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Exploring the stability of DNA/RNA chimeras by MD simulations: Could early life have utilized mixed DNA/RNA duplexes?

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In the current study we extend previous experimental work [1] on the (in-) stability of heterogeneous chimeric DNA-RNA duplexes by exploring the possible structural basis of experimental observations with Molecular Dynamics Simulations. In this study the DNA duplex $d(CGATTTAGCG)_2$ has been gradually converted into all RNA analog $r(cgauuuagcg)_2$ by two different paths. In Transition I all pyrimidine nucleotides in Strand 1 and then in Strand 2 were sequentially converted from the DNA form to their RNA equivalents followed by the analogous mutation of the puine nucletides. Transition II was generated by the conversion of the purine nucleotides in Strands 1 and 2, followed by the mutation of pyrimidine nucleotides. The changes in the free energies between each step in both transition paths were computed by the Free Energy Perturbation method. The intermediate hetero-duplexes along the Transition I appeared to be substantially less stable (up to 4.5 kcal/mol) than the corresponding homodimers, while along Transition II the intermediates were predicted to have a stability similar to that of the homoduplexes. Although the calculated changes in the thermodynamic stability for some individual species along Transition I and Transition II differ from experimental results, the predicted relative stability of most chiemeric dimers largely agrees with those revealed by experiment.

Our detailed structural analysis of the chimeric structures reveals that Transitions I and II explore different intermediate conformational space, which could be the origin of the observed experimental difference between the stabilities of duplexes along these two transition paths. While during Transition I a B-form helix is gradually converted to an A-form helix, some chimeric intermediates during Transition II occupy states outside of the canonical A/B conformations. Overall, the conformational changes in the systems studied here appear to be driven by the complex energy landscapes that account for the local changes near the mutation sites as well as for the global cooperative processes of backbone helical structure remodeling. The results of this study suggest that a few chimeric systems may be at least as stable as the pure RNA or DNA oligonucleotides of the same composition, while the others may be severely destabilized by the heterogeneity. These results could have important implications regarding the possible participation of chimeric systems in earlier stages of life, and further suggests a mechanism by which these two substantial biopolymers may have been purified and segregated [1].

[1]Gavette JV, Stoop N, Hud NV and Krishnamurthy R (2016) *Angewante Chemie* 55:13204–13209.

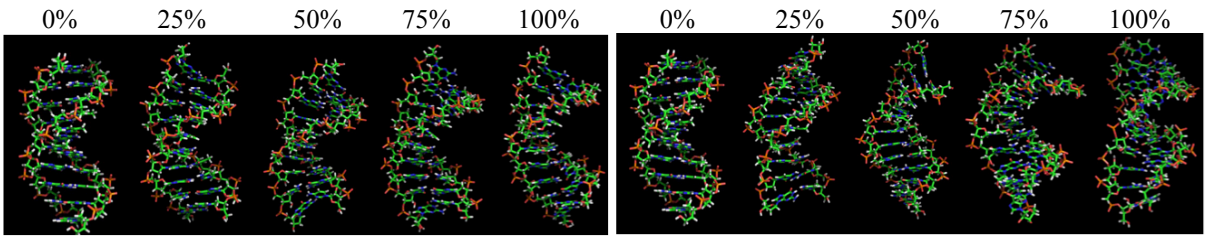

Figure 1. – Snapshots from MD trajectory for the Initial, final and intermediate conformations for Transitions I (left) and II (right) as a fraction of RNA nucleotides added into the system. 0% is all DNA, 100% all RNA.