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Simulations of vibrational spectra from classical trajectories: Calibration with *ab initio* force fields

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An algorithm allowing simulating vibrational spectra from classical time-dependent trajectories was applied for infrared absorption, vibrational circular dichroism, Raman, and Raman optical activity of model harmonic systems. The implementation of the theory within the TINKER molecular dynamics (MD) program package was tested with ab initio harmonic force fields in order to determine the feasibility for more extended MD simulations. The results suggest that sufficiently accurate frequencies can be simulated with integration time steps shorter than about 0.5 fs. For a given integration time step, lower vibrational frequencies ($\sim 0-2000 \text{ cm}^{-1}$) could be reproduced with a higher accuracy than higher-frequency vibrational modes (e.g., O-H and C-H stretching). In principle, the algorithm also provides correct intensities for ideal systems. In applied simulations, however, the intensity profiles are affected by an unrealistic energy distribution between normal modes and a slow energy relaxation. Additionally, the energy fluctuations may cause weakening of the intensities on average. For *ab initio* force fields, these obstacles could be overcome by an arbitrary normal mode energy correction. For general MD simulations, averaging of many shorter MD trajectories started with randomly distributed atomic velocities provided the best spectral shapes. α -pinene, D-gluconic acid, formaldehyde dimer, and the acetylprolineamide molecule were used in the tests. © 2007 American Institute of Physics. [DOI: 10.1063/1.2756837]

I. INTRODUCTION

Computation of spectroscopic properties via the classical approximations, particularly those based on the autocorrelation functions and the Fourier transformation of timedependent properties, have been extensively used for nuclear magnetic resonance,¹ Raman, infrared, and vibrational circular dichroism spectra in the past.^{2–4} The possibility to get vibrational spectra from classical trajectories was also investigated for anharmonic systems.^{3,5} These techniques partially receded from the mainstream molecular dynamics computations as the *ab initio* techniques became broadly available.⁶ Lately a renewed interest in the generation of the spectra via Fourier transformations appeared in connection with combined quantum mechanics-molecular mechanics (QM/MM) methods.^{7,8} Also, the interpretations required in numerous new spectroscopic techniques, such as the vibrational circular dichroism (VCD) or the two-dimensional infrared spectroscopy, are quite complex and they can often conveniently utilize variously modified Fourier techniques.^{9,10} Regularly, ab initio parameters are transferred, simplified, and used in combination with classical MD trajectories.¹¹ These generations of the spectra can be found not only in classical but also in *ab initio* molecular dynamics studies.¹²

In spite of the frequent applications, many ad hoc theo-

retical assumptions are made in the classical generations of the spectra, and their precision is seldom checked against reliable data. Therefore, in this work, we want to investigate the accuracy with which the vibrational optical activity spectra can be obtained from time-dependent variables of harmonic systems. Special attention is paid to the optical activity, and the classical approximation is newly applied to the generation of the Raman optical activity (ROA) spectra. The optical activity differential techniques, including ROA or the VCD, are sensitive to different interactions of molecules with left- and right-circularly polarized light, and as such, they bring enhanced information about the molecular structure.¹³ Advanced spectral simulation techniques, involving the time-frequency transformations, can thus substantially contribute to structural studies of complex molecular systems.

As various authors approach the quasiclassical approximation differently, we will review a self-standing theory for the harmonic systems based on an approximation of the quantum uncertainty by temperature averaging. For absorption and VCD intensities, we will obtain the same formulas as previously found by Abbate *et al.*⁴ The method will be tested with *ab initio* harmonic force field calculated for model optically active systems. The molecules were selected rather arbitrarily to represent a variety of molecular types: the gluconic acid, α -pinene, two formaldehyde molecules as

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FIG. 1. Model molecules used in the simulations: (A) D-gluconic acid, (B) α -pinene, (C) formaldehyde dimer, and (D) acetylprolineamide.



II. THEORY

A. Classical and quantum averages

For a molecule, the vibrational harmonic Hamiltonian is given by

$$H = \frac{1}{2} \sum_{j=1,...,M} (P_j^2 + \omega_j^2 Q_j^2),$$
(1)

where Q_j , P_j , and ω_j are the coordinate, momentum, and frequency of the normal mode *j*, respectively. The respective quantum mechanics and classical coordinate root averages are¹⁴

$$\langle Q_j^2 \rangle_{\rm QM} = \langle 0 | Q_j^2 | 0 \rangle = \frac{\hbar}{2\omega_j},$$
 (2a)

$$\langle Q_j^2 \rangle_{\text{classical}} = \frac{kT}{\omega_j^2},$$
 (2b)

where \hbar is the Planck constant, k the Boltzmann constant, T the temperature, and $|0\rangle$ is the molecular ground state. Thus the quantum integral can be obtained from the classical average as

