Supporting Information

How Ligand Protonation State Controls Water in Protein-Ligand Binding

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Supplementary Figures

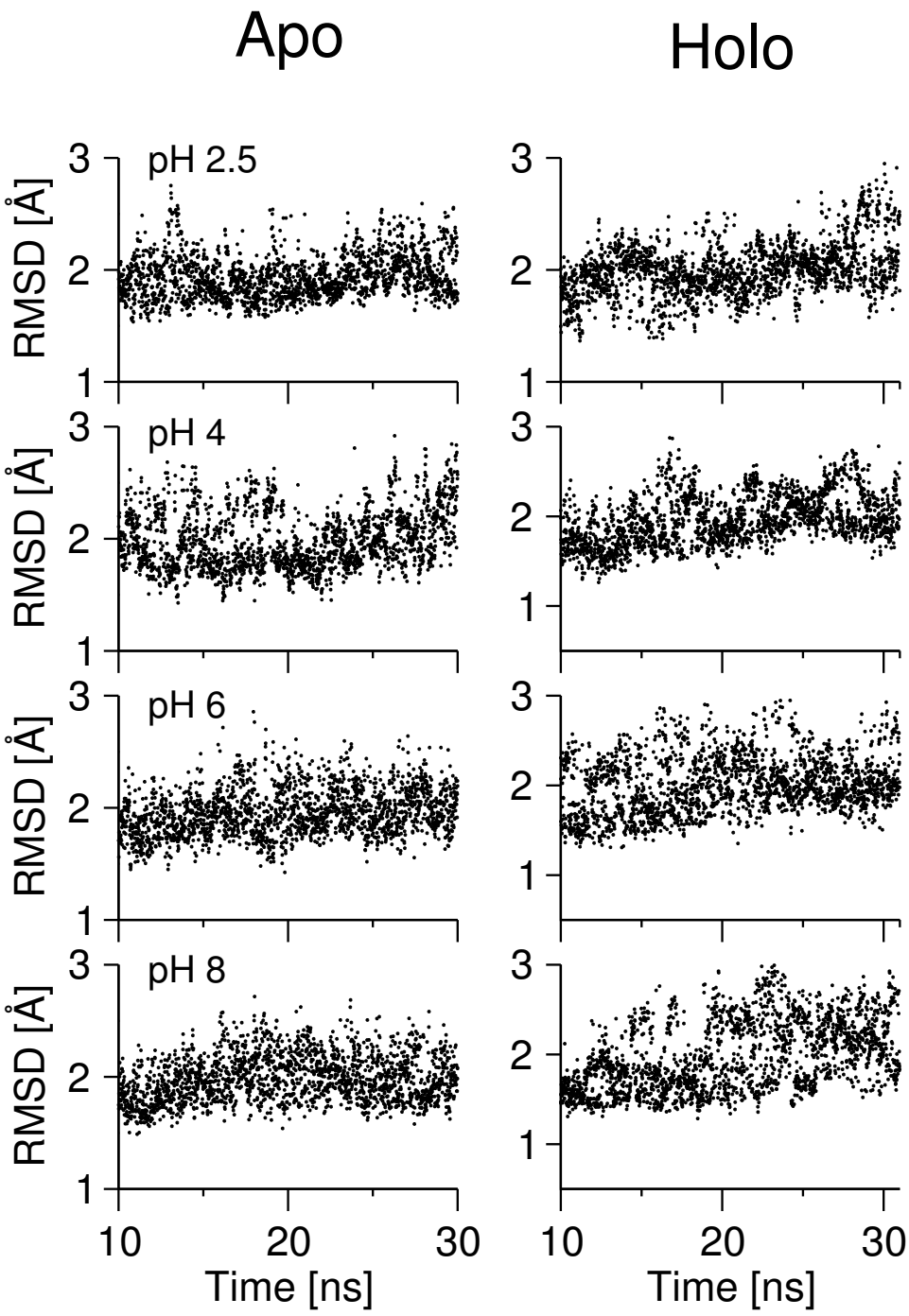

Figure 1: Time series of the backbone root-mean-square deviation (RMSD) from the crystal structure in the simulations of the apo and holo BACE2 at pH 2.5, 4, 6, and 8.

