Amide-I excitations in molecular-mechanics models of α helix structures

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A three-dimensional model of an α helix is built applying a molecular-mechanics approach. The potential-energy function describing the system is based on empirical data and implemented in the molecular-dynamics computer program CHARMM. The time evolution of amide-I vibrations has been examined numerically. In order to examine the coupling mechanism of an amide-I oscillator to other amide-I oscillators along the backbone as well as along the so-called spines, a simple analytical model has been set up. From this model the coupling along the backbone is estimated to be more than 50% stronger than the coupling along the spines.

I. INTRODUCTION

One of the main tasks in biophysics is to understand how proteins work. A protein structure can be described (roughly speaking) as a three-dimensional folding of a linearly linked chain of amino acids. The three-dimensional structure of proteins is in general very complicated. However, a number of structural patterns have been identified in proteins. Of particular interest is the α helix because of its frequent occurrence and the conceptual simplicity of its structure.[1] The helix is tightly coiled about its longitudinal axis and is stabilized by hydrogen bonds linking peptide groups together to form three spines that span the length of the helix. These spines are not exactly linear or parallel to the axis of the helix. However, the electric dipole moments induced by the amide-I vibrations are essentially in the same direction as the hydrogen bonds that define the spine. The α helix as a whole constitutes a very strong dipole moment.

The energy supply for many enzyme reactions is provided by hydrolysis of adenosine triphosphate (ATP). An ATP molecule binds to a specific site on the protein, reacts with water, and releases under normal physiological conditions 0.49 eV (11.5 kcal/mol) of energy.[1] One hypothesis is that the energy is converted to a vibrational excitation within the protein, namely, the amide-I vibration. This vibration is primarily a stretch and contraction of the C=O bond—the energy of one quantum amide-I vibration is about 0.21 eV or 1665 cm^{-1}.

Recently, considerable effort has been devoted to model energy exchange modes in proteins.[2-11] One of the simplest structural units, namely, the α helix mentioned above, has been used in these attempts. A variety of models are based on the existence of the spines which has been the main justification for applying very simple one-dimensional (1D) dynamic models of α-helix structures focusing in particular on the propagation of excitations.

The first attempt to model energy exchange modes in proteins was formulated by Davydov[2,3] who suggested that the amide-I energy would stay localized (trapped) through the nonlinear interaction of the vibrational excitation and the deformation in the protein structure caused by the presence of the excitation. Thus the amide-I vibration in the Davydov model is coupled to low-frequency phonon modes at around 100 cm^{-1}. The coupling is modeled by inclusion of a nonlinear interaction term in the Hamiltonian. The idea was applied to the α helix but assuming the single-spine model. Scott[4-6] generalized this theory by taking dipole-dipole coupling between the three spines into account. This theory showed how a pulse could travel along the three hydrogen-bonded spines of the α helix. The theory is semiclassical in the sense that it considers one quantum of amide-I vibration. Since then, a considerable amount of work has been done on the original Davydov model.[2-8]

While the Davydov model and the related models have considered intramolecular modes, another kind of model has been set up which focuses on large-amplitude motions, so-called lattice vibrations.[9-11] The proposed lattice excitations are established solely through the nonlinearity and asymmetry of the hydrogen bonds that stabilize the α-helix structure. These models also restrict themselves to the 1D spines.

Recently, a three-dimensional (3D) model of an α helix has been examined by numerical computations.[12] The model is completely classical in the sense that it is based on a potential-energy function (i.e., an empirical energy of molecular-mechanics type[13]) from which Newton's equations of motion are derived. The parameters used to describe the interactions among the atoms are based on experiments and have been tested in models of macromolecules (Ref. 14 and references therein). Numerical experiments were performed in the spirit of some of the theories mentioned above. In particular, the time evolution of excitations was examined. No localized pulses were found. Further, it was concluded that for the numerical experiments considered the system was linear, which means that dispersion governs the time evolution of excitations.

