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# Perturbation Approach for Computing Infrared Spectra of the Local Mode of Probe Molecules

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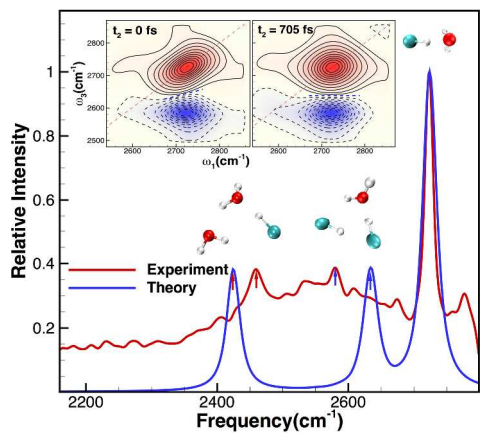
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**ABSTRACT:** Linear and two-dimensional infrared (IR) spectroscopy of site-specific probe molecules provides an opportunity to gain a molecular-level understanding of the local hydrogen-bonding network, conformational dynamics and long-range electrostatic interactions in condensed-phase and biological systems. A challenge in computation is to determine the time-dependent vibrational frequencies that incorporates explicitly both nuclear quantum effects of vibrational motions and an electronic structural representation of the potential energy surface. In this paper, a nuclear quantum perturbation (QVP) method is described for efficiently determining the instantaneous vibrational frequency of a chromophore in molecular dynamics simulations. Computational efficiency is achieved through the use of discrete variable representation of the vibrational wave functions, a perturbation theory to evaluate the vibrational energy shifts due to solvent dynamic fluctuations, and a combined QM/MM potential for the systems. It was found that first-order perturbation is sufficiently accurate, enabling time-dependent vibrational frequencies to be obtained on the fly in molecular dynamics. The QVP method is illustrated on the mode-specific linear and 2D-IR spectra of the H-Cl stretching frequency in the HCl-water clusters, and the carbonyl stretching vibration of acetone in aqueous solution. To further reduce computational cost, a hybrid strategy was proposed, and it was found that the computed vibrational spectral peak position and line shape are in agreement with experiment. In addition, it was found that anharmonicity is significant in the H-Cl stretching mode and hydrogen-bonding interactions further enhance anharmonic effects. The present QVP method complements other computational approaches, including path integral-based molecular dynamics, and represents a major improvement over the electrostatics-based spectroscopic mapping procedures.

TOC GRAPHICS



**KEYWORDS:** IR Probe Spectra, 2D IR spectra, frequency correlation, intermolecular potential perturbation, vibrational frequency shift

## 1. Introduction

Molecular vibrations and infrared spectroscopy of small chromophore probes embedded in molecular clusters, solutions, and biomacromolecules have been widely used to investigate solute-solvent interactions, hydrogen-bonding dynamics, and the local electric fields in enzymes.<sup>1-9</sup> Vibrational frequency shifts are especially sensitive to the local electrostatic environment, which can be easily and accurately measured. Thus, the study of vibrational frequency shifts is an efficient way to analyze the local structure and its consequent electric field.<sup>2,10</sup> Furthermore, measurements of the time-dependent frequency fluctuations or spectral diffusion can provide dynamic information, and it is useful to carry out condensed-phase simulations of solutions or biomacromolecules. To this end, a range of computational methods have been developed for the study of molecular vibration in condensed phases, including path integral simulations.<sup>4,11,12</sup> Still, it is a challenging task to determine the instantaneous vibrational frequencies of probe molecules that include nuclear quantum effects on the fly in molecular dynamics simulations.<sup>1,4,13</sup> In this study, we present a combined quantum mechanical and molecular mechanical (QM/MM) perturbation approach to efficiently and accurately determine the vibrational frequency of a probe molecule to construct its linear and two-dimensional infrared (2D-IR) spectra.<sup>14,15</sup>

We use the HCl-water cluster system to illustrate and validate the present first-order quantum vibration perturbation (QVP1) approach because strong hydrogen-bonding and dispersion interactions are important, and because it has been extensively investigated experimentally<sup>16-27</sup> and theoretically.<sup>25-53</sup> Although this appears to be a small test case, it is in fact challenging because of the strong bond-dissociation character in the oscillator mode. We emphasize that the QVP1 method is equally efficient for condensed-phase simulations as in a

combined QM/MM approach.<sup>54</sup> This is illustrated on the vibrational spectral shifts of the carbonyl stretch mode of acetone in aqueous solution. The C=O stretch vibration is widely used as the probe to the secondary structure of proteins,<sup>55,56</sup> including acetone in water.<sup>57,58</sup>

Experimentally, Suhm and coworkers reported the first IR spectrum of HCl-water clusters,<sup>16,17</sup> and found that a minimum of four water molecules is required for HCl dissociation. Recently, Havenith and coworkers confirmed that the broad band at 2675 cm<sup>-1</sup> is due to the dissociated cluster, H<sub>3</sub>O<sup>+</sup>(H<sub>2</sub>O)<sub>3</sub>Cl<sup>-</sup>.<sup>59</sup> On the theoretical side, Born-Oppenheimer molecular dynamics (BOMD) simulations with DFT-based potentials have been used to model HCl(H<sub>2</sub>O)<sub>n</sub> (n=1 to 4) clusters.<sup>38,40-45,47,60</sup> Marx and coworkers<sup>47</sup> obtained the IR spectra of the HCl-water clusters using the BLYP density functional. A sequential solvation process was proposed to account for the HCl dissociation mechanism, involving the interplay of quantum tunneling and thermal fluctuations from path integral simulations.<sup>33,37,43-45</sup> Employing a semiempirical PM3-MAIS potential, Lin and Paesani extended the investigation to larger clusters up to n = 21.<sup>26</sup> The IR spectra assignment was analyzed on the basis of atomic velocity autocorrelation functions, in which the vibrational quantum effects were ignored.<sup>26</sup> In this regard, Paesani and coworkers have developed highly accurate empirical potential energy functions for liquid water and solutes.<sup>61-63</sup> Various approximate methods are available to account for the time-dependent nuclear quantum effects, including linearized semiclassical initial value representation (LSC-IVR),<sup>64-66</sup> centroid molecular dynamics,<sup>13,67-73</sup> and ring-polymer molecular dynamics.<sup>72,74-78</sup> One can, of course, solve numerically the vibrational Schrödinger equation.<sup>13,67-73</sup> Mancini and Bowman<sup>50-53,79</sup> employed diffusion Monte Carlo simulations to investigate the high-frequency fundamental modes of HCl-water clusters. Good agreement was observed between the calculated vibrational

frequencies and experimental peak positions when the delocalized zero-point vibrational motion was taken into account.<sup>50</sup>

The IR signature of  $\text{H}_3\text{O}^+$  in the dissociated configuration of  $\text{H}_3\text{O}^+(\text{H}_2\text{O})_3\text{Cl}^-$  was investigated using vibrational configuration interaction (VCI) with the local monomer (LMon) potential energy surface,<sup>79</sup> providing peak positions and intensities. The VCI calculations employed eight states for each vibrational mode, coupled to up to four other modes, on 10G integration points per mode. Although these studies provided significant insights on mode coupling and peak positions of  $\text{H}_3\text{O}^+$  for a single fixed water- $\text{Cl}^-$  configuration, the method does not provide spectral line shape and is too time-consuming to obtain time-dependent frequencies in dynamics simulations.

