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Theoretical Model for HIV-1 PR That Accounts for Substrate Recognition and Preferential Cleavage of Natural Substrates

The Human Immunodeficiency Virus type 1 (HIV-1) protease is a crucial target for HIV/AIDS treatment and understanding its catalytic mechanism is the basis on which HIV-1 enzyme inhibitors are developed. Several experimental studies have indicated that HIV-1 protease facilitates the cleavage of the Gag and Gag-Pol polyproteins and it is highly selective with regards to the cleaved amino acid precursors and physical parameters. However, the main theoretical principles of substrate specificity and recognition remain poorly understood theoretically. By means of a one-step concerted transition state modeling, the recognition of natural substrates by HIV-1 PR subtypes (B and C-SA) was studied. This was carried out to compare the activation free energies at varying peptide bond regions (scissile and non-scissile) within the polypeptide sequence using ONIOM calculations.

The computational resources (CPUs/GPUs) used in this research were provided by CHPC under project name: HEAL0839 workspace (lustre file system) on lengau cluster. The Gaussian 09 and Amber 18 were the two software programs utilized on the cluster to execute the project, using 24 cores, 1 node and 48 hours wall time.

We studied both P3-P3' and P5-P5' natural substrate systems. For P3-P3' substrates, excellent recognition was observed for the MA-CA family but not for the RH-IN substrates. Satisfactory recognition for the latter was only observed for the longer sequence (P5-P5') after the substrate was subjected to an MD run to maximise the interaction between the enzyme and the substrate. These results indicate that both sequence and structure are important for correct scissile bond recognition of these natural substrates.

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