8].

Here we apply such theories of VER to the problem of estimating the vibrational population relaxation time of a CD stretching mode—in short, a CD mode—in the protein cytochrome c [9]. (We will define the CD mode to be the system and define the remainder of the protein to be the bath.) Recently Romesberg's group succeeded in selectively deuterating a terimnal methyl group of a methionie residue in cytochrome c [10]. The resulting CD mode has a frequency $\omega_S \simeq 2100$ cm^{-1}, which is located in a transparent region of the density of states of the protein. As such, spectroscopic detection of this mode provides clear evidence of the protein dynamics, including the VER of the CD vibrational mode. Note that at room temperature ($T = 300$ K) $\beta\hbar\omega_S \simeq 10$, where $\beta = 1/(k_B T)$; hence quantum effects are not negligible for this mode.

Let us mention a little more about cytochrome c (cyt c). Cyt c is a protein known to exist in mitochondrial inner membranes, chloroplasts of plants, and bacteria [11]. Its functions are related to cell respiration [12]; and cyt c, using its heme molecule, "delivers" an electron from cytochrome bc 1 to cytochrome oxidase—two larger proteins both embedded in a membrane. Recently it was also found that cyt c is released when apoptosis occurs [13]. In this sense, cyt c governs the "life and death" of a cell.

The heme molecule in cyt c has a large oscillator strength, and it serves as a good optical probe. As a result, many spectroscopic experiments have been designed to clarify VER and the (un)folding properties of cyt c [14]. Cyt c is often employed in numerical simulations [15,16] because a high-resolution structure was obtained [17] and its simulation has become feasible. Attempts have also been made to characterize cyt c through ab initio (DFT) calculations [18,19].

VER of the selected CD mode in the terminal methyl group of methionine (Met80) was previously addressed by Bu and Straub [9]: They used equilibrium simulations for cyt c in water with the quantum-correction factor (QCF) method

[20], and they predicted that the VER time for the CD mode is on the order of 0.3 ps. However, their results are approximate: The use of the QCF method is not justified a priori, and their analysis is based on a harmonic model for cyt c. To extend that previous analysis, in this work, we model cyt c in vacuum as a normal mode system and include the lowest anharmonic coupling elements. A similar analysis has been completed for another protein myoglobin by Kidera's group [21] and by Leitner's group [22]. Use of a reduced model Hamiltonian allows us to investigate the VER rate of the CD mode in cyt c more "exactly" and to move beyond the use of quantum correction factors and the harmonic approximation.

This chapter is organized as follows: In Section I.B, we derive the principal VER formula employed in our work, and we mention the related Maradudin–Fein formula. In Section I.C, we apply those theoretical results for the rate of VER to the CD mode in cyt c, and we compare our results with (a) the classical simulation by Bu and Straub and (b) the experiments by Romesberg's group. In Section I.D, we provide a summary of our results, and we discuss further aspects of VER processes in proteins.

II. VIBRATIONAL ENERGY RELAXATION (VER)

A. Perturbation Expansion for the Interaction

We begin with the von Neumann equation for the complete system written as

$$ i\hbar \frac{d}{dt} \rho(t) = [\mathscr{H}, \rho(t)] \tag{1} $$

The interaction representation for the von Neumann equation is

$$ i\hbar \frac{d}{dt} \tilde{\rho}(t) = [\tilde{\mathscr{V}}(t), \tilde{\rho}(t)] \tag{2} $$

where

$$ \mathscr{H} = \mathscr{H}_0 + \mathscr{V} = \mathscr{H}_S + \mathscr{H}_B + \mathscr{V} \tag{3} $$

and

$$ \tilde{\rho}(t) \equiv e^{i\mathscr{H}_0 t/\hbar} \rho(t) e^{-i\mathscr{H}_0 t/\hbar}, \qquad \tilde{\mathscr{V}}(t) \equiv e^{i\mathscr{H}_0 t/\hbar} \mathscr{V} e^{-i\mathscr{H}_0 t/\hbar} \tag{4} $$

Here $\mathscr{H}_S$ is the system Hamiltonian representing a vibrational mode, $\mathscr{H}_B$ the bath Hamiltonian representing solvent or environmental degrees of freedom, and

$\mathscr{V}$ the interaction Hamiltonian describing the coupling between the system and the bath. An operator with a tilde means the one in the interaction picture. If we *assume* that $\mathscr{V}$ is small in some sense, we can carry out the perturbation expansion for $\mathscr{V}$ as

$$\tilde{\rho}(t) = \rho(0) + \frac{1}{i\hbar} \int_0^t dt' [\tilde{\mathscr{V}}(t'), \tilde{\rho}(t')]$$

$$= \rho(0) + \frac{1}{i\hbar} \int_0^t dt' [\tilde{\mathscr{V}}(t'), \rho(0)]$$

$$+ \frac{1}{(i\hbar)^2} \int_0^t dt' \int_0^{t'} dt'' [\tilde{\mathscr{V}}(t'), [\tilde{\mathscr{V}}(t''), \rho(0)]] + \cdots \quad (5)$$

Let us calculate the following probability:

$$P_v(t) \equiv \text{Tr}\{\rho_v \rho(t)\} = \text{Tr}\left\{\rho_v e^{-i\mathscr{H}_0 t/\hbar} \tilde{\rho}(t) e^{i\mathscr{H}_0 t/\hbar}\right\} \quad (6)$$

$$\rho_v \equiv |v\rangle\langle v| \otimes 1_B \quad (7)$$

$$\rho(0) = \rho_S \otimes \rho_B = |v_0\rangle\langle v_0| \otimes e^{-\beta\mathscr{H}_B}/Z_B \quad (8)$$

$$Z_B = \text{Tr}_B\left\{e^{-\beta\mathscr{H}_B}\right\} \quad (9)$$

where the initial state is assumed to be a direct product state of $\rho_S = |v_0\rangle\langle v_0|$ and $\rho_B = e^{-\beta\mathscr{H}_B}/Z_B$. Here $|v\rangle$ is the vibrational eigenstate for the system Hamiltonian $\mathscr{H}_S$, that is, $\mathscr{H}_S|v\rangle = E_v|v\rangle$. The VER rate $\Gamma_{v_0 \to v}$ may be defined as follows:

$$\Gamma_{v_0 \to v} \equiv \lim_{t \to \infty} \frac{d}{dt} P_v(t) \quad (10)$$

Note that the results derived from this definition are equivalent to those derived from Fermi's golden rule [23]. Hence we refer to them as a Fermi's golden rule formula.

