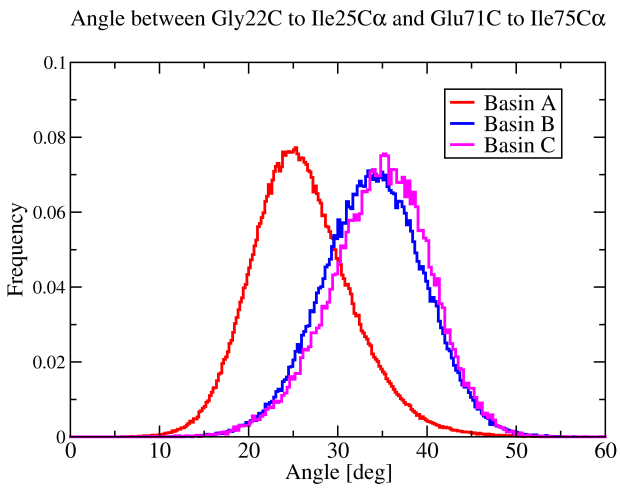

Figure 1: **Basin specific histograms for alternative tilting angle.** Histograms of $\alpha 2$ tilting angle for subbasins A, B and C. For subbasin A the average angle is 26 with a standard deviation of 6, for subbasin B it is $average = 34 \pm 6$, and for subbasin C $average = 35 \pm 6$.

Supplementary Material for: Peptide binding to the PDZ3 domain by conformational selection

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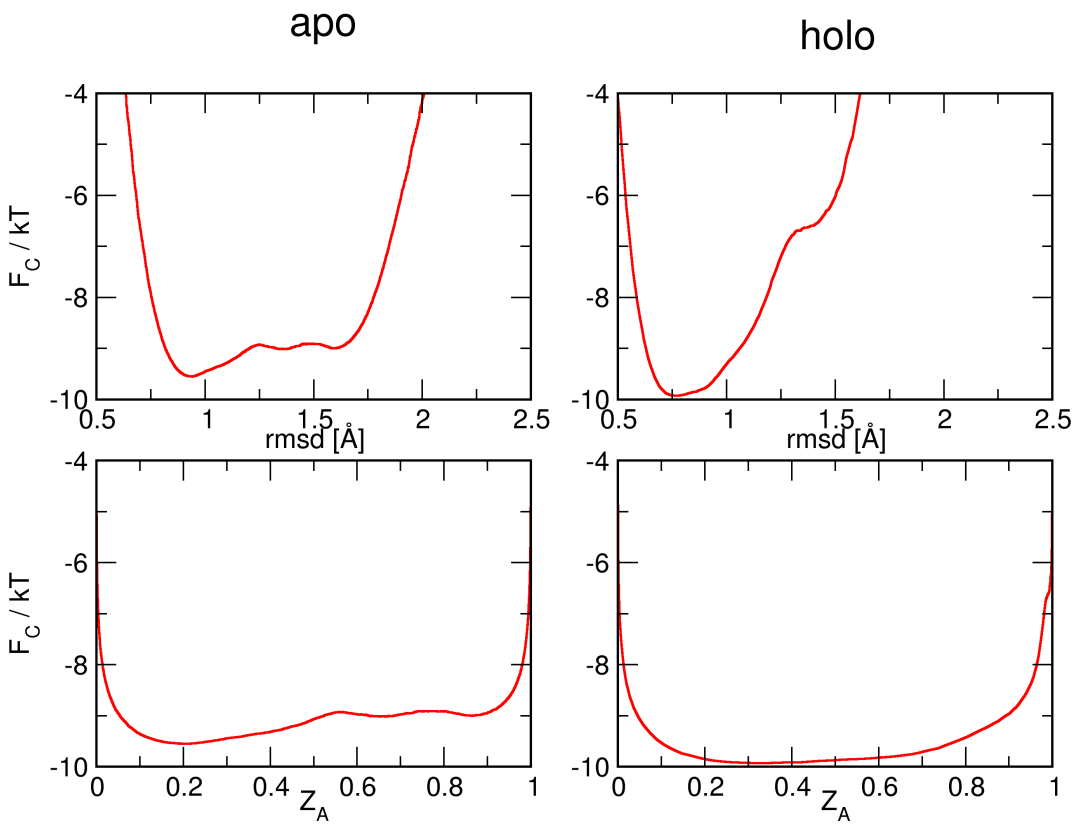

