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Quantum mechanical studies on the effect of ions at phosphate and sugar groups of DNA

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Abstract

Many studies have demonstrated the interaction of cation with the polyanionic regions of DNA. Different quantum mechanical methods are used to analyze the ion affinities around phosphate-sugar region. The proton affinities are found much larger than Na^+ and Mg^{2+} affinities. Further, we find that in most cases the ions can interact with multiple atomic sites of sugar-phosphate group.

Keywords : *Ab initio,* DNA, Ion affinities, MP2, Proton affinities, Quantum mechanics.

1 Introduction

The complexity of molecular system in solution due to the effect of ions present in it has attracted researchers to understand the exact nature of chemical system (Asad *et. al.,* 1991, Andrushchenko et al 2002, Mrevlishvili *et. al.,* 2003, Iyandurai et al 2009). The structure of DNA in solution is found to be considerably influenced by the surrounding water molecules and ions. It is not so easy to know the exact nature of such complex molecular system in solution environment. The DNA is a large poly-anionic molecule, and many biological chemists aim to describe the structural changes as well as chemical behaviour of this biomolecule in different solution environments (Bhattacharyya *et. al.,* 1988, Spotheim *et. al.,* 1992, Andrushchenko *et. al.,* 2002, Mrevlishvili *et. al.,* 2003, Iyandurai et al 2009). The phosphate groups of oligonucleotide are the active sites for the accumulation of water molecules and ions (Bhattacharyya *et. al.,* 1988, Spotheim *et. al.,* 1992, Shuguang *et. al.,* 2005). The water molecules can associate around phosphate groups either through hydrogen bonds or through donor acceptor interactions. In turn, the conformation of DNA changes in presence of different ions, which may be related to many biochemical processes.

The difference of dielectric constants for the minor and major grooves of DNA is more likely to be as a result of electrostatic interaction between water molecules and phosphate groups, and the number of water molecules or ions accumulated around these regions may not be equal. Slight disturbances of structurally well organized solvent molecules in solution environment might cause drastic change of

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DNA conformation. The structure and stability of DNA in the presence of monovalent and divalent cations have been reported in some studies (Spotheim *et. al.,* 1992, Shuguang *et. al.,* 2005). The divalent cations are expected to contribute for the stabilization of DNA double helix, but the presence of transition metal cations can destabilize the double helix by weakening the base pair and the stacking interactions among nucleobases. In addition, the distortion sugar backbone may produce drastic change of DNA conformation (Spotheim et al 1992, John *et. al.,* 1996, Parajuli *et. al.,* 2004, Shuguang *et. al.,* 2005, Masanori *et. al.,* 2008). Although the conformational change of DNA depends on the sequence combination of the whole nucleotides, the interaction of metal ions with various sites may also change the conformation of double helical DNA. The metal ions may bind with the heterocyclic atoms of nucleobases, and with the phosphates groups. Hence the sugar and phosphate groups may be considered as important molecular fragments for computing ion affinities. The study may indirectly demonstrate the accumulation of certain cations around phosphate and sugar groups of DNA.

2 Methodology

We have used different level of theories for computing the ion affinities, so that the accuracies of the results obtained from these theories may be assessed. The proton(PA), MA (Na^+)and MA (Mg^{2+}) affinities are computed to assess the ionic effect around sugar-phosphate reion of DNA. The inclusion of large basis set as well as electron correlation has been recommended in most of the studies (Cramer et al 1999, Tarakeshwar *et. al.,* 2001, Tarakeshwar 2001, Parajuli *et. al.,* 2004, Parajuli *et. al.,* 2005, Talukdar et al 2006, Zhao *et. al.,* 2006). Henceforth, the HF, DFT and MP2 calculations with different basis set have been used to compute ion affinities. The inaccuracy of super molecular calculation arises from the basis set superposition error in the interaction energies (Tarakeshwar *et. al.,* 2001, Tarakeshwar *et. al.,* 2001, Zhao *et. al.,* 2006). Indeed, such corrections have been automatically taken into account in Gaussian 03 program code during geometry optimization (Gaussian *et. al.,* 2003). Here the geometries of phosphate-sugar fragment and the corresponding ion interacted fragment are completely optimized with Gaussian 03 before computing ion affinities. The ion affinities are obtained from the following equation.

$$\text{Interaction energy} = \mathbf{E_3 - (E_1 + E_2)}.$$

$$\text{Ion affinity} = -\Delta \mathbf{E}$$

E_1, E_2 and E_3 are the energies of phosphate-sugar fragment, ion and ion-phosphate-sugar complex respectively.

