Nonequilibrium molecular dynamics simulation of the energy transport through a peptide helix

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Recent progress in transient infrared spectroscopy has made it possible to monitor the transient flow of vibrational energy along a peptide helix [V. Botan et al., Proc. Natl. Acad. Sci. U.S.A. 104, 12749 (2007)]. To provide a theoretical description of these experiments, extensive nonequilibrium molecular dynamics simulations of the photoinduced energy transport in a photoswitchable Aib peptide are performed. By calculating the response of the molecule caused by its excitation via optical and infrared pulses as well as temperature jump and stationary heating, it is shown that these methods are equivalent in that they provide approximately the same molecular energy transfer times. The resulting thermal diffusivity of 10 Å² ps⁻¹ qualitatively agrees with the results of previous normal mode calculations for proteins and with experimental bulk values (e.g., 14 Å² ps⁻¹ for water). To compare to experiment, a new way of approximating the measured signals is suggested which leads to an improved agreement with the experimental results and explains previous discrepancies. To elucidate the mechanism of energy transfer, modifications to the molecular dynamics force field are introduced, which reveal that the energy transfer occurs mainly through the peptide backbone and depends surprisingly little on the force field parametrization. Employing a harmonic model, quantum-mechanical effects are estimated to moderately (about a factor of 2) speed up the energy transport along the peptide. © 2010 American Institute of Physics. [doi:10.1063/1.3284742]

I. INTRODUCTION

The transport of vibrational energy in molecular systems plays an important role in the operation of mechanical and electronic machines.¹ In order to avoid overheating, for example, molecular electronic devices as well as photoproteins, there is a need to dissipate excess energy on very short time and length scales.²,³ Furthermore, proteins and nucleic acids transport energy through specific pathways to function as molecular machines.⁴–⁷ On the theoretical side, biomolecular energy flow has been described by harmonic theories⁸–¹⁴ and by equilibrium and nonequilibrium molecular dynamics (MD) simulations.⁴–⁷,¹⁵–²³ These calculations have revealed that the transport of vibrational energy in biomolecules may be highly specific and anisotropic. On the experimental side, several recent works exist that attempt to unravel the mechanism of energy transport on a molecular level, including the study of bridged azulene-anthracene compounds,²⁴ small molecules in solution,²⁵ single amino acids,²⁶ long-chain hydrocarbon molecules,²⁷ reverse micelles,²⁸ and heme proteins.²⁹–³²

In a series of recent papers, Hamm and co-workers³³–³⁸ studied the photoinduced energy transport through a short peptide ₃₁₀-helix, see Fig. 1. Employing either ultraviolet (UV) excitation via a synthetically attached azobenzene moiety or direct pumping of a localized infrared (IR) vibration, they measured the transient flow of vibrational energy by employing C=O probes at various distances from the heat source as local thermometers.³⁹ Interestingly, it was found that the peptide helix appears not to be a particularly good conductor of vibrational energy. Its measured heat diffusivity of 2 Å² ps⁻¹ is significantly smaller than values obtained for bulk materials (10–20 Å² ps⁻¹) and only slightly exceeds the heat diffusivity of the competing cooling process into the CHCl₃ solvent. Accompanying nonequilibrium MD simulations qualitatively reproduced the overall experimental findings but differ in terms of quantitative numbers.³³,³⁴ The calculations overestimate the experimentally obtained cooling time (1/kₜ=7 ps) by a factor of 2.5, which seems to be mainly caused by the neglect of the internal motion of the solvent molecules.²¹ Moreover, the simulations yield a significantly shorter energy transport time along the peptide (1/kₜ=0.4 ps) than in experiment (2 ps). However, the resulting calculated heat diffusivity (10 Å² ps⁻¹) is consistent with experimental bulk values and other computational works.⁹

The deviations between theory and experiment raise various questions, which indicate that several aspects of molecular energy flow are not yet well understood: What are the molecular parameters determining the speed and efficiency of the energy transport in peptides? Does the energy transfer depend on, e.g., electrostatic interactions (as expected for the transport via hydrogen bonds), on through-bond interactions (as expected for the transport through the backbone), or on the interaction between solute and solvent? What about
quantum effects, i.e., is a simple quasiclassical MD description at all suited for the modeling of energy transfer? Furthermore, to what extent do nonequilibrium MD simulations directly mimic the experiment under consideration? Is the specific laser excitation scheme (e.g., optical or IR excitation) important for the subsequent energy transport, or can one simply assume an instantaneous temperature jump? Is it sufficient to calculate the molecular energy flow or do we need to explicitly simulate the transient vibrational spectrum measured in experiment?