TABLE I. Overview of the simulated systems.

| | Force field | Solvent |
|--------------------|------------------|------------------------------|
| D-gluconic acid | BPW91/6-311++G** | CPCM dielectric ^a |
| α-pinene | B3LYP/6-31G** | Vacuum |
| Formaldehyde dimer | HF/6-31G** | Vacuum |
| Acetylprolineamide | Amber99 | Explicit TIP3P ^b |

^aReference 37. ^bReference 35. J. Chem. Phys. 127, 084502 (2007)

 $\langle 0|Q_j^2|0\rangle = \frac{\hbar\omega_i}{2kT} \langle Q_j^2 \rangle_{\text{classical}}.$ (3) For the harmonic oscillator, we can express also the transi-

tion coordinate integral to the first excited state $|0\rangle$ as¹⁵ (0) 0 |1) $\sqrt{\hbar}$ $\sqrt{000}$ (4)

$$\langle 0|Q_j|1\rangle = \sqrt{\frac{n}{2\omega_j}} = \sqrt{\langle 0|Q_j^2|0\rangle}.$$
(4)

By combining Eqs. (3) and (4), we obtain the quantum transitional integral from the classical trajectories

$$\langle 0|Q_j|1\rangle = \sqrt{\frac{\hbar\omega_i}{2kT}} \langle Q_j^2 \rangle_{\text{classical}}.$$
 (5a)

An analogous derivation for the vibrational momenta P_j leads to

$$\langle 0|P_j|1\rangle = \sqrt{\frac{\hbar\omega_i}{2kT}} \langle P_j^2 \rangle_{\text{classical}}.$$
 (5b)

B. Absorption and circular dichroism intensities

In resolved spectra, the absorption peak area of a transition $0 \rightarrow 1$ is proportional to the dipole strength, $D = \langle 0 | \boldsymbol{\mu} | 1 \rangle \cdot \langle 1 | \boldsymbol{\mu} | 0 \rangle$. Similarly, the circular dichroic peak area is proportional to the rotational strength, $R = \text{Im}\langle 0 | \boldsymbol{\mu} | 1 \rangle \cdot \langle 1 | \mathbf{m} | 0 \rangle$.^{16,17} The symbols $\boldsymbol{\mu}$ and \mathbf{m} denote the electronic and magnetic dipole moments. The strengths for each fundamental transition $(0 \rightarrow 1)$ associated with a normal mode *j* can be obtained with the aid of Eqs. (5a) and (5b) as

$$D = \mathbf{p}_{j} \cdot \mathbf{p}_{j} \frac{\hbar \omega_{j}}{2kT} \langle Q_{j}^{2} \rangle_{\text{classical}},$$

$$R = \mathbf{p}_{j} \cdot \mathbf{m}_{j} \frac{\hbar \omega_{j}}{2kT} \sqrt{\langle Q_{j}^{2} \rangle_{\text{classical}} \langle P_{j}^{2} \rangle_{\text{classical}}},$$
(6)

where the derivatives $\mathbf{p}_j = \partial \boldsymbol{\mu} / \partial Q_j$ and $\mathbf{m}_j = \partial \mathbf{m} / \partial P_j$ are often referred to as the polar and axial tensors, respectively. Note

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that Eq. (6) is valid for harmonic systems exactly, without any approximation.

In the case of harmonic motion, the electric moment is proportional to the coordinate, and the magnetic dipole is proportional to the momentum,

$$\boldsymbol{\mu}(t) = \frac{1}{2} \sum_{j} \mathbf{p}_{j} Q_{j0} (e^{i\omega_{j}t} + e^{-i\omega_{j}t}),$$

$$\mathbf{m}(t) = \frac{i}{2} \sum_{j} \omega_{j} \mathbf{m}_{j} Q_{j0} (e^{i\omega_{j}t} - e^{-i\omega_{j}t}).$$
(7)

Let us define the Fourier pictures of the dipoles as

$$\boldsymbol{\mu}(\omega) = \int_{t_0}^{t} \boldsymbol{\mu}(\tau) e^{i\omega\tau} d\tau$$

$$= \frac{1}{2i} \mathbf{p}_j Q_{j0} \left(\frac{e^{i(\omega_j + \omega)t} - e^{i(\omega_j + \omega)t_0}}{(\omega_j + \omega)} + \frac{e^{i(\omega - \omega_j)t} - e^{i(\omega - \omega_j)t_0}}{(\omega - \omega_j)} \right),$$

$$\mathbf{m}(\omega) = \int_{t_0}^{t} \mathbf{m}(\tau) e^{i\omega\tau} d\tau$$
(8)

