Witcha Treesuwan 2009: Molecular Dynamics Simulations of Wild Type, Y181C Mutant HIV-1 RT/Nevirapine and Minor Groove Binder, Thiazotropsin A, Complex: The Energetic and Interactions by Means of MM-PBSA Calculations. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor:
Associate Professor Supa Hannongbua, Dr.rer.nat. 156 pages.

The combination of Molecular Dynamics simulations/MM-PBSA calculations were used to explore thermodynamic properties of two systems; the HIV-1 Reverse Transcriptase (RT) complex to nevirapine and the minor groove binder, thiazotropsin A, complex to DNA, which are comparable to the available experimental data. First, the simulations of wild type and Y181C HIV-1 RT/nevirapine complexes revealed the characteristic hydrogen bonds from the bridge water molecule (WAT1075), which was the key in the stabilizing of the bound complex. Improvement of binding energies calculations was observed when an explicit solvent, WAT1075, was included in the MM-PBSA calculations. Binding energies of -37.65 and -29.82 kcal/mol found in the wild type and Y181C HIV-1 RT, respectively. The attractive interactions via the bridge water brought His235 and Leu234 became major contributions. However, the presence of WAT1075 in the Y181C RT complex presented the weaker hydrogen bond distance formation, lack of attractive force to nevirapine and lack of binding efficiency leaded to the fail of nevirapine against the Y181C HIV-1 RT. Quantitative understanding of the role of bridge water will help to develop and design for novel HIV-1 RT inhibitors active against mutant enzyme. Second, the simulations of thiazotropsin A and DNA dodecamer, $d(GCGACTAGTCGC)_2$, at 2:1 ratio were performed using several combination of parameter sets and simulation protocols. Evaluation of the model revealed that combination of ligand charges from HF/6-31G*, polarizable force field for DNA and loop protocol equilibration reproduced the best binding energy of -10.06 kcal/mol, compared to the experimental data of -10.0 kcal/mol from the Isothermal Titration Calorimetry (ITC). The reproducible energy was observed only when the isolate trajectories were used in the MM-PBSA calculations. The major and minor interactions also revealed the recognition pattern of thiazotropsin A to the floor of the DNA minor groove. High correlation between protocols was observed, but not models and parameter sets. These will be used as a benchmark for the side-by-side simulations in term of the Quantitative Protocol Activities Relationship (QPAR) in the future.

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