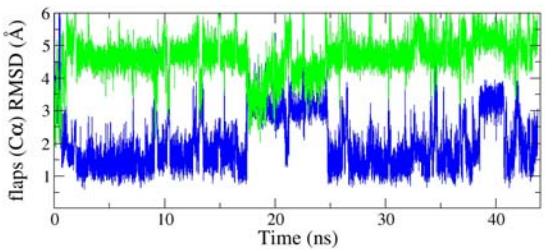

Figure S1. Flaps RMSD for both monomers in the dimer, fit to the 1HHP (semi-open) flaps in blue and the 1TW7 (wide-open) flaps in green. Data is from simulation of the unrestrained dimer in implicit solvent. The initial 1TW7 structure is unstable and the simulated HIV-PR adopts the semi-open flap conformation as seen for the wild-type (PDB code 1HHP).

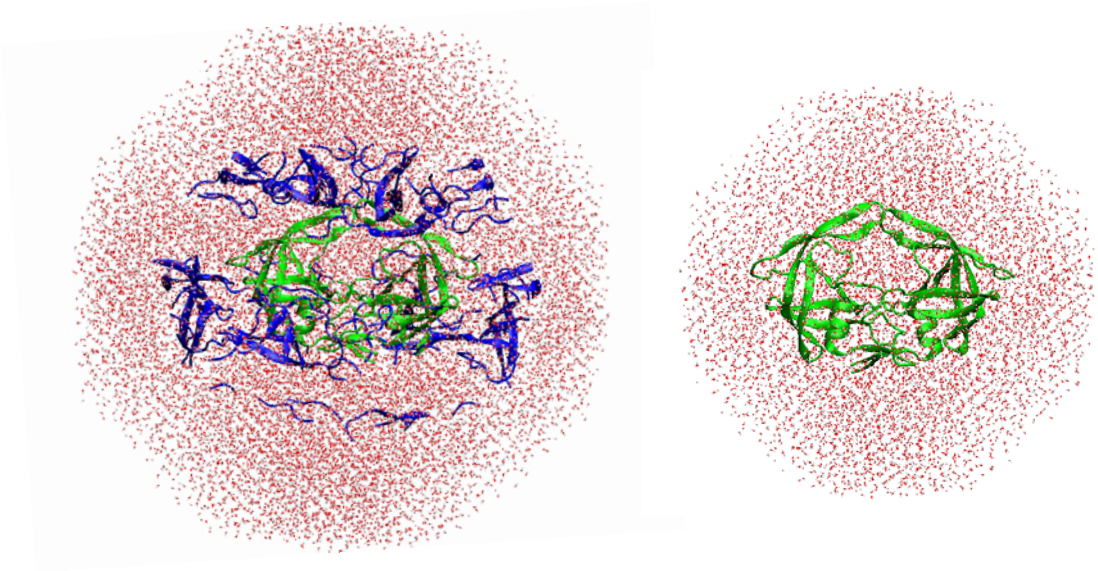

Figure S2. Images of solvated systems used for the simulations. The HIV-PR dimer is shown in a green cartoon diagram and the explicit water is shown in red and white. **Left**: simulations with crystal packing contacts, with packing residues shown in blue and 20,196 water molecules. **Right**: The dimer in solution with 8,572 water molecules and no packing contacts.

Simulation Details:

All simulations employed Amber 8[1] and the ff99SB forcefield[2]. Simulations with implicit solvent used a modified generalized Born model[3] and no cutoff on nonbonded interactions. Simulations with explicit solvent used the TIP3P water model[4] and truncated octahedral periodic boundary conditions. A cutoff of 8Å was used on nonbonded interactions, with long-range electrostatic interactions included using the PME method[5]. RMSD of the flap region was calculated using Cα atoms in residues 46-55 in both monomers. These protocols are the same as we employed previously for HIV-PR simulations[6,7].

Positional restraints were applied only to heavy atoms of residues representing crystal packing contacts and not to the central HIV-PR dimer. A force constant of 10 kcal/mol-Å was employed.

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