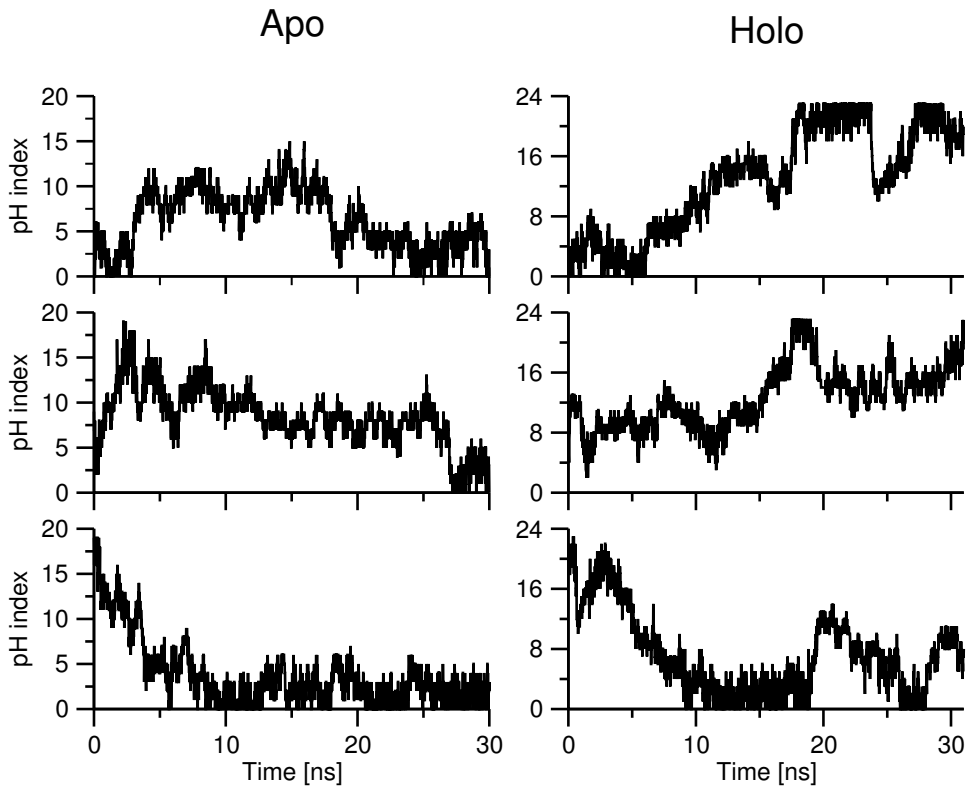

Figure 2: Time series of the replica walks through the pH ladders in the apo and holo simulations. Three randomly chosen replicas are shown. For the apo simulation, a pH index in the range of 1–20 corresponds to a pH condition in the range of 1.3–8. For the holo simulation, a pH index in the range of 1–24 corresponds to a pH condition in the range of -1–8. See Methods section in the main text for the pH conditions.