To provide an answer to these questions, in this work we present extensive nonequilibrium MD simulations of the photoinduced energy transport of a photoswitchable Aib peptide forming a $3_{10}$-helix (Fig. 1), which was considered in the studies of Hamm and co-workers.33–35 By changing the MD force field model (e.g., by switching off some type of interaction), we find that the energy transfer occurs mainly through the peptide backbone and depends surprisingly little on the force field parametrization. This behavior is explained by adopting a harmonic theory of heat transport set forward by Leitner and co-workers.89 To compare to experiment, we consider various excitation schemes and observable quantities. Apart from calculating the energy flow through the peptide, we suggest a new way of approximating the experimental results and clarifies previous discrepancies.

II. COMPUTATIONAL METHODS

A. Equilibrium MD simulations

All simulations were performed with the GROMACS program suite,40 using the GROMOS96 force field 43a1 (Ref. 41) to model the photoswitchable Aib peptide and the rigid all-atom model of Ref. 42 to describe the chloroform solvent. Additional force field parameters for the azobenzene unit were derived from density functional theory, as described in Ref. 43. The equation of motion was integrated by using a leap-frog algorithm with time step of 0.2 ps. We employed the particle-mesh Ewald method to treat the long-range electrostatic interaction.47 The nonbonded interaction pair list was updated every 10 fs, using a cutoff of 1.4 nm. Bonds containing a hydrogen atom were constrained via the SHAKE (Ref. 48) procedure with a relative geometric tolerance of $10^{-4}$. This assures that these high-frequency vibrations (which are ground state dominated in a quantum description) are not spuriously excited in the classical simulation.

Starting with a $3_{10}$-helical conformation, the Aib peptide was placed in an octahedral box containing $\approx$700 chloroform molecules. After energy minimization, the system was simulated for 40 ns at constant temperature (300 K) and pressure (1 atm), using the Berendsen coupling44 procedure with coupling times of 0.1 and 0.5 ps, respectively. From this equilibrium trajectory, 400 statistically independent conformations were sampled for the subsequent nonequilibrium simulations. The procedure was repeated for the temperatures 220, 250, 260, 270, and 280 K in order to account for the temperature dependence of the energy transport.

B. Modeling of the excitation process

To study energy transport in and within molecules, we have recently developed several protocols of nonequilibrium MD simulations, which are designed to mimic the experimental preparation by either an optical laser pulse triggering a molecular photoswitch (UV excitation)45 or an IR pumping of a local vibrational mode (IR excitation).20,34 In the absence of a concrete experiment, moreover, one may approximately assume an initial temperature jump of some atom group in order to initiate nonstationary energy flow (T-jump excitation).21 To achieve a better signal-to-noise ratio, one can also continuously heat a part of the molecule, which generates a stationary energy flow (stationary excitation).2 In the following, we briefly describe the various methods to generate MD initial conditions that account for these excitation techniques. The corresponding MD results are compared in Sec. III below.

1. UV excitation

To model the laser-induced isomerization process of the azobenzene photoswitch, we use a minimal model for the corresponding potential-energy surfaces that diabatically connects the excited-state $S_1$ of the cis isomer with the ground state $S_0$ of the trans isomer (see Ref. 45 for details). The photoexcitation of the system by an ultrafast laser pulse is mimicked by instantly switching from the ground-state $N=\text{N}$ torsional potential to the excited-state potential. Following this nonequilibrium preparation at time $t=0$ with the excess energy of 320 kJ/mol, the system isomerizes along excited-state $N=\text{N}$ potential within $\approx$0.2 ps. After isomerization (i.e., for times $\geq$0.5 ps), the N= N torsional potential is switched back to its ground-state form, and the excess energy will transfer into the peptide.

FIG. 1. (a) Structure of the photoswitchable Aib peptide used in the studies of Hamm and co-workers (Refs. 33–35). To initiate energy flow along the peptide $3_{10}$-helix, either UV excitation via cis $\rightarrow$ trans photoisomerization of the azobenzene photoswitch or IR pumping of a localized C-O mode was considered. In the MD simulations, moreover, we employed a temperature jump and a stationary heating excitation of the C$_{\alpha}$ atom, which connects the photoswitch to the peptide. (b) Simple kinetic scheme of the energy flow in the system, which describes the energy transport along the peptide by the transport rate constant $k_p$ and the energy loss to the solvent by the cooling rate constant $k_c$.
2. IR excitation

In order to model the IR excitation of a local C=O group, we represent the C=O stretch vibration as a harmonic oscillator with the reduced mass \( \mu=(m_C+m_O)/m_{C+O} \), coordinate \( q_{CO}=q_C-q_O-\langle q_{CO} \rangle \), and momentum \( p_{CO}=p_C-p_O \). In terms of classical action-angle variables \( n, \phi \), these variables are represented as

\[
q_{CO} = \sqrt{(2n+\gamma)} \sin \phi,
\]

\[
p_{CO} = \sqrt{(2n+\gamma)} \cos \phi,
\]

where the factor \( \gamma=1 \) accounts for the zero-point energy of the oscillator. To obtain the initial positions and momenta of the initially excited C=O, we associate the action \( n \) with the initial quantum state of an oscillator, e.g., \( n=1 \) for the first excited state. The vibrational phases \( \phi \) are picked randomly from the interval \([0,2\pi]\). This way, an ensemble of positions and momenta are calculated which provides a quasi-classical representation of the quantum-mechanical initial state of the C=O oscillator with an energy of \( \approx 30 \) kJ/mol.

