# Chemistry of Self Assembled DNA-Nanostructures- An Overview

[1]S Baby Gayathri, [2]P Kamaraj

Department of Chemistry, SRM University, Kattankulathur 603203, India
Email: [1]babygayathri@gmail.com, [2]kamaraj97@yahoo.co.in

**Abstract-** **DNA structure exists in two forms namely single stranded (ss) and double stranded (ds) DNA structures. The ss-DNA consists of the purine and pyramidine nucleotides covalently linked via phosphodiester bonds. The structure of ds-DNA consists of two helical single stranded DNA coiled around each other with a pitch of 3.4 nanometers and radius of 1.0 nanometer. DNA nanotechnology utilizes the unique molecular recognition properties of nucleic acids to create self-assembling DNA complexes at the nanoscale termed as nanostructured DNA. This article deals with the concept of DNA self assembly. A major focus has been given for the thermodynamics of the self assembled nucleic acid structures forming DNA nanostructures.**

**Key words: DNA nanostructures, DNA origami, Nearest-Neighbor thermodynamics, Self assembly.**

## I. INTRODUCTION

Double stranded DNA is the most stable form of DNA found in biological system. The structure of ds-DNA consists of two helical single stranded DNA coiled around each other with a pitch of 3.4 nanometers and radius of 1.0 nanometer. The two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule which holds the chain together and a nucleobase, which interacts with other DNA strand in the helix. Although each individual nucleotide is very small, DNA as a polymer can be very large macromolecule containing millions of nucleotides. Each strand of the ds-DNA has a direction namely parallel and antiparallel direction. The direction of the polynucleotides in one strand is opposite to the direction of other strand and hence the name "antiparallel".

There are two forces which plays a major role in the structural stability of DNA: hydrogen bonds between the nucleotides and base-stacking interactions among aromatic nucleobases. Hydrogen bonding is done between the purines and the pyramidines. In the aqueous environment, the phi bonds of nucleotide bases align perpendicular to the axis of the DNA molecule minimizing their interaction with the solvent shell [1].

DNA nanotechnology utilizes the unique molecular recognition properties of nucleic acids to create self-assembling DNA complexes at the nanoscale termed as nanostructured DNA. Here, DNA is used as astructural material rather than a carrier of biological codes. This has lead to the creation of two-dimensional structures and three-dimensional structures of DNA nanostructures using DNA origami method. DNA origami is the nanoscale folding of DNA to create arbitrary two and three- dimensional shapes of DNA at the nanoscale. Inorganic nanostructure synthesis have been proven to vary in crystal structure, size and shape depending on the method and mode of synthesis [2] and sometimes unpredictable. Whereas, the DNA nanostructure construction involves the application of an individual's basic understanding about the stability of DNA under various conditions.

## II. THERMAL STABILITY OF DNA

Before understanding the DNA nanostructure synthesis, it is important to understand the structural and thermo dynamical stability of double stranded DNA. In double stranded helical DNA, each nucleobase of one stand pair with their complementary nucleobases in the other strand via hydrogen bonds in other words purines form hydrogen bonds with pyramidines. In general, adenine form double hydrogen bonding with thymine and guanine forms triple hydrogen bonding with cytosine. This process of nucleotide binding across the ds-DNA is known as base pairing. The hydrogen bonds formed between the two strands are non-covalent and they can be easily broken either by mechanical force or high temperature and this process is reversible. Although weak hydrogen bond is established between the purines and pyramidines, the sugar phosphate backbone of the DNA forms a strong covalent bonding. The sugar phosphate backbone is due to phosphodiester bond which is a group of strong covalent bonds. Apart from base pairing, base stacking is another important phenomenon to be considered for the stability of DNA. DNA with high GC content is

considered to highly stable as the interstrand base stacking is strongest for GC stacks. The free energy gained on stacking base pairs in the helical structure was estimated to be about 7 kcal, per mole of base pairs and forms a major part of free energy stabilizing the helix [3]. Base paring and base stacking together contribute to the thermal stability of DNA irrespective of salt concentration and pH [4].

## III.  MAJOR AND MINOR GROOVES

The helical DNA take one complete turn about its axis in every 10.4 base pairs in solution. This helical pattern depends greatly on the stacking force exhibited by nucleobases on its neighboring bases. During the formation of this helical pattern, major and minor grooves are formed between the strands. As the strands are not symmetrical, the grooves are not equally sized. The nucleobases at the edges of the minor groove are more accessible in the major groove. Large proteins and enzymes can bind to specific sequence which forms major grooves by making contact with the sides of the nucleobases exposed in the major groove [5]. Whereas, small molecules have been reported to bind in the minor groove region of DNA through fluorescence quenching and molecular docking methods [6]. In the following pages, thermodynamics and kinetics of DNA hybridization and folding have been explained to explore the knowledge of DNA self assembly.

