Atomistic Details of the Ligand Discrimination Mechanism of
SMK/SAM-III Riboswitch

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SAM-III riboswitch, involved in regulating sulfur metabolic pathways in lactic acid bacteria, is capable of differentiating S-adenosyl-L-methionine (SAM) from its structurally similar analog S-adenosyl-L-homocysteine (SAH). Atomic level understanding of the ligand recognition mechanism of riboswitches is essential for understanding their structure-function relationships in general. In the present study, we have employed molecular dynamics (MD) simulations on five model systems to elucidate the discrimination mechanism adopted by the SAM-III riboswitch that enables differential binding of SAM with respect to SAH. The structures of the binding pocket of the riboswitch, and the modes of binding of the adenine moiety of SAM obtained from the MD simulations are similar to the experimental structure. However, MD simulations of the riboswitch-SAH complexes lead to partial unbinding of the ligand and structural changes in the RNA binding pocket. Detailed analyses were performed to examine the structural and energetic factors involved in such a differentiation. The calculations reveal a novel mechanism by which the aptamer domain specifically recognizes the adenine moiety of SAM/SAH, but SAM is better stabilized in the binding pocket due to nonspecific electrostatic interactions involving the sulfonium group. Additionally, the results support less dependence of the ligand conformation in the bound form on the effective binding of SAM to the riboswitch.