The aim of the present paper is to evaluate the assumption used in the development of 1D models, namely, that the genuine 3D problem can be reduced to a 1D problem by considering only the interaction along the hydrogen-bonded spines. In order to undertake this evaluation we use the 3D α-helix structure presented in Ref. 12. Fur-

ther, we only consider the time evolution of amide-I vibrations which we examine numerically. Two cases are investigated. In one case the surroundings of the helix are a vacuum, while in the other case the presence of solvent is modeled in a simple way. In the latter case the presence of solvent is modeled using a distance-dependent dielectric constant. If the system is in the linear regime it is possible to generate a simple model which reproduces the numerical results and gives an estimate of the strength of the coupling of a single amide-I oscillator to other amide-I oscillators along the backbone as well as along the spines. The results of this investigation show that the amide-I oscillators couple stronger to amide-I oscillators placed on the backbone than to oscillators placed on the spines. In the following section we shortly describe the method of calculation (which follows Refs. 12 and 14), outline the analytical model, and present the estimated coupling constants.

II. METHOD OF CALCULATION

The energy function used for macromolecules in the molecular-mechanics approach in the present work is composed of terms representing bonds, bond angles, torsional angles, van der Waal's interactions, and electrostatic interactions. The resulting form of the potential energy function is

$$E_{\text{pot}}=0.5\sum_b K_b(b-b_0)^2+0.5\sum_\theta K_\theta(\theta-\theta_0)^2 +0.5\sum_\phi K_\phi[1+\cos(n\phi)]+0.5\sum_\omega K_\omega(\omega-\omega_0)^2 +\sum_{i,j}\left[\frac{A}{r_{ij}^{12}}+\frac{C}{r_{ij}^{6}}\right]+\sum_{i,j}\frac{q_iq_j}{Dr_{ij}} \quad . \tag{1}$$

This is a general form of the energy expression. The first four terms represent the covalent potential which is assumed to be harmonic in bond lengths (b), bond angles (θ), periodic and even in dihedral angles (ϕ), and harmonic in the improper torsion angle (ω).[13] The K's are the associated force constants. Hydrogen bonds are not included explicitly in the potential—the last two terms in the expression take care of these. These terms represent the noncovalent potential which is assumed to consist of a Lennard-Jones potential and Coulombic electrostatic contributions—here r_{ij} is interparticle distance, q_i atomic charge, and D is the static dielectric constant. In the vacuum case, $D=\epsilon_0$. In order to model the presence of solvent we have applied a distance-dependent dielectric constant, i.e., $D=\epsilon_0 r_{ij}$, which acts as an approximate solvent screening term in which the electrostatic interaction experiences a progressively larger attenuation as the two charges are separated. Further, an extended-atom representation has been used, i.e., one extended atom replaces a nonhydrogen (carbon) atom and any hydrogen atoms bonded to it. This approach has been implemented in the molecular-dynamics (MD) computer program CHARMM.[14] Essentially, the various force constants (K_x) have been obtained by fitting to vibrational data, while the geometric constants (b_0, etc.) have been derived from crystallographic data.[14] The force constants and the mass of the atoms determine the frequency of oscillation. The numerical scheme used to integrate Newton's equations of motion is based on the so-called central-difference approximation. It should be noted that the energy (kinetic as well as potential) can be partitioned into contributions from single atoms or groups of atoms.

We have applied CHARMM to build the 3D model of an α helix and to perform numerical experiments, see Ref. 12. The α helix considered is a polyalanine chain consisting of 72 amino acids which corresponds to 24 amino acids on each spine. Each amino acid consists of six atoms: N, H, C_α, C_β, C, and O. The termini were chosen as $-NH_3^+$ and $-COO^-$. The total number of atoms is 435 (the dynamics of each atom is described by three ordinary differential equations). For further details we refer to Ref. 12.