Explicit quantum mechanical treatments of both the nuclear motion and the potential energy surface are required to understand the solute-solvent interaction dynamics in 1-D and 2-D vibrational spectroscopic experiments. In principle, path-integral molecular dynamics employing an on-the-fly QM potential can be used; however, the high computational costs limit its broad applications, especially when excitation involving higher vibrational states are investigated. In practice, empirical spectroscopic maps that relate the frequency change to the local electric field have been widely used. The method has been shown to be quite reliable for systems dominated by electrostatic interactions.<sup>1-3,80,81</sup> However, the electrostatics-based spectroscopic map does not fully take into account exchange and dispersion interactions, nor explicit polarization effects and charge transfer contributions. Thus, large deviations were found in simulations of N-methyl acetamide (NMA) in  $\text{CDCl}_3$  solution in which dispersion forces are dominant.<sup>39</sup> To this end, combined QM/MM methods, in which the probe molecule is treated explicitly by electronic structure theory, provide the most general, efficient and systematic approach to represent the

potential energy surface.<sup>82,83</sup> It also avoids the need to fit a secondary dipole moment surface that is typically inconsistent with the electrostatic properties of the empirical potential function.<sup>1,4,13,79</sup> The instantaneous vibrational energy levels can be determined by solving the vibrational Schrödinger equation for a given mode or coupled modes based on the QM/MM potential,<sup>13,82</sup> but the increased computational costs prevent it from being effectively used to obtain the frequency time correlation function (FTCF). Thus, it is useful to develop computationally efficient methods to accurately determine the time-dependent vibrational frequencies of a specific vibrational mode of a probe oscillator in solution and biological systems.

In this paper, we describe a perturbation approach to efficiently determine the instantaneous vibrational frequency of one or two specific target modes. The method is based on quantum vibrational perturbation (QVP) theory by means of potential-optimized discrete variable representation (PODVR).<sup>84,85</sup> The key in the QVP method is **to estimate the vibrational energy shift of the solute (probe) molecule induced by interactions with the solvent environment without the need to solve the vibrational Schrödinger equation.**<sup>86,87</sup> The QVP method incorporates nuclear quantum effects of the vibrational probe as well as the influence of dynamic fluctuations of the environment, and it can be applied to large molecular systems directly in molecular dynamics simulations with a combined QM/MM potential. The QVP method is illustrated and validated by an application to the small yet challenging HCl-water clusters to determine the IR spectra in the HCl stretching region.

## 2. Method

In the present QVP approach, the energy of each vibrational state of the oscillator is obtained by treating the solvent fluctuation as a perturbation,  $\Delta H(Q, R)$ , to the reference



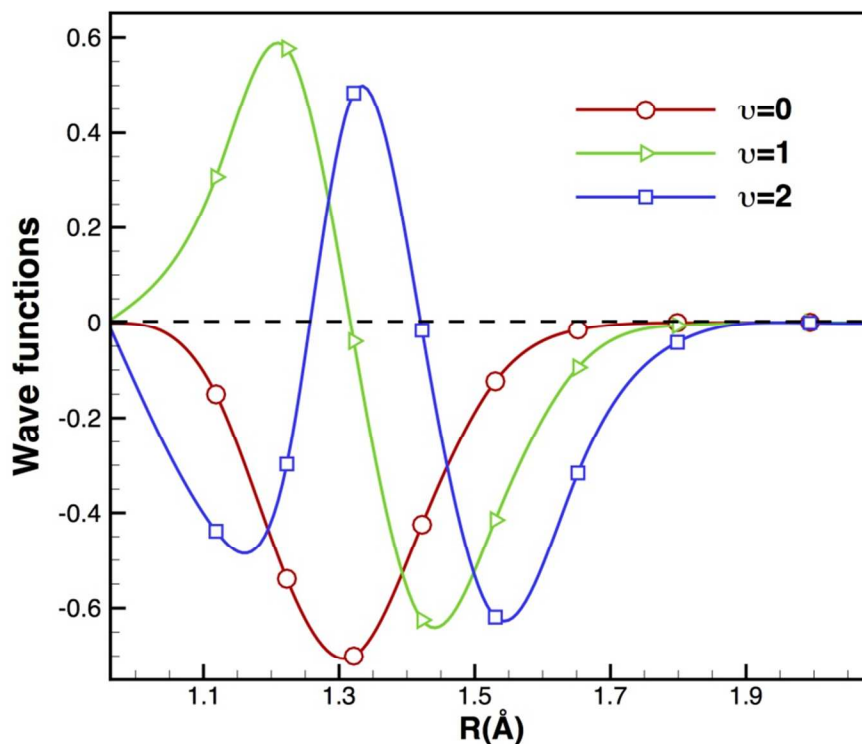
configuration  $H^0(Q, R_0)$ , where  $Q$  and  $R$  refer to solute and solvent coordinates, and  $R_0$  is the coordinates at the referenced state. Consequently, the instantaneous transition frequency from the ground vibrational state ( $\nu = 0$ ) to the first excited state ( $\nu = 1$ ) for the mode of interest is given by

$$\omega_{10}(t) = \omega_{10}^0 + \Delta\omega_{10}(t) \quad (1)$$

where  $\omega_{10}^0$  is the vibrational frequency of the reference state, which is the minimum-energy structure of the ClH–OH<sub>2</sub> complex. In eq 1, the frequency shift  $\Delta\omega_{10}(t)$  is related to the perturbation energies of the instantaneous structure at time  $t$ :

$$\Delta\omega_{10}(t) = \frac{\Delta V_1(t) - \Delta V_0(t)}{\hbar} \quad (2)$$

where  $\Delta V_0(t)$  and  $\Delta V_1(t)$  are the perturbation energies for the ground and first excited states of the quantum oscillator in the bath of a given solvent configuration.



**Figure 1.** Computed vibrational wave functions of the ground, and the first and second excited states of the HCl stretch mode in the optimized HCl(H<sub>2</sub>O) structure. Discrete variable representation (DVR) at the eight optimized grid points are indicated.

Specifically, we first solve the vibrational Schrödinger equation for the reference structure defined by  $H^0(Q, R_0)$  to yield the vibrational wave functions  $\phi_v$ , based on which the optimal number of PODVR points is obtained.<sup>85,88</sup> For the ClH–OH<sub>2</sub> complex, we found that just eight PODVR points are sufficient to obtain convergent energies and wave functions for the lowest three vibrational states (see Supporting Information). They are depicted in Figure 1. Then, we use perturbation theory to determine the energy shifts for each vibrational level relative to that of the reference state. Importantly, the perturbation energies converge quickly, and the first order approximation (QVP1) is sufficient in the present test cases (see below).

