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Free Energy Landscape and Conformational Kinetics of Hoogsteen Base Pairing in DNA vs. RNA

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Abstract

Genetic information is encoded in the DNA double helix, which, in its physiological milieu, is characterized by the iconical Watson-Crick nucleo-base pairing. Recent NMR relaxation experiments revealed the transient presence of an alternative, Hoogsteen (HG) base pairing pattern in naked DNA duplexes, and estimated its relative stability and lifetime. In contrast with DNA, such structures were not observed in RNA duplexes. Understanding HG base pairing is important because the underlying "breathing" motion between the two conformations can significantly modulate protein binding. However, a detailed mechanistic insight into the transition pathways and kinetics is still missing. We performed enhanced sampling simulation (with combined metadynamics and adaptive force-bias method) and Markov state modeling to obtain accurate free energy, kinetics, and the intermediates in the transition pathway between Watson-Crick and HG base pairs for both naked B-DNA and A-RNA duplexes. The Markov state model constructed from our unbiased MD simulation data revealed previously unknown complex extrahelical intermediates in the seemingly simple process of base flipping in B-DNA. Extending our calculation to A-RNA, for which HG base pairing is not observed experimentally, resulted in relatively unstable, single-hydrogen-bonded, distorted Hoogsteen-like bases. Unlike B-DNA, the transition pathway primarily involved base paired and intrahelical intermediates with transition timescales much longer than that of B-DNA. The seemingly obvious flip-over reaction coordinate (i.e., the glycosidic torsion angle) is unable to resolve the intermediates. Instead, a multidimensional picture involving backbone dihedral angles and distance between hydrogen bond donor and acceptor atoms is required to gain insight into the molecular mechanism.

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