B. General Formula for VER

First we notice that

$$P_v(t) = \text{Tr}\left\{\rho_v e^{-i\mathscr{H}_0 t/\hbar} \tilde{\rho}(t) e^{i\mathscr{H}_0 t/\hbar}\right\} = \text{Tr}\{\rho_v \tilde{\rho}(t)\} \quad (11)$$

as ρ_v commutes with $\mathcal{H}_0$. If we assume that $v \neq v_0$, then $\rho_v \rho(0) = 0$. Using this fact, we obtain the lowest (second)-order result

$$
\begin{aligned}
P_v(t) &\simeq \frac{1}{(i\hbar)^2} \int_0^t dt' \int_0^{t'} dt'' \, \mathrm{Tr} \{ \rho_v [\tilde{\mathcal{V}}(t'), [\tilde{\mathcal{V}}(t''), \rho(0)]] \} \\
&= \frac{1}{\hbar^2} \int_0^t dt' \int_0^{t'} dt'' \, \mathrm{Tr} \{ \rho_v \tilde{\mathcal{V}}(t') \rho(0) \tilde{\mathcal{V}}(t'') + \rho_v \tilde{\mathcal{V}}(t'') \rho(0) \tilde{\mathcal{V}}(t') \} \\
&= \frac{1}{\hbar^2} \int_0^t dt' \int_0^{t'} dt'' [e^{i\omega_{v_0 v}(t'-t'')} C(t' - t'') \\
&\quad + e^{i\omega_{v_0 v}(t''-t')} C(t'' - t')]
\end{aligned}
\tag{12}
$$

where

$$
C(t) \equiv \langle \tilde{\mathcal{V}}_{v_0 v}(t) \mathcal{V}_{v v_0}(0) \rangle \equiv \mathrm{Tr}_B \{ \rho_B \tilde{\mathcal{V}}_{v_0 v}(t) \mathcal{V}_{v v_0}(0) \} \tag{13}
$$

$$
\tilde{\mathcal{V}}_{v v_0}(t) = \langle v | \tilde{\mathcal{V}}(t) | v_0 \rangle \tag{14}
$$

$$
\omega_{v_0 v} = (E_{v_0} - E_v)/\hbar \tag{15}
$$

Hence the lowest-order estimate of the VER rate is given by

$$
\begin{aligned}
\Gamma_{v_0 \to v} &= \lim_{t \to \infty} \frac{1}{\hbar^2} \int_0^t dt'' [e^{i\omega_{v_0 v}(t-t'')} C(t - t'') + e^{i\omega_{v_0 v}(t''-t)} C(t'' - t)] \\
&= \frac{1}{\hbar^2} \int_{-\infty}^{\infty} dt \, e^{i\omega_{v_0 v} t} C(t)
\end{aligned}
\tag{16}
$$

If we *assume* that a system variable q is small in some sense, the interaction Hamiltonian is expressed as

$$
\mathcal{V} = -q \mathcal{F}(\{q_k\}, \{p_k\}) \tag{17}
$$

where $\{q_k\}, \{p_k\}$ are position and momentum variables for the bath. This $\mathcal{F}(\{q_k\}, \{p_k\})$ is a force applied to the system by the bath. Thus we finally obtain the following Fermi's golden rule formula [3–6]:

$$
\Gamma_{v_0 \to v} = \frac{|q_{v_0 v}|^2}{\hbar^2} \int_{-\infty}^{\infty} dt \, e^{i\omega_{v_0 v} t} \langle \tilde{\mathcal{F}}(t) \tilde{\mathcal{F}}(0) \rangle \tag{18}
$$

with

$$q_{v_0 v} = \langle v_0 | q | v \rangle \tag{19}$$

$$\tilde{\mathscr{F}}(t) = e^{i\mathscr{H}_B t/\hbar} \tilde{\mathscr{F}} e^{-i\mathscr{H}_B t/\hbar} \tag{20}$$

$$\langle \tilde{\mathscr{F}}(t)\tilde{\mathscr{F}}(0)\rangle = \mathrm{Tr}_B\{\rho_B \tilde{\mathscr{F}}(t)\tilde{\mathscr{F}}(0)\} \tag{21}$$

In most situations, the transition from $v_0 = 1$ to $v = 0$ is considered. In such a case, $q_{10} = \sqrt{\hbar/2m_S\omega_S}$, where m_S is the system mass and $\omega_S = \omega_{10}$ is the system frequency in the harmonic approximation. Hence

$$\Gamma_{1\to 0} = \frac{1}{2m_S\hbar\omega_S} \int_{-\infty}^{\infty} dt\, e^{i\omega_S t} \langle \tilde{\mathscr{F}}(t)\tilde{\mathscr{F}}(0)\rangle \tag{22}$$

C. Use of a Symmetrized Autocorrelation Function

It is useful to define a *symmetrized* force–force correlation function as [3–6]

$$S(t) = \tfrac{1}{2}[\langle \mathscr{F}(t)\mathscr{F}(0)\rangle + \langle \mathscr{F}(0)\mathscr{F}(t)\rangle] \tag{23}$$

Since $S(t)$ is real and symmetric with respect to t, $S(t) = S(-t)$, we consider it to be analogous to $S_{cl}(t)$, the classical limit of the correlation function. Hereafter we drop the tilde on $\mathscr{F}$ for simplicity. By half-Fourier transforming $S(t)$ with the use of the relation $\langle \mathscr{F}(0)\mathscr{F}(t)\rangle = \langle \mathscr{F}(t - i\beta\hbar)\mathscr{F}(0)\rangle$, we have

$$\begin{aligned}
\int_0^\infty dt\, e^{i\omega t} S(t) &= \tfrac{1}{2}\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t)\mathscr{F}(0)\rangle + \tfrac{1}{2}\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(0)\mathscr{F}(t)\rangle \\
&= \tfrac{1}{2}\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t)\mathscr{F}(0)\rangle + \tfrac{1}{2}\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t - i\beta\hbar)\mathscr{F}(0)\rangle \\
&= \tfrac{1}{2}\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t)\mathscr{F}(0)\rangle + \tfrac{1}{2}e^{-\beta\hbar\omega}\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t)\mathscr{F}(0)\rangle \\
&= \tfrac{1}{2}(1 + e^{-\beta\hbar\omega})\int_0^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t)\mathscr{F}(0)\rangle
\end{aligned} \tag{24}$$

Taking the real parts of both sides, we have

$$\int_0^\infty dt\, \cos(\omega t)\, S(t) = \tfrac{1}{4}(1 + e^{-\beta\hbar\omega})\int_{-\infty}^\infty dt\, e^{i\omega t}\langle \mathscr{F}(t)\mathscr{F}(0)\rangle \tag{25}$$

where we have used the fact that $S(-t) = S(t)$ is real and $\langle \mathscr{F}(t)\mathscr{F}(0)\rangle^* = \langle \mathscr{F}(0)\mathscr{F}(t)\rangle = \langle \mathscr{F}(-t)\mathscr{F}(0)\rangle$. Hence, Eq. (22) can be rewritten as [6]

$$\Gamma_{1\to 0} = \frac{1}{m_S\hbar\omega_S}\frac{2}{1 + e^{-\beta\hbar\omega_S}}\int_0^\infty dt\,\cos\left(\omega_S t\right)S(t) \qquad (26)$$

Note that this expression diverges in the classical limit because $\Gamma_{1\to 0} \propto 1/\hbar$. According to Bader and Berne [4], to make contact with the classical limit, we introduce another VER rate as

$$\frac{1}{T_1} = (1 - e^{-\beta\hbar\omega_S})\Gamma_{1\to 0}$$
$$= 2C(\beta, \hbar\omega_S)\int_0^\infty dt\,\cos\left(\omega_S t\right)S(t) \qquad (27)$$

where

$$C(\beta, \hbar\omega_S) = \frac{1}{m_S\hbar\omega_S}\frac{1 - e^{-\beta\hbar\omega_S}}{1 + e^{-\beta\hbar\omega_S}} \qquad (28)$$

This is a final quantum expression, which can be interpreted as an energy relaxation rate and be used to estimate the VER rate.[1]

D.   Quantum Correction Factor Method and Other Methods

Though Eq. (27) is exact in a perturbative sense, it is demanding to calculate the *quantum mechanical* force autocorrelation function $S(t)$ even for small molecular systems. Hence, many computational schemes have been developed to approximate the quantum mechanical force autocorrelation function.