3. T-jump excitation

In the above described excitation techniques, the energy of the photon is converted into randomized vibrational energy in the vicinity of the photoexcited moiety.\(^3\)\(^4\) For the sake of simplicity, we may therefore approximate the photoexcitation by an initial temperature jump of the C\(_a\) atom which connects the photoswitch to the peptide.\(^2\)\(^1\) Starting from an equilibrium initial configuration (see Sec. II A), the C\(_a\) atom is heated up through the coupling to a heat bath at 600 K, while the remaining atoms of the peptide and solvent are coupled to a 300 K heat bath. This way, the thermally excited atom reaches the desired temperature of 600 K within \( \approx 2 \) ps. Following this preparation, a nonstationary heat flow is generated that allows us to follow the energy transfer from the thermally excited atom to the peptide.

4. Stationary excitation

The impulsive excitation techniques described above generate a nonstationary energy flow in the peptide, which rapidly decreases due to dissipation into the solvent. Alternatively, to facilitate the detection of temperature-induced fluctuations at distant sites with reasonable signal-to-noise ratio, one may continuously heat the atoms in the vicinity of the photoexcited moiety to a high temperature, while the remaining atoms are kept at a low temperature.\(^7\) To maintain this high temperature during the nonequilibrium simulations, the C\(_a\) atom is coupled to a heat bath at 600 K, while the temperature coupling is turned off for all other atoms. This way, heat in the form of kinetic energy will propagate from the C\(_a\) atom into the peptide.

C. Nonequilibrium MD simulation

Following the calculation of initial conditions described above, nonequilibrium MD simulations were performed in CHCl\(_3\) solvent and \textit{in vacuo}. All simulations were performed at constant energy (NVE ensemble) for 100 ps, and data were collected every 0.02 ps. For the constant heat simulation, only the hot C\(_a\) atom is coupled to a heat bath, using the Berendsen coupling method.\(^4\)\(^\dagger\) \textit{In vacuo} simulation, the same procedure was employed except that the periodic boundary conditions were turned off and no cutoffs were used.

As a straightforward quantity to study biomolecular energy flow, we consider the time evolution of the kinetic energy per atom of the \( i \)th peptide unit CONH, \( E_i(t) \). Performing nonequilibrium simulations, we are concerned with the ensemble average

\[
\langle E_i(t) \rangle = \frac{1}{N} \sum_{r=1}^{N} E_i^{(r)}(t),
\]

where \( E_i^{(r)}(t) \) is the residue energy along trajectory \( r \) and \( N \) =400 denotes the number of nonequilibrium trajectories. Alternatively, we consider the energy transfer from residue \( i \) to residue \( j \) described by the two-time energy correlation function

\[
K^{(2)}_{ij}(t, \tau) = \langle \delta E_i(t) \delta E_j(t+\tau) \rangle,
\]

where \( \delta E_i(t) = E_i(t) - \langle E_i^{eq} \rangle \). In the case of continuous heating of the system, one may simplify matters by considering the time-integrated function

\[
K_{ij}(\tau) = \frac{1}{\sigma_i \sigma_j} \int dt \delta E_i(t) \delta E_j(t+\tau),
\]

where we have also introduced a normalization factor with \( \sigma_i = \langle E_i^2(t) \rangle^{1/2} \) denoting the variance of the fluctuations of \( E_j \) (and similar for \( \sigma_j \)).

III. COMPARISON OF EXCITATION TECHNIQUES

In what follows, we compare the four nonequilibrium excitation schemes introduced in Sec. II B. In particular, we wish to study if these techniques provide equivalent information on the energy transfer process and discuss their computational advantages and shortcomings. Displaying the time evolution of the mean kinetic energy of the first, third, and fifth residues of the Aib peptide, Fig. 2 compares the nonequilibrium MD results obtained for excitation via (a) a UV pulse, (b) an IR pulse, (c) a T-jump, and (d) stationary heating.
ing. Following the excitation at time $t = 0$, the excess energy is transferred into the peptide and solvent. In all cases, the time-delayed rise of the kinetic energies of the subsequent peptide units nicely illustrates the propagation of energy along the peptide backbone. The various methods clearly differ in the amount of available excess energy, the initial evolution of the energy of residue 1 close to the heater, and the feature that the molecule is excited impulsively or stationary.