3 Results and discussions

The O1, O2 and O3 are the three electron donor sites in phosphate and sugar groups of DNA that can interact with ions(Fig.1). All these atomic sites are located in substantially separated positions along the DNA chain, hence can not equally accessible for the ions and water molecules in solution environment. The ion affinities of these donor sites are computed to understand the accumulation of ions, and also hydrogen bond formation with these sites. We consider both the monovalent and divalent cations for neutralizing these donor sites in two different ways. Initially, the oxygen atom(O1) of phosphate group is taken for interaction with ions, since this atomic site may exist as anion that naturally serves as prominent site for neutralizing the cations present in solution. Secondly, the oxygen atom of sugar(O2) and the other oxygen atom(O3) that links sugar and phosphate groups are also taken for computing ion affinity.

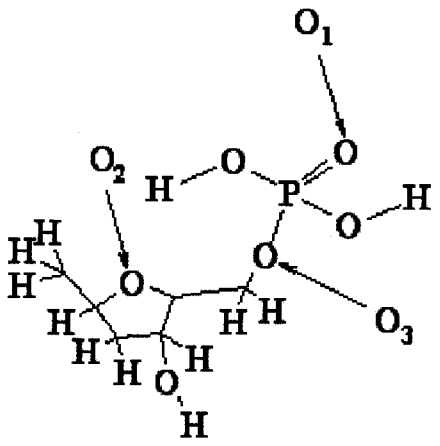

Fig. 1: Various interaction sites of phosphate-sugar region.

In this paper, the effects of monovalent (H^+ and Na^+) and divalent (Mg^{2+}) ions on O1, O2 and O3 are studied by using different methods. Table 1 shows the substantial changes of ion affinities of these three atomic sites. Moreover in most cases, these ions can interact with multiple atomic sites, and the nature of the complexes formed with the ion depend on its position with donor sites (Figs.2 (a),(b), (c),(d),(e) and (f)). The Na^+ and H^+ ions can also interact with multiple atomic sites, however the ions are found interacted more preferably with a particular donor site. Fig. 2(a) shows the ions towards O1 of phosphate group. Again the Mg^{2+} is found interacted with O1 and O2 at different interaction distances (Fig. 2(b), Table 2). The other preferred orientation for the interaction of Na^+ with O1 is shown in Fig. 2(c), however Na^+ and H^+ can also interact simultaneously with O1 and O2 in a different manner as shown in Fig. 2 (d). In this orientation, unlike that of Fig.2(a), the ions are more towards O2 atomic site. Based on the orientation of ions, the Mg^{2+} can interact either with O1 and O3 or with O1 and O2, hence the exact location of Mg^{2+} around these donor sites is also crucial due to its bivalent nature.