Figure S1: **Cut-based free energy profiles for apo and holo PDZ3.** The root mean square deviation (RMSD) of the C_α atomss of residues 6 to 97 from the first frame computed along the apo or holo trajectory was used as reaction coordinate (RC). The top plots show the profiles projected onto the RMSD while the bottom plots show the projection onto the relative partition function Z_A as introduced by Krivov[31]. Apo PDZ3 shows three distinguishable subbasins while the profile of holo PDZ3 consists of a single free energy basin. The lack of barriers for holo PDZ3 hinders the optimization of RC. For apo PDZ3, the cut-based free energy profile projected onto the optimized RC is shown in S2.

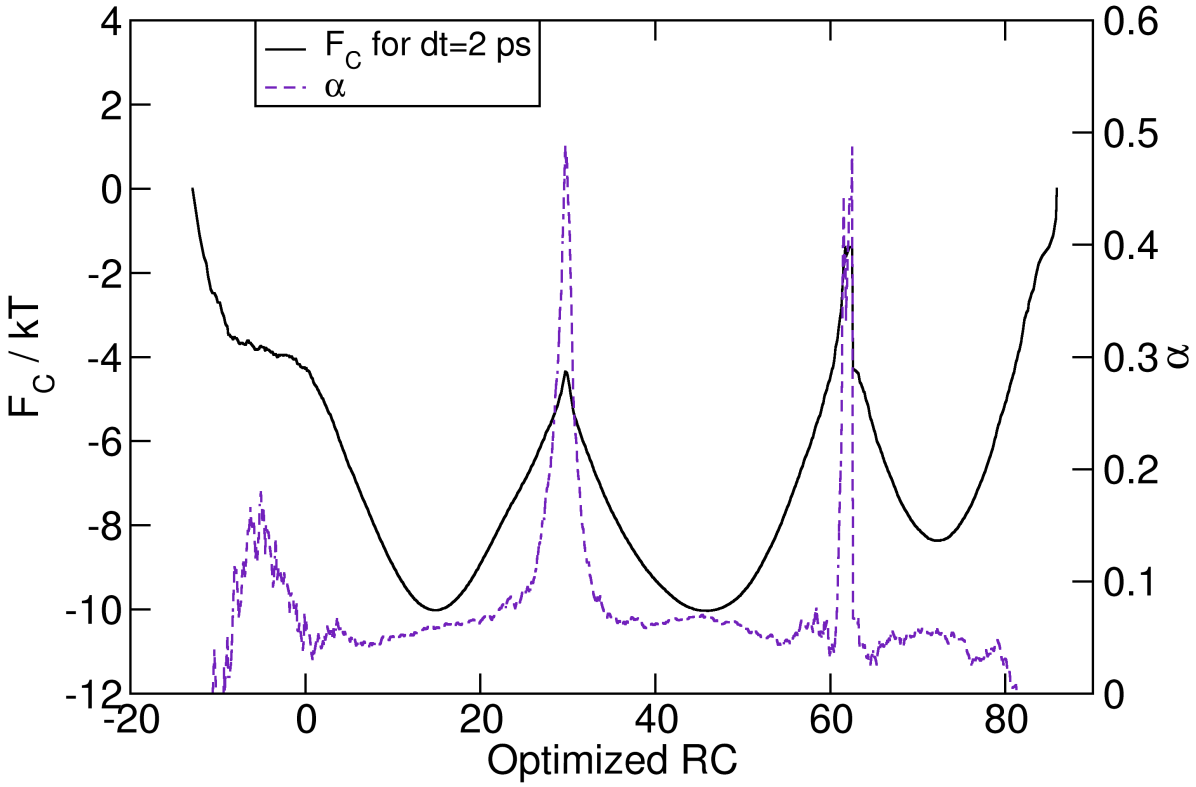

Figure S2: **Free energy profile of apo PDZ3 along optimized RC.** The cut-based free energy F_C along the optimized RC (seed coordinate was RMSD) for sampling interval $dt = 2$ ps (solid line) together with the sub-diffusion coefficient α (dashed line). Three free energy subbasins are present and they correspond to the subbasins observed when constructing the cFEP using RMSD as RC.