Skinner and coworkers advocated to use the quantum correction factor (QCF) method [20], which is the replacement of the above formula Eq. (18) with

$$\Gamma_{v_0\to v} = Q(\omega_S)\frac{2|q_{v_0v}|^2}{\hbar^2}\int_0^\infty dt\,\cos\left(\omega_{v_0v}t\right)S_{cl}(t) \qquad (29)$$

where $S_{cl}(t) = \langle \mathscr{F}(t)\mathscr{F}(0)\rangle_{cl}$ and the bracket means a classical ensemble average (not a quantum mechanical average). This approach is very intuitive and easily applicable for large molecular systems because one only needs to calculate the *classical* force autocorrelation function $S_{cl}(t)$ multiplied by an

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[1]Although the experimental observable is $\Gamma_{1\to 0}$, we note that $1/T_1 \simeq \Gamma_{1\to 0}$ because $\beta\hbar\omega_S \gg 1$ for our case of a CD stretching mode.

appropriate QCF $Q(\omega_S)$. There exist several QCFs corresponding to different VER processes [20].

However, one challenge that arises in the application of the QCF method is that we do not know *a priori* which VER process is dominant for the system considered. Furthermore, it is possible that several VER processes compete [24]. Hence one must be careful in the application of the QCF method, and Skinner and coworkers have provided a number of examples of how this can be accomplished.

In this chapter, we employ the harmonic approximation for the relaxing oscillator, and the vibrational relaxation time T_1^{QCF}. Hence Eq. (29) is transformed to

$$\frac{1}{T_1^{QCF}} = \frac{Q(\omega_S)}{m_S \hbar \omega_S} \int_0^\infty dt \, \cos(\omega_S t) \, S_{cl}(t) = \frac{Q(\omega_S)}{\beta \hbar \omega_S} \frac{1}{T_1^{cl}} \tag{30}$$

where we have introduced the classical VER rate $1/T_1^{cl}$

$$\frac{1}{T_1^{cl}} = \frac{\beta}{m_S} \int_0^\infty dt \, \cos(\omega_S t) \, S_{cl}(t) \tag{31}$$

which is the classical limit $\hbar \to 0$ of Eq. (27). This result can also be derived from a classical theory of Brownian motion, and is known as the Landau-Teller-Zwanzig (LTZ) formula.

Alternatively, one may calculates $S(t)$ *itself* systematically using controlled approximations. Calculating a correlation function for large systems has a long history in chemical physics [25], including recent applications to VER processes in liquid [26,27]. The vibrational self-consistent field (VSCF) method [28] will also be useful in this respect.

On the other hand, if we *approximate* $\mathcal{F}$ as a simple function of $\{q_k\}, \{p_k\}$, we can calculate $S(t)$ rather easily and, in a sense, more "exactly." In the next section, we explore such an approach.

E. Approximations for the Force–Force Correlation Function

1. Taylor Expansion of the Force

We can formally Taylor-expand the force as a function of the bath variables $\{q_k\}, \{p_k\}$:

$$\mathcal{F}(\{q_k\}, \{p_k\}) = \sum_k A_k^{(1)} q_k + \sum_k B_k^{(1)} p_k + \sum_{k,k'} A_{k,k'}^{(2)} q_k q_{k'} + \sum_{k,k'} B_{k,k'}^{(2)} p_k p_{k'} + \cdots \tag{32}$$

where the expansion is often truncated in the literature following the first term. Depending on the system–bath interaction considered, higher-order coupling including the third and fourth terms can be relevant. For example, the fourth term appears in benzene to represent the interaction between the CH stretch and CCH wagging motion [29] through the Wilson G matrix [30]. In the case of a CD stretching mode in cyt c, as discussed below, or a CN$^-$ stretching mode in water [24], the third term is relevant for VER.

2. Contribution from the First Term

If the first term $\sum_k A_k^{(1)} q_k$ is dominant in the force, then the force–force correlation function becomes

$$\langle \mathscr{F}(t)\mathscr{F}(0)\rangle = \sum_{k,k'} A_k^{(1)} A_{k'}^{(1)} \langle q_k(t)q_{k'}(0)\rangle = \sum_k \frac{\hbar(A_k^{(1)})^2}{2\omega_k}[(n_k+1)e^{-i\omega_k t} + n_k e^{i\omega_k t}]$$

(33)

where we have used

$$q_k(t) = \sqrt{\frac{\hbar}{2\omega_k}}(a_k e^{-i\omega_k t} + a_k^\dagger e^{i\omega_k t})$$

(34)

and $\langle a_k^\dagger a_{k'}\rangle = n_k \delta_{k,k'}$ with $n_k = 1/(e^{\beta\hbar\omega_k} - 1)$ because

$$\rho_B \propto e^{-\beta\mathscr{H}_B} = e^{-\beta\sum_k \hbar\omega_k(a_k^\dagger a_k + 1/2)}$$

(35)

Here we have *assumed* that the bath Hamiltonian is an ensemble of harmonic oscillators:

$$\mathscr{H}_B = \sum_k \hbar\omega_k(a_k^\dagger a_k + 1/2) = \sum_k \left(\frac{p_k^2}{2} + \frac{\omega_k^2}{2}q_k^2\right)$$

(36)

where ω_k is the kth mode frequency for the bath, and

$$p_k = -i\sqrt{\frac{\hbar\omega_k}{2}}(a_k - a_k^\dagger)$$

(37)

Thus we obtain

$$S(t) = \sum_k \frac{\hbar(A_k^{(1)})^2}{2\omega_k}(2n_k + 1)\cos \omega_k t$$

(38)

and

$$\frac{1}{T_1} = \pi \hbar C(\beta, \hbar \omega_S) \sum_k \frac{(A_k^{(1)})^2}{\omega_k} (2n_k + 1)[\delta(\omega_S - \omega_k) + \delta(\omega_S + \omega_k)] \qquad (39)$$

The contribution from the second term $\sum_k B_k^{(1)} p_k$ is calculated in the same way.

