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Thermal compaction of the intrinsically disordered protein tau: entropic, structural, and hydrophobic factors

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1 Fit of SAXS curves

We report in Fig. 1 the residuals of the fits of the SAXS data at 293 K and 333 K shown in Fig. 3 and Fig. 4 of the article. The fits have been obtained by means of the EOM procedure applied to the pools of conformers produced by 10 ns of metadynamics simulations at the two temperatures.

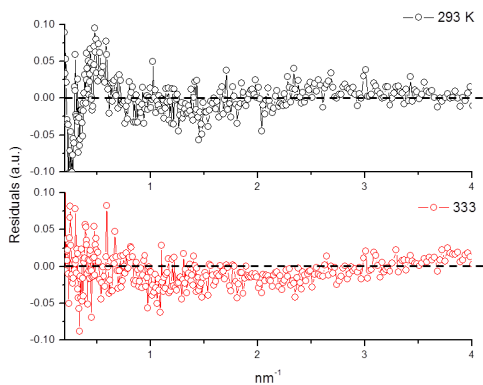


Fig. 1 Residuals of the fit of the SAXS curves shown in Fig. 3 and in Fig. 4 of the article. Here the vertical scale is linear.

2 H-bonds

We report in Fig. 2 the number of intra-molecular H-Bonds as a function of the corresponding value of R_g . The average values in Table 4 increase with the temperature, and Fig. 2 clearly shows that all the lowest values (below 140) belong to the low temperature simulation C1, while all the highest values (above 200) belong to the high temperature simulation C2; but the bulk of the values in the intermediate range can belong to either temperature.

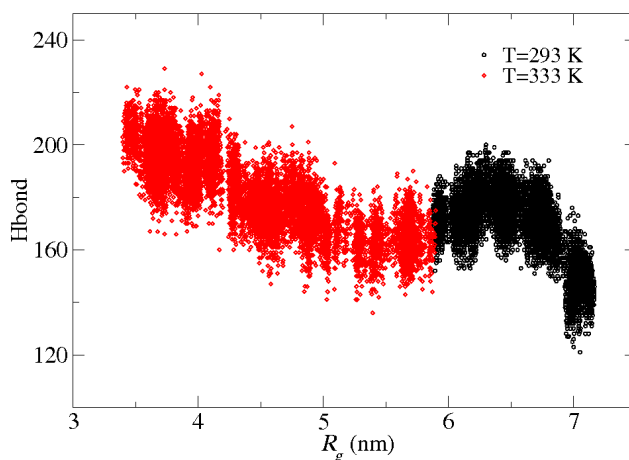


Fig. 2 Number of intramolecular H-bonds vs. R_g for configurations recorded at 1 ps intervals during the 10 ns MD runs in explicit water.

3 Metadynamics simulation

The time evolution of R_g displayed in Fig. 3 shows how the metadynamics algorithm forces the system to leave the regions of the phase space already explored, and to wander in other regions of the phase space. The system thus samples a portion of the phase space much larger than the one sampled in an equal time of a standard molecular dynamics (MD) simulation [†].

The many large oscillations of the variable highlight the extension of the phase space sampling, and their growing amplitude reflects the molecule's progressive wandering in less populated regions of the phase space.

The time evolution of R_g in Fig. 3 shows that the overall structure of the molecule, from time to time, is in a basin of local equilibrium, moving then from one basin to another under the action of the metadynamics algorithm. When the molecule is temporarily trapped in an energy well, this algorithm progressively “fills” the well, reducing the amplitude of the oscillations until the molecule is forced to leave the well and move to a different region of the phase space. This feature of the dynamics is shown by the darker spots in Fig. 3; as the dynamics progresses and the wells are “filled”, their number diminishes. An enlargement of three of these spots, corresponding to the sections framed in

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[†]The collective variable used to implement the metadynamics method was the gyration radius. The metadynamics parameters were set as follows: $CV = R_g$; deposition stride $\tau = 10$ ps; height $W = 0.5$ kJ/mol; Gaussian width $\sigma = 0.35$ nm; limits on R_g : upper $UWALL = 7.0$ nm, lower $LWALL = 5.5$ nm.

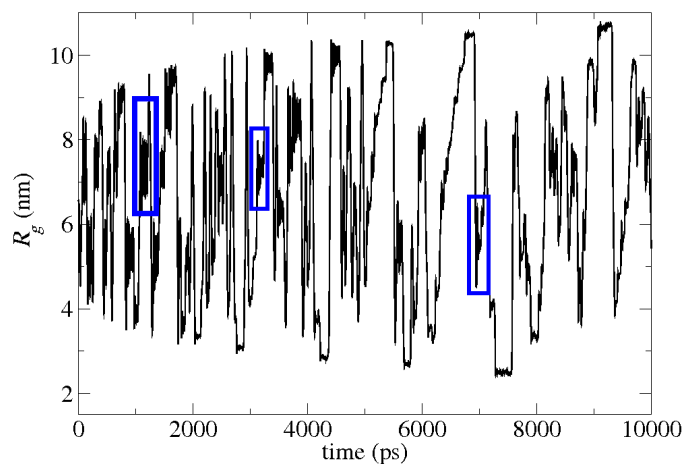


Fig. 3 Time evolution of the radius of gyration of protein tau during the metadynamics simulation at $T = 293$ K in implicit water. The experimental average value of R_g is 6.9 nm, the standard deviation 0.2 nm. The areas framed in blue are expanded in Fig. 4.

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The metadynamics algorithm progressively forces the system to span less probable regions of the phase space; this can be seen in

Fig. 3, where R_g reaches progressively more extreme values. As a consequence, the conformers selected by the EOM method are not evenly distributed in the 10 ns metadynamics. As an example, taking into account the multiplicity of the conformers, less than 16% of the selected ensemble at $T = 293$ K turns out to be located in the second half of the dynamics.

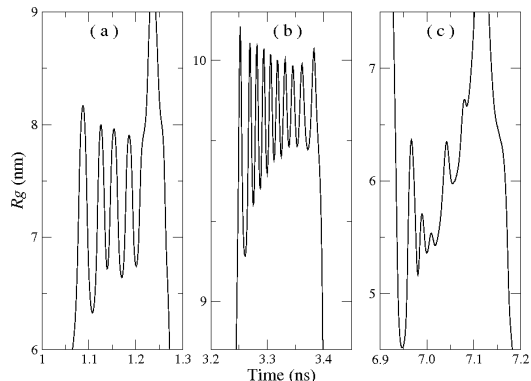


Fig. 4 Time evolution of the radius of gyration of protein tau during the metadynamics at $T = 293$ K in implicit water. The oscillations in each time segment correspond to a transitory stay in an energy well.