In the case of UV excitation [Fig. 2(a)], the photon energy of $\approx 320$ kJ/mol deposited in the $\mathrm{N} = \mathrm{N}$ double bond of the photoswitch is converted to the kinetic energy of the azobenzene photoswitch, which rises and reaches the maximum value of 225 kJ/mol within 0.1 ps (data not shown). This energy is subsequently transferred to the peptide, and the CONH unit of residue 1 is seen to attain about 22 kJ/mol of kinetic energy within 0.3 ps. The subsequent energy transfer to the farther peptide units is much slower, that is, units 3 and 5 reach the peak energy in about 2 and 10 ps, respectively. To quantitatively account for the energy flow in the system, we adopt the simple kinetic scheme shown in Fig. 1(b), which describes the energy transport along the peptide by the transport rate constant $k_p$ and the energy loss to the solvent by the cooling rate constant $k_c$. A global fit yields $1/k_p = 0.5(\pm 0.1)$ ps and $1/k_c = 20(\pm 2)$ ps, which—apart from the initial rise of the energy of unit 1 during the photoexcitation—is seen to at least qualitatively match the time evolution of the system. Within the given boundaries for $k_p$ and $k_c$, the quality of the fit is similar. As already mentioned, the calculation overestimates the experimental transport rate $(1/k_p = 2$ ps) but underestimates the experimental cooling rate $(1/k_c = 7$ ps). When the propagation rates are related to the heat diffusivity $D = k_p \Delta \omega$ [with $\Delta \omega \approx 2$ Å being the helical translation per residue for a $3_{10}$ helix (Ref. 50)], we obtain $D = 2$ and $10 \, \text{Å}^2 \, \text{ps}^{-1}$ from experimental and calculated data, respectively.

Interestingly, we obtain essentially the same values for these rates from the other three excitation methods (IR and impulsive or continuous heating). This indicates that all methods are equivalent in that they provide the molecular energy transfer times (independent of the specific excitation method). The invariance to the initial conditions also indicates that the photoinduced energy is rapidly converted via intramolecular vibrational relaxation into randomized vibrational energy. (We note, however, that for IR excitation the energy of unit 1 decays somewhat slower as expected, which might indicate an initial vibrational redistribution process from the excited C–O group to the peptide backbone.) The main difference in UV, IR, and T-jump excitation is the amount of available excess energy and the way that this energy is transferred to unit 1. In the case of IR excitation, the initial total energy of the excited C=O oscillator is about 30 kJ/mol, which is much lower than that of the UV excitation. Due to the spatial proximity of the C=O group to the first peptide residue [see Fig. 1(a)], a large part of this energy is almost instantaneously transferred to unit 1. This is even more so in the case of T-jump excitation, where $\approx 5 \, \text{kJ/mol}$ (corresponding to $600 \, \text{K}$) of kinetic energy is deposited into a single C$_a$ [Fig. 1(a)]. Due to the smaller initial excess energy, the energy peak height of units 3 and 5 is significantly smaller than for UV excitation. Because of the signal-to-noise ratio obtained from the average over 400 trajectories, the energy increase at residues beyond unit 5 is hard to detect.

To facilitate the simulation of long-distance energy transfer to distant residues, one may continuously excite the molecule by keeping the C$_a$ atom at 600 K. In this case, we obtain a transient rise of the residues’ energies until stationary energy current in the peptide is being established for times $\gtrsim 100$ ps [Fig. 2(d)]. The energy transport along the peptide can be extracted from the delayed onset of the energy rise, i.e., units 1, 3, and 5 start to increase after about 0.5, 1, and 2 ps, respectively. Compared to the impulsive excitation methods, the energy rise of sites 3 and 5 is clearly larger and hence much easier to monitor in a MD simulation with a modest number of trajectories.

Alternatively, the energy transport of the system can be studied via the energy correlation function $K_{ij}(\tau)$ defined in Eq. (4). This quantity reflects the energy flow from site $j$, playing the role as a heat source, to site $i$, receiving the heat. In the present case, site $j$ is the heated C$_a$ atom and we consider peptide units 1, 3, and 5 as site $i$. Figure 3 shows the time evolution of the nonequilibrium correlation for these residues; their corresponding kinetic energies are shown in Fig. 2(d). The correlation function of unit 1 starts at its maximum value, reflecting the fact that this unit feels the hot C$_a$ atom almost immediately [see Fig. 2(d)] and decays on a time scale of 1 ps. The correlation functions of units 3 and 5 reach their maximum values at about 1 and 2 ps, respectively, which roughly coincide with the rise times of the kinetic energies shown in Fig. 2(d). As has been shown in Ref. 7, the energy correlation function is advantageous for the study of energy transfer over long distances because this quantity is less affected by the noise of the complete system.

