Conformational Selection Drives Antibiotic Sequestration

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Deciphering the molecular mechanisms underlying multi-drug resistance in bacteria is crucial for the development of novel therapeutics. One such mechanism is the sequestration of antibiotics via protein-based sensors. TipA and AlbA, synthesized by *Streptomyces lividans* and *Klebsiella oxytoca,* respectively, bind and sequester antibiotics through their effector binding domains. The precise extent and role of protein dynamics in enabling antibiotic binding in otherwise occluded binding sites are open questions. Combining equilibrium and time-resolved spectroscopy with kinetics, calorimetry, HDX-MS and statistical modeling, we show that the natural isoforms TipAS and AlbAS display vastly different mechanisms of sequestration involving not just local unfolding but also large-scale order-disorder transitions. However, the underlying phenomenon appears to be conformational selection wherein there exists a pre-equilibrium between binding-incompetent and competent substates. Our work highlights how conservation of dynamics, but not sequence or structure, could drive function.