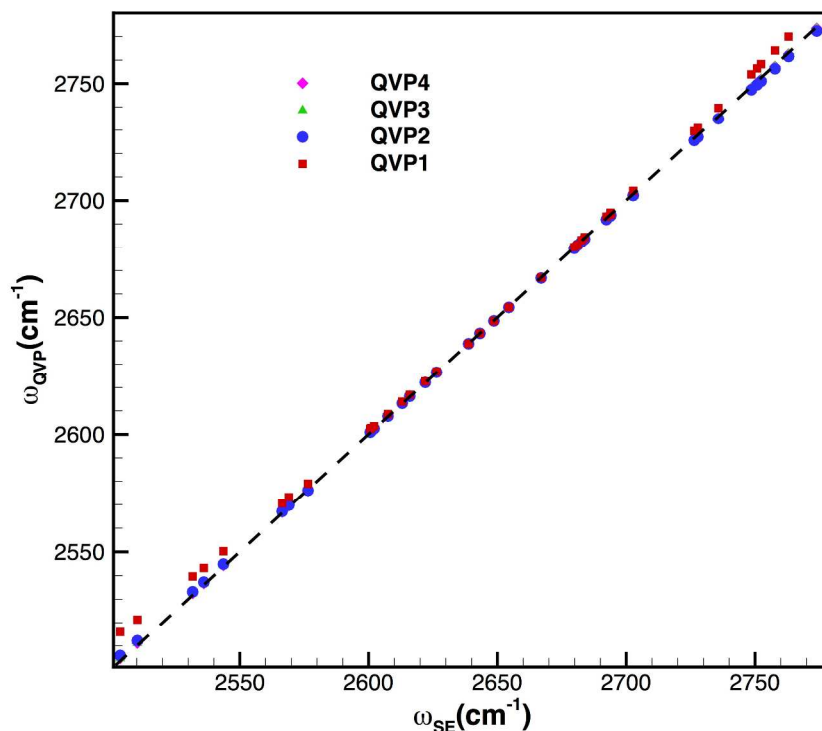
In the PODVR basis  $\{\chi^2(Q_i; R_0), i=1, \dots, 8\}$  over the discrete points along the HCl stretching mode for the reference state,  $R_0$ , the first order perturbation energy for state  $\nu$  is given by

$$\begin{aligned} \Delta V_\nu(t) &= \int dQ \Delta H(Q, R[t]) |\phi_\nu(Q; R_0)|^2 \\ &= \sum_{i=1}^8 \Delta H(Q_i, R[t]) c_{\nu i}^2 \chi^2(Q_i; R_0) \end{aligned} \quad (3)$$

where  $Q_i$  is the coordinates of the  $i$ th PODVR point,  $\{c_{\nu i}\}$  are the optimized and normalized coefficients for state  $\nu$  in the PODVR basis, and  $\Delta H(Q_i, R[t])$  is the perturbation energy corresponding to the chromophore at the discrete point  $Q_i$  and the instantaneous bath coordinates at  $R[t]$  at time  $t$ . Equation 3 is based on the separation of inter- and intra-molecular motions, which ignores the nuclear quantum mechanical effects on their coupling. This approximation is justified for situations in the present study (except when HCl dissociation occurs with four water molecules) and is valid for most applications in biological systems, where the vibrational frequency of the probe molecule is designed to clearly separate from the bath modes. Nevertheless, coupling to higher quanta of bath modes could be important and a procedure developed by Skinner and coworkers can be applied here to treat such situations.<sup>12</sup> In practice,  $\Delta H(Q, R[t])$  can be evaluated using a combined QM/MM potential, or by a mixed fragmental QM model in which the solute and its nearest neighbors are described by a high-level theory embedded in the solvent environment to model long-range electrostatic effects.<sup>89</sup> In the latter case, short-range repulsion, dispersion and charge transfer effects between the oscillator and solvent molecules in close proximity are naturally included in the QM model. For the present HCl-water clusters, the entire system is treated quantum-mechanically using two QM methods: M06-2X<sup>90</sup>/cc-pVTZ and CCSD(T)-F12B<sup>91-93</sup>/cc-pVTZ.

Equations 2 and 3 show that the present QVP1 method can be extremely efficient for computation of vibrational frequencies, which involve two weighted averages of the perturbation term. Thus, the computational cost is equivalent to that needed to determine the perturbation energy at the discrete points without explicitly solving the vibrational Schrödinger equation. The weighting coefficients in eq 3, defined by  $\{\omega_i = c_{vi} \chi^2(Q_i, R_0), v = 1, 2\}$ , are predetermined for the chromophore oscillator in the reference structure, and optimized to represent the vibrational wave function in the PODVR method. Higher order perturbation terms can be used if greater computational accuracy is desired or becomes necessary.

To quantify convergence of the present perturbation strategy, we selected 40 structures from the molecular dynamical trajectory of HCl(H<sub>2</sub>O) at equal interval, and determined the exact vibrational frequencies by solving numerically the Schrödinger equation and those estimated by the QVPn method up to the fourth-order perturbation ( $n = 1 - 4$ ). The results are compared in Figure 2 spanning a range of vibrational frequency from 2500 cm<sup>-1</sup> to 2775 cm<sup>-1</sup>. Figure 2 reveals that while the first-order perturbation approach QVP1 has a good agreement with the exact result in the medium range of 2600-2700 cm<sup>-1</sup>, increased deviations are observed at higher and lower frequencies with an average error of 3.0 cm<sup>-1</sup>. As the order of perturbation increases, the computation accuracy increases sharply to root-mean-square deviations of 0.1, 0.04 and 0.04 cm<sup>-1</sup> for the second, third, and forth-order perturbation theory, respectively. However, higher vibration excited states are needed to obtain high-order perturbation energies, which translate to more discrete points in the PODVR evaluation. Since the frequency shifts are relatively large in the present test cases, the first-order perturbation QVP1 is used throughout.



**Figure 2.** Correlation of the exact and the QVP vibrational frequencies for HCl in 40 complex structures from an ab initio molecular dynamics trajectory of the  $\text{H}_2\text{O}\dots\text{HCl}$  cluster using CCSD(T)-F12b/cc-pVTZ-F12. The exact results are obtained by solving the vibrational Schrödinger equation (abscissa) for each complex structure, whereas up to the fourth-order perturbation is used in the quantum vibrational perturbation (QVP) approach (ordinate). The black dashed line represents a perfect match.