$$= \frac{1}{2}\omega_{j}\mathbf{m}_{j}Q_{j0}\left(\frac{e^{i(\omega_{j}+\omega)t} - e^{i(\omega_{j}+\omega)t_{0}}}{\omega_{j}+\omega} - \frac{e^{i(\omega-\omega_{j})t} - e^{i(\omega-\omega_{j})t_{0}}}{\omega-\omega_{j}}\right),$$

and the absorption (ε) and circular dichroic ($\Delta \varepsilon$) spectra as

$$\varepsilon(\omega) = A \boldsymbol{\mu}^{*}(\omega) \cdot \boldsymbol{\mu}(\omega),$$

$$\Delta \varepsilon(\omega) = \operatorname{Im} B(\boldsymbol{\mu}^{*}(\omega) \cdot \mathbf{m}(\omega) - \boldsymbol{\mu}(\omega) \cdot \mathbf{m}^{*}(\omega)),$$
(9)

where A and B are real constants. The spectra should oblige the usual spectroscopic identities¹⁸

$$R = 2.296 \cdot 10^{-3} \int_{-\infty}^{\infty} \Delta \varepsilon(\omega) \frac{d\omega}{\omega},$$

$$D = 9.184 \cdot 10^{-3} \int_{-\infty}^{\infty} \varepsilon(\omega) \frac{d\omega}{\omega},$$
(10)

where *D* and *R* are in debye² (1 D=10⁻¹⁸ esu cm=3.335 46 $\times 10^{-30}$ C m), and ε and $\Delta \varepsilon$ in L/mol/cm. Performing the integration of equations for $\omega \rightarrow \omega_j$, we get

$$\int_{-\infty}^{\infty} \varepsilon(\omega) \frac{d\omega}{\omega} = \frac{A}{2\omega_j} \mathbf{p}_j \cdot \mathbf{p}_j Q_{j0}^2 \pi(t - t_0),$$

$$\int_{-\infty}^{\infty} \Delta \varepsilon(\omega) \frac{d\omega}{\omega} = B \mathbf{p}_j \cdot \mathbf{m}_j Q_{j0}^2 \pi(t - t_0).$$
(11)

The proportionality constants can be obtained by comparison

of Eqs. (10) and (11), and by realizing that $\langle Q_j^2 \rangle_{\text{classical}} = Q_{j0}^2 \langle \cos^2(\omega_j t) \rangle = Q_{j0}^2 / 2$ and $\langle P_j^2 \rangle_{\text{classical}} = \omega_j^2 Q_{j0}^2 / 2$, as

$$A = \frac{\hbar \omega_j^2}{2(9.184 \times 10^{-3})\pi(t - t_0)kT},$$

$$B = \frac{\hbar \omega_j}{4(2.296 \times 10^{-3})\pi(t - t_0)kT}.$$
(12)

C. Transition dipole coupling

The transition dipole coupling (TDC) is an important mechanism for inducing molecular optical activity, particularly for circular dichroism.^{16,19,20} Let us discuss the TDC behavior for the classical case. Consider two oscillating chromophores with time-dependent dipole moments, $\boldsymbol{\mu}_i(t) = \boldsymbol{\mu}_{0i}Q_i(t)$, i=1,2. The interaction potential is restricted to the dipole-dipole interaction,

$$V_{12} = -\boldsymbol{\mu}_1 \cdot \mathbf{T}_{12} \cdot \boldsymbol{\mu}_2 = -\boldsymbol{\mu}_{01} \cdot \mathbf{T}_{12} \cdot \boldsymbol{\mu}_{02} Q_1 Q_2 = 2\nu Q_1 Q_2,$$
(13)

where

$$\mathbf{T}_{12} = \frac{1}{4\pi\varepsilon_0} \frac{3\mathbf{r}_{12}\mathbf{r}_{12} - \mathbf{1}r_{12}^2}{r_{12}^5},$$

and \mathbf{r}_{12} is the distance vector. The Hamiltonian of this system is

$$H = E_{\rm kin} + \frac{\omega_1^2}{2}Q_1^2 + \frac{\omega_2^2}{2}Q_2^2 + 2\nu Q_1 Q_2.$$
(14)

