



**Figure S14. WPD loop conformational transition on the reduced PC planes.** Small black dots represent the whole trajectory of WPD loop during TMD<sub>1</sub> simulation. Pink and green lines represent the WPD loop trajectory during the first loop closing (WPD<sub>open</sub> → WPD<sub>closed</sub>) and the first loop opening (WPD<sub>closed</sub> → WPD<sub>open</sub>), respectively. Blue and red filled circles represent the WPD<sub>open</sub> and WPD<sub>closed</sub> crystal structures, respectively. Yellow filled square and purple filled circles connected by gray arrows denote the trajectory of WPD loop in the absence of active water molecules in the WPD<sub>closed</sub> state. Light gray crosses represent an equilibrium simulation in WPD<sub>closed</sub> conformation. The numbers in parenthesis on the axis labels denote the percentage of explanation offered by PCA.