### 3. Computational Details

Born-Oppenheimer molecular dynamics simulations were performed using the meta-GGA M06-2X density functional theory with the cc-pVTZ basis for  $\text{HCl}(\text{H}_2\text{O})$  and using BLYP density functional theory augmented by dispersion corrections<sup>88,89</sup> for other cases with a plane wave basis set<sup>86,87,94</sup>. For each cluster, the dynamics simulations were carried out at 200 K for a total of 25 ps with an integration step of 30 au (0.72 fs). Additional details of the ab initio simulation procedure are given in the SI. For accuracy in the computed vibrational frequency, all

the perturbation energies were determined using the M06-2X/cc-pVTZ and CCSD(T)-F12b/cc-pVTZ-F12 methods.<sup>95</sup> Basis set superposition errors (BSSE)<sup>96</sup> were corrected following the counter poise scheme. Note that as the number of water increases in the HCl(H<sub>2</sub>O)<sub>n</sub> clusters, HCl dissociation is observed when *n* is 4 as shown in Figure S1. This is consistent with the aggregation-induced dissociation mechanism<sup>22,40</sup> in previous simulations.<sup>40,42-44,59,97</sup>

For comparison, we have determined the linear absorption line shape by classical and mixed quantum/classical approaches.<sup>1,4</sup> In the classical approach, the line shape function is computed by Fourier transform of the autocorrelation function of the total molecular dipole moment from classical molecular dynamics simulations

$$I_{cl}(\omega) = Q_H(\omega) \int d\omega < \mu(0) \cdot \mu(t) > e^{-i\omega t} \quad (4)$$

where  $Q_H(\omega)$  is the harmonic quantum correction factor,<sup>98,99</sup> and the brackets specify a classical statistical mechanical average. In the mixed quantum/classical method,<sup>1,4</sup> where the HCl vibrational mode is treated quantum mechanically and all other degrees of freedom are modeled classically by molecular dynamics, a key quantity of interest is the 0 → 1 transition frequency and its dependence on the environment (eq 1). Then, within the Condon approximation, the magnitude of the vibrational transition moment is assumed to be independent of the bath fluctuations,<sup>1</sup> and the semiclassical absorption line shape can be written as

$$I_{sc}(\omega) = \int dt e^{-i\omega t} < e^{i \int_0^t d\tau \omega_{10}(\tau)} > e^{-t/2T_1} \quad (5)$$

where  $T_1$  is the vibrational energy relaxation time (224 fs), which is estimated following the work of Straub and co-workers<sup>100-103</sup> by computing the classical autocorrelation function of the force along the H-Cl bond. To evaluate the average in eq 5, the time evolution for  $\omega_{10}(t)$  are

computed using the QVP1 method on the classical molecular dynamics trajectory. Equation 5 can be written in terms of cumulant expansion at the second-order truncation:

$$I_{cum}(\omega) = \int dt e^{-i(\omega - \langle \omega_{10} \rangle)t} e^{-\int_0^t d\tau (t-\tau)C(\tau)} e^{-t/2T_1} \quad (6)$$

Where  $\langle \omega_{10} \rangle$  is the average transition frequency, and  $C(t)$  is the frequency-frequency time-correlation function given by

$$C(t) = \langle \delta\omega(0)\delta\omega(t) \rangle \quad (7)$$

where  $\delta\omega(t) = \omega_{10}(t) - \langle \omega_{10} \rangle$ .

## 4. Results and Discussion

We first present results on the hydrogen chloride-water clusters to demonstrate the performance of the quantum vibrational perturbation approach for determining on-the-fly vibrational frequencies. Here, the full system is represented by an electronic structure method. Then, we illustrate the applicability of the QVP method in condensed-phase simulations, making use of the carbonyl stretching mode of acetone in water as an example. In this case, combined QM/MM molecular dynamics simulations are performed to evaluate the perturbation energy using a semiempirical Hamiltonian.

### 4.1. HCl-Water Clusters.

**HCl(H<sub>2</sub>O).** The computed and experimental IR spectra in the HCl stretching region of the bimolecular complex HCl(H<sub>2</sub>O) are displayed in Figure 3. In this discussion, we first address nuclear quantum effects on the computed frequency, and then, examine a hybrid procedure to increase the accuracy of the results, making use of the M06-2X trajectory. Figure 3(a) displays the line shape functions using the classical molecular dipole autocorrelation function (DAF) in blue (scaled by the harmonic quantum correction factor), and using eq 5 based on the QVP1

transition frequencies in green. The spectrum determined from the DAF shows a series of side peaks with an interval of about  $50\text{ cm}^{-1}$ , attributed to the coupling with rotations of the water molecule about the H-Cl axis. This effect is not included in the instantaneous frozen-bath approximation in the QVP1 model. The maximum peak position from the QVP1 method is located at  $2653\text{ cm}^{-1}$ , red-shifted by  $185\text{ cm}^{-1}$  from the strongest peak position ( $2838\text{ cm}^{-1}$ ) displayed on the spectrum based on the classical DAF. Since M06-2X/cc-pVTZ was used in both approaches, consistent with the dynamic trajectory, the difference between the two methods is primarily due to nuclear quantum effects of the oscillator, which clearly have significant contributions to the computed vibrational frequencies in Figure 3(a). Nevertheless, the full widths at half maximum (FWHM) of the spectrum peak are similar from both methods ( $21$  and  $23\text{ cm}^{-1}$ , respectively).

Figure 3(b) compares the results obtained using three different electronic structure methods; M06-2X (green line), CCSD(T)-F12b (red line), and a composite of M06-2X spectral shift and the CCSD(T)-F12b frequency. In the latter approach, the CCSD(T)-F12b frequency for the reference state is used, but the spectral shift due to dynamic fluctuations of the solvent is determined at the M06-2X level using QVP1. We designate this method as CCSD(T)/M06 in Figure 3(b), which significantly reduces the computational costs compared with that when the perturbation theory is also carried out at the CCSD(T)-F12b level. Figure 3(b) shows that the maximum peak position from QVP1 using CCSD(T)-F12b is only  $14\text{ cm}^{-1}$  greater than the experimental value ( $2723.5\text{ cm}^{-1}$ ).<sup>16,17</sup> The M06-2X frequency in the HCl(H<sub>2</sub>O) complex is blue-shifted by  $84.6\text{ cm}^{-1}$  from the coupled-cluster value, and this is mainly due to the difference in the reference state between the two methods;  $80.6\text{ cm}^{-1} = 2650.5\text{ cm}^{-1}$  (CCSD(T)-F12b) -  $2569.9\text{ cm}^{-1}$  (M06-2X). Thus, the solvatochromic shifts are not very sensitive to the quantum chemical

