Simulation of Antibiotics that interfere with the Ribosomal Machinery

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GENTAMICIN is a potent antibiotic often used in therapy for methicillin-resistant Staphylococcusaureus. Gentamicin works by flipping a conformational switch on the ribosome, disrupting the reading head (i.e., 16S ribosomal decoding bases 1492-1493) used for decoding messenger RNA. We use explicit solvent all-atom molecular simulation to study the thermodynamics of the ribosomal decoding site and its interaction with gentamicin. The replica exchange molecular dynamics simulations allow enhanced sampling of the unbinding free-energy landscape, including a rigorous treatment of enthalpic and entropic effects. The decoding bases flip on a timescale faster than that of gentamicin binding, supporting a stochastic gating mechanism for antibiotic binding, rather than an induced-fit model where the bases only flip in the presence of a ligand. The study also allows us to explore the nonspecific binding landscape near the binding site and reveals that, rather than a two-state bound/unbound scenario, drug dissociation entails shuttling between many metastable local minima in the free-energy landscape. Special care is dedicated to validation of the obtained results, both by direct comparison to experiment and by estimation of simulation convergence.