**IV. MECHANISM OF ENERGY TRANSPORT**

To learn how energy is transported within the peptide, we consider the interaction energy of the peptide, which in terms of the contributions to the MD force field can be written as

$$V = V_b + V_{nb} + V_s.$$  

(5)

Here $V_b$ denotes the bonded interactions of the peptide, including bonds, bond angles and dihedral angles; $V_{nb}$ accounts for the nonbonded interactions, i.e., Coulomb and Lennard-
Jones interactions between peptide atoms with a distance larger than three covalent bonds, and \( V_i \) represents the Coulomb and Lennard-Jones interactions between the peptide and the solvent. Since no energy flow within the peptide is possible for \( V = 0 \), we can study the relevance of the various interactions by weighting the corresponding force field terms. While doing so, we keep all remaining force field parameters, involving, e.g., the azobenzene photoswitch or the solvent, constant. In all cases, UV excitation is considered.

Let us first study the effects of the CHCl₃ solvent on the energy transport through the Aib peptide. To this end, we performed MD simulations in vacuo (i.e., \( V_i = 0 \)), and compared the resulting time-dependent residue energies to the corresponding results of the simulations in chloroform, see Figs. 4(a) and 4(b). In the absence of energy dissipation to the solvent, the total energy of the photoswitchable peptide is constant. After several tens of picoseconds, this energy is distributed equally among all peptide residues, resulting in a long-time value for the residue energies of \( \approx 5 \) kJ/mol. Furthermore, we observe higher values of the energies at short times due to the lack of dissipation. Employing the kinetic model shown in Fig. 1(b) with \( k_p = 0 \), we obtain from the in vacuo simulations the same results for the transfer time \( (1/k_p) = 0.4 \) ps as we found for the simulations in solution. This outrules the possibility that the transport process is “slaved by the solvent,” as it has been discussed for various dynamical processes in proteins.²⁵ Hence, we conclude that—apart from obvious effects caused by the additional relaxation channel—the solvent does not effect the energy transport through the peptide.

In the next numerical experiment we switched off the nonbonded Coulomb and Lennard-Jones interactions within the peptide, i.e., \( V_i = 0 \). Hardly any effect is observed in solution (results not shown) as well as in vacuo (panel (c)). This is remarkable since no intramolecular hydrogen bonds can exit in the absence of Coulomb interactions, which renders the structure of the 3_{10}-helix unstable at longer times. Apparently, energy transport through intramolecular hydrogen bonds can be ruled out as well.

As a consequence, we have found that the energy transport occurs (almost) exclusively through the bonded interactions along the backbone. Since the exclusion of the dihedral angle potentials does not change the situation either, it is the bond and bonding angle potentials that are responsible for the transport. To further study their effect, we either softened or constrained those degrees of freedom. In the latter case, the overall time evolution of the residue energies hardly changes [panel (d)], except that less kinetic energy is available because the number of flexible degrees of freedom of the CONH unit is reduced from \( 4 \times 3-1=11 \) (NH bond is constrained) to \( 12-5=7 \) (all bonds and angles are constrained). Surprisingly little effect is also observed in the opposite limit of softening bonds and bonding angles [panel (e)]. As maybe expected from harmonic models (see below), softer bonds react slower and absorb somewhat more energy. However, the overall transfer rate hardly changes. For the same reason we also do not expect that (relatively small) anharmonic corrections would make a significant effect to the energy transfer. A true overall scaling of the time scale can be achieved when the peptide masses are changed [panel (f)]. Increasing the atom masses by a factor of 4, we obtain about twice the transfer time \( (1/k_p) = 0.9 \) ps. This finding is in line with the prediction of a linear chain model that the velocity of sound \( c \approx 1/\sqrt{M} \) would be reduced by a factor 2.

In summary, we have shown that the energy transport through the peptide helix occurs primarily through the bonds of its backbone, while neither the solvent nor the nonbonded Coulomb and Lennard-Jones interactions within the peptide play an important role. Moreover, we have found that the energy flow through the backbone depends surprisingly little on the force constants of bonds and bonding angle.

To obtain a microscopic understanding of these findings, we follow Leitner and co-workers⁸–¹⁰,⁵² and adopt a harmonic description of energy transfer by calculating the vibrational normal modes of the peptide. Within the Kubo formalism, the thermal conductivity is then given by

\[
\kappa = \sum_i C_V(\omega_i)D(\omega_i) = \int d\omega \rho(\omega)C_V(\omega)D(\omega),
\]

where \( \omega_i \) denotes the frequency of the \( i \)th normal mode, \( C_V(\omega_i) \) denotes its specific heat, \( D(\omega_i) \) represents its energy diffusion coefficient, and \( \rho(\omega) \) is the density of states. For low-frequency modes, the diffusion coefficient can be approximated by \( D(\omega) \approx \frac{2}{3}C_V(\omega)l(\omega) \), where \( C_V(\omega) \) is the speed of sound and \( l(\omega) \) accounts for the mean free path for the normal mode.⁸ The thermal diffusivity is then given by \( D_T = \kappa/C_V \), where \( C_V \) is the mean heat capacity.