III. NUMERICAL RESULTS

In this section we present results from numerical experiments on the α-helix structure described above. The time step was 0.001 psec. In the present model the electric dipole moments of the carbonyl groups interact electrostatically through the Coulombic potentials in Eq. (1). Phonons will propagate along the molecule. Further, the amide-I vibration and the phonons are coupled through the nonlinear potentials in Eq. (1). The amide-I vibration is primarily a stretch and compression of the C=O bond. Thus a reasonable mode of excitation has been achieved by stretching the C=O bond in amino acid number 36 a distance Δa (the C and O atoms have been moved $\Delta a/2$ in opposite directions). We note that in the present model such an excitation will influence the bond angle and the torsion angle terms of Eq. (1) as well, albeit only slightly.

In Fig. 1(a) the potential-energy increase ΔE_{pot} is shown as a function of Δa. In this figure we have used a distant-dependent dielectric constant, which is a simple model of the effect of solvent. The picture is qualitatively the same for a constant dielectric constant modeling vacuum. Figure 1(a) shows the total potential energy as well as the contributions from the bond potential, the angle potential, and the electrostatic potential. The contributions from the van der Waals potential and improper potential are less than 1.15 kcal/mol and 0.23 kcal/mol, respectively. In order to evaluate the importance of anharmonicities, the difference δE_{pot} between a harmonic approximation for the potential energy and the actual potential has been displayed in Fig. 1(b). The approximation has been determined from the relation $\Delta E_{\text{harmonic}}=0.5k_{\text{harmonic}}\Delta a^2$, where k_{harmonic} is determined from $k_{\text{harmonic}}=2\Delta E/\Delta a$ and $\Delta a=0.02$. From Fig. 1(b) it is seen that for $\Delta a<0.12$ the deviation between the harmonic approximation of the potential energy and the actual potential energy is negligible. Thus the system is expected to be governed by dispersion in this range.

The influence of anharmonicity on the time evolution of amide-I oscillations is shown in Fig. 2. Again we have used a distance-dependent dielectric constant. Here the kinetic energy of each amino acid (n being the number of the amino acid) is calculated as the sum of the kinetic energies of its individual atoms. In Fig. 2(a), Δa is below

the threshold value for the onset of anharmonicities. In Ref. 12 it was shown (by means of a power spectrum of the total kinetic energy) that the main part of the energy is preserved as amide-I vibration energy. In Fig. 2(b) the anharmonicities influence the time evolution. A power spectrum shows that a large range of frequencies are activated in this case. Thus a linear approximation based on a single vibration frequency is not appropriate in this case.

In order to further elucidate the influence of anharmonicity on the time evolution of amide-I excitations we have displayed the kinetic energy as a function of time for a selected carbonyl group of the helix. Figure 3(a) shows the kinetic energy of the C=O group number 39. Here Δa is below the threshold value for the onset of anharmonicity. The excited mode is coherent in the sense that most of the energy is preserved as amide-I oscillations. In Fig. 3(b) we show the response when Δa is above the threshold value. Pronounced differences are observed. A large range of frequencies is activated because of the initial excitation.

IV. MODEL OF AMIDE-I EXCITATIONS BASED ON NORMAL MODES

In order to describe analytically the time evolutions observed for amide-I vibrations in the linear regime a model was proposed in Ref. 12. This model is based on a system consisting of point masses connected by linear springs (i.e., the potential describing the interaction between two masses is harmonic). The masses represent the amide-I oscillators and the springs represent the interaction (bonded and nonbonded) between the amide-I oscillators. In the following we show how the procedure presented in Ref. 12 can be generalized to systems consisting of n interacting residues. If periodic boundary conditions are assumed, solutions to the simple model can be found. Further, for single residue interaction the solution can be approximated by a Bessel function provided the coupling constant is small. The results from Sec. III indicate that each amino acid has two equal

