Internal Abstraction of Dynemicin A: An MD Approach

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Abstract

Dynemicin A has the ability to undergo the Bergman cyclization, forming a *para*-benzyne moiety which has the ability to induce strand scission of DNA. This property of dynemicin A makes it a promising anti-tumor agent. Past research has shown conclusively that dynemicin A binds to and abstracts a hydrogen atom (H5') from the DNA backbone, but the molecular mechanism of this abstraction is not fully understood. We have used AMBER Molecular Dynamics simulations to investigate these reaction mechanisms. Previously, two mechanisms have been proposed, of which the second is more supported: 1.) dynemicin A intercalates between two base pairs and directly abstracts a hydrogen atom from DNA, 2.) dynemicin A inserts into the minor groove and directly abstracts a hydrogen atom from DNA. We propose a third mechanism, where dynemicin A intercalates, then undergoes a proximate, intramolecular hydrogen atom abstraction (internal abstraction). The resulting radical subsequently abstracts a hydrogen atom from DNA.