Figure 5 shows these quantities for the Aib peptide in solution, obtained from instantaneous normal mode calculations, using 400 statistically independent molecular structures. The density of states was obtained by histogramming the normal mode frequencies \( \omega_i \), the specific heat is given by \( C_V(\omega) = k_B(\beta\omega)^2e^{\beta\omega}/[V\{e^{\beta\omega}-1\}]^2 \) with \( \beta = 1/k_BT \) and \( T = 300 \) K, and the mean free path was estimated.
nated from the decay length of the atomic displacement correlation function. The most prominent frequency dependence is exhibited by the mean free path, which for the vast majority of modes is $\sim 2$ Å, which corresponds to a typical distance between nearest-neighbor atoms. Only modes with $\omega \leq 100$ cm$^{-1}$ are seen to provide a longer free path length up to $\sim 10$ Å, which reflects the length of the peptide. The main contributions to the quantum-mechanical heat capacity, as well as being achieved by low-frequency modes satisfying $\hbar \omega / k_B T \approx 1$ because only these modes are thermally excited at 300 K. Taken together, it is clear from Eq. (6) that these delocalized low-frequency vibrational modes are the main cause for energy flow in a molecular system.

When we use $c_v = 23$ Å$^2$ ps$^{-1}$ as average value of the speed of sound in a peptide, we obtain a heat diffusivity of $20$ Å$^2$ ps$^{-1}$ from the above theory. This in good agreement with previous calculations of Leitner and co-workers, who found 21 and 19 Å$^2$ ps$^{-1}$ for the heat diffusion of green fluorescent protein and myoglobin, respectively. Interestingly, though, the heat diffusivity $D_V = \kappa / C_v$ calculated from Eq. (6) is a factor of 2 larger than the heat diffusivity estimated from our nonequilibrium MD simulations above. This is caused by the fact that in Eq. (6) we used a quantum-mechanical expression for the heat capacity, while the MD simulations represent a classical description which predicts $C_V = k_B q$ for harmonic vibrations instead of the frequency-dependent behavior found in Fig. 5. Employing the classical expression for $C_V$, we obtain 12 Å$^2$ ps$^{-1}$ for the heat diffusivity of the normal mode model, which is in good agreement with the nonequilibrium MD results of 10 Å$^2$ ps$^{-1}$.

We are now in a position to employ the harmonic theory to explain the above observed insensitivity of the heat transport with respect to the MD force field of the peptide. When we calculated the density of states $\rho(\omega)$, the heat capacity $C_V(\omega)$, and the mean free path $l(\omega)$ for the various cases discussed in Fig. 4, we indeed found that these quantities are quite robust with respect to the force field parametrization. As an example, Fig. 5 compares $\rho(\omega)$, $C_V(\omega)$, and $l(\omega)$ obtained from the standard force field model and a modification with considerably softened bonds, which caused the most significant effect in the energy transfer (Fig. 4). Apart from the expected change in the density of states for frequencies $\omega \approx 1000$ cm$^{-1}$, all three quantities are quite similar in both cases. Moreover, the integration over normal mode frequencies in Eq. (6) affects an averaging that obscures many details and therefore explains why the energy flow through the backbone depends only little on the MD force field.

V. COMPARISON TO EXPERIMENT

As discussed in Sec. I, our nonequilibrium MD simulations seem to overestimate the experimentally measured heat diffusivity of the Aib peptide by a factor of 5. From the discussion above, it has become clear that this effect cannot be explained by deficiencies of the force field. Furthermore, one would not expect quantum-mechanical effects to be the reason for this finding since they typically speed up the energy transfer rather than slowing it down. For example, by using the quantum-mechanical rather than the classical expression for the heat capacity in Eq. (6), we obtain a two-fold increase of the transport rate (see above).

Another possibility that might explain the significant deviation between theory and experiment is that the calculated observable, i.e., the time-dependent kinetic energy $E_i(t)$ of the $i$th residue [Eq. (2)], is not equivalent to the measured observable, i.e., the transient redshift $\Delta \omega_i$ of the $i$th isotope-labeled C$\equiv$O vibration. The calculated residue energy $E_i(t)$ by construction directly measures the transient energy flow through the peptide. However, this definition takes into account the high temperature-induced motion of all atoms of the residue, while the measured redshift is only caused by vibrational modes that couple to the C$\equiv$O vibration of this residue. Since one expects that mostly the motion of nearby atoms couple to the local C$\equiv$O vibration, so far the working hypothesis has been that $E_i(t) \approx \Delta \omega(t)$. Because of the unexpected deviation between theory and experiment, in the following we attempt to inspect the validity of this approximation.

