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Standard binding free energy calculation for theophylline-RNA aptamer system: alchemical transformation and metadynamics

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Binding affinity of theophylline to RNA apatamer (PDB *id*: 1EHT) is calculated using alchemical transformation, in which the interactions of the ligand with its surroundings are decreased to zero [1]. The parmbsc0 force field is used for describing potential functions of RNA to improve the accuracy of simulation [2]. A quadratic potential restraining the translation of the ligand is added to keep the relation to the standard state condition. The calculated binding free energy is -8.9 kcal/mol, which agrees well with the experimental value of -8.9 kcal/mol. This result indicates that experimental binding energy is well reproduced by simulations for alchemical route.

In order to realize the computer-aided drug design (CADD), understanding of the kinetics of association/dissociation phenomena is also necessary. Then, we perform metadynamics simulation to explore the free energy surface (FES) starting from the equilibrated binding geometry [3]. The distance between U23(C1') and TEP(C8) and the angle of G26(C6)-TEP(C2)-TEP(C8) are chosen as a set of collective variables (CVs) used here as shown (Figure 1). Metadynamics is a dynamics in the space of the CVs. In Figure 2, the FES shows a physical path for the ligand from the binding site to the external solution. A barrier from the binding site to the unbound state is estimated to be 13.5 kcal/mol while taking the experimental binding affinity into account. This value gives us information for recognizing the dissociation process of the ligand from the binding site and for ligand optimization.

It is shown that alchemical transformation and metadynamics simulation are powerful methods for exploring the properties of ligand in rational drug design.

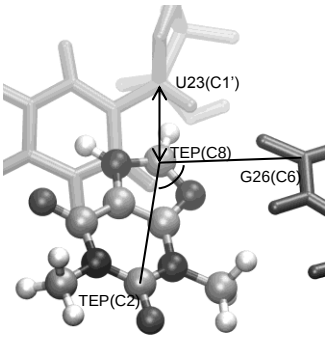

Figure 1. Theophylline-RNA binding geometry after equilibrium procedure. Particular atoms used are also shown.

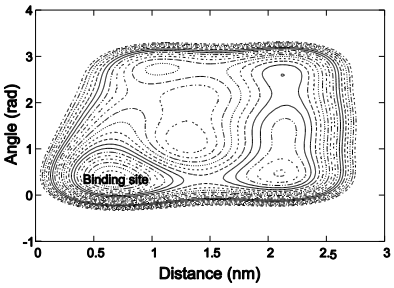

Figure 2. Free energy surface reconstructed using metadynamics as a function of the angle G26(C6)-TEP(C2)-TEP(C8) and of the distance U23(C1')-TEP(C8).

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