Nucleic Acids Chemistry beyond the Watson-Crick Double Helix (79) : Application of the nearest-neighbor model for the stability prediction of intramolecular i-motif DNAs

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The stability prediction of nucleic acids structures is significant to understand and regulate the biological reactions related to genomic information such as replication and transcription.[1] In particular, the development for non-canonical structures such as tetraplex structures is highly demanded because these non-canonical structures are important motifs for gene expressions in cells.[2] The i-motif is one of the tetraplexes formed by cytosine-hemi protonated base pairs (denoted as C-C$^+$) with cytosine-rich nucleic acid sequences clustered at the promoter regions, which controls replication and transcription.[3,4] The most successful approach for the stability prediction is the nearest-neighbor (NN) model, in which the stability of the nucleic acids is determined by the interactions between the nearest base pairs. We recently reported the stability prediction of DNA duplex and RNA/DNA hybrid under physiological conditions. However, the prediction for non-canonical structures have not been developed yet. In this study, we have investigated to develop the stability prediction of i-motif based on the NN model.

To find out the rule of the stabilization of i-motif, we systematically analyzed thermodynamic parameters ($\Delta H°$, $\Delta S°$, $\Delta G°_{37}$, and T_m) for the formation of i-motif DNAs having different numbers of C-C$^+$ base pairs and thymine bases within loop regions. For the NN model prediction, we considered the energetic contributions to the i-motif stability from the C-C$^+$ base pairing, loops, junctions, and helix initiation with those pH-dependency as a following equation (1):

$$\Delta G°_{\text{i-motif}} = f(\text{pH})_{\text{NN}} * a + f(\text{pH})_{\text{int}} + f(\text{pH})_{\text{loop}} * b + f(\text{pH})_{\text{junction}} \quad (1)$$

, where $f(\text{pH})_{\text{NN}}$ is pH function of $\Delta G°$ of C-C$^+$ base pairing, $f(\text{pH})_{\text{int}}$ is pH function of $\Delta G°$ initiation factor, $f(\text{pH})_{\text{loop}}$ is pH function of $\Delta G°$ of loop, $f(\text{pH})_{\text{junction}}$ is pH function of $\Delta G°$ junction, a is C-tract length, and b is loop length

By using our developed equation, we could accurately predict the stability of i-motif by linking the sequence information and corresponding thermodynamic parameters. Thus, this approach could be a standard and general method to predict the stability.

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