As outlined in Ref. 39, the temperature-induced redshift can be estimated as

$$\Delta \omega_i(t) \approx \sum_j c_j n_j(t),$$

(7)

where $n_j(t)$ denotes the mean excitation number of the $j$th normal mode $q_j$ and $c_j$ accounts for the anharmonic coupling of this normal mode to the $i$th local C$\equiv$O vibration. This expression can be obtained via second-order perturbation theory by considering the model Hamiltonian

$$H = \frac{\omega_{CO}}{2} (q_{CO}^2 + p_{CO}^2) + \sum_j \frac{\omega_j}{2} (q_j^2 + p_j^2) + c_{CO} q_j p_j,$$

(8)

which describes the cubic coupling of a C$\equiv$O mode to a number of “bath” modes $q_j$. Hence the temperature-induced redshift is caused by vibrational modes which satisfy two requirements: Their frequency needs to be sufficiently low to get thermally excited (i.e., $n_j > 0$) and they must exhibit significant coupling $c_{CO}$ to the local C$\equiv$O vibration under consideration.
From the above model, we learn that the time evolution of the redshift is caused by the excitation $n_j(t)$ of the low-frequency modes $q_j$. It is important to note, however, that $\Delta \omega_j(t)$ does not, in general, directly reflect the time evolution of the corresponding residue energy $E_i(t)$. This is because the latter mainly involves the energy of the "transporting modes" (essentially the backbone vibrations), which by definition first receive the excess energy due to the thermal excitation. The low-frequency modes, on the other hand, become excited subsequently through some kind of energy transfer from the transporting modes. As a consequence, the redshift occurs with some delay after the rise of the residue energy $E_i(t)$. This effect is enhanced by the fact that the response of the low-frequency modes is slower than the response of the backbone vibrations with comparatively high frequency.

Although the temperature-induced redshift can, in principle, be calculated directly, in practice, this calculation is rather challenging because $\Delta \omega_j$ is small ($\approx 10$ cm$^{-1}$) and the quantum-chemical calculation of anharmonic couplings of polypeptides is quite cumbersome. To nevertheless illustrate the basic effect with the aid of our MD calculations, we note that model (8) also gives rise to the vibrational energy redistribution process

$$\omega_j(n_j \rightarrow n_j - 2) = \omega_{CO}(0 \rightarrow 1).$$

That is, the C==O mode is excited, provided that the resonance condition of the process, $2\omega_j = \omega_{CO}$, holds at least roughly. Since $\omega_{CO} \approx 1700$ cm$^{-1}$, however, we find that low-frequency vibrational modes that are thermally excited at room temperature of 300 K ($k_BT=200$ cm$^{-1}$) only create a negligible excitation of a C==O mode via process (9), e.g., $n_j=1/[(e^{\hbar\omega_j/k_BT}−1)]=0.02$ for $\omega_j=800$ cm$^{-1}$. This is different in a classical calculation, though, because the excitation number of a classical harmonic oscillator is $n_j=k_BT/\hbar\omega_j$, which gives $n_j=0.25$ in the above example. Although this is clearly an artifact of the classical approximation, it nevertheless facilitates the calculation of this energy transfer process from our nonequilibrium MD simulations with reasonable signal-to-noise ratio.

Figure 6 shows the resulting time evolution of the kinetic energy of the local C==O modes, which were calculated via an ensemble average [Eq. (2)] using the velocities of the C==O stretch motion. Compared to the residue energies $E_i(t)$ shown in Fig. 2(a), the time evolution of the C==O energies is significantly slower, which yields a transport time that is about one order of magnitude lower than the transport time along the backbone. Since the energy transfer (9) and redshift (7) are caused by the same anharmonic couplings, it is tempting to speculate that the slow rise of the C==O energies explains the slow (five times slower than calculated) experimentally observed time evolution, the redshift. Because the classical calculation spuriously overestimates the size of the energy transfer and the time evolution of energy transfer and redshift need not be the same, it is clear though that Fig. 6 can only qualitatively demonstrate this effect.

Another intriguing experimental finding has been the temperature dependence of the energy transport in the peptide. As showed by Backus et al., the overall transport efficiency stays approximately constant from 220 to 260 K, but rises steeply for higher temperatures. A similar behavior was found for the homogeneous dephasing rate $1/T_2$ of the C==O vibration. Accompanying nonequilibrium MD simulations revealed the signatures of a "dynamical transition" at a transition temperature of 270 K, in particular, they showed a prominent rise of the atomic fluctuations of the peptide. The biphasic behavior of the fluctuations and the energy transport efficiency resembled the behavior of proteins at the so-called glass transition at 200 K in aqueous solution, where the transition temperature appears to reflect the solvent rather than the solute dynamics. A similar transition has also been found for denatured proteins and small peptides.