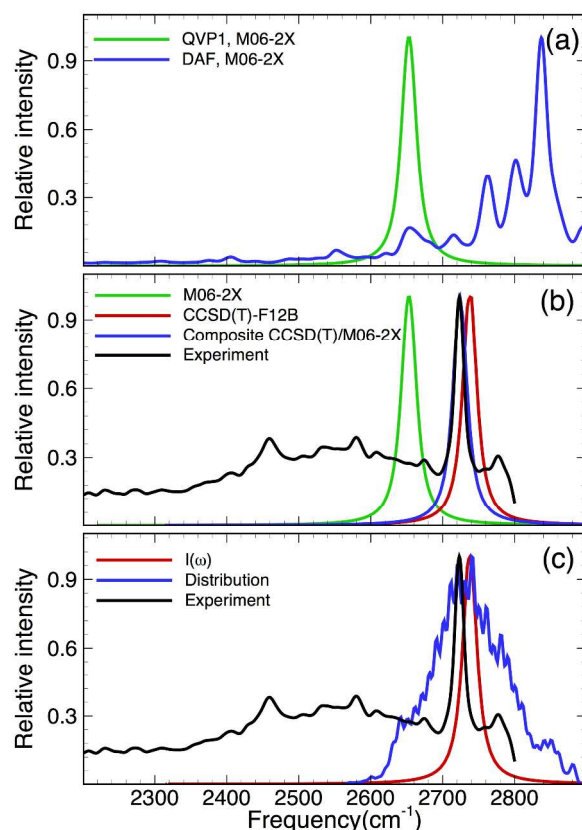


models used, here, differing only by  $4\text{ cm}^{-1}$ . Clearly, it can be a major time-saving approach to use density functional theory to estimate the spectral shift, but the reference frequency value is evaluated using coupled cluster theory (eq 1) since the latter only needs to be computed once. As the computational cost of the QVP method is equivalent to that required to determine the perturbation energy at the discrete points, allowing the instantaneous vibrational frequency of the oscillator to be determined on-the-fly of dynamics simulations. Indeed, the composite approach, employing the CCSD(T) zeroth order frequency (reference state) and QVP1 frequency shift from M06-2X (blue curve in Figure 3b), yields a maximum peak position at  $2725\text{ cm}^{-1}$ , only  $13\text{ cm}^{-1}$  different from the CCSD(T)-F12b value ( $2738\text{ cm}^{-1}$ ). Interestingly, the composite result is in better accord with experiment than CCSD(T)-F12b, perhaps due to fortuitous error cancellations. Furthermore, the predicted FWHM from the composite strategy is  $21\text{ cm}^{-1}$ , also in good agreement with experiment ( $18\text{ cm}^{-1}$ ),<sup>16,17</sup> and consistent with pure CCSD(T)-F12b and M06-2X calculations. The agreement between theory and experiment both in peak position and in line shape suggests that the QVP1 composite approach can be used for studying IR spectra of condensed-phase and biomolecular systems.

In Figure 3(c), we compare the distribution of instantaneous vibrational frequencies (blue) computed along an MD trajectory with the line shape function (eq 6) determined at the CCSD(T)-F12b/cc-pVTZ-F12 level (red). Although the average peak positions are the same, the statistical distribution of the computed frequencies is clearly not an adequate approximation to the spectral line shape due to motion narrowing effects. Similar features were found in the study of HOD vibration in  $\text{H}_2\text{O}$  and in  $\text{D}_2\text{O}$  employing a polarizable empirical potential for water.<sup>13</sup>

The 2D pump-probe spectra for the HCl stretching vibration in  $\text{HCl}(\text{H}_2\text{O})$  are computed using the instantaneous vibrational frequencies determined by the CCSD(T)/M06-2X composite

strategy along with  $t_2$  evolution (additional details are given in the SI). In Figure 3, the  $\omega_1$  axis represents the pump pulse, while the  $\omega_3$  axis specifies the probe pulse. The projection on  $\omega_3$  is the dynamical line shape both for the vibrational bands of the 1-0 resonance (red) and the 2-1 resonance (blue). The 2D IR spectra are displayed in Figure 3 for  $t_2$  waiting times of 0, 302, 504 and 705 fs. At  $t_2 = 0$  fs, the spectrum is diagonally elongated and anti-diagonally narrowed, which demonstrates the anisotropy of the two vibrational bands and indicates a strong correlation of the vibrational bands. The anti-diagonal direction is broadened and the nodal slope (separating the positive region of the 1-0 resonance from the negative region of the 2-1 resonance in the 2D spectra and the slope lines are shown as the blue dashed lines in Figure 3) decreases as  $t_2$  increases, indicating reduction of correlation. At  $t_2 = 705$  fs, the nodal slope is closer to zero, where the coupling of the two vibrational bands vanishes.



**Figure 3.** Normalized IR line shapes from experiment (black) and computations for the HCl stretching vibrational mode in the HCl(H<sub>2</sub>O) complex. (a) The spectrum obtained by Fourier transform of DAF (eq 4) is given in blue, and that from instantaneous QVP1 frequencies (eq 5) is displayed in green, both at the M06-2X/cc-pVTZ level. (b) Spectral line shapes determined by the second-cumulant expression based on the frequency-frequency time correlation function (eq 6) are shown at the CCSD(T)-F12b (red) and M06-2X (green) levels along with the composite of CCSD(T)-F12b frequency for the reference state and M06-2X frequency shifts (blue). The distribution of computed H-Cl stretching frequency (blue) at the CCSD(T)-F12b level is illustrated in (c) along with the corresponding spectral line shape function (red) and the experimental spectrum (black).

**Table 1.** Computed HCl stretching vibrational frequency  $\omega_{Cl-H}$  and the shift  $\Delta\omega_{Cl-H}$  of the HCl(H<sub>2</sub>O) complex using harmonic normal mode analysis (NMA), Fourier transform of the dipole autocorrelation function (DAF) and the spectral expansion (eq 6) of the frequency-frequency time correlation function from the QVP1 method, along with the experimental value. Vibrational frequencies are given in  $cm^{-1}$ .

	Method	Basis Set	$\omega_{Cl-H}$	$\Delta\omega_{Cl-H}^a$
NMA <sup>15</sup>	HF	Q <sup>b</sup>	3033.0	309.5
	MP2	T <sup>b</sup>	2791.0	67.5
	CCSD(T)	D <sup>b</sup>	2782.0	58.5
DAF	M06-2X	cc-pVTZ	2837.6	114.1
	M06-2X	cc-pVTZ	2653.0	-70.5
QVP1	M06-2X+ CCSD(T)-F12b	cc-pVTZ+cc-pVTZ-F12 <sup>c</sup>	2724.8	1.3
	CCSD(T)-F12b	cc-pVTZ-F12	2737.6	14.1
EXP <sup>15,16</sup>			2723.5	

