CHAPTER 5

CONCLUSIONS

The main finding of this study is the accurate predictions of binding affinities for HIV-1 protease complexed with inhibitors using MMPB/SA-type free energy analysis. The enzyme protonation states of complex were determined carefully. HIV-1 protease is predicted to maintain D25 protonation of the free enzyme when LPV, SQV, or IDV are bound, but is assumed to change protonation to D25' when the inhibitors RTV, NFV, or APV are embedded. Furthermore, it is found that the inclusion of explicit water molecules in a hybrid implicit/explicit MMPB/SA slightly scheme improves absolute agreement of calculated binding affinities with the experimental data. On the other hand, the use of the Generalized Born approximation significantly diminishes the accuracy of the obtained results. However, the energy obtained from the GBMV method is in good agreement with that of the PB and also maintains the relative ranking between different snapshots fairly well. While the results from GB method in AMBER are far from PB estimation and do not rank some of energy data correctly.

For the prediction of HIV-1 PR mutation due to 6 FDA-approved drugs, the decomposition free energy method can predict the possible mutated residues of high and intermediate levels. The prediction using decomposition free energy does not depends on the complex. In addition, the predicted model was also found to valid for the influenza virus enzyme, neuraminidase subtypes N1, N2, and N9 complexed with the oseltamivir.

Mutation at Gly48 and Ile84 was investigated in details for the SQV complexed with HIV-1 PR. It was found that conformational change is a primary

source of mutation for I84. In contrast, G48 mutation can be described in terms of indirect displacement of F53 in the flap regions.