For a degenerate case with $\omega_1 = \omega_2 = \omega_0$, the Hamiltonian can be transformed to a sum of two oscillators with coordinates $Q_+ = (Q_1 + Q_2)/\sqrt{2}$ and $Q_- = (Q_1 - Q_2)/\sqrt{2}$, and frequencies $\omega_{\pm}^2 = \omega_0^2 \pm 2\nu$. In general, the new oscillators may oscillate with a phase difference φ , $Q_+ = Q_{+0} \cos(\omega_+ t)$ and $Q_- = Q_{-0} \cos(\omega_- t + \varphi)$. For long time integrations, the frequencydependent dipole moment

$$\boldsymbol{\mu}(\boldsymbol{\omega}) = \int_0^t (\boldsymbol{\mu}_{01} Q_1(\tau) + \boldsymbol{\mu}_{02} Q_2(\tau)) e^{i\boldsymbol{\omega}\tau} d\tau$$

becomes

$$\boldsymbol{\mu}(\omega) = \boldsymbol{\mu}_{+} Q_{+0}(t - t_0)/2 \quad \text{for } \omega_{+} = \omega,$$

$$\boldsymbol{\mu}(\omega) = \boldsymbol{\mu}_{-} Q_{-0}(t - t_0)/2 \quad \text{for } \omega_{-} = \omega,$$
(15)

where $\boldsymbol{\mu}_{\pm} = (\boldsymbol{\mu}_{01} \pm \boldsymbol{\mu}_{02})/\sqrt{2}$. If the origin is placed at the first chromophore, the total magnetic moment becomes $\mathbf{m}(t) = (1/2)\mathbf{r}_{12} \times \boldsymbol{\mu}_2$, which gives

$$\mathbf{m}(\omega) = -\frac{i}{4\sqrt{2}}\mathbf{r}_{12} \times \boldsymbol{\mu}_{02}\omega_{+}Q_{+0}(t-t_{0}) \quad (\omega_{+} = \omega)$$
$$= \frac{i}{4\sqrt{2}}\mathbf{r}_{12} \times \boldsymbol{\mu}_{02}\omega_{-}Q_{-0}(t-t_{0})\cos(\varphi) \quad (\omega_{-} = \omega).$$
(16)

Inserting Eqs. (15) and (16) into Eq. (9) we get

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$$\Delta \varepsilon(\omega) = -\frac{\omega}{8} B \boldsymbol{\mu}_{01} \cdot \mathbf{r}_{12} \times \boldsymbol{\mu}_{02} Q_{+0}^2 (t - t_0)^2 \quad \text{for } \omega_+ = \omega$$
(17)
$$\Delta \varepsilon(\omega) = \frac{\omega}{8} B \boldsymbol{\mu}_{01} \cdot \mathbf{r}_{12} \times \boldsymbol{\mu}_{02} Q_{-0}^2 (t - t_0)^2 \quad \text{for } \omega_- = \omega.$$

The classical case thus provides two VCD bands of the same magnitude (because $\omega_{-} \sim \omega_{+}$) and opposite signs, as was obtained also in the quantum TDC model.^{16,19}

D. Raman and Raman optical activities

The Raman and ROA intensities are dependent on the derivatives of the electric dipole–electric dipole (α), electric dipole–electric quadrupole (**A**), and electric dipole–magnetic dipole (**G**') polarizabilities. The common backscattering (180°) nonpolarized Raman and ROA intensities simulated in this study are ^{16,21,22}

$$\begin{split} I_{R} + I_{L} &= 6K(7\alpha_{\alpha\beta}^{j}\alpha_{\alpha\beta}^{j} + \alpha_{\alpha\alpha}^{j}\alpha_{\beta\beta}^{j})|\langle 0|Q_{j}|1\rangle|^{2}, \\ I_{R} - I_{L} &= (48K/c)[3\alpha_{\alpha\beta}^{j}G_{\alpha\beta}^{\prime j} - \alpha_{\alpha\alpha}^{j}G_{\beta\beta}^{\prime j} \\ &+ \omega\varepsilon_{\alpha\beta\gamma}\alpha_{\alpha\beta}^{j}A_{\beta,\gamma\delta}^{j}/3]|\langle 0|Q_{j}|1\rangle|^{2}, \end{split}$$
(18)

where the normal mode derivatives were abbreviated by the upper index (e.g., $\alpha_{\alpha\beta}^{j} = \partial \alpha_{\alpha\beta} / \partial Q_{j}$), and ω is the excitation frequency. Therefore, we can use Eq. (5a) for the classical analog of the transition moment $\langle 0|Q_{j}|1\rangle$ and obtain the Raman and ROA spectra from frequency-dependent polarizabilities $[\alpha(\omega) = \int_{t_0}^{t} \alpha(\tau) e^{i\omega\tau} d\tau$, etc.], similarly as for the absorption intensities. Temperature-corrected intensity profiles can be obtained by considering the Boltzmann statistics. The absolute differential scattering cross section²³ is then

$$\partial \sigma_i / \partial \Omega = k \omega^4 \{ \omega_j [1 - \exp(-\hbar \omega / (k_B T))] \}^{-1} I, \qquad (19)$$

where k_B is the Boltzmann constant.