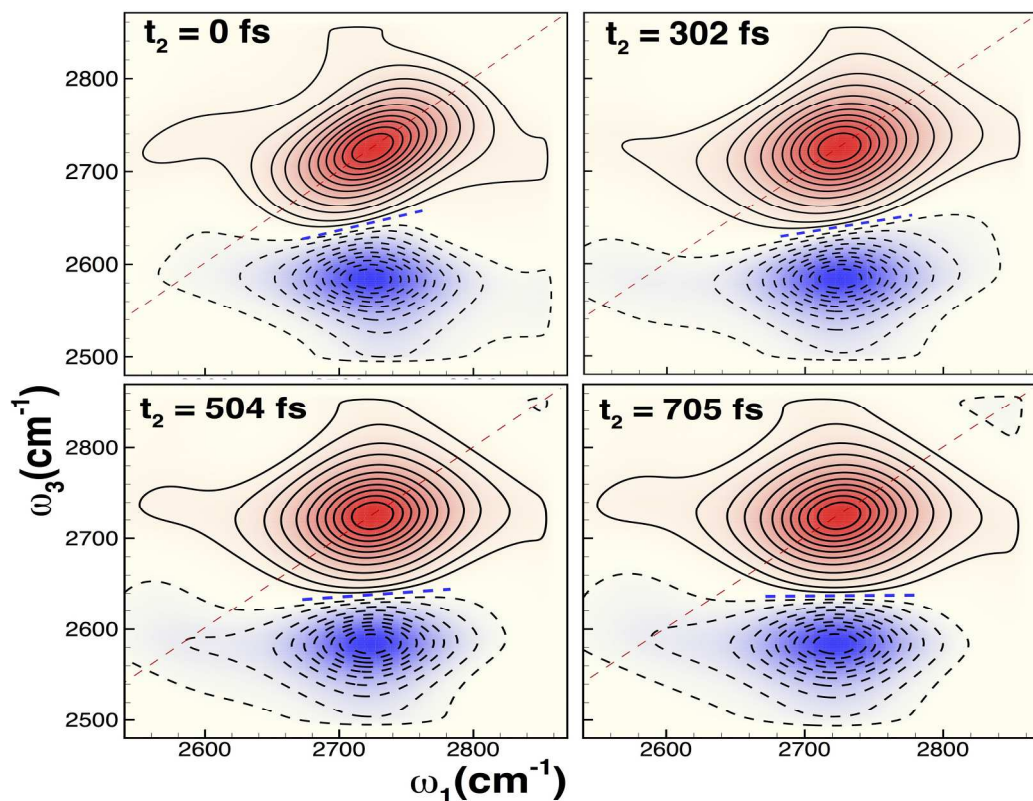
<sup>a</sup>  $\Delta\omega_{Cl-H} = \omega_{Cl-H} - \omega_{exp}$ .

<sup>b</sup> aug-cc-pVXZ, X=D,T,Q.

<sup>c</sup> M06-2X/cc-pVTZ+CCSD(T)-F12b/cc-pVTZ-F12

The 2D IR spectra provide a direct measure of the anharmonicity of the probe mode. Figure 4 indicates that the anharmonic frequency shift from the QVP1 approach is 140  $cm^{-1}$  for H-Cl stretching vibration in the HCl(H<sub>2</sub>O) complex, which is the difference between the central frequencies at positive (red) and negative (blue) peak regions. In comparison with the anharmonic frequency shift of 104  $cm^{-1}$  estimated for an isolated HCl molecule, hydrogen bonding interactions as well as dispersion contributions further increase anharmonicity in the

HCl(H<sub>2</sub>O) cluster. It is interesting to note that 1-0 and 2-1 transitions for the HCl stretching mode in HCl(H<sub>2</sub>O) are red-shifted, respectively, by 161 and 197 cm<sup>-1</sup> relative to an isolated HCl. Apparently, hydrogen bonding interactions have a greater effect on the higher vibrational energy levels than the ground state.



**Figure 4.** The 2D pump-probe spectra of the HCl stretching vibration in the HCl(H<sub>2</sub>O) complex are given at the evolution time  $t_2$  equaling to 0 fs, 302 fs, 504 fs and 705 fs respectively. See text for specific details.

(HCl)<sub>2</sub>(H<sub>2</sub>O). There are two HCl stretching vibrations in (HCl)<sub>2</sub>(H<sub>2</sub>O). Here, we focus on the HCl stretching mode in which the hydrogen atom is hydrogen-bonded to the oxygen of water. Figure 4 depicts the line shape of the main peak, which is in good agreement with the

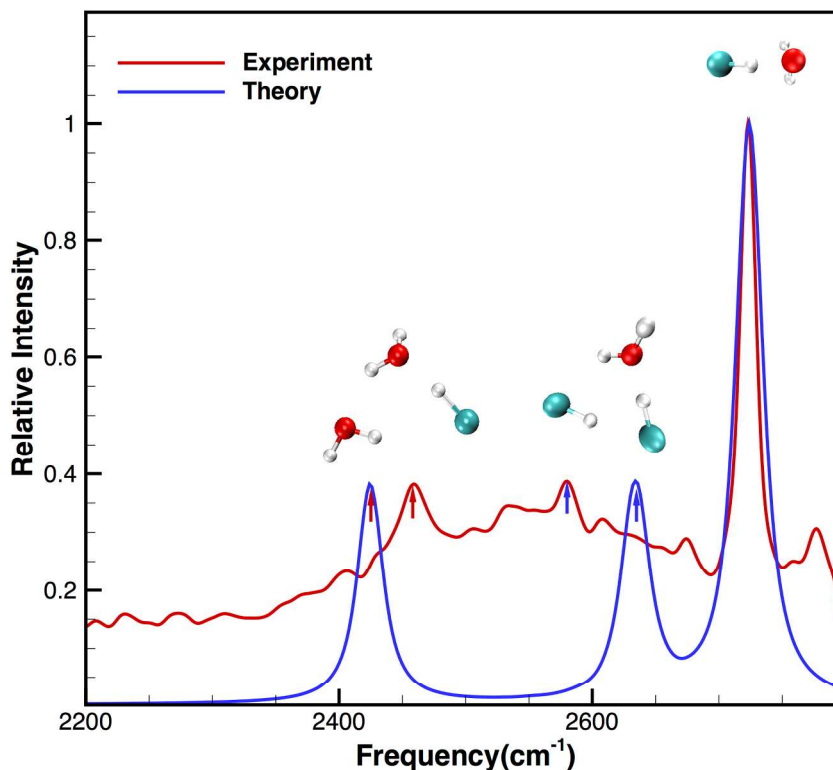
experimental peak.<sup>16,17</sup> The peak position is centered at 2634 cm<sup>-1</sup> which is 54 cm<sup>-1</sup> greater than the experimental value. The calculated line shape is similar to that from experiment, indicated by the blue arrow of the spectrum in red. For this system, the time-dependent trajectories, including the HCl(H<sub>2</sub>O)<sub>2</sub> cluster below, were sampled at the BLYP/Plane wave level, but the vibrational frequencies were determined by using the composite QVP1 strategy.

