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Replica-exchange molecular dynamics simulation of small peptide in water and in ethanol

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Abstract

Replica-exchange molecular dynamics simulations have been performed on a 10-residue peptide in ethanol as well as in water that were treated explicitly with 32 replicas in the range of 298–600 K. It has been found that the peptide tends to form compact structures in ethanol whereas it is extended in water. The numbers of intramolecular hydrogen bonds and turn structures are both larger in ethanol than in water, and this difference enhances the tendency of forming secondary structures in ethanol.

1. Introduction

Alcohol-induced denaturation of peptides and proteins that enhances the α-helical structure has widely been used in protein technology [1]. Solvent effects on denaturation of proteins have often been discussed in terms of electrostatic interactions by treating medium as a dielectric continuum in biophysics and biochemistry fields, but the underlying mechanism has yet to be clarified at the microscopic level [2]. Kinoshita et al. [3] applied the reference interaction site model (RISM) theory to calculate the thermodynamic properties of various conformations of Met-enkephalin and C-peptide fragment of ribonuclease A in methanol, ethanol, and water. Their results showed that alcohols facilitate the peptide molecules to form the secondary structures with intramolecular hydrogen bonds such as the α-helix. They concluded that the free energy of solvation in alcohols becomes less dependent on the conformational change than in water because of less solvation number of peptide in alcohols than that in water and that the conformational stability in alcohols is governed mostly by the conformational energy [3]. However, these results are based on calculations of solvation energy of a few fixed solute structures [3]. They selected a few typical structures of the peptide (native, extended, in vacuum, and others). Because the solute molecules in water and in ethanol are always changing their structures, the solute and solvent molecules should be treated on an equal basis to discuss the solvent effects more exactly.

Recently, we have investigated liquid structures in *tert*-butanol (TBA)–water mixtures without peptides with a RISM theory [4]. The calculated radial distribution functions showed that hydrogen-bond formation between hydrophilic pairs was enhanced as the concentration of large hydrophobic TBA increases (here water was treated as a hydrophilic molecule). It is thus expected that hydrophilic interactions within peptides are more enhanced in ethanol than in water [4].

In simulations of protein folding, a generalized-ensemble algorithm has been proven effective because

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it overcomes the common problem in protein simulations that they can easily get trapped in one of a huge number of local-minimum-energy states (for a review, see [5]). In the present study, one of the generalized-ensemble algorithms called the replica-exchange molecular dynamics (REMD) [6] was performed with a 10-residue model peptide in water and in ethanol that were treated explicitly as individual molecules in order to compare solvent effects on the peptide conformations. We have indeed observed quite significant differences in the behaviors of the peptide in these solvents.

2. Methods

A model peptide of 10 residues was taken from the α-helix part of 28-residue designed peptide with β–β–α motif whose 3D structure have been determined by 2D NMR [7]. The amino-acid sequence is GLU$^-$-LEU-ARG$^+$-ASP$^-$-PHE-ILE-GLU$^-$-LYS$^+$-PHE-LYS$^+$. The N-terminus and the C-terminus were taken to be the usual zwitter ionic groups (NH_3^+ and COO^-, respectively). REMD [6] was incorporated in the MD package program DL_POLY [8]. The utilities of DL_PROTEIN [9], which is a version of DL_POLY specified for larger and complex biomolecular simulations, were used to construct the input files for the model peptide. The force-field parameters were taken from CHARMM22 [10,11]. For water and ethanol, the TIP3P model [12] and the OPLS united atom model [13] were used, respectively. Periodic boundary conditions were imposed. The unit cell sizes of water and ethanol systems were 31.08 and 41.03 Å, respectively, which were determined from the densities of the corresponding bulk solvents at 298 K and 0.1 MPa. The volume of the cell was fixed and the temperature was controlled by the Berendsen method (NVT ensemble). The potential cut-off distance for the Lennard-Jones interactions was 10 Å. The electrostatic interaction was calculated by the Ewald method. The structure of the model peptide was taken from the corresponding part of the PDB file (PDB code: 1FSD) and solvated in water. The solvent molecules within 1.5 Å from the atoms of the peptide were removed. The numbers of water and ethanol molecules finally adopted were 910 and 702, respectively. The time step was set to 1.0 fs. A canonical MD simulation of this system was performed at 600 K for 100 ps (i.e., 10^5 MD steps), from which we randomly extracted an extended structure of the peptide without any secondary structures. This structure was used as the initial conformation for all the replicas in both solvent conditions.

Replicas at 32 temperatures from 298 to 600 K were used for the REMD simulations. Their values were 298, 305, 311, 316, 323, 330, 337, 345, 353, 361, 369, 378, 387, 396, 405, 414, 424, 433, 443, 454, 464, 475, 486, 498, 510, 523, 535, 547, 560, 573, 587, and 600 K. After an equilibration canonical MD run at each temperature for 10 ps, a production REMD simulation of 10^6 time steps (1.0 ns) for each replica was finally performed. Replica exchange was tried every 100 MD steps (0.1 ps). The data from trajectories were stored every 1000 MD steps (1 ps) for later analysis.

3. Results and discussion

3.1. Results of REMD simulations

We first examine whether the REMD simulations were performed properly. Each replica of the REMD simulations should realize a random walk in the temperature space, which in turn induces a random walk in the potential energy space. We depict in Fig. 1 the time series of temperature and potential energy for one of the replicas during the REMD simulation in ethanol. We observe a random walk between the lowest temperature (298 K) and the highest temperature (600 K) in Fig. 1a. Likewise, we do observe in Fig. 1b a random walk in the potential energy space, which covers a range as large as ≈2300 kcal mol^{-1}. Note that there is a strong

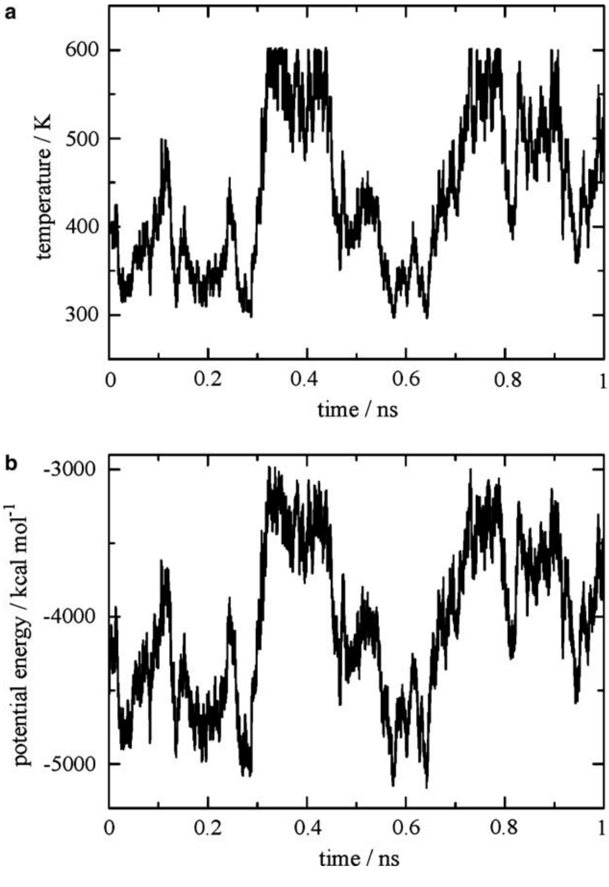

Fig. 1. Time series of: (a) temperature and (b) total potential energy in ethanol for one of the replicas.