E. Implementation

The *ab initio* harmonic force fields (second energy derivatives with respect to the nuclear coordinates) were computed for equilibrium geometries with the GAUSSIAN program.²⁴ Then the field was imported into the TINKER software package²⁵ and used in place of usual MD fields within classical simulations. Similarly, the dipole and polarizability derivatives were computed with GAUSSIAN and used for the spectra generations in an adapted version of TINKER.

The Fourier accumulations were obtained after a *per* partes integral transformation. For the electric dipole, for example, the integral (8) becomes $\int_{t_0}^t \boldsymbol{\mu}(\tau)e^{i\omega\tau}d\tau = \int_{t_0}^t (i/\omega) \times (\partial \boldsymbol{\mu}(\tau)/\partial \tau)e^{i\omega\tau}d\tau$. The dipole and polarizability time derivatives were obtained from the *ab initio* Cartesian derivatives as

$$\frac{\partial \boldsymbol{\mu}(\tau)}{\partial \tau} = \sum_{\lambda,\alpha} \frac{\partial \boldsymbol{\mu}(\tau)}{\partial r_{\lambda\alpha}} \frac{\partial r_{\lambda\alpha}(\tau)}{\partial \tau} = \sum_{\lambda,\alpha} \mathbf{p}_{\lambda\alpha} \dot{r}_{\lambda\alpha}(\tau),$$
$$\frac{\partial \mathbf{m}(\tau)}{\partial \tau} = \sum_{\lambda,\alpha} \frac{\partial \mathbf{m}(\tau)}{\partial \dot{r}_{\lambda\alpha}} \frac{\partial \dot{r}_{\lambda\alpha}(\tau)}{\partial \tau} = \sum_{\lambda,\alpha} \mathbf{m}_{\lambda\alpha} \ddot{r}_{\lambda\alpha}(\tau),$$

$$\frac{\partial \boldsymbol{\alpha}(\tau)}{\partial \tau} = \sum_{\lambda,\alpha} \frac{\partial \boldsymbol{\alpha}(\tau)}{\partial r_{\lambda\alpha}} \frac{\partial r_{\lambda\alpha}(\tau)}{\partial \tau} = \sum_{\lambda,\alpha} \boldsymbol{\alpha}_{\lambda\alpha} \dot{r}_{\lambda\alpha}(\tau), \quad (20)$$

and so on. A fully empirical model was implemented as an alternative, based on atomic partial charges²⁶ obtained from the AMBER force field²⁷ and isotropic atomic polarizabilities.²¹ The empirical polarizability calculations were used for testing purposes only and are not shown. In order to avoid uncontrollable narrowing of spectral lines during longer integration times, accumulated spectra were convoluted with Lorentzian functions each n steps ($n \sim 100$). The resolution Δ was set to 5 cm⁻¹ according to the usual liquid-phase experiment. For this bandwidth, a minimum integration time of a few picoseconds ($T \sim 1/\Delta$) is needed.

F. Normal mode energy redistribution

In MD simulations, the vibrational normal modes are normally unknown and their indirect extraction is a rather difficult procedure.²⁸ For our test systems, however, we could construct the Cartesian-normal mode transformation matrix **S** and obtain the normal mode frequencies $\{\omega_j\}$ directly, by diagonalization of the harmonic force field. The mode energies ε_i could be calculated from the Cartesian atomic velocities, ν_{λ} , and the deviations from the equilibrium positions, Δx_{λ} , as¹⁵

$$\varepsilon_{i} = \frac{1}{2} (\dot{Q}_{i}^{2} + \omega_{i}^{2} Q_{i}^{2}) = \frac{1}{2} \left(\sum_{\lambda,\lambda'} m_{\lambda} S_{i,\lambda} \nu_{\lambda} m_{\lambda'} S_{i,\lambda'} \nu_{\lambda'} + \omega_{i}^{2} \sum_{\lambda,\lambda'} m_{\lambda} S_{i,\lambda} \Delta x_{\lambda} m_{\lambda'} S_{i,\lambda'} \Delta x_{\lambda'} \right).$$

$$(21)$$

In an equilibrium, all average energies ε_i should oscillate around $kT = \overline{\varepsilon}$. This was difficult to achieve in normal MD simulations within a reasonable time. Therefore, we experimented with a coupling parameter α , enforcing the equilibrium already at shorter MD times. Let us look for corrected velocities $\nu'_{\lambda} = \nu_{\lambda} + \Delta \nu_{\lambda}$, that would bring the new mode energies closer to the average,

$$\varepsilon_{i}' = \varepsilon_{i} + \alpha(\overline{\varepsilon} - \varepsilon_{i}) \approx \frac{1}{2} \left(\dot{Q}_{i}^{2} + 2\sum_{\lambda} \dot{Q}_{i} m_{\lambda} S_{i,\lambda} \Delta \nu_{\lambda} + \omega_{i}^{2} Q_{i}^{2} \right).$$
(22)