3.   Contribution from the Third Term

If the third term $\sum_{k,k'} A_{k,k'}^{(2)} q_k q_{k'}$ is dominant in the force, then

$$\langle \mathscr{F}(t) \mathscr{F}(0) \rangle = \sum_{k,k',k'',k'''} A_{k,k'}^{(2)} A_{k'',k'''}^{(2)} \langle q_k(t) q_{k'}(t) q_{k''}(0) q_{k'''}(0) \rangle$$

$$= R_{--}(t) + R_{++}(t) + R_{+-}(t) \qquad (40)$$

where

$$R_{--}(t) = \frac{\hbar^2}{4} \sum_{k,k',k'',k'''} D_{k,k',k'',k'''}^{(2)} \langle a_k a_{k'} a_{k''}^\dagger a_{k'''}^\dagger \rangle e^{-i(\omega_k + \omega_{k'})t} \qquad (41)$$

$$R_{++}(t) = \frac{\hbar^2}{4} \sum_{k,k',k'',k'''} D_{k,k',k'',k'''}^{(2)} \langle a_k^\dagger a_{k'}^\dagger a_{k''} a_{k'''} \rangle e^{i(\omega_k + \omega_{k'})t} \qquad (42)$$

$$R_{+-}(t) = \frac{\hbar^2}{4} \sum_{k,k',k'',k'''} D_{k,k',k'',k'''}^{(2)} \left[\langle a_k a_{k'}^\dagger (a_{k''}^\dagger a_{k'''} + a_{k''} a_{k'''}^\dagger) \rangle e^{-i(\omega_k - \omega_{k'})t} \right.$$

$$\left. + \langle a_k^\dagger a_{k'} (a_{k''}^\dagger a_{k'''} + a_{k''} a_{k'''}^\dagger) \rangle e^{i(\omega_k - \omega_{k'})t} \right] \qquad (43)$$

with

$$D_{k,k',k'',k'''}^{(2)} = \frac{A_{k,k'}^{(2)} A_{k'',k'''}^{(2)}}{\sqrt{\omega_k \omega_{k'} \omega_{k''} \omega_{k'''}}} \qquad (44)$$

Using the following

$$\langle a_k a_{k'} a_{k''}^\dagger a_{k'''}^\dagger \rangle = (1 + n_k)(1 + n_{k'})(\delta_{kk''} \delta_{k'k'''} + \delta_{kk'''} \delta_{k'k''}) \quad (45)$$

$$\langle a_k^\dagger a_{k'}^\dagger a_{k''} a_{k'''} \rangle = n_k n_{k'} (\delta_{kk''} \delta_{k'k'''} + \delta_{kk'''} \delta_{k'k''}) \qquad (46)$$

$$\langle a_k a_{k'}^\dagger (a_{k''}^\dagger a_{k'''} + a_{k''} a_{k'''}^\dagger) \rangle = (1 + n_k)(1 + 2n_{k'}) \delta_{kk'} \delta_{k''k'''}$$

$$+ (1 + n_k) n_{k'} (\delta_{kk''} \delta_{k'k'''} + \delta_{kk'''} \delta_{k'k''}) \qquad (47)$$

$$\langle a_k^\dagger a_{k'} (a_{k''}^\dagger a_{k'''} + a_{k''} a_{k'''}^\dagger) \rangle = n_k (1 + 2n_{k'}) \delta_{kk'} \delta_{k''k'''}$$

$$+ n_k (1 + n_{k'})(\delta_{kk''} \delta_{k'k'''} + \delta_{kk'''} \delta_{k'k''}) \qquad (48)$$

we have

$$R_{--}(t) = \frac{\hbar^2}{2} \sum_{k,k'} D^{(2)}_{k,k',k,k'}(1 + n_k)(1 + n_{k'})e^{-i(\omega_k + \omega_{k'})t} \tag{49}$$

$$R_{++}(t) = \frac{\hbar^2}{2} \sum_{k,k'} D^{(2)}_{k,k',k,k'} n_k n_{k'} e^{i(\omega_k + \omega_{k'})t} \tag{50}$$

$$R_{+-}(t) = \langle \mathscr{F}(0) \rangle^2 + \hbar^2 \sum_{k,k'} D^{(2)}_{k,k',k,k'}(1 + n_k)n_{k'} e^{-i(\omega_k - \omega_{k'})t} \tag{51}$$

where we have used $A^{(2)}_{k,k'} = A^{(2)}_{k',k}$, and

$$\langle \mathscr{F}(0) \rangle^2 = \frac{\hbar^2}{4} \sum_{k,k'} D^{(2)}_{k,k,k',k'}(1 + 2n_k)(1 + 2n_{k'}) \tag{52}$$

Hence we obtain

$$S(t) = \sum_{k,k'} \left[\zeta^{(+)}_{k,k'} \cos(\omega_k + \omega_{k'})t + \zeta^{(-)}_{k,k'} \cos(\omega_k - \omega_{k'})t \right] + \langle \mathscr{F}(0) \rangle^2 \tag{53}$$

and

$$\frac{1}{T_1} = \pi C(\beta, \hbar\omega_S) \sum_{k,k'} \left\{ \zeta^{(+)}_{k,k'} [\delta(\omega_k + \omega_{k'} - \omega_S) + \delta(\omega_k + \omega_{k'} + \omega_S)] \right.$$
$$\left. + \zeta^{(-)}_{k,k'} [\delta(\omega_k - \omega_{k'} - \omega_S) + \delta(\omega_k - \omega_{k'} + \omega_S)] \right\} \tag{54}$$

where we have assumed $\omega_S \neq 0$ and defined

$$\zeta^{(+)}_{k,k'} = \frac{\hbar^2}{2} D^{(2)}_{k,k',k,k'}(1 + n_k + n_{k'} + 2n_k n_{k'}) \tag{55}$$

$$\zeta^{(-)}_{k,k'} = \frac{\hbar^2}{2} D^{(2)}_{k,k',k,k'}(n_k + n_{k'} + 2n_k n_{k'}) \tag{56}$$

Though its appearance is rather different, Eq. (54) is equivalent to that derived by Kenkre, Tokmakoff, and Fayer [5] as well as by Shiga and Okazaki [24]. There is

also a similar result known as the Maradudin–Fein formula [31]

$$W = W_{\text{decay}} + W_{\text{coll}} \tag{57}$$

$$W_{\text{decay}} = \frac{\pi\hbar}{2m_S\omega_S} \sum_{k,k'} \frac{(A_{k,k'}^{(2)})^2}{\omega_k\omega_{k'}} (1 + n_k + n_{k'}) \, \delta\left(\omega_S - \omega_k - \omega_{k'}\right) \tag{58}$$

$$W_{\text{coll}} = \frac{\pi\hbar}{m_S\omega_S} \sum_{k,k'} \frac{(A_{k,k'}^{(2)})^2}{\omega_k\omega_{k'}} (n_k - n_{k'}) \, \delta\left(\omega_S + \omega_k - \omega_{k'}\right) \tag{59}$$

which has been utilized to describe VER processes in glasses [32] and in proteins by Leitner's group [22]. As was demonstrated in Ref. 5, this formula is also equivalent to Eq. (54); in the following we make use of Eq. (54). A problem with this formula is that we cannot take its continuum limit in the case of finite systems like proteins. As a remedy, a *width parameter* related to the vibrational lifetime is usually introduced leading to a definite value for the VER rate. We will discuss this problem in Section III.C.

