

P003 Thermodynamic characterization of HIV-1 protease-inhibitor interactions

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HIV-1 protease has been extensively studied, making it not only a medically relevant target, but also a suitable model protein for the study of protein-ligand interactions. Interaction kinetic analysis using biosensor technology has previously been shown to provide an improved description of the interactions between HIV-protease and inhibitors. This type of analysis was extended to provide a characterization of the interaction energetics. Interaction kinetic analysis of seven HIV-1 protease inhibitors at different temperatures revealed distinguishing kinetic and thermodynamic characteristics for the inhibitors. The kinetics showed non-linear temperature dependencies for some of the inhibitors, and the enthalpy and entropy of these interactions were also temperature dependent. The free energy change (ΔG) was in the same range for all inhibitors and was dominated by the entropy term. The association and dissociation free energy changes (ΔG_{on} and ΔG_{off}) were also similar for all inhibitors. However, the enthalpy and entropy terms contributed differently to association and dissociation, distinguishing these phases energetically. Association of all inhibitors, except lopinavir, was accompanied by positive entropy changes ($\Delta S_{on} > 0$), whereas dissociation had positive enthalpy ($\Delta H_{off} > 0$) and negative entropy ($\Delta S_{off} < 0$) changes. Thus, resolution of the energetics of association and dissociation (ΔG_{on} , ΔG_{off} , ΔH_{on} , ΔH_{off} , ΔS_{on} and ΔS_{off}) revealed unique characteristics for lopinavir. This study indicates that resolution of the energetics of interactions will be useful for the characterization of molecular interactions, such as those between inhibitors and target proteases.