Dipolar nanodomains in protein hydration shells. Supporting Information

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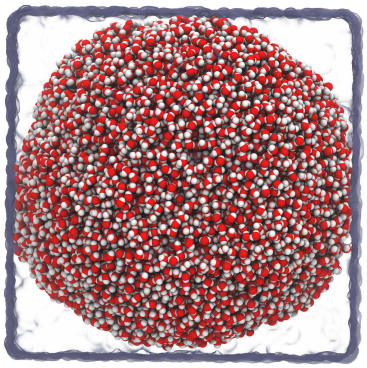

FIG. S1. The hydration shell 30 Å thick around lysozyme (not shown) displayed in respect to the simulation box.

I. GENERAL SYSTEM SETUP AND SIMULATION DETAILS

Molecular Dynamics (MD) simulations were performed for the solvated lysozyme system using the initial structure PDB entry 3FE0 solvated with TIP3P water. The simulation cell contained a total of 85056 atoms, with 27673 water molecules and 8 Cl^- ions to neutralize the system (the total charge of lysozyme in the simulation box was +8). An initial optimization of the simulation cell was performed using the conjugate gradient minimization for 10000 steps, followed by a 20–40 ns NPT equilibration run depending on the temperature. Longer equilibration was required for lower temperatures. The constant pressure-temperature equilibration simulations were done using the Langevin temperature-pressure control with the damping coefficient of 5 ps^{-1}, a piston pressure of 1 atm, a piston decay time of 50 fs, and a piston oscillation period of 100 fs.

Proceeding from this equilibration run, production simulations were carried out for 100–200 ns under the NVE simulation protocol: 100 ns runs at $T > 190$ K and 200 ns runs at $T < 190$ K. Overall, twelve different temperatures (140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280 and 300 K) were studied. All simulations (both NPT and NVE) were performed with a 2.0 fs timestep, a cutoff radius of 12 Å, and full electrostatics using the particle mesh Ewald (PME) technique. NAMD 2.8[1] with the CHARMM27 force field was used to produce the MD trajectories. The NVE production runs 20-40 ns long were separated by additional 5 ns NPT runs to stabilize the temperature.

The analysis of the hydration shells around the protein was performed by varying their thickness a measured from the van der Waals surface of the protein. The range of a values is limited by 30 Å in order to avoid potential artifacts from the finite size of the simulation shell. Figure S1 shows that the shell with $a = 30$ Å fits the simulation cell without including the periodic images of the water molecules within the cell.

Since lysozyme is not spherical, the hydration shell is most closely an ellipsoid. We have analyzed the distance between the hydration shell and the edges of the simulation box along the simulation trajectory. The hydration shell starts touching the side of the box along the longest axis of the ellipsoid at the shell size of $24-26$ Å depending on the temperature.

II. p_1 AND p_2 ORIENTATIONAL ORDER PARAMETERS

The one-particle order-parameters of waters in the hydration shell of lysozyme are defined as

$$p_1^i = \hat{\boldsymbol{m}}_i \cdot \hat{\mathbf{r}}_i \tag{S1}$$

and

$$p_2^i = \frac{1}{2}\left[3(\hat{\boldsymbol{m}}_i \cdot \hat{\mathbf{r}}_i)^2 - 1\right] , \tag{S2}$$

where $\hat{\boldsymbol{m}}_i$ is the unit vector along the water's dipole moment and $\hat{\mathbf{r}}_i$ is the unit vector connecting the water oxygen to the protein atom closest to it.

The calculation of p_1^i and p_2^i for lysozyme's amino acids first involved the location of the closest water to each lysozyme atom. This means that for each atom in lysozyme, there is initially a single water molecule associated with it. After this list of water molecules is determined, the cut-off distance is applied: if the position of the center-of-mass of the water molecule falls within the cut-off distance, then the calculation of p_1^i and p_2^i for that water is performed. The values of these two parameters are accumulated for each protein atom along the simulation trajectory, updating the closest water list at each frame. The results presented in Figure 1 in the main text are for those water molecules identified in the calculation with $r_i < 3$ Å and averaged over 20 ns long trajectories of the hydrated lysozyme.

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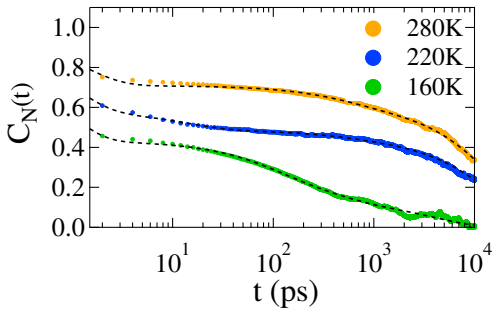

FIG. S2. Time autocorrelation function of the number of waters in the hydration shell of lysozyme of $a = 3$ Å thick. The points are simulation data and the lines are fits to two-exponential decay functions. Shown are the results at different temperatures indicated in the plot.

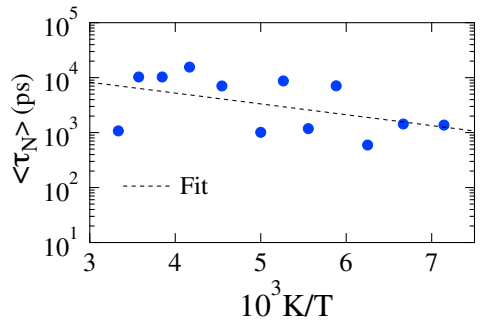

FIG. S3. Average relaxation time determined from the time autocorrelation function $C_N(t)$ of the number of waters in the hydration shell of lysozyme of $a = 3$ Å thick. The points are relaxation times determined from eq S3 and the straight line is the fit with the slope $H_a = -0.9$ kcal/mol.

III. DENSITY DYNAMICS OF THE HYDRATION SHELL

The density dynamic of the hydration shell was studied by recording trajectories of the number of waters in the shell $N(t)$ of thickness $a = 3$ Å extended from the van der Waals surface of the protein. The time autocorrelation function $C_N(t) = \langle \delta N(t) \delta N(0) \rangle$ was calculated, where $\delta N(t) = N(t) - \langle N \rangle$. These functions were calculated at different temperatures and fitted to the bi-exponential decay function. The average relaxation time was calculated according to the equation

$$\tau_N = \int_0^\infty C_N(t)/C_N(0) dt. \qquad \text{(S3)}$$

As is seen already from Figure S2, the decay of density fluctuations becomes faster with lowering temperature. This is confirmed in Figure S3 displaying the Arrhenius plot of the average relaxation time. The relaxation time shows a negative activation enthalpy of $H_a = -0.9$ kcal/mol.

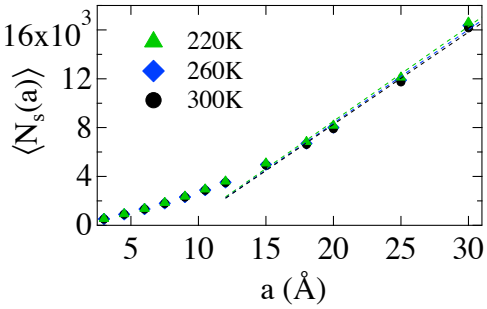

FIG. S4. The number of waters in hydration shells of lysozyme at different temperatures.

Figure S4 shows the number of water molecules in the shells of thickness a at different temperatures. The function $\langle N_s(a) \rangle$ can be approximated by a straight line at $a \geq 15$ Å, as shown by the dashed lines in the plot.

REFERENCES

[1] J. C. Phillips, R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R. D. Skeel, L. Kale, and K. Schulten, J. Comp. Chem. **26**, 1781 (2005).