DYNAMICS OF A SMALL PEPTIDE SIMULATED IN WATER MODELS WITH VARYING VISCOCITY

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Summary The following paper concerns analysis of structure and dynamics of peptides in solution. We have studied the dipeptide N-acetyl-trypthophanamide (NATA) in water using molecular dynamics simulations, with solvent viscosity tuned by mass scaling. Increasing the viscosity of water had strong effects on the external and internal dynamics of NATA peptide. As expected, the rates of external peptide motions, describing overall translations and rotations, were inversely proportional to the effective solvent viscosity. Internal motions, representing conformational transitions, which may exhibited a more complicated pattern of change, will be studied in future work. Numerical results from molecular dynamics simulations were also compared with experimental measurements obtained by fluorescence anisotropy decay.

INTRODUCTION

The dynamics of small peptides have been considered numerically and experimentally [1-3]. The fundamental behavior of small peptides, like NATA, give us information about the internal and external dynamics of the basic biological protein systems immersed in the liquids with different viscosity. Interactions of biological particles with the solvent are manifested by a conformation changes of the molecule and its translation and reorientation in relation to the molecules of the solvent in which the particle is located [3]. The study of reorientation of the biological particles allows the recognition and isolation of the preferred behaviors of molecules in a contact with specific solvent. In this work, molecular simulations of peptide dynamics are compared with experimentally available measurements to verify the numerical results and microscopic effects that are difficult to investigate in the lab. The purpose of this analysis was to study the influence the solvent viscosity on the internal and external dynamics of the NATA peptide.

METHODS

Molecular dynamics (MD) simulations were used to study the behavior of NATA (see Fig.2) in a water-based liquid. Simulations of a single NATA molecule placed in water were performed using the GROMACS program with the OPLS/AA force field [4]. The TIP3P model was chosen for water modeling. Calculations of NATA peptide in a box of 1185 molecules of water were performed at the temperature T=300K using periodic boundary conditions in canonical ensemble (NVT) with the Nose–Hoover thermostat. To vary the viscosity of the liquid surrounding the peptide without changing the potential energy parameters, an artificial method of increasing the mass of the water molecule was used. With increasing the mass m in the molecular model, the viscosity of the modeled fluid increases proportionally to $m^{1/2}$. Numerical calculations were made for liquid models with viscosity $\eta = n \cdot \eta_0$, where n = 1,2,3,4,5 and η_0 is the basic viscosity of the the regular TIP3P model [7]. 200-nanosecond all-atom trajectories of NATA in water were generated with the five mass-scaled water models. The trajectories were analyzed by calculating peptide and solvent translational and rotational diffusion coefficients, as well as by following changes in internal structure like end-to-end distance and backbone and sidechain dihedral angles. Parameters calculated from the molecular dynamics simulations were compared with experimental measurements obtained for NATA in water [3].

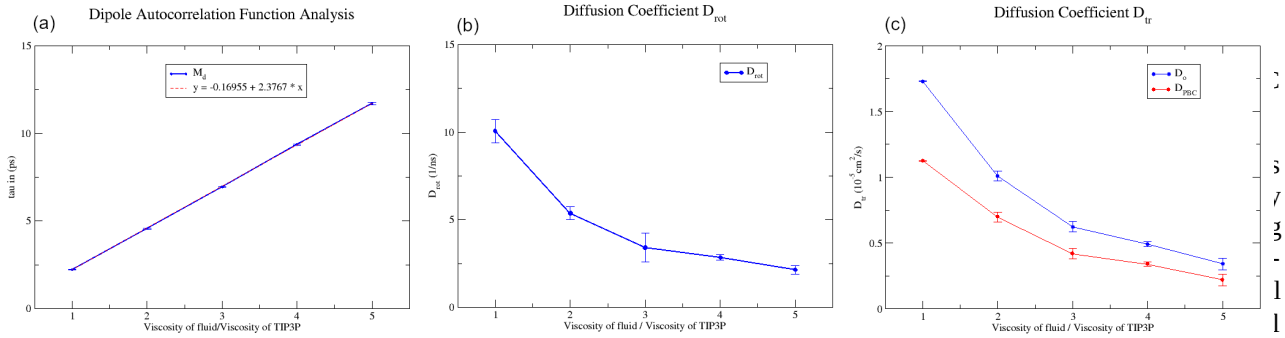
RESULTS

Numerical studies of the peptide dynamics were concentrated on determining how the change of viscosity of the solvent effects peptide behavior. Studying this phenomenon, first of all, the viscosity of the solutions surrounding the peptide were calculated. According to the fact, that the water viscosity is proportional to the rotational orientation time τ for dipoles [2], we determined the reorientation time τ from simulations for different models of solvent comparing the results with the assumed relative viscosity of the solution η . As is shown on the graph (see Figure 1a), the dependence between the reorientation times τ and modeled viscosity of solvent is linear and reproduce very well the expected hydrodynamical relation between these parameters.

Analyzing the external dynamics of NATA in different solutions, the translational D_{tr} and rotational D_{rot} diffusion coefficients of the peptide were calculated and presented in Figure 1b and 1c. Taking into account the hydrodynamic correction due to the difference between the Stokes friction in an infinite system and in a system under periodic boundary conditions (PBC), the parameters were recalculated with respect to the following forms:

$D_{rot} = D^r_{PBC} + \frac{k_b T}{6\eta V}$ (1) and $D_{tr} = D^t_{PBC} + \frac{k_b T \xi}{6\pi\eta L}$ (2), where D^r_{PBC} , D^t_{PBC} are the diffusion coefficients from PBC simulations (rotational and translational respectively), k_B- Boltzmann constant, T – temperature, ξ=2.837297, η -

TIP3P water viscosity, V – volume of the calculated box and L –length of the simulated cell [5,6]. In Figure 1c, the red line represents D^{t}_{PBC} values obtained from simulations and the blue line D_{tr} after correction for PBC effects, illustrating relatively large influence of the geometry of the simulation box on the global diffusion coefficient values.



dynamics of NATA by proportional increasing of characteristic relaxation times. MD results are consisted with results obtained experimentally.

The natural follow-up question is, how does the internal dynamics of the peptide react to the increasing of the solvent viscosity. The detailed analysis of this problem will be realized in future studies based on results obtained from structural clustering of peptide conformers and investigation of the kinetics of transitions between preferred conformers of NATA in water-based solutions with different viscosity (Figure 2).

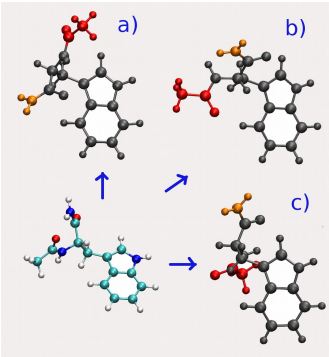


Figure 2. NATA molecule – typical conformations from MD simulation in TIP3P water (molecules of water not shown).

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