III. APPLICATION TO A CD STRETCHING MODE IN CYTOCHROME c

A. Definition of System and Bath

We take horse heart cytochrome c (cyt c) as an example of how one may estimate the rate of VER for selected modes in proteins. We use the CHARMM program [33] to describe the force field, to minimize the structure, and to calculate the normal modes for the system. Starting from the 1HRC structure for cyt c in Protein Data Bank (PDB) [34], one hydrogen atom of the terminal methyl group of Met80 was deuterated. The energy of the protein structure was minimized in vacuum using the conjugate gradient algorithm. We diagonalized the Hessian matrix (second derivatives of the potential) for that mechanically stable configuration of the protein:

$$K_{ij} = \frac{\partial^2 V_{\text{CHARMM}}}{\partial \bar{x}_i \, \partial \bar{x}_j} = \frac{1}{\sqrt{m_i m_j}} \frac{\partial^2 V_{\text{CHARMM}}}{\partial x_i \, \partial x_j} \tag{60}$$

where V_{CHARMM} is the CHARMM potential, and $\bar{x}_i = \sqrt{m_i} x_i$ are mass-weighted Cartesian coordinates. The number of atoms in cyt c is 1745 (myoglobin has 2475 atoms), so the Hessian matrix is 5235×5235, and its diagonalization was readily accomplished using the `vibran` facility in CHARMM [33].

The result of this calculation was the density of states (DOS) for the system as shown in Fig. 1. The DOS consists of three regions: (1) below around
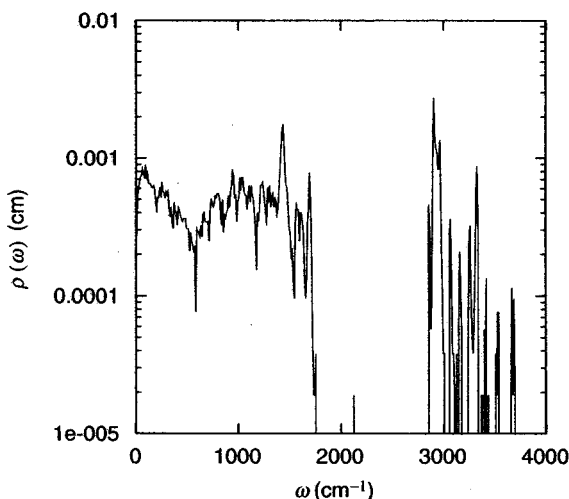
Figure 1. Density of states for cytochrome c in vacuum.

1700 cm^{-1}, (2) from around 1700 cm^{-1} to around 2800 cm^{-1}, and (3) above around 2800 cm^{-1}. The first region corresponds to rotational and torsional motions of the protein, and the third corresponds to bond stretching motions such as CH bonds. The second is rather "transparent," but one can observe one mode localized around the CD bond stretching mode in Met80 with frequency 2129.1 cm^{-1} as shown in Fig. 2a. Hence we refer to this as a CD stretching mode, or CD mode, the dynamics of which is the focus of our study. The other two modes in Fig. 2b and 2c are strongly coupled modes with the CD mode: 3330th mode (1330.9 cm^{-1}), an angle bending mode of Met80, and the 1996th mode (829.9 cm^{-1}), a stretch-bend mode in Met80. In the following, we will discuss the detail of the coupling and how it affects the VER rate.

At this level of description, the system is an ensemble of harmonic oscillators—that is, normal modes. Since we are interested in VER of the CD mode, we represent it as a system

$$\mathscr{H}_S = \frac{p_{CD}^2}{2} + \frac{\omega_{CD}^2}{2} q_{CD}^2 \tag{61}$$

while other degrees of freedom are treated as a bath:

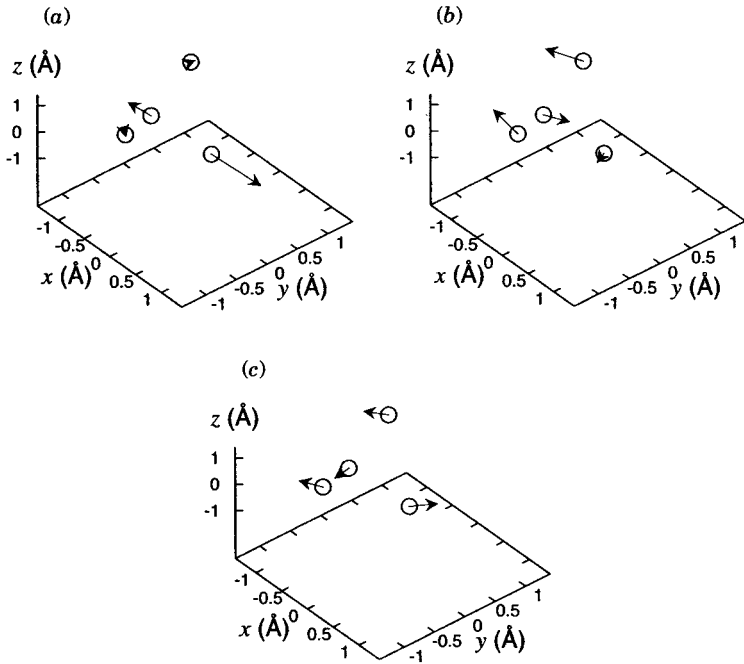$$\mathscr{H}_B = \sum_k \left(\frac{p_k^2}{2} + \frac{\omega_k^2}{2} q_k^2 \right) \tag{62}$$

Figure 2. Normal modes of cytochrome c in vacuum. (a) 4357th mode (CD mode) with $\omega = 2129.1$ cm^{-1}, (b) 3330th mode (angle bending mode of Met80) with $\omega = 1330.9$ cm^{-1}, (c) 1996th mode (a stretch-bend mode in Met80) with $\omega = 829.9$ cm^{-1}. Only vectors on the terminal methyl group of Met80 in cyt c are depicted. These modes are strongly coupled with the Fermi resonance.

The interaction between the system and bath is described by the interaction Hamiltonian

$$\mathscr{V} = \mathscr{H}_{\text{cytc}} - \mathscr{H}_S - \mathscr{H}_B \tag{63}$$

where $\mathscr{H}_{\text{cytc}}$ is the Hamiltonian for the full cyt c protein. We will discuss the content of $\mathscr{V}$ in the following section.

B. Calculation of the Coupling Constants

As in Eq. (17), we *assume* that the interaction Hamiltonian is of the form

$$\mathscr{V} = -q_{CD}\mathscr{F} \tag{64}$$

and Taylor expand the force as Eq. (32). The first and second terms do not appear because this is a normal mode expansion, and the fourth term does not appear as

the original coordinates are Cartesian coordinates. As in the first approximation, we take the force to be

$$\mathscr{F} = \sum_{k,k'} A^{(2)}_{k,k'} q_k q_{k'} \tag{65}$$

The coupling coefficients $A^{(2)}_{k,l}$ are calculated as

$$A^{(2)}_{k,l} = -\frac{1}{2} \frac{\partial^3 V}{\partial q_{CD} \, \partial q_k \, \partial q_l} \tag{66}$$

A problem arises: How does one calculate these coupling coefficients? The most direct approach is to use a finite difference method:

$$A^{(2)}_{k,l} \simeq -\frac{1}{2} \frac{V_{+++} - V_{-++} - V_{+-+} - V_{++-} + V_{--+} + V_{-+-} + V_{+--} - V_{---}}{(2\Delta q_{CD})(2\Delta q_k)(2\Delta q_l)} \tag{67}$$

where $V_{\pm\pm\pm} = V(\pm\Delta q_{CD}, \pm\Delta q_k, \pm\Delta q_l)$. However, this is rather cumbersome. Instead, we use the approximation [22,24]

$$A^{(2)}_{k,l} \simeq -\frac{1}{2} \sum_{ij} U_{ik} \, U_{jl} \, \frac{K_{ij}(\Delta q_{CD}) - K_{ij}(-\Delta q_{CD})}{2\Delta q_{CD}} \tag{68}$$

where U_{ik} is an orthogonal matrix that diagonalizes the Hessian matrix at the mechanically stable structure K_{ij}, and $K_{ij}(\pm\Delta q_{CD})$ is a Hessian matrix calculated at a shifted structure along the direction of the CD mode with a shift $\pm\Delta q_{CD}$. This expression is approximate but readily implemented using the CHARMM facility to compute the Hessian matrix. A comparison between Eqs. (67) and (68) is made in Table I. We also examined the convergence of the results by changing Δq_{CD}, and we found that $\Delta q_{CD} = 0.02\text{Å}$ is sufficient for the following calculations.

