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The enzymatic mechanism of Human Immunodeficiency Virus type 1 (HIV-1) protease: are we there yet?

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Introduction
The catalytic mechanism of the Human Immunodeficiency Virus type 1 (HIV-1) protease (PR) is one of the most studied aspartate protease representative. Both experimental and theoretical techniques have been harnessed to provide profound understanding on a number of possible reaction pathways for the catalysis of HIV-1 PR on its natural substrate/ligand. Most of these studies have investigated the stepwise general acid/base mechanism with little attention on a synchronous model in which the proteolytic reaction could occur as a one-step concerted process. Jaskólski et al. first put this proposal forward in 1991 in which the hydrolytic reaction is viewed as a one-step process; the nucleophile (water molecule) and electrophile (an acidic proton) attack the scissile bond in a concerted manner.
Aim and objective
Herein, the one-step concerted catalytic mechanism of HIV-1 PR on its natural substrate and a fluoride derivative was studied using density functional theoretical (DFT) method.
Method
The reaction was modeled to proceed through the formation of a six-membered ring transition state structure, which was facilitated by a pre-reaction enzyme-substrate complex at B3LYP/6-31+G(d) level of theory using Gaussian 09 program suite. The applied in silico model allows the elucidation activation parameters, kinetics, solvent contributions and quantum chemical properties for this system.
Result
Theoretically determined activation free energy of 19 kcal mol-1 obtained was very close to approximately 18 kcal mol-1 reported from experiment. The fluorinated peptide substrate has an activation free energy of 12 kcal mol-1 which is 7 kcal mol-1 lower than natural substrate.
Implications of result
This investigation could potentially serve as a basis towards understanding the enzymatic mechanism of homodimeric enzymes and could also guide future design of better HIV-1 PR inhibitors through fluorinating the scissile nitrogen of the natural substrates; an ongoing perspective from our research group.

HPC content

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