## IV.  NEAREST-NEIGHBOUR THERMODYNAMICS

Hybridization, denaturation and annealing are the three steps which commonly occur in DNA of the living cell. These steps follow the neareast-neighbour theromodynamic approach for the over stability of DNA in the cell. One of the major drawbacks associated with understanding the concept of NN thermodynamic is that different methods in different conditions have been adopted in the literature for presenting the NN parameters. The nearest neighbor model for nucleic acids assumes that the stability of a base pair in the sequence depends on the structure and orientation of the neighboring base pairs [7]. The free energy of forming double stranded DNA is given as follows:

$\Delta G°(total) = \Sigma_i\ n_i\ \Delta G°(i)$

$+ \Delta G°(Initiation\ with\ terminal\ GC)$

$+ \Delta G°(Initiation\ with\ terminal\ AT) + \Delta G°(sys)$

Where $\Delta G°(i)$ are the standard free-energy changes for the 10 possible Watson and Crick nearest neighbours (AA/TT, AT/TA, TA/AT, CA/GT, GT/CA, CT/GA, GA/CT, CG/GC, GC/CG, GG/CC), $n_i$ is the number of occurrences of each nearest neighbor and $\Delta G°$ (sys)I

equal "+0.43 kcal/mol" if the DNA is self-complementary and "zero" if it is non-self-complementary.

The enthalpy and entropy parameters can be determined as follows:

$\Delta G°(total) = \Delta H°(total) - T\Delta G°(total)$

Melting temperature (TM) is the temperature at which half of the DNA in the double helical state and other half in the random helical state, calculated as follows:

$T_M = \Delta H° / (\Delta S° + R\ ln\ CT)$

Where R is the gas constant (1.98 cal/K mol). If strands are in equal concentration and non-self complementary, CT is replaced by CT/4. (CA – CB)/2 if the strands are at different concentrations; CA and CB are the concentrations of the more concentrated and less concentrated strands.

Hence the stability of the double helical DNA depends greatly on the total free energy involved in the forming of duplex DNA which is difficult to estimate. Dipole-dipole, dipole-induced and London dispersion forces of interactions among the bases are large. This makes the free energy of the helix to depend on the nucleobases and its sequence [8]. Dipole-dipole interaction involves the attraction between the positive end of one dipole and the negative end of another dipole, in this case between the two bases while stacking and paring (own thought- have to find out if this is true). London dispersion forces are weak attractive forces between two atoms or molecules caused by electrostatic attraction between temporary induced dipole [9]. Dipole-dipole interaction and London dispersion forces are weaker than thermal energy (2.4 KJ/mole) at room temperature and are referred to as Vander Waals force [10]. DNA with free energy value near "zero" and with greater melting temperature is considered to be more stable.

## V.  DNA SELF ASSEMBLY

Self assembly is a process in which the disordered components of a system form an organized pattern or structure due to specific local interactions among the components without any external influence. DNA is known to form an ordered self assembled structure through bottom up approach due to the following reasons [11]:

A.  Complementary base pairing

Complementary base pairing of the DNA refers to the pairing of nucleotide bases of one strand to another opposite strands via hydrogen bonds to form double stranded DNA helix. The base pairing rule with respect to DNA is that the purine can pair only to pyramidine and vice versa (Adenine to Thymine and Guanine to cytosine

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forming double and triple hydrogen bonds respectively).

B.  Sense and Antisense DNA

In DNA, sense strand is referred to coding strand, is the segment of double stranded DNA running from 5' to 3' direction. It should be noted that the sense strand is always complementary to the anti-sense strand which runs in 3' to 5' direction. In practice, the top strand is generally written 5' to 3' while the bottom strand is written in 3' to 5' direction.