**Table 2.** Computed H-Cl stretching vibrational frequencies (cm<sup>-1</sup>) for (HCl)<sub>2</sub>(H<sub>2</sub>O) by solving two independent one-dimensional (E<sub>1D</sub>) Schrodinger equation and a two-dimensional (E<sub>2D</sub>) vibrational Schrodinger equation. The potential energy surfaces were determined using M06-2X/cc-pVTZ. Q<sub>1</sub> and Q<sub>2</sub> represent, respectively, the H-Cl stretch associated with the HCl molecule directly hydrogen-bonded to water and hydrogen-bonded to the probe HCl molecule (Figure 4).

Mode	E <sub>1D</sub>	E <sub>2D</sub>	Δv
Q <sub>1</sub>	2617.0	2612.3	4.7
Q <sub>2</sub>	2692.6	2693.7	-1.1

The present QVP method is applied to a single mode of interest, which ignores vibrational mode coupling in order to increase computational efficiency. For applications to biological systems, in which the vibrational frequency of the probe molecule (e.g., chromophores with triple bond or C-D stretch), the effect is expected to be small. However, because of the proximity of two similar HCl vibrations, mode coupling could be important. To address this question, we have determined the frequencies both HCl molecules in the optimized (HCl)<sub>2</sub>(H<sub>2</sub>O) complex (see Figure 5) by solving one-dimensional and two-dimensional vibrational Schrodinger equations, *i.e.*, one based on the potential energy surface of independent modes, and the second employing the full potential of the two modes, both at the M06-2X/cc-pVTZ level (Table 2). Mode coupling is

included in the latter approach. It was found that the mode corresponding to the HCl molecule directly hydrogen-bonded to water is lowered by  $4.7\text{ cm}^{-1}$  due to coupled interactions with the second HCl molecule, whereas the stretch frequency of the other HCl is enhanced by  $1.1\text{ cm}^{-1}$ . Thus, the effect due to mode coupling is not significant in this case.



**Figure 5.** The experimental spectra and the overall computed HCl stretching vibrational spectra for a mixture of  $(\text{HCl})(\text{H}_2\text{O})$ ,  $(\text{HCl})_2(\text{H}_2\text{O})$  and  $(\text{HCl})(\text{H}_2\text{O})_2$  clusters with weighting factors of 1, 0.41 and 0.46 for the relative intensities. The blue and red arrows specify the HCl stretching mode in the  $(\text{HCl})_2(\text{H}_2\text{O})$ ,  $(\text{HCl})(\text{H}_2\text{O})_2$  clusters, respectively, and the strongest peaks correspond to that in the  $\text{HCl}(\text{H}_2\text{O})$  complex. The latter was sampled by M06-2X/cc-pVTZ, whereas the remaining systems were sampled using BLYP-D Born-Oppenheimer molecular dynamics simulations.

**HCl(H<sub>2</sub>O)<sub>2</sub>.** The peak position of the HCl stretching vibrational mode of the 1:2 cluster, illustrated in Figure 5, is found at 2424 cm<sup>-1</sup>, which is close to the peak at 2460 cm<sup>-1</sup> found experimentally.<sup>16,17</sup> The computed line shape for HCl(H<sub>2</sub>O)<sub>2</sub> complex is somewhat narrower than that from experiment, highlighted by the red arrows in Figure 4.

Finally, we note that Figure 5 was constructed by summing up the individual HCl stretching vibrational spectra of the (HCl)(H<sub>2</sub>O), (HCl)<sub>2</sub>(H<sub>2</sub>O) and (HCl)(H<sub>2</sub>O)<sub>2</sub> clusters with weighting factors for relative intensities of 1, 0.41 and 0.46, respectively. Both the peak positions and line shapes are in reasonable agreement with the experimental spectra, which further support our assignments of those peaks as the HCl stretching mode in the (HCl)(H<sub>2</sub>O), (HCl)<sub>2</sub>(H<sub>2</sub>O), (HCl)(H<sub>2</sub>O)<sub>2</sub> clusters, respectively. The molecular structures for the clusters, (HCl)(H<sub>2</sub>O), (HCl)<sub>2</sub>(H<sub>2</sub>O) and (HCl)(H<sub>2</sub>O)<sub>2</sub>, are shown in Figure S2 along with key geometrical parameters indicated.

#### 4.2. Acetone in Aqueous Solution.

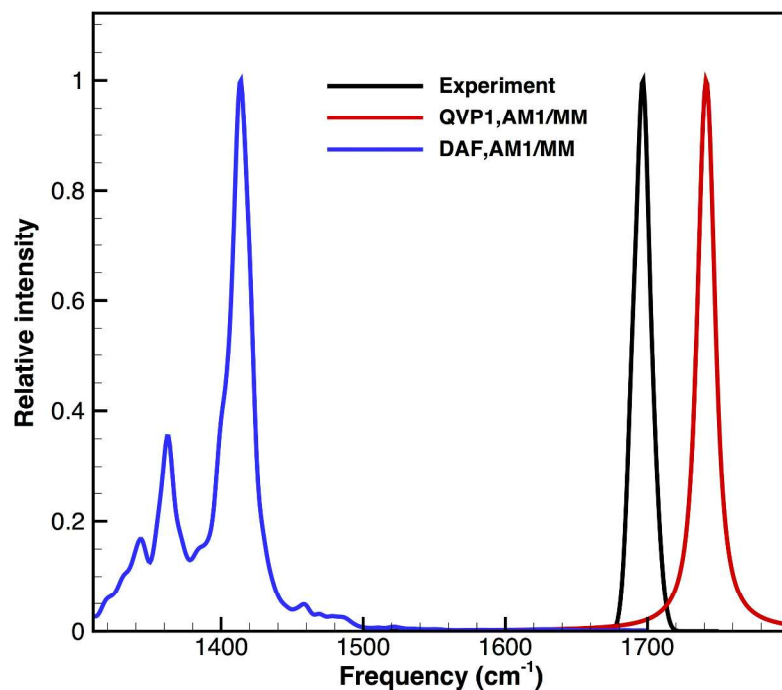
To illustrate the general applicability of the QVP method in condensed-phase simulations, we carried out “on-the-fly” vibrational frequency for the carbonyl stretching mode of acetone in aqueous solution. Combined quantum mechanical and molecular mechanical (QM/MM) potential<sup>54,104</sup> is employed, in which the chromophore is approximated by the semiempirical Austin Model 1 (AM1)<sup>105</sup> Hamiltonian, and the solvent is represented by the TIP3P model for water. A single solute molecule is embedded in a cubic box of 467 water molecules using the isothermal-isobaric (NPT) ensemble at 25 °C and 1 atm. The time-step in the simulation is 1 fs and a convergent QVP spectrum of C=O vibration is obtained using a 50 ps trajectory. All computations are carried out using CHARMM. Here, the instantaneous vibrational frequency of



the carbonyl stretch in water is determined using the composite approach described in the previous section, where the reference state is determined at a high level of theory, whereas the perturbation energy is obtained at the combined QM/MM level to account for solvent effects. In particular, the C=O vibrational wave functions for the first three vibrational states of an isolated acetone molecule in the gas phase are determined using the potential energy curve from CCSD(T)-F12/cc-pVTZ-F12 calculations along the C=O normal mode coordinate. The 0→1 transition frequency is estimated to be 1776 cm<sup>-1</sup>, in reasonable agreement with the experimental value of 1738 cm<sup>-1</sup> in the vapor phase, and the small difference of +38 cm<sup>-1</sup> will be fully transferred to the solution result.