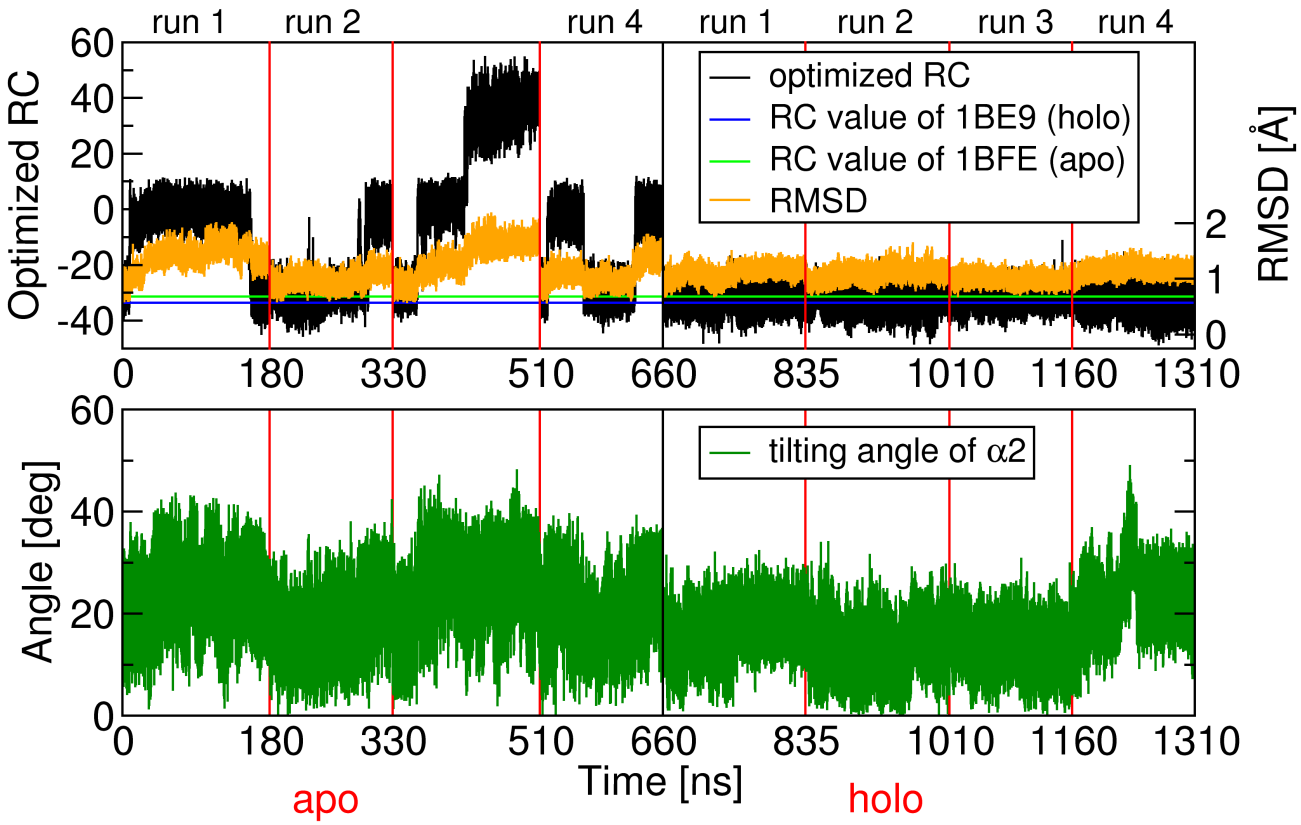

Figure S3: **Tilting angle and optimized RC.** Time series of tilting angle between $\alpha 2$ and $\beta 2$ (green, bottom panel) along the total trajectory together with the time series of the RMSD (orange, top panel, y-axis on the right) and the optimized RC (black, top panel, y-axis on the left). The tilting angle between $\alpha 2$ and $\beta 2$ was computed as the angle between two directional vectors given by $\beta 2$ (from C_α of Ile25 to carbonyl C of Gly22) and $\alpha 2$ (from carbonyl C of Glu71 to carbonyl C of Lys78). Vertical lines indicate the beginning/end of each MD run and the black vertical line separates apo from holo runs. The values of the optimized RC of the X-ray structures of apo (pdb code 1BFE) and holo (pdb code 1BE9)[3] are shown with green and blue horizontal lines, respectively (top panel).