Comparing Eqs. (22) and (21), and introducing matrix $B_{i,\lambda} = \dot{Q}_i m_\lambda S_{i,\lambda}$, we obtain a linear equation for the corrections, $\alpha(\bar{\varepsilon} - \varepsilon_i) = \Sigma_\lambda B_{i,\lambda} \Delta \nu_\lambda$. After multiplying by $B_{i,\mu}$ and summing over *i*, we get $\Sigma_{i=1,...,M} B_{i,\mu} \alpha(\bar{\varepsilon} - \varepsilon_i)$ $= \Sigma_{i=1,...,M} B_{i,\mu} \Sigma_{\lambda=1,...,N} B_{i,\lambda} \Delta \nu_\lambda$, which, finally, provides the corrections

$$\Delta \mathbf{v} = \mathbf{C}^{-1} \mathbf{V},\tag{23}$$

where $C_{\mu\lambda} = \sum_i B_{i,\mu} B_{i,\lambda}$ and $V_{\mu} = \sum_i B_{i,\mu} \alpha(\bar{\epsilon} - \epsilon_i)$. For M = N, the matrix **C** might be singular as the translational and rotational modes are not well defined. Therefore, the velocity corrections were applied iteratively for *x*, *y*, and *z* coordinates, for which M > N.

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FIG. 2. Dependence of the O–H (top, *ab initio* limit $\omega_0=3268 \text{ cm}^{-1}$) and C==O stretching (bottom, ω_0 = 1552 cm⁻¹) band frequencies of gluconic acid on the MD integration time step. Parts of the absorption spectra (intensities are scaled arbitrarily) containing the bands are plotted at the right hand side for selected steps. The BPW91/CPCM(H₂O)/6-311++G^{**} harmonic force field was used for the simulations.

III. RESULT AND DISCUSSION

A. Time-step dependence

The MD integration time step is significantly limited by the energy-conservation and stability criteria. Longer steps are more efficient for sampling of the conformational space, but it can be achieved with special methods only.²⁹ On the other hand, exact spectral simulations require rather shorter simulation times, as is apparent from Fig. 2, where the dependence of the center band frequency for the C=O stretching and O-H stretching motions of D-gluconic acid on the time step is plotted. The BPW91/6-311++ G^{**} /CPCM force field was used in 50 ps MD simulations (temperature of 298 K and pressure of 1 atm). Clearly, the MD default²⁵ step of 1 fs is already introducing a notable error of about 4 cm⁻¹ for the medium-frequency C=O stretching band. An unacceptable error of 50 cm⁻¹ appears at the higher-frequency O-H stretching band. A step of 2 fs, although still providing numerically stable MD trajectories, increases the errors of the C=O and O-H bands to 24 and 250 cm⁻¹ (!), respectively. Fortunately, the frequency inaccuracy quickly decreases for steps below 0.5 fs. The frequency convergence can also be followed at the right hand side of Fig. 2, where parts of the absorption spectrum are simulated for selected steps. For the shortest steps (~ 0.1 fs), the central band frequencies obtained from the classical trajectories agree within the numerical accuracy (about $\sim 0.1 \text{ cm}^{-1}$), with the normal mode frequencies obtained directly by the force field diagonalization. The error clearly stems from the finite-step Verlet³⁰ integration algorithm, and the same dependence was also observed for the Beeman modification of the integration.³¹ For practical spectral simulations, however, such need of shorter steps is no serious obstacle because usable spectra can be accumulated within a few picoseconds.

B. Intensity distribution

The simulation of spectral intensities is more difficult than frequency simulations. The primary reason is uneven energy distribution among the vibrational degrees of freedom. At the beginning of MD simulations, the atomic velocities are distributed randomly among atoms, but the distribution of the energy among the normal modes is far from equilibrium $\overline{\varepsilon} = kT$. For harmonic systems, the normal modes do not interact. In applied simulations, the equilibrium is achieved after a very long time. A similar behavior, however, was observed for more general (anharmonic) MD force fields of TINKER and even for a solvated molecule in a box of solvent. Thus the coupling³² of Berendsen *et al.* applied to a thermal bath apparently does not guarantee an equal energy redistribution among individual vibrations on the time scale of the simulations.