Figure 5 displays the computed vibrational spectra for the C=O stretching mode of acetone in water using the Fourier transform of the dipole autocorrelation function (DAF) (blue curve) and that from the cumulant expansion of the QVP1 frequency fluctuation autocorrelation function (red curves), along with the experimental results (black curve).<sup>57</sup> The peak position at 1741 cm<sup>-1</sup> from the QVP1 method represents a solvent-induced red shift of -35 cm<sup>-1</sup>, which may be compared with a solvent effect of -41 cm<sup>-1</sup>, corresponding to a maximum peak position at 1697 cm<sup>-1</sup>. The agreement indicates that the AM1 model used in combined QM/MM simulations can capture the large bulk of solvation effects. In addition, the calculated FWHM (14.8 cm<sup>-1</sup>) is in good accord with the experiment (15.1 cm<sup>-1</sup>).<sup>57,58</sup> On the other hand, the maximum peak position is found at 1414 cm<sup>-1</sup> by Fourier transform of DAF, which is red-shifted by -30 cm<sup>-1</sup> from the corresponding gas-phase value. The AM1 Hamiltonian severely underestimate the carbonyl stretch frequency of acetone by 294 cm<sup>-1</sup> compared with experiment, which is fully translated into the condensed-phase results by direct application of the molecular dipole autocorrelation function. Since the Fourier transform of DAF includes anharmonicity and

captures the same solvent effect as that in the QVP1 calculations, the small difference of  $5\text{ cm}^{-1}$  between the two methods is attributed to nuclear quantum effects. The difference between the QVP1 and DAF results also illustrates the use of the composite approach to effectively correct errors in the low-level QM/MM representation of the absolute vibrational frequency.



**Figure 5.** Experimental (black) and computed vibrational spectra of the carbonyl stretching region of acetone in water. The spectrum from the first-order quantum vibration perturbation (QVP1) calculation employing a composite of the CCSD(T) reference frequency and a QM(AM1)/MM perturbation potential is shown in red, and that from the Fourier transform of the molecular dipole autocorrelation function determined using AM1 directly in QM/MM simulations is given in blue.

#### 4. Conclusions

We have presented a nuclear quantum perturbation (QVP) method for efficiently determining the instantaneous vibrational frequency of a chromophore in molecular dynamics simulations. The QVP approach is a semiclassical approach that combines quantum mechanical treatment of nuclear motions of specific vibrational modes with classical dynamics simulations. The method treats intermolecular interactions as a perturbation to the vibrational Hamiltonian on a predefined reference state. Computational efficiency is achieved as a result of three key ingredients, including (a) the use of potential optimized discrete variable representation (PODVR) of the vibrational wave functions for all levels of interest, (b) the application of perturbation theory to evaluate the energy shifts due to solvent dynamic fluctuations, and (c) the representation of the potential energy surface by a combined QM/MM approach for condensed-phase and macromolecular systems. Furthermore, we found that first-order perturbation is sufficiently accurate for the present HCl-water cluster system, a small but challenging test case due to strong bond-dissociation character associated with the vibrational mode as well as hydrogen bonding interactions. The use of the PODVR representation and perturbation theory to determine the energy shifts avoids the need to solve the vibrational Schrödinger equation. Thus, the computational cost of the QVP method is equivalent to that needed to determine the potential energies at the PODVR points. The use of a combined QM/MM approach incorporates naturally the effects of solvent dynamics on the potential energy surface, which can be systematically improved in accuracy and is computationally efficient. It also avoids the need to develop empirical potential energy surface and offer the accompanying dipole moment surface for every new system. Since time-dependent vibrational frequencies can be determined on the fly in molecular dynamics simulations, the mode-specific linear and 2D-IR spectra can be extracted from the frequency time correlation function. Although the QVP method is validated using the

HCl-water clusters, we emphasize that the approach can easily be extended to macromolecular systems since the perturbation theory calculation is only concerned with one-electron integrals in a combined QM/MM potential. Thus, as long as it is possible to carry out QM/MM simulations at the desired QM level, the QVP1 method can be used to determine on-the-fly vibrational frequencies at the same or better accuracy.

Intra and intermolecular mode coupling can be important, but it is not specifically included in the present QVP method except the effect due to intermolecular interactions in the QM/MM potential energy surface. This is a subject of future research, though one can straightforwardly extend the present single mode approach to two or more coupled modes (as illustrated in the text), making use of the PODVR numerical method. Intramolecular (and intermolecular) mode-coupling can also be treated by using vibrational configuration interaction (VCI) as implemented in the MULTIMODE program, but the computational costs are prohibitive for computation of time-dependent vibrational frequencies. A linear scaling strategy is clearly desired.

To further reduce computational costs, we examined a hybrid, or composite strategy that can yield accurate peak position and line shape. In this scheme, the reference-state vibrational frequency (eq 1) is determined with a highly accurate method only once, but the vibrational frequency shifts at each instantaneous configuration along the MD trajectory are evaluated using the QVP method with a lower-level QM/MM potential. In the HCl-water cluster test cases, we compared the spectral result determined by using CCSD(T)-F12b on the entire system with that from the hybrid strategy with CCSD(T)-F12b reference frequency and M06-2X frequency shift. The agreement is very good, especially considering the tremendous cost-saving. Importantly, the inclusion of nuclear quantum effects, either using the semiclassical (eq 5) or cumulant expansion (eq 6) algorithm, has a large effect on the computed spectra and is found to be in better

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3 agreement with experiment than that obtained by Fourier transform of the classical dipole  
4 autocorrelation function. We found that anharmonicity in the H-Cl stretch is significant and has a  
5 large solvent effects in the relaxation process exhibited in the computed 2D-IR spectra. To  
6 illustrate the general applicability, solvent effects on the carbonyl stretch of acetone in water  
7 were determined using QVP1 with a dual-level approach using the CCSD(T) results as the  
8 reference state coupled with combined QM(AM1)/MM simulations to account for solute-solvent  
9 interactions. The computed solvent-induced spectral shifts is in accord with experiment. The  
10 present QVP method complements other computational approaches, including path integral-  
11 based molecular dynamics, and represents a major improvement over the electrostatics-based  
12 spectroscopic mapping procedures.  
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29 **Supporting Information.** The Supporting Information is available free of charge on the [ACS](#)  
30 [Publications website](#) at DOI:  
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34 The convergent test of HCl stretch vibration within HClH<sub>2</sub>O complex, the perturbation approach  
35 test, ab initio molecular simulation setup, the response function of rephrasing and non-rephrasing  
36 processes are described in the text.  
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