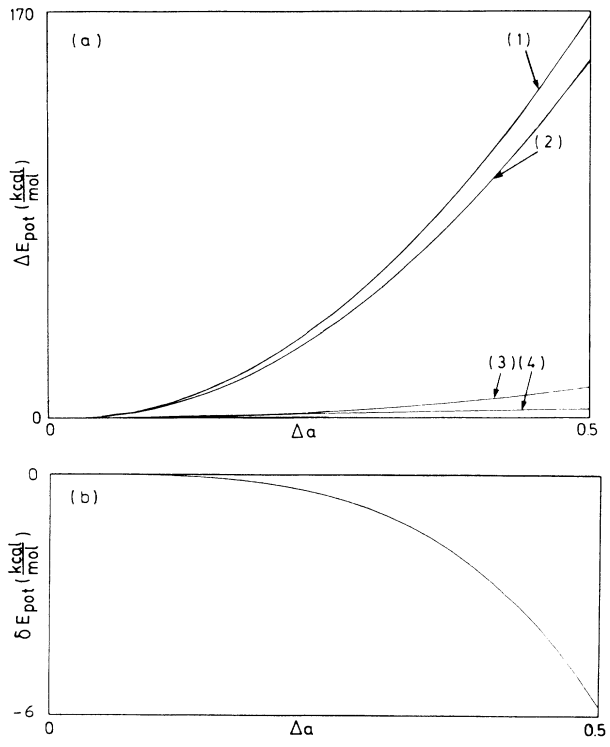

FIG. 1. (a) Total potential-energy increase as a function of C=O bond stretch for amino acid number 36, curve 1. The most important contributions to the potential energy are bond energy (2), angle energy (3), and electrostatic energy (4). (b) Deviation of the total potential energy from a harmonic approximation. The potential is harmonic for $\Delta a < 0.12$.

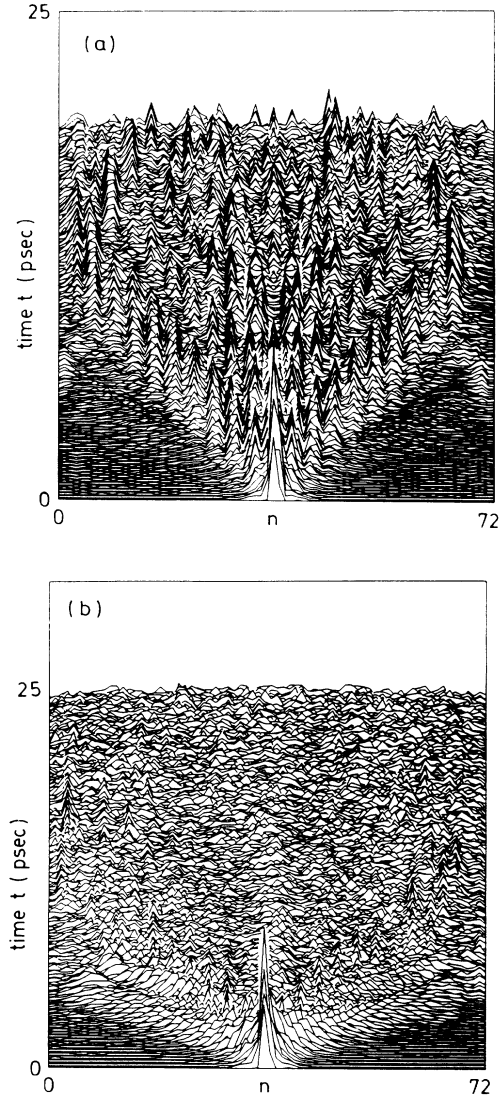

FIG. 2. (a) Time evolution of an amide-I excitation for $\Delta a = 0.1$. Total kinetic energy of each amino acid as a function of time (0–25 psec). Linear response. (b) Time evolution of an amide-I excitation for $\Delta a = 0.40$. Nonlinear response.

nearest- (bonded) neighbor interactions plus a third- and fourth-nearest- (nonbonded) neighbor interaction. The nearest-neighbor interactions represent interaction along the backbone, while the two other interactions represent the nonbonded interactions through potentials, i.e., van der Waals and electrostatic potentials. From the solution to the simple problem an estimate of these constants can be given. These constants give a quantitative measure of the importance of taking the backbone coupling into account when simplifying the 3D models.