Typical developments of the energy distribution are shown in Fig. 3 for α -pinene harmonic force field. The individual mode energies (Eq. (21)) could be traced with the aid of the Cartesian-normal mode transformation matrix obtained by the field diagonalization.¹⁵ The plain MD simulation (at the top of the figure) provides energies converging slowly to the right limit (kT, marked by the black horizontalline for T=298 K). However, several modes are still inactive even after 200 000 MD steps. On the other hand, two "hyperactive" modes (degenerate C-H bending in the middle of the mid IR region) accumulate the energy much more quickly than the others, and they do not stabilize within the captured time scale. Nevertheless, as documented in the middle and lower panel of Fig. 3, the normal mode energies can be stabilized by the arbitrary velocity correction. For larger value of the α parameter (0.04 in the bottom panel as compared to $\alpha = 0.01$ in the middle), equilibrium is established more quickly. However, because of the approximations involved, the average mode values often deviate from the Boltzmann kT target. As can be seen on the right hand side of Fig. 3, such energy distribution differences have a significant influence on the spectral intensities. The IR absorption and VCD and Raman intensities (not shown) behaved similarly as the ROA spectra selected as an example.

An alternative view of the mode intensity and energy time dependence can be provided by a partial Fourier transformation of the molecular dipole shown in Fig. 4. For this purpose, the intensity was obtained as $I(\omega,t) = |u_x|^2 + |u_y|^2$ $+|u_z|^2$, where $u_i = \int_0^t \mu_i(\tau) \exp[-(t-\tau)^2/\Delta^2] d\tau$ are the partially transformed dipole components with the Gaussian time window of $\Delta = 3$ ps. Clearly, a qualitatively similar pic-



FIG. 3. (Color) Evolution of the instantaneous normal mode energies of α -pinene for three values of the equilibrium coupling parameter (α =0, 0.01, and 0.04). The ROA intensities collected during each run are plotted on the right hand side.

ture is obtained for the partially transformed intensities as for the energy distributions in Fig. 3: for a plain MD simulation (left hand side of Fig. 4), the peak intensities vary during the simulation time, while for the simulation with the energy correction (right hand side), the band intensities are stable except for short-time oscillations.

C. Spectral averaging

Although the arbitrary energy correction could reasonably well stabilize the spectra, it is not fit for general MD simulation, where the second energy derivatives are not known or cannot be directly diagonalized. Fortunately, averaging of sufficient number of independent MD trajectories provides well-stabilized spectral intensities. For the *ab initio* force fields, the obtained spectral patterns are very close to the quantum chemical benchmark. The stabilization of the intensities by averaging is documented in Fig. 5 for inte-



FIG. 4. (Color) Visualization of the evolution of the absorption intensities via a partial Fourier transformation. The intensities are plotted in the logarithmic scale for α -pinene. In the plain MD simulation (left), the intensities change on a longer time scale, while with the normal mode energy stabilization (right) average intensities are more stable.



FIG. 5. Integrated absorption α -pinene intensities: top, plain MD simulation; bottom, simulation with random energy redistribution, each 100 ps. Low (0–2000 cm⁻¹) and high (2000–4000 cm⁻¹) frequency regions were integrated separately.

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FIG. 6. The VCD, ROA, absorption, and Raman α -pinene spectra obtained from (a) one, (b) 10, and (c) 100 MD trajectories, as compared to the *ab initio* result (d). One MD simulation comprised 20 000 steps of 1 fs, T = 300 K.

grated IR absorption of α -pinene. The intensities obtained by the continuous MD run (upper panel of the figure) stabilize relatively slowly and do not provide realistic spectral shapes. On the other hand, averaging of shorter MD runs with random redistributions of atomic energies (the lower panel) provides much quicker convergence. The latter method also leads to a better relative intensity pattern. The absolute intensity scale [fulfilling, for example, Eq. (11)] could be reproduced only approximately, because of the numerical approximations and deviations from the ideal harmonic trajectories. Nevertheless, we find the absolute intensity error acceptable from the point of practical simulations, where the system properties depend mostly on relative peak intensities (and signs, in case of optical activity).

Individual band intensities can be seen in Fig. 6, where simulated VCD, ir absorption, ROA, and Raman spectra of α -pinene are compared to the *ab initio* results. The single run intensity distribution (traces "a" in the figure) is rather unrealistic. The VCD and ROA vibrational optical activity spectra are hampered not only by incorrect relative intensity ratios, but also by wrong signs of many peaks. These errors, however, are mostly corrected in the ten-spectra averages Fig. 6(b); the averaging of 100 MD runs Fig. 6(c) further improves the spectral profiles, including signs and relative intensities of weaker bands. The absolute y scales are less realistic and, as pointed out above, at this point we did not attempt to reproduce the benchmark qualitatively. Instead, the spectra were uniformly scaled for comparison. However, the circular intensity difference ratios (VCD/absorption, ROA/Raman) were reproduced correctly by the classical method. The spectra appear stable throughout the entire frequency part captured in Fig. 6, and a similar behavior was observed also for higher-frequency C-H stretching bands (not shown).

