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Influence of Dielectric Constant on Codon-Anticodon pairing in mRNA and tRNA triplets by Theoretical Studies: Hartree-Fock and Density Functional Theory Calculations.

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ABSTRACT

In this paper we have focused on the dielectric constant effect between various solvents with theoretical model in the biochemical process. Thereby, AAA, UUU, AAG and UUC triplex sequences have been optimized in water, methanol, ethanol and DMSO with proposed SCRF Model of theory. The solvation of biomolecules is important in molecular biology since numerous processes involve to interacting a protein with changing of solvent-molecule.

The hydrogen bond is one of the important predictions of structural and functional in biochemical and biophysical of biological complexes such as proteins. mRNA-tRNA pairing as a fundamental step in protein

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synthesis is a complexes process controlled by hydrogen bonding between two anti-parallel trinucleotides, namely the mRNA codon and the tRNA anticodon.
In order to determine the optimized structural biology including of bond lengths, bond angles and dihedral angles energies, dipole moments and other properties of codons and anticodon, we have performed ab initio calculations of Quantum Mechanics (QM) at HF/sto-3G, 3-21G, 6-31G levels in gas phase and a few solvents with different dielectric constans via the SCF method using the GAUSSIAN 98 software package. Optimization at the HF/6-31G level has yielded results in better agreement with the experimental data.

INTRODUCTION

The Watson-Crick type base pair formation is fundamental for molecular recognition in the duplex formation of nucleic acids [1, 2]. The processes of transcription from DNA to mRNA [3], and of translation from mRNA to protein via tRNA [4] are also based on the formation of the Watson –Crick type base pairs.

Each amino acid in a protein is specified by a group of the three adjacent nucleotide bases, denoted a codon, on the messenger RNA (mRNA) strand. Three special nucleotide bases in the tRNA molecule, the anticodon, interact with the three complementary codon bases in the mRNA molecule through hydrogen bonds and joining of the amino acid into a chain is realized inside the ribosome. In a process called translation, the mRNA molecule directs the collection of amino acids into the specific linear sequence characteristic of a given protein [5].

Theoretical nucleic acid conformational investigations have, thus far, mainly been concerned with the elucidation of the factors that govern sequence-dependent conformational properties.

Codon-anticodon pairing is not merely a simple process controlled by hydrogen bonding between two anti-parallel trinucleotides, namely the mRNA codon and the tRNA anticodon. For example, peculiarities of the codon-anticodon interaction such as the absence of non-canonical base pairing at the first two positions of the codon cannot be explained just by the internal stability of the codon-anticodon mini helix and the influence of the tRNA anticodon loop. It is known that a wide variety of non-canonical base pairs is observed in different regions of the double helices of RNA molecules [6-9], and even in different positions of the anti-codon-anticodon mini helices [8,10]. There is also a series of indications that the translation of the codon can depend on adjacent codons (codon context effects [11-13]).

Although we know which anticodon-codon complexes are recognized as "correct," we have never understood why only they are acceptable. Crick (1966), based on the emerging structure of the genetic code and base pair stereochemistry, and proposed his famous wobble rules for identifying correct duplexes. He proposed that only canonical base pairing should occur at the first and second codon positions, and that certain wobble pairing would be possible at the third codon position. In succeeding years these general rules have been amply confirmed, although the range of acceptable wobble pairs has been expanded (Osawa et al., 1992; Boren et al., 1993; Inagaki et al., 1995). There has also been progress towards an understanding of how nucleoside modifications affect wobbling (e.g., Agris, 1991; Björk, 1992, 1998; Osawa et al., 1992; Yokoyama & Nishimura , 1995; Curran, 1998).

In fact, some of these mispaired complexes are just as stable as duplexes that contain only correct base pairs. Clearly, both correct and wrong codon-anticodon duplexes can be stable in solution. Notice that ribosomal proofreading, which can in principle amplify small energetic differences (Hopfield, 1974; Ninio, 1975; Kurland et al, 1990; Yarus, 1992), cannot distinguish duplexes that have essentially the same stabilities. Therefore, in addition to using a proofreading mechanism, ribosomes must rely on features other than duplex stability as predicted from solution and structural studies.

In the solution and while interacting with other materials, nucleic acids have also shown to adopt conformations not at all similar to the original Watson and Crick model (Srinivasan and Olson, 1987; Jaworski et al., 1987; Wu et al., 2002). Rigid body docking and static models have been used to examine the codon–anticodon–ribosome interactions, and ternary complex initial selection. Smaller scale molecular dynamics simulation studies of cognate codon–anticodon interactions in the absence of