C.  Structural motifs

Theoretically, DNA is considered as a linear biopolymer which upon conformation can undergo primary, secondary and tertiary structure. The structural motifs in DNA includes Watson-Crick base pairs, internal mismatch, terminal mismatches, terminal dangling ends, hairpins, bulges, internal loops and multi branched loops [12]. The relationship between primary structure and tertiary structure is not straight forward, and hence the two biopolymers share same motif yet lack significant primary structure similarity.
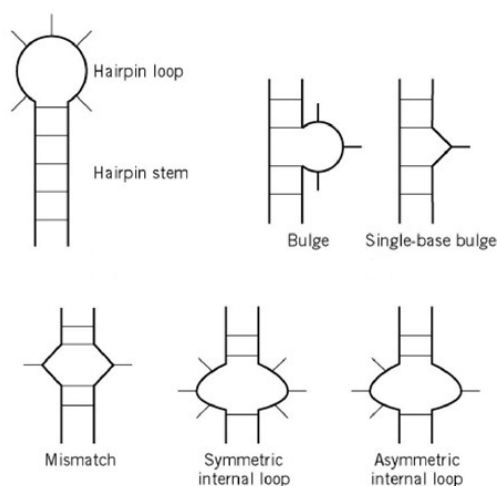


Figure 1: Few of the known structure motifs in genome

D.  Coaxial stacking of DNA

Coaxial stacking is formed when two DNA duplexes forms a contiguous helix which is stabilized by base stacking at the interface of two helices. Figure explains the formation of pseudo knot with coaxial stacking of the two helices. Two common motifs involving coaxial stacking are kissing loops and pseudo knots. In kissing loop interactions, the single-stranded loop regions of two hairpins interact through base pairing, forming a composite, coaxially stacked helix. Notably, this structure allows all of the nucleotides in each loop to participate in base-pairing and stacking interactions.
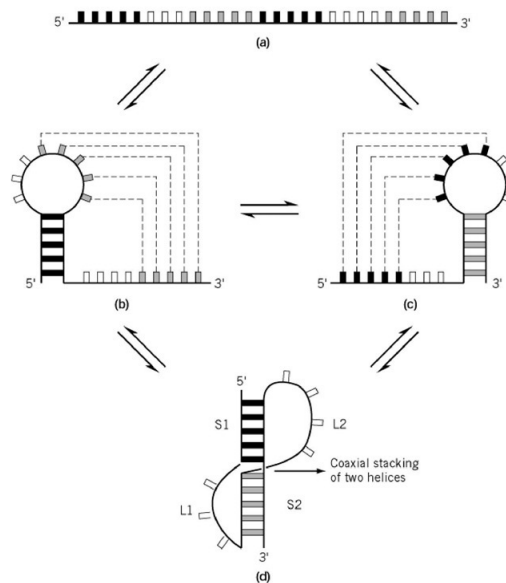


Figure 2: Formation of pseudo knot with coaxial stacking of the two helices, (a) Original strand, (b,c) Kissing loops interactions and (c) Coaxial stacking of two helices.

In 1994, Walter and Turner determined the free energy contributions of nearest neighbor stacking interactions within a helix-helix interface between a short oligomer and a four-nucleotide overhang at the end of a hairpin stem . Their experiments confirmed that the thermodynamic contribution of base-stacking between two helical secondary structures closely mimics the thermodynamics of standard duplex formation (nearest neighbor interactions predict the thermodynamic stability of the resulting helix). The relative stability of nearest neighbor interactions can be used to predict favorable coaxial stacking based on known secondary structure. Walter and Turner found that, on average, prediction of RNA structure improved from 67% to 74% accuracy when coaxial stacking contributions were included [13].

DNA origami structures contain a large number of double helixes with exposed blunt ends. These structures were observed to stick together along the edges that contained these exposed blunt ends, due to the hydrophobic stacking interactions [14].

The process of DNA self assembly can be divided into four categories [15]:

A.  Quick Mix approach

A set of unique sequenced basic unit strands are designed with unique sticky ends. During the self assembly, these strands associate at particular positions to form the entire architecture.

B.  Hierarchical Self assembly

An approach to minimize the unique set of strands

required to generate individually formed multi-tile DNA structure, thus sequences can be reused by generating the unique tiles separately and mix them in a particular order.

C. Algorithmic self assembly

The tiles are programmed with built in instructions which code for the next layer of tiles to self-assemble on the previous layer following algorithmic rules.

D. Nucleated self assembly

A longer strand acts as a nucleation site for the attachment of the associated strands to generate a complex pattern.

The DNA nanostructures generated up to date range from simple 1D structures to highly complex 2D structures. Some 3D objects have also been successfully constructed.

## VI. CONCLUSIONS

By understanding the chemistry behind the DNA stability, it is possible to obtain DNA nanostructures in the form of cubes, polyhydra, tiles, bare code etc. The literature on the stability of DNA has paved the way for easy design of the DNA sequence to construct DNA nanostructures. One can simply draw the desired structure to be constructed and later fill in the DNA sequence and create DNA nanostructures using any one of the DNA self assembly process with the possible applications in DNA computing, NEMS based biosensor, drug delivery, DNA nanomachines, microelectronics etc.

## VII. ACKNOWLEDGEMENTS

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