Although the MD simulations nicely reveal the dynamical transition at 270 K (see Fig. 3 in Ref. 35), the simulated residue energies do not show a significant dependence on temperature such as found in experiment. This is demonstrated in Fig. 7(a) which shows the overall transferred vibrational energy $\Delta E_i = E_i(t) - E_i(\infty)$ to the $i$th residue, where $t_i$ denotes the time where the maximum of $E_i(t)$ occurs. While there is some overall increase in $\Delta E_i$ with temperature, the calculated energy transfer along the peptide backbone does not show a pronounced biphasic behavior. Interestingly, this is different when the transferred energy along the C==O modes of these residues is considered. Figure 7(b) shows that the C==O mode energy of residue 1 exhibits quite clearly a biphasic behavior around 270 K with a 60%
increase. The effect is weaker but still visible for the C=O mode of residue 3. This finding indicates that it is the above discussed energy transfer to the low-frequency modes rather than the energy transport along the peptide that reflects the characteristic temperature dependence of a dynamical transition.

VI. CONCLUDING REMARKS

We have presented a detailed description of nonequilibrium MD simulation techniques to model photoinduced energy transport along a peptide helix. By comparing the response of the molecule caused by its excitation via UV and IR pulses as well as T-jump and stationary heating, we have shown that all considered methods are equivalent in that they provide similar molecular energy transfer times. While the simulation of UV and IR excitation allows us to directly compare to experiment, the usage of stationary heating is computationally advantageous since its improved signal-to-noise ratio facilitates the study of energy transfer to distant residues. To elucidate the mechanism of energy transfer, we have introduced modifications to the MD force field which revealed that the energy transfer occurs mainly through the peptide backbone. Furthermore, the energy transport depends surprisingly little on the force field parametrization, which could be explained by adopting a harmonic theory of heat transport that showed that neither the density of states nor the mean free path changes significantly for realistic changes (≤10%) in the force field.

Nonequilibrium MD simulations are per se classical calculations [with the possible exception of their quantumlike initial conditions, see Eq. (1)]. This raises the question on the importance of quantum effects for the peptide energy transfer. Interestingly, we have obtained a similar thermal diffusivity from the nonequilibrium MD simulations (10 Å² ps⁻¹) and from the harmonic theory [Eq. (6)] with a classical heat capacity (12 Å² ps⁻¹). Using a quantum-mechanical-expression for the heat capacity, on the other hand, the latter yields 20 Å² ps⁻¹, which is in good agreement with previous calculations for proteins (20 Å² ps⁻¹) and experimental bulk values (e.g., 14 Å² ps⁻¹ for water). This suggests that the main quantum effect in the peptide energy transport is of statistical nature [i.e., \( n_j = k_B T / \hbar \omega_j \) versus \( n_j = 1 / (e^{\hbar \omega_j / k_B T} - 1) \)] and confirms recent theoretical work which revealed that classical nonequilibrium MD simulations typically reproduce the correct quantum energy transfer rate up to a factor of 2.5

To explain the origin of the significant deviation between calculated and measured energy transport time (0.4 versus 2 ps), we could rule out deficiencies of the force field as well as quantum-mechanical effects which typically speed up the energy transfer rather than slowing it down. It rather turned out that the calculated observable, i.e., the time-dependent kinetic energy \( E_k(t) \) of the ith peptide residue is not equivalent to the measured observable, i.e., the transient redshift \( \Delta \omega_i \) of the ith isotope-labeled C=O vibration. The residue energies \( E_i(t) \) by construction directly account for the transient energy flow through the peptide. They mainly involve the energy of the transporting modes (essentially the backbone vibrations), which by definition first receive the excess energy due to the thermal excitation. The measured redshift, on the other hand, is caused by thermally excited low-frequency vibrational modes that couple to the C=O vibration of this residue. Because these modes are excited through energy transfer from the transporting modes, the redshift occurs with some time delay.

As the transient redshift of the C=O modes is difficult to extract from MD simulations, we have calculated the time evolution of the kinetic energy of these local modes. This yielded a transport time for the C=O modes that is about one order of magnitude smaller than the transport time along the backbone. Since the C=O energy transfer and the measured redshift are caused by the same anharmonic couplings, this finding may qualitatively explain the slow time evolution of the redshift observed in experiment. Unlike to the residue energies, moreover, the C=O energies reveal the experimentally measured biphasic dependence on temperature. That is, the C=O energy transfer stays approximately constant up to a temperature of \( ≈ 270 \) K but rises steeply for higher temperatures, thus reflecting the dynamical transition of the peptide at 270 K. This finding indicates that the characteristic temperature dependence of the dynamical transition is caused by the above discussed energy transfer to the low-frequency modes rather than by the energy transport along the peptide. Ongoing work may hopefully also shed some light on the underlying dynamical processes of this transition which seem to be not well understood yet.

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