# Investigating the Atypical Protonation State of the Catalytic Dyad of HIV-1 Protease

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**Abstract**

The protonation state of the HIV-1 protease (HIVPR) has been the subject of much debate because it has two aspartates in the active site that exist in an atypical protonation state. Modeling the correct protonation state of the aspartates is vital in computation drug design. Using Constant pH Molecular Dynamics, we simulated the apo and bound forms of HIVPR with thirteen different protease inhibitors to determine the protonation state of each specific system. All of the HIVPR complexes were begun with three initial protonation states different initial protonation states – dianionic, mono-protonated, and di-protonated – to show that each converges to the same result. We observe that all simulations converge to the same protonation state, converge to the mono-protonated state suggesting that there is no change in protonation state transitioning from the apo to bound form of HIVPR for the inhibitors utilized in this study.