QM insights into the catalytic mechanism of the SARS-CoV-2 main protease (M^{pro}) using Hexapeptide substrates

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The SARS-CoV-2 main protease is crucial for the coronavirus's replication cycle and pathogenesis. Due to its high conservation and absence of human analogues, it is an attractive drug target whose inhibition promises therapeutic relief against COVID-19 morbidity. The present study aimed to profile the M^{pro} catalytic mechanism by characterising and leveraging key mechanistic events for rational drug design. A multi-conformer library of hexapeptide substrates was generated and complexed with the crystal structure of M^{pro} (PDB ID 6XHM) through extensive molecular docking calculations[1]. The hexapeptides comprised residues with high frequency that follow the known sequence for recognition and cleavage. Classical equilibrations were performed in the NPT ensemble at 300 K, on the best-docking and high-binding-efficiency complexes using the NAMD program. QM/MM systems comprising the catalytic dyad, scissile residues, the oxyanion loop and a water molecule in the QM region were treated to equilibration with NAMD, wherein the tight-binding GFN2-xTB method was applied to the QM region *via* the ORCA 4.2.1 program[2-3]. Potential energy surface calculations for each catalytic step on the QM atoms using the tight-binding GFN2-xTB method. Transition State Optimization and Intrinsic Reaction Coordinate calculations were performed with Gaussian09 and GFN2-xTB to gain insights into the reaction mechanisms and kinetics. Adaptive Partitioning Molecular Dynamics calculation will elucidate the free energy profile of the proteolysis in dynamic simulations, within the context of the plasticity of the M^{pro} active site.

References:

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