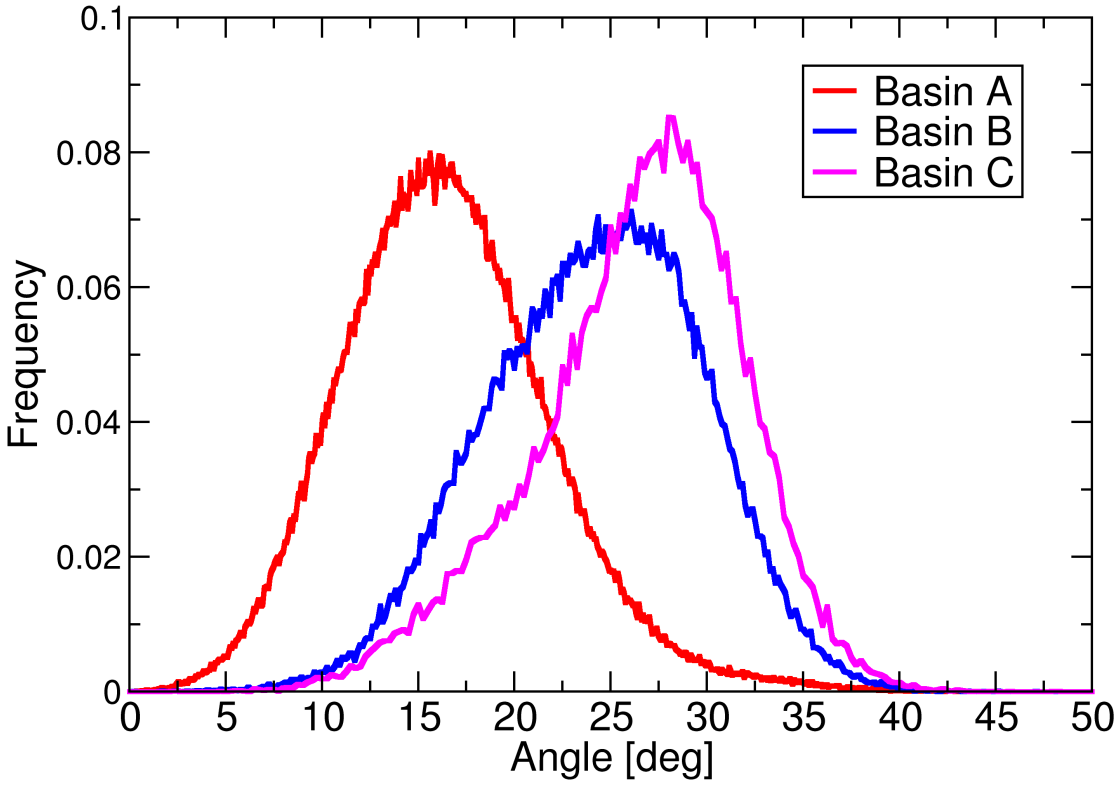

Figure S4: **Basin specific histograms for the tilting angle.** Histograms of $\alpha 2$ tilting angle for subbasins A, B and C. For subbasin A the average angle is 16 with a standard deviation of 5, for subbasin B it is average $= 24 \pm 6$, and for subbasin C average $= 26 \pm 5$.