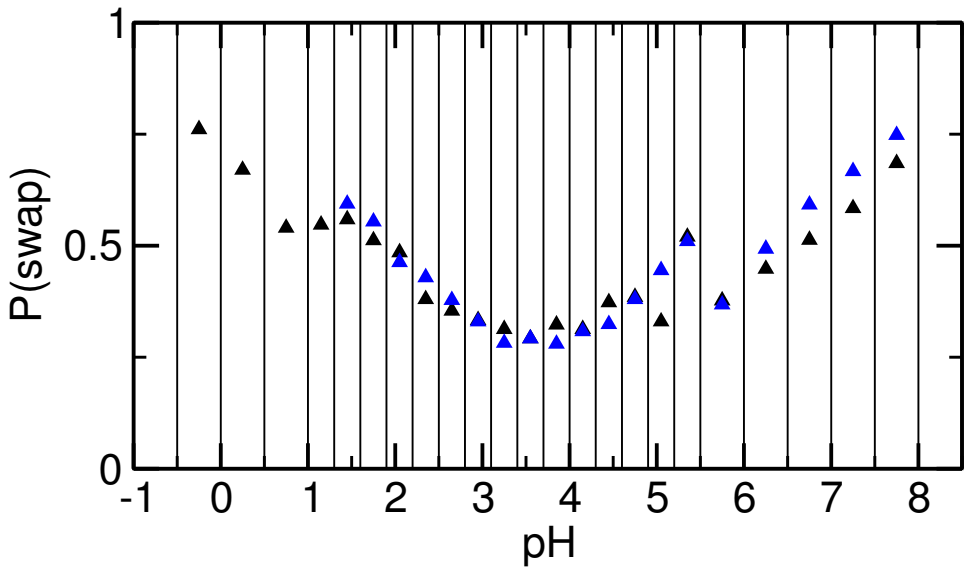

Figure 3: Average acceptance ratios of replica-exchange walks in the apo and holo BACE2 simulations.

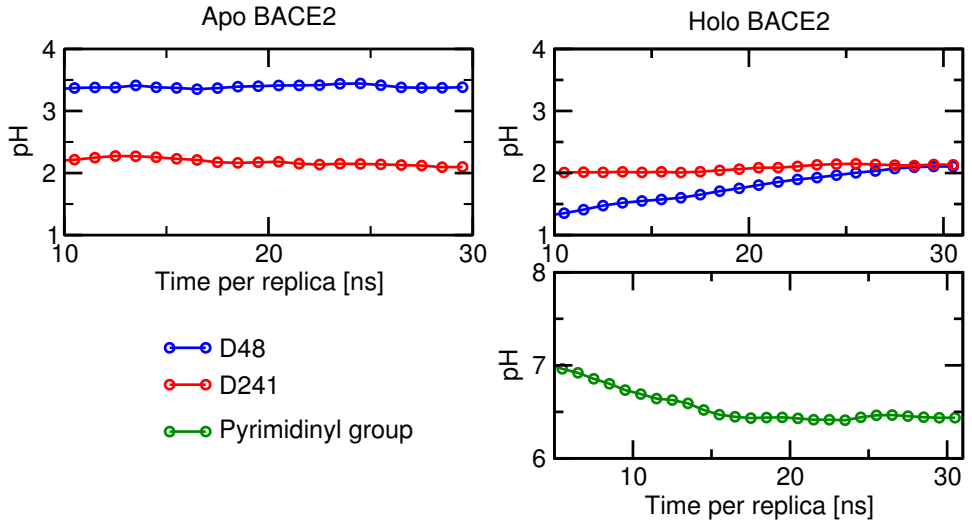

Figure 4: Time series of the cumulatively calculated pK_{a}'s of the catalytic dyad and inhibitor. pK_{a} calculation was performed every 1 ns.

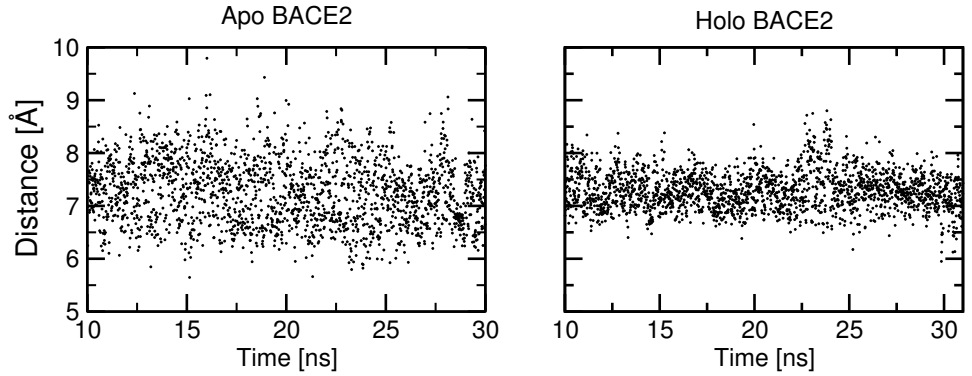

Figure 5: Time series of the S3 pocket width in the simulations of apo and holo BACE2 at pH 6. The data was used to plot the distributions shown in Figure 4c.