D. Two-chromophore interaction

To estimate the performance of the time-dependent method for the transition dipole coupling mechanism,^{16,18} we



FIG. 7. The VCD ($\Delta \varepsilon$) and absorption (ε) signals of the C=O stretching band for the two formaldehyde (2CH₂CO) molecules. Comparison of the MD (left) and *ab initio* (right) simulations.

chose the idealized system composed of two formaldehyde molecules separated by 2, 2.5, 3.5, and 5 Å (Fig. 1). The torsion angle $O=C\cdots C=O$ was kept at 45°. The C=O stretching formaldehyde vibration was selected as an example of a well-defined relatively localized dipolar chromophore. As can be seen in Fig. 7, where the *ab initio* and MD spectra are compared, the time-dependent MD simulation is able to reproduce the typical TDC spectral pattern.^{19,20} At the shortest distance of 2 Å, the equal sign scheme breaks down as the dipolar interactions cease to dominate and the VCD couplet is strongly negatively biased. For the larger distances, however, the splitting is given by the dipolar term. Therefore the VCD signal becomes more conservative and the energy separation quickly decreases.

Finally, the acetylprolineamide molecule in the aqueous environment was chosen as a less abstract example. Experimental spectra of this system were analyzed and reproduced faithfully with advanced combined MM/QM models in the past.^{7,9} In this study, the IR absorption and VCD spectra were simulated with the fixed partial charge model^{26,33} using the TINKER atomic charges. Such a simulation might not provide realistic spectral intensities,³³ but we still use it in order to estimate the general behavior and the geometry dependence of simulated spectra. Particularly, we concentrate on the signal from the two carboxyl groups that form a system of two chromophores coupled, in this case, mostly by a non-electrostatic through-bonds interaction.

The spectra were collected during a 1 ns MD run, where various acetylprolineamide conformers were placed in a cubic water box (18.62 Å a side). The ψ angle (Fig. 1) was constrained via a penalty potential function and allowed to vary slightly around the desired value ($\sim \pm 5^{\circ}$). The AM-BER99 (Ref. 34) force field [with the TIP3P (Ref. 35) water parameters] was used at the temperature of 298 K, pressure of 1 atmosphere, and the integration time step set to 0.5 fs. One hundred spectra were averaged during each simulation. In order to speed up the spectral accumulation, only the solute atom contribution to the electric and magnetic dipoles was collected in the Fourier transformation. If all atoms in the box were allowed to contribute, the simulation would



FIG. 8. The VCD (top) and absorption (bottom) spectra of the acetylproline Ac-Pro-NH₂ molecule in a water box obtained for six torsional ψ angles. Spectra of natural (A) and N-deuterated (B, in heavy water) systems are compared.

have to be much longer. The acetylprolineamide signal would be difficult to detect in strong water background. In fact, this feature of the simulations reminds one of the problems that can be encountered in experiment.

Nevertheless, as can be seen in Fig. 8, the solute provides a smooth signal which is dependent on molecular geometry. In natural (protonated, left part of Fig. 8) peptide, the absorption spectra are dominated by the NH₂ bending motion at ~1825 cm⁻¹. The ND₂ bands, however, shift out of the plotted region and only the carbonyl stretching bands $(\sim 1650 - 1770 \text{ cm}^{-1})$ remain in the deuterated system (simulated with D_2O , right hand side of Fig. 8). It is somewhat surprising that the geometry dependence of the carbonyl VCD is not the same for natural and deuterated cases, differing within a transitional region for $\psi = 270^{\circ}$, 330°, and 30°. An analysis of the MD results did not indicate any significant geometry changes under the isotopic substitution. Nevertheless, such a profound effect of the deuteration was observed for the carbonyl stretch experimentally: a single-couplet VCD pattern of α -helices often splits to a W-shaped pattern in heavy water.³⁶

IV. CONCLUSION

The simulation of the vibrational spectra based on the classical trajectories was implemented and analyzed for harmonic systems within an adaptation of the TINKER software. The results confirmed the possibility of obtaining very accurate harmonic frequencies with this method, albeit shorter integration steps have to be used than those used in common MD simulations. In practical simulations, spectral intensities faithfully mimicked the *ab initio* benchmark only when many spectra collected in shorter time intervals were averaged, in order to ensure correct energy distribution among the normal modes. By this method, the transition dipole VCD coupling pattern could be reproduced as well. The computation with the hydrated acetylprolineamide molecule suggests that obtained results are quite general and that the

method can be adapted for biomolecular conformational studies when accurate force fields become available.

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