HIV Protease Inhibition Seen by X-ray Diffraction and Molecular Dynamics

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Binding of inhibitor into the complex with HIV protease is accompanied by a large movement of protease flaps. X-ray crystallography shows the stable inhibited protease complexes [1], or unliganded proteases with "semi-opened" flaps and larger atomic displacement parameters. This work inspects conformational mobility of the HIV protease flaps and the process of inhibitor unbinding using molecular dynamics (Amber, Oral) [2] under influence of external forces (with variable magnitudes and directions) making the system pass through different conformations in a reasonable computer time. Energies of individual components of the system were monitored to judge on feasibility of the states acquired. For unliganded protease, the flaps can accommodate a large range of opened conformations allowing direct entry of inhibitor into the binding cleft. Therefore, the protease without inhibitor is in a relaxed state with its flaps in large spectrum of conformations of similar energy. On the complexation the protease flaps close over the inhibitor as necessary and thus can accommodate inhibitors of different sizes. Forced unbinding of inhibitor simulated with HIV protease in a "water box" shows that the flaps stick to the inhibitor and follow it up to a large distance from the protein. The energy profiles show that the process of unbinding has many steps and must be slow relatively to the natural movement of the flaps to keep their deformation energies low. The project was supported by GA AV CR KJB4050312 and MSMT 1K05008.

[1] Petroková H., et al., *Eur.J.Biochem*, 2004, **271**, 4451. [2] Zimmermann K., *J. Comput. Chem*., 1991, **12**, 310-319.

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