TABLE I
Comparison Between the Finite Difference Method [Eq. (67)]
and Eq. (68)[a]

(k, l)	Equation (68)	Finite Difference
(3330, 1996)	22.3	22.4
(3330, 4399)	−29.6	−29.5
(3327, 1996)	−5.7	−5.8
(1996, 678)	0.64	0.63

[a]We have used $\Delta q_{CD} = 0.02 \text{ Å}$, and $A^{(2)}_{k,l}$ is given in kcal/mol/Å^3.
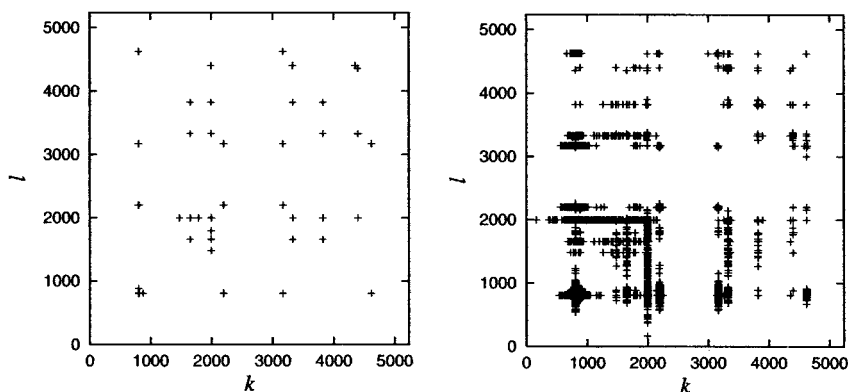
Figure 3. Distribution of the coupling elements. **Left:** $50.0 > |A_{k,l}^{(2)}| > 5.0$. **Right:** $5.0 > |A_{k,l}^{(2)}| > 0.5$. The value of $A_{k,l}^{(2)}$ are given in kcal/mol/$\overset{\circ}{A}{}^3$. Note that (k, l) are mode numbers, not wavenumbers.

The numerical results for the coupling elements are shown in Fig. 3. The histogram for the elements is shown in Fig. 4. As one can see from these figures, most of the elements are small, while the largest coupling elements are rather large. See Table II. Note that the combination (3330, 1996) is particularly significant for the CD mode because it approximately satisfies the
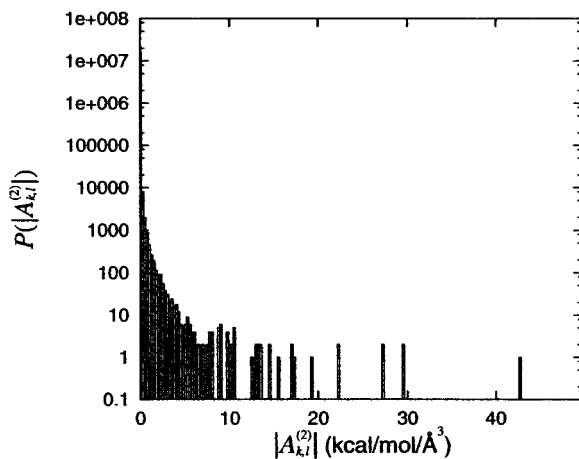

Figure 4. Histogram for the amplitude of the coupling elements.

TABLE II
The Largest Coupling Elements[a]

(k, l)	$|A_{k,l}^{(2)}|$
(1996, 1996)	42.9
(4399, 3330)	29.6
(4622, 3170)	27.3
(3330, 1996)	22.3

[a]The value of $A_{k,l}^{(2)}$ are given in kcal/mol/Å^3.

resonant condition [21]:

$$|\omega_{CD} - \omega_k - \omega_l| \ll \mathcal{O}(|A_{k,l}^{(2)}|) \tag{69}$$

As shown in Figs. 2b and 2c, these modes are localized near the terminal methyl group of Met80 as well as near the CD mode. In such a case, resonant energy transfer (Fermi resonance) is expected as shown by Moritsugu, Miyashita, and Kidera [21]. We have observed similar behavior in cyt c when the CD mode was excited, and the energy immigration to other normal modes facilitated by resonance was followed.

C. Assignment of the "Lifetime" Parameter

We cannot directly evaluate Eq. (54) because it contains delta functions. Evaluation of this expression for a finite system like a protein leads to a null result. To circumvent this problem, we "thaw" the delta function $\delta(x)$ as

$$\delta(x) = \frac{1}{\pi} \frac{\gamma}{\gamma^2 + x^2} \tag{70}$$

using a width parameter γ. Physically this means that each normal mode should have a lifetime $\simeq 1/\gamma$ due to coupling to other degrees of freedom—that is, the surrounding environment including water (or we might be able to interpret $1/\gamma$ as a time resolution). It is difficult to derive γ from first principles, so we take it to be a phenomenological parameter as in the literature [22,32].