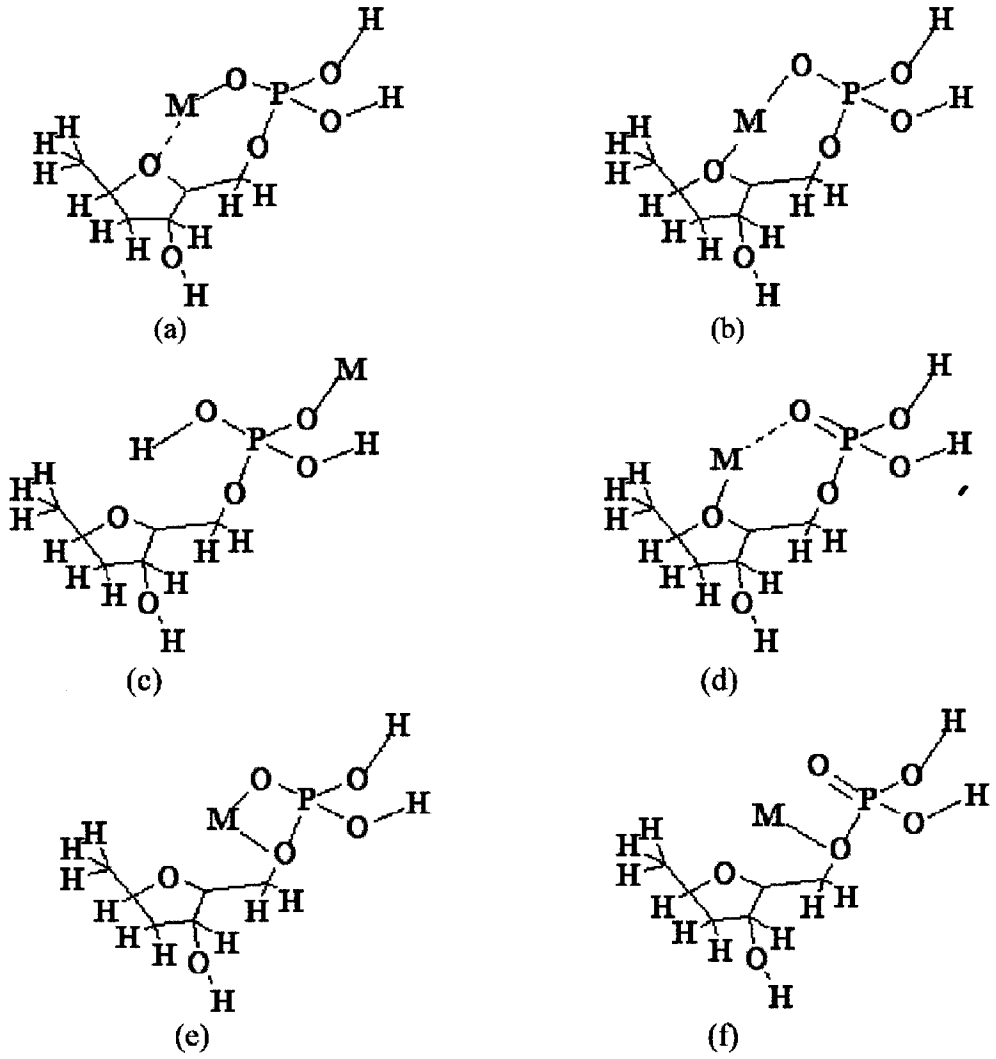

Fig. 2: Interaction of (a)Na^+ and H^+ with O1(M= Na^+, H^+) (b) Mg^{2+} with O1 & O2 (M= Mg^{2+}) (c) Na^+ with O1 (M= Na^+) (d) Na^+ and H^+ with O2 (M= Na^+, $H+$) (e) Mg^{2+} with O1 & O3(M= Mg^{2+}) (f) H^+ with O3(M= H^+).

The H affinities(PA) for these sites are found to be more than that of MA (Na^+)and MA (Mg^{2+}), and the differences between PA and MA(Mg^{2+}) affinities are not large. The PA for O1 is found more than that of O2 and O3, and the order follows as PA(O1)>PA(O2)>PA(O3). The MA(Na^+) affinities around O1, O2 and O3 are comparatively very less than the corresponding values of MA(Mg^{2+}). The findings indicate that Na+ ion may not approach very close to phosphate-sugar region in presence of H+ and Mg^{2+}. Hence, the association of ions around certain sites may largely depend on the differences of PA(H^+), MA(Na^+) and MA(Mg^{2+}). The observed variation of ion affinities within these sites might be useful to demonstrate the accumulation of these ions around phosphate-sugar region. The difference between the MA(Na^+) and MA(Mg^{2+}) around O1, O2 and O3 atomic sites might be due to the higher cationic charge

Table1- Computed ion affinities within various sites of phosphate-sugar with different methods.

Ions (Interaction sites) (Interaction distances)	Ion affinities(kcal/mol) HF/ 6-31G	MP2/ 6-31G	*HF/ 6-31G***	*DFT/ 6-31G***	*HF/ 6-31+G(d,p)*
H^+ (O1,O2H) (0.999,1.623)	229.27	212.15	222.33	224.48	224.73
Na^+ (O1) (2.042)	57.60	52.52	55.24	54.89	51.32
Mg^{2+} (O1,O2) ((1.837,1.917)	211.98	201.47	208.80	214.35	203.37
H^+ (O1H,O2) (1.549,1.009)	221.76	214.55	223.90	221.92	220.54
Na^+ (O1H,O2) (2.251,2.146)	52.72	46.51	49.56	46.51	45.90
H^+ (O3) (0.963)	197.10	197.63	190.79	192.88	192.33
Mg^{2+} (O1,O 3) (1.963,2.132)	196.63	195.57	190.20	191.35	186.35

Multiple interaction sites and interaction distances are shown in the brackets.

Table2 - The computed net charges (Mulliken) on the interaction sites of free and interacted phosphate - sugar complex w ith ions (HF/6 -31G**)

	Sites of interaction O1	O2	O3
Free	-0.820	-0.800	-0.762
H^+	-0.847(0.525)	-0.862(0.617)	-0.951(0.554)
Mg^{2+}	-0.960(1.626)	-1.079(1.626)	-1.047(1.658)
Na^+	-0.986(0.920)	-0.843(0.863)	-

The values in bracketed () show the charges on respective ions (Mg^{2+}, Na^+, H^+) in phosphate - sugar - ion complexes.

Here the interaction ability of H^- with polyanionic phosphate(O atom) groups present in DNA is found to be more significant than the metal ion, and it indicates that some of the cations may not exist very close to phosphate group. The PA of phosphate oxygen may also be indirectly used for understanding the hydrogen bond formation with the surrounding water molecules. So the characteristic behavior of different ions at the phosphate group is that the metal ions may not interact so easily with the donor sites of phosphate-sugar region in presence of H^- or hydrogen bonding molecules like water.

