ABSTRACT

ANALYSIS OF NUCLEIC ACIDS THROUGH COMPUTATIONAL APPROACHES

Nucleic acids are essential biomolecules when it comes to replication, transcription and translation of genetic information. Understanding nucleic acid functions is integrated with thorough knowledge of structural variations and interactions present in the system. In this thesis molecular dynamics simulation have been used to gain insight into two different aspects of nucleic acids: interactions in ionic environment and temperature induced melting. Stacking interactions is another important aspect of nucleic acid duplexes which is extensively analyzed in this thesis employing quantum chemical tools.

Four simulations of 100 ns each are performed on DNA in presence and absence of Mg$^{2+}$ ion. The Mg$^{2+}$ is found to reside in the major groove where the selection is governed by steric effects rather than electrostatic interactions. Mg$^{2+}$ imposes rigidity in the duplex and the metal ion and DNA atom/water interacting distances in crystal database is explored which is in agreement with the simulation data. Water exchange in the primary hydration shell of Mg$^{2+}$ coordination is not observed which is in agreement with the experimental residence time (1 μs) of coordinated water molecules.

Poly(dA),poly(dT) sequence being quite interesting in its properties, are simulated at temperatures 300 K - 400 K. The DNA is simulated in different temperatures, where covalent bonds between terminal residues of the DNA in the primary simulation box and the DNA in the image boxes along z-direction is incorporated in the oligomeric DNA sequences. This gives rise to a model polymeric DNA where the terminal fraying is avoided. The analysis of hydrogen-bond, bending and ion distribution indicate that the polymer also undergoes partial melting at high temperature. Major restructuring of counterions were observed in the minor groove with temperature which could be an important factor for increased flexibility or premelting of poly(dA),poly(dT). Temperature induced melting of nucleic acids for d(CGC)CGCGAATTCGCGCGCG sequence show that higher standard deviation of base pair parameters is seen in the central AATT region compared to CG base paired part of the sequence even at 300 K. At 460 K, the polymer show melting start-point through the central AATT region and propagates to the ends of the sequence in cooperative way. This establishes the success of polymeric melting which was until now only restricted to the terminal melting only.

A battery of ab-initio quantum chemical methods along with dispersion corrections are evaluated for prediction of stacking interactions in AU/AU dinucleotide step. Roll and slide dinucleotide parameters are statistically established as the most sequence dependent. The calculations included a wide variation in dinucleotide structures in generated roll-slide energy hyperspace, which is beyond the scope of single energy minimized structure or crystal structure. The best description of stacking interaction with AU/AU step was taken as knowledge for evaluating roll-slide parameter energy hyper-space for all 10 dinucleotide steps in DNA and RNA and compared with experimental data. Incorporation of solvent effect in the calculation of stacking energy was done through CPCM method of self-consistent reaction field. Stabilization of B-DNA like conformation with small slide and small roll even for smaller twist is seen due to solvation. This relates the appearance of BDNA structures at high water activity and the transformation of the DNA to A-form in presence of dehydrating agents. BII substate is observed in TA/TA, TG/CA and GCGG steps.