As a result, the VER rate, Eq. (54), for the CD mode becomes

$$\frac{1}{T_1} = C(\beta, \hbar\omega_S) \sum_{k,k'} \left[\frac{\gamma \zeta_{k,k'}^{(+)}}{\gamma^2 + (\omega_k + \omega_{k'} - \omega_S)^2} + \frac{\gamma \zeta_{k,k'}^{(+)}}{\gamma^2 + (\omega_k + \omega_{k'} + \omega_S)^2} \right.$$
$$\left. + \frac{\gamma \zeta_{k,k'}^{(-)}}{\gamma^2 + (\omega_k - \omega_{k'} - \omega_S)^2} + \frac{\gamma \zeta_{k,k'}^{(-)}}{\gamma^2 + (\omega_k - \omega_{k'} + \omega_S)^2} \right] \tag{71}$$
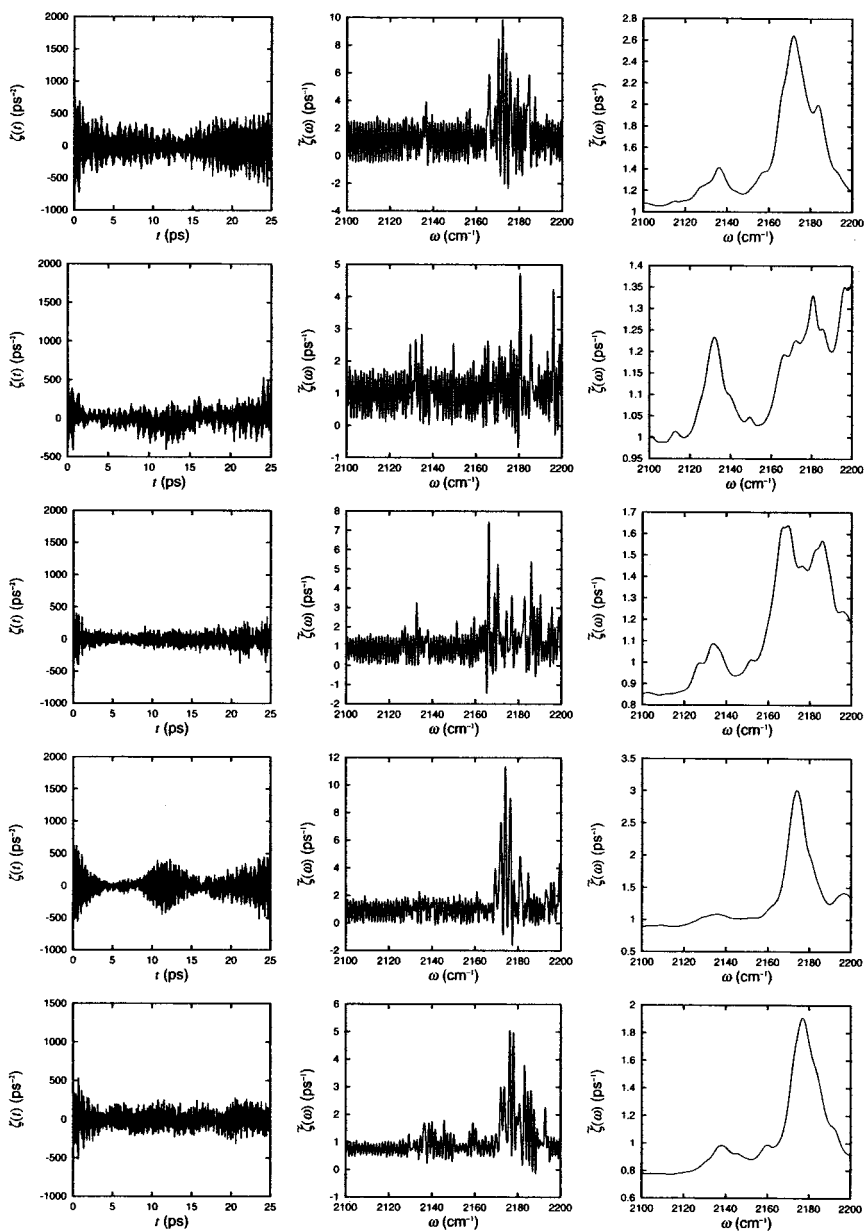
We employ this expression in our subsequent calculations.

Figure 5. **Left:** Classical data for the force–force correlation function. **Middle:** Fourier spectra for the correlation function. **Right:** The corresponding coarse-grained Fourier spectra. The "lifetime" width parameter $\gamma = 3$ cm^{-1}.

D. Results

1. Classical Calculation

Classical force–force correlation functions and their (cosine) Fourier transformations are shown in the left and middle column of Fig. 5 for five different trajectories. Here we have defined a ζ function as

$$\zeta(t) = \frac{\beta}{m_S} S_{cl}(t) \tag{72}$$

and have defined its (cosine) Fourier transformation as $\tilde{\zeta}(\omega)$, that is, $1/T_1^{cl} = \tilde{\zeta}(\omega_S)$. Note that these data are obtained from molecular dynamics simulations of cyt c in water [9]. As can be seen, the correlation functions oscillate wildly, and the (cosine) Fourier transformations are messy. As such, it is difficult to extract a reliable and stable value for the VER rate.

To address this problem, we introduce the window function

$$w(t) = \exp(-\gamma t) \tag{73}$$

The ζ functions are multiplied by this function and are (cosine) Fourier transformed. This corresponds to broadening each peak of a spectrum with a Lorentzian with width γ. The results for five trajectories are shown in the right column of Fig. 5. (The width parameter is taken as $\gamma = 3$ cm^{-1}.) The results in the right column are better behaved than those in the middle column, but there still remain some fluctuations.

According to Bu and Straub simulations of cyt c in water [9], we take $\omega_S = 2135$ cm^{-1} to investigate the γ dependence of the result as shown in the left of Fig. 6. We see that $\tilde{\zeta}(\omega_S) \simeq 1.1 \sim 1.2$ ps^{-1} for $\gamma \simeq 3 \sim 30$ cm^{-1}. Since $Q(\omega_S)/(\beta\hbar\omega_S) \simeq 2.4 \sim 3.0$ for two-phonon processes [9], this corresponds to a VER time of 0.3–0.4 ps according to Eq. (29).[2]

2. Quantum Calculation

We use the formula Eq. (71) as a quantum mechanical estimate of the VER rate. The γ dependence of the result is shown on the right-hand side of Fig. 6. We see that, for $\gamma \simeq 3 \sim 30$ cm^{-1}, the quantum mechanical estimate gives $T_1 \simeq 0.2 \sim 0.3$ ps, which is similar to the classical estimate Eq. (29): $T_1 \simeq 0.3 \sim 0.4$ ps.

In Table III, we list the largest contributions to the VER rate for different width parameters. For the case of $\gamma = 3$ cm^{-1}, the largest contribution is due to modes (3823,1655). This combination of modes is nearly resonant with the CD

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[2]In the VER calculation of myoglobin [22], Leitner's group took $\gamma = 0.5 \sim 10$ cm^{-1} to be the width, and confirmed that the result is relatively insensitive to the choice of γ in this range.
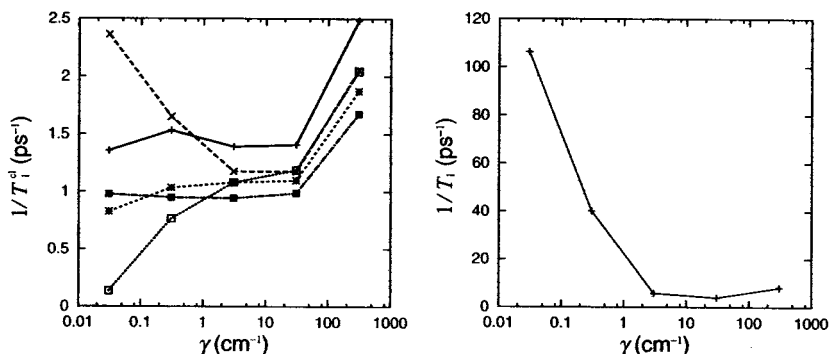
Figure 6. **Left:** Classical VER rate for five trajectories as a function of the "lifetime" width parameter γ. **Right:** VER rate calculated by Eq. (71) as a function of γ.

mode as $|\omega_{3823} + \omega_{1655} - \omega_{CD}| \simeq 0.03$ cm^{-1}. Though the coupling element for the combination is small ($|A^{(2)}_{3823,1655}| = 5.1$ kcal/mol/Å^3), this mode combination contributes significantly to the VER rate. On the other hand, for the case of $\gamma = 30$ cm^{-1}, the largest contribution results from the combination of modes (3330,1996). This combination is somewhat off-resonant—that is, $|\omega_{3330} + \omega_{1996} - \omega_{CD}| = 32$ cm^{-1}—but the coupling element is very large ($|A^{(2)}_{3330,1996}| = 22.3$ kcal/mol/Å^3), and the contribution is significant. In both cases, one combination of modes dominates the VER rate ($\simeq 20\%$), though there are nonnegligible contributions from other combinations of modes.