Using the approach from Ref. 12, it is straightforward to express the force on the nth residue

$$m\ddot{u}_n = -k_0 u_n + \sum_{j=1}^{N} k_j (u_{n+j} + u_{n-j} - 2u_n) , \quad n = 1, \ldots, N . \tag{2}$$

Here u_n is the deviation of the internal coordinate (being the C=O group of nth residue) from its equilibrium position and m is the reduced mass of the C=O group. The "spring" constant k_0 is connected to the amide-I vibration frequency through the relation $k_0 = m\omega_0^2$. The other coupling constants describe bonded and nonbonded interaction constants. These constants are not given *a priori* but must be determined from numerical experiments. Using the expression $c_j = k_j/(m\omega_0^2)$ ($j = 1, \ldots, N$), Eq. (2) yields

$$\ddot{u}_n = -\omega_0^2 u_n + \omega_0^2 \sum_{j=1}^{N} c_j (u_{n+j} + u_{n-j} - 2u_n) , \quad n = 1, \ldots, N . \tag{3}$$

Now we introduce the variable $x = na$, where a is the equilibrium distance between two C=O oscillators along the backbone and look for traveling-wave solutions to Eq. (3) of the type $u = e^{i(kx - \omega t)}$. Insertion of this function into Eq. (3) gives the dispersion relation

$$\omega^2(k) = \omega_0^2 \left[1 + \sum_{j=1}^{N} c_j \sin^2 jka/2 \right] . \tag{4}$$

In order to determine the relation between k and a we assume periodic-boundary conditions

$$u_{n+N} = u_n . \tag{5}$$

This assumption is of course only valid as long as the excitation has not reached the terminations of the helix. From Fig. 2(a) is seen that this assumption is valid for the first 12.5 psec. In these experiments, however, the boundary conditions at $n = 1$ and $n = N$ approximate periodic-boundary conditions, i.e., the excitations are reflected at the ends without any phase jumps. Insertion of Eq. (5) into the traveling-wave solution yields

$$ka/2 = n\pi/N . \tag{6}$$

Now the solution to Eq. (2) imposing the initial value problem consisting of a single amide-I vibration is given by

$$u_j(t) = \sum_{n=1}^{N} e^{i[2\pi n/N(j - j_0) - \omega(n)t]} , \tag{7}$$

where $u_j(t)$ is the displacement of residue j, $\omega(n)$ is given by Eq. (4), and the excitation has been initiated in residue $j_0 = 36$. Similar solutions can be found for other initial excitations, e.g., a triple excitation, see Ref. 12. The solution of Eq. (7) represents the situation where all amide-I oscillators interact.

In order to determine the constants c_1, c_3, and c_4 we have fitted the constants, such that Eq. (7) reproduces the numerical results in Fig. 2(a). This has been done by visual comparison. Using these constants the time evolution for the first 15 psec is reproduced extremely well, see Ref. 12. The results are shown in Table I. The constant c_1 determines the slow modulation, while the two other constants influence the fine structure. The signs of the constants c_i can be understood from the geometry of the helix—the spiral structure requires opposite signs for the nearest-neighbor interaction constant and the two other