The PA and MA values, and the interaction distances shown in Table 1 may be useful for demonstrating ionic effect around phosphate-sugar fragment. We have also computed Mulliken net charges on the ions and donor sites of free and interacted complexes. There observed significant variation of net charges of the donor sites after interaction with these ions (Table 2). From these results, it is questionable whether the H^- ion is well accessible towards this nucleotide fragments. It may also indicate a good criterion for the accumulation of H_2O molecules around this molecular fragment through H bonds. The interaction distances of Na^- and Mg^- are much larger than that of H^-. Moreover H^- ion is found very close to the specific donor site, at a distance of 1.0 Å approximately. In addition, the results clearly indicate that the other ions, Na^- and Mg^- may not assemble very close to this molecular fragment in aqueous solution if the H^- affinity may be taken as a good validation of H-bond formation with H_2O.

4 Conclusion

From these results, it has been found that the H+ ion is well accessible towards this nucleotide fragments. It may also indicate a good criterion for the accumulation of H_2O molecules around this molecular fragment through hydrogen bonds. The H+ occur at much closer distance than Na^- and Mg^- ions, approximately at a distance of 1.0 Å.

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References

Andrushchenko V, Tsankov D & Wieser H, 2002.Analytical methods in supramolecular chemistry. Thermochimica Acta, 394: 83-85.

Asad N R & Leitao A C, 1991.Effects of metal ion chelators on DNA strand breaks and inactivation. J Bacteriol, 173(8): 2562-2568.

Bhattacharyya D, Boulden A M, Foote R S & Mitra S,1988. Phenolic hydroxyl ionistion in Calotropins from Calotropis gigantea latex. Carcinogenesis, 9: 683-685.

Cramer C J, Truhlar D G, 1999. Universal approach for continuum solvent pKa calculations. Chem Rev, 99: 2161, and references therein.

Gaussian 03, (Gaussian Inc, Pittsburgh PA) 2003.

Iyandurai N & Sarojini R, 2009. Effect of Metal Ion on the Structure of DNA: An FT-Raman Study. J of Appl Sci Res, 5(3): 283-285.

John G D & Victor A B, 1996. Electrostatic Effects on the Stability of Condensed DNA in the Presence of Divalent Cations. Biophysical Journal, 2838-2846.

Masanori Y & Taro S, 2008. Utilisation of DNA-metal ion. Polymer Journal, 40 : 327–331.

Mrevlishvili G M, Sottomayor M J, Ribeiro da Silva M A V, 2003. Epoxidation of pinene catalysed by tetrameric cobalt(III). J of Mol Struct, 661: 541-543.

Parajuli R &.Medhi C, 2004. Basicities of some 9-substituted acridine-4-carboxamides: A Density functional theory (DFT) calculation. J Chem Sci, 116(4): 235-241.

Parajuli R & Medhi C, 2005. Which base triplet stabilises triple helix? Ab initio SCF and Density functional methods of calculations on some base triplets. J Mol Struct (Theochem), 717: 59-66.

Spotheim M, Garnier F, Sabattier R & Charlier M, 1992. Sites of strand breakage in DNA irradiation by fast neutrons. Int J of Radiation Biol, 62 (6): 659-666.

Shuguang W & Hongtao Y, 2005. Pyrene and its derivatives. Int. J. Environ Res. Public Health, 2(1), 132-137.

Talukdar D, Parajuli R, Kalita R & Medhi C, 2006. Are there variations in hydrogen bonding abilities of Watson Crick region and other donor-acceptor sites of nucleobases? An ab-initio method of studying proton and metal ion affinities of nucleobases. Ind. J.of Chem., 45A: 1804-1812

Tarakeshwar P, Kim K S, Brutschy B, 2001. Nuclear Magnetic Resonance and ab initio studies of small complexes J. Chem. Phys, 114: 1295-1305.

Tarakeshwar P, Kim K S, Djafari S, Buchhold K, Reimann B, Barth H-D, Brutschy B, 2001. Structure of microstate molecules. J Chem Phys, 114: 4016-4024.

Zhao Y, Schultz N E, Truhlar D G, 2006. Design of Density Functionals by Combining the Method of Constraint Satisfaction with Parametrization for Thermochemistry, Thermochemical Kinetics, and Noncovalent Interactions. J. Chem. Theory Comput, 2 (2): 364–382.

Zhao Y, Truhlar D G, 2006. Assessment of Model chemistries for nonvalent interactions. J. Chem. Theory Comput, 2 (4): 1009-1018.