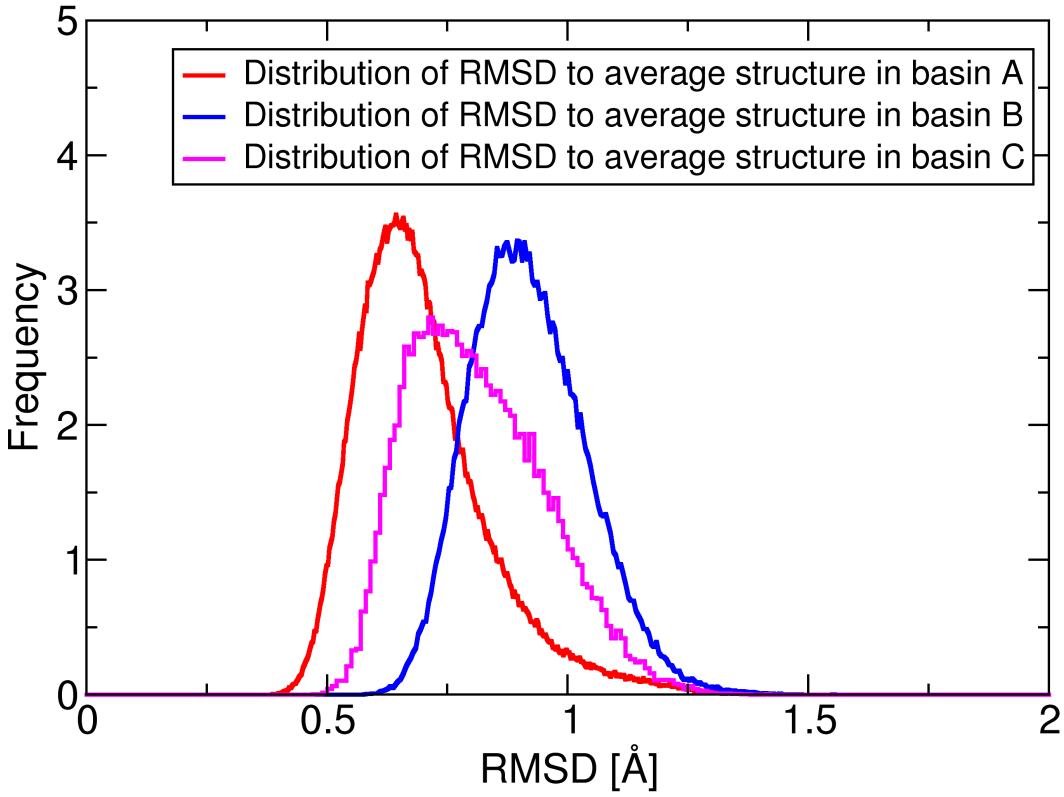

Figure S5: **Basin specific histograms of RMSD values from average structure.** For each basin the average structure was computed in order to find a representative snapshot. Here histograms of RMSD values from average structure within the respective basins are plotted. The RMSD was computed for the C_α atoms of residues 6 to 97.

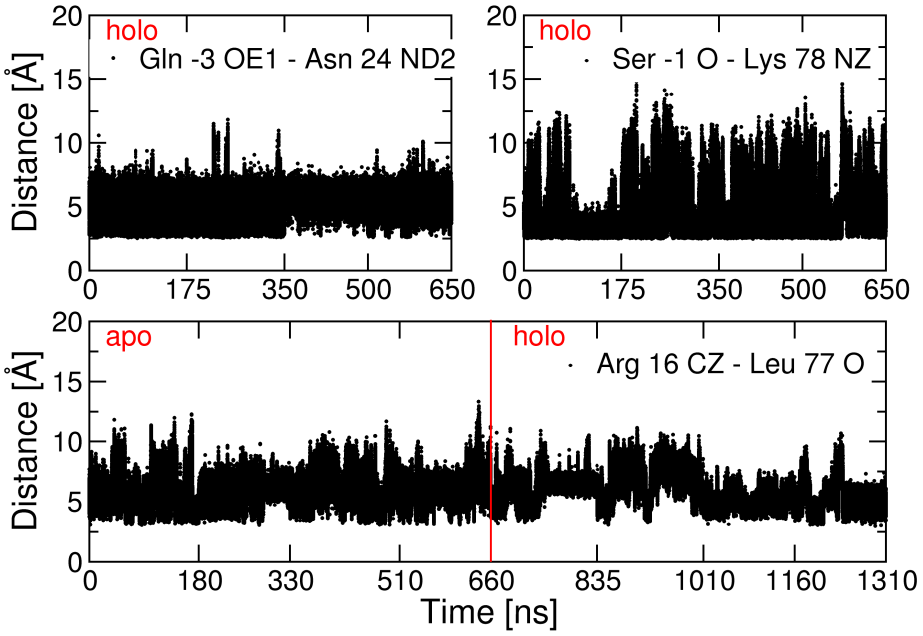

Figure S6: **Further hydrogen bonds involved in binding.** Time series of distances between atoms involved in different hydrogen bonds found in the crystal structure of complexed PDZ3[3]. For Arg16 the central carbon atom of the guanidinium group was used in the distance calculation to account for the symmetry. The red line in the bottom plot marks the concatenation point of apo and holo trajectories while the tick marks on all the three x-axes represent the concatenation of individual, independent MD runs.