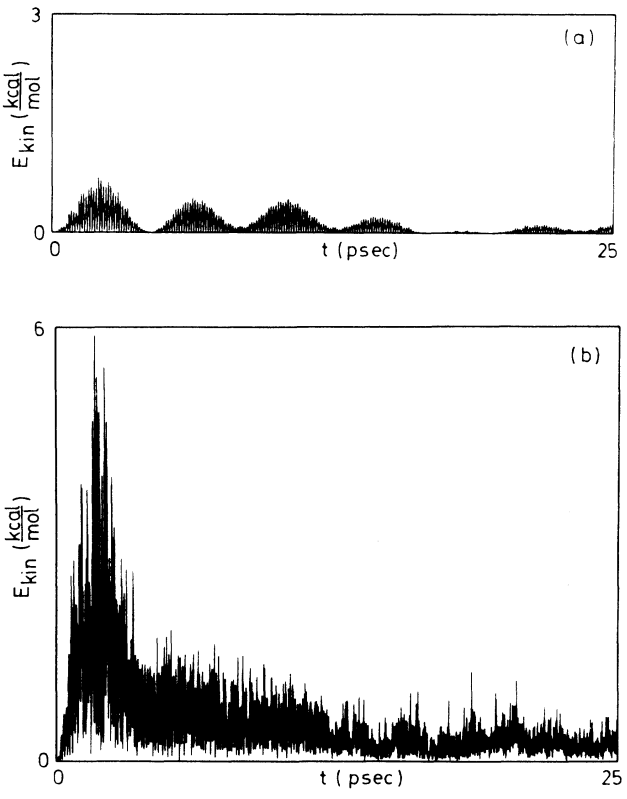

FIG. 3. Time evolution of C=O energy on amino acid number 36. (a) $\Delta a = 0.1$, linear response. (b) $\Delta a = 0.4$, nonlinear response.

TABLE I. Coupling constants describing bonded and nonbonded interactions determined numerically.

	c_1	c_3	c_4
Solvent	−0.0016	0.0010	0.0003
No solvent	−0.0020	0.0014	0.0005

constants. It is seen from Table I that the coupling along the backbone is approximately 50% stronger than the coupling along the spines. Thus the present rather elaborate, molecular-mechanics model shows no evidence of spines, which can be used as an argument for the simplification of the 3D problem to a 1D problem. It is at least obvious that the coupling along the backbone should be considered.

Finally, in this section we show how the solution to Eq. (2), Eq. (7), can be approximated by a Bessel function if only single-neighbor interaction is assumed and provided that the coupling constant is small.

For $|c_j| \ll 1$, Eq. (4) can be approximated by

$$\omega(k)=\omega_0\left[1-0.5\sum_{j=1}^{N} c_j[1-\cos(jka)]\right] . \tag{8}$$

If only single-residue interaction (i.e., jth-nearest-neighbor interaction) is assumed, we get for the modulation of the displacement [being the real part of Eq. (7)] for residue number i

$$A_i(t)=(1/2\pi) \times \sum_{n=1}^{N} (2\pi/N)\cos[(2\pi n/N)(i-i_0) +(c_j\omega_0 t/2)\cos(j2\pi/N)] , \tag{9}$$

which can be approximated by

$$A_j(t)=1/(2\pi j)\int_0^{2\pi j} dx\ \cos[x(i-i_0)/j+(c_j\omega_0 t/2)\cos x] =J_{(i-i_0)/j}(-c_j\omega_0 t/2) . \tag{10}$$

Here i_0 is the residue where the initial excitation is placed and J is the Bessel function of order $(i-i_0)/j$. This expression reproduces the first time interval ($t<7.5$ psec) in the numerical experiments, provided that $\Delta a<0.12$ Å.

V. CONCLUSION

In the present work we have examined dynamic aspects of α-helical structures modeled in three spatial dimensions. The model is based on a molecular-mechanics approach. Numerical experiments have been performed in order to evaluate the assumption used in the development of 1D models namely that the 3D problem can be reduced to a 1D problem by considering only the hydrogen bonded spines in the helix.

First, we note that the system is linear for energies corresponding to an initial stretching, Δa, less than 0.12 Å, which means that dispersion governs the time evolution of excitations. In this region a simple linear approach can essentially explain the time evolution of amide-I vibrations. For values of Δa larger than this threshold value a wide range of frequencies is activated.

Second, an estimate of the magnitudes of the coupling constants can be obtained from the simple linear approach. Thus coupling along the backbone is found to be the most important, while the coupling along the spine is just two-thirds of the backbone coupling. The present, rather elaborate, molecular-mechanics model shows no evidence for the existence of nonbonded directions in the helix which can serve as an argument for the reduction of the 3D problem to a 1D problem.

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