We have also examined the temperature dependence of the VER rates using Eq. (71). As shown in Fig. 7, for $T < 300$ K there is little temperature dependence as has been addressed in the case of myoglobin [22]. Thus we can say that the relaxation of the CD mode is quantum mechanical rather than thermal because the decay at 300 K is similar to that at 0.3 K.

TABLE III
The Largest Contributions to the VER Rate (in ps^{-1}) for $\gamma = 3$ cm^{-1} (left) and $\gamma = 30$ cm^{-1} (right)

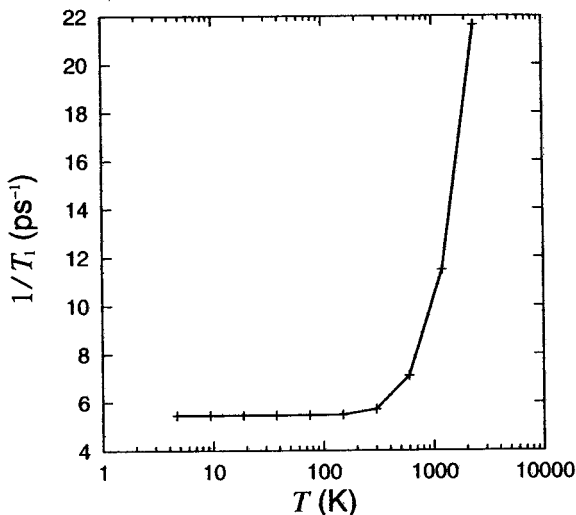| (k, l)	Contribution	(k, l)	Contribution
(3823, 1655)	1.10 (19%)	(3330, 1996)	0.88 (22%)
(3823, 1654)	0.43 (8%)	(3823, 1655)	0.11 (3%)
(3822, 1655)	0.37 (6%)	(3170, 2196)	0.07 (2%)
(3330, 1996)	0.17 (3%)	(1996, 1996)	0.05 (1%)
(3822, 1654)	0.15 (3%)	(3823, 1654)	0.04 (1%)
(3823, 1661)	0.14 (3%)	(3170, 2202)	0.04 (1%)
(3822, 1661)	0.05 (1%)	(3822, 1655)	0.04 (1%)
(3822, 1656)	0.05 (1%)	(3327, 1996)	0.03 (1%)
(3823, 1658)	0.04 (1%)	(3330, 1655)	0.02 (1%)

Figure 7. Temperature dependence of the VER rate calculated by Eq. (71). The width parameter is $\gamma = 3$ cm^{-1}.

3. Discussion

We examine the relationship between the theoretical results described above and the corresponding experiments of Romesberg's group, which has studied the spectroscopic properties of the CD mode in cyt c [10]. They measured the shifts and widths of the spectra for different forms of cyt c; the widths of the spectra (FWHM) were found to be $\Delta\omega_{FWHM} \simeq 6.0$–13.0 cm^{-1}. A rough estimate of the VER rate leads to

$$T_1 \sim 5.3/\Delta\omega_{FWHM} \quad (ps) \tag{74}$$

which corresponds to $T_1 \simeq 0.4$–0.9 ps. This estimate is similar to the "semi"-classical prediction computed using Eq. (29) and appropriate QCFs (0.3–0.4 ps) and the perturbative quantum mechanical estimate using the reduced model (0.2–0.3 ps). This result appears to justify the use of QCFs and the reduced model in this situation, and it suggests that the effects of the protein solvation (by water) are negligible in describing the VER of the CD mode. Of course, we must be careful in comparing the estimate derived from Eq. (74) because there may be inhomogeneity in the experimental spectra.[3] As such, it is more desirable to

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[3] We have confirmed that the methyl group does not rotate during the equilibrium simulations. Thus we might exclude the rotation as a possible reason of inhomogeneity.

calculate not only VER rates but spectroscopic observables themselves to compare with experiments.

Finally we discuss the relation between this work and previous work on carbon monoxide myoglobin (MbCO). Though there are many experimental studies on Mb [35], we focus on the experiments of Anfinrud's group [36] and Fayer's group [37] on MbCO. The former group found that the VER time for CO in the heme pocket (photolyzed MbCO) is $\simeq$ 600 ps, whereas the latter group found that the VER time for CO bounded to the heme is $\simeq$ 20 ps. This difference is interpreted as follows: CO is covalently bonded to the heme for the latter case, whereas CO is "floating" in the pocket in the former case; that is, the force applied to CO for the latter case is stronger than that for the former case. This difference in the magnitude of the force causes the slower VER for the "floating" CO. In this respect, the CD bond is expected to be stronger than the CO–heme coupling. This may explain a VER time $\sim$ 0.1 ps, which is similar to the VER times for the CH(CD) stretching modes in benzene (or perdeutero-benzene) [29,38]. It will be interesting to apply a similar reduced model to the analysis of the VER of CO in MbCO.

IV. SUMMARY AND FURTHER ASPECTS

After reviewing the VER rate formula derived from quantum mechanical perturbation calculations, we applied it to the analysis of VER of a CD stretching mode in cyt c. We modeled cyt c in vacuum as a normal mode system with the third-order anharmonic coupling elements, which were calculated from the CHARMM potential. We found that, for the width parameter $\gamma = 3 \sim 30$ cm^{-1}, the VER time is 0.2–0.3 ps, which agrees rather well with the previous classical calculation using the quantum correction factor (QCF) method, and is consistent with the experiments by Romesberg's group. This result indicates that the use of QCFs or a reduced model Hamiltonian can be justified a posteriori to describe the VER problem. We decomposed the VER rate into contributions from two modes, and we found that the most significant contribution, which depends on the "lifetime" width parameter, results from modes most resonant with the CD mode.

Finally we note several future directions which should be studied: (a) Our final results for the VER rate depend on a width parameter γ. Unfortunately we do not know which value is the most appropriate for γ. Nonequilibrium simulations (with some quantum corrections [39]) might help this situation, and they are useful to investigate energy pathways or sequential IVR (intramolecular vibrational energy redistribution) [40] in a protein. (b) This work is motivated by pioneering spectroscopic experiments by Romesberg's group. The calcula-tion of the VER rate and the linear or nonlinear response functions, related to absorption or 2D-IR (or 2D-Raman) spectra [41–44], is desirable. (c)

Romesberg's group investigated a spectroscopic change due to the oxidation or reduction of Fe in the heme; such an electron transfer process [45] is fundamental for the functionality of cyt c. To survey this process dynamically, it will be necessary to combine some quantum chemistry (ab initio) calculations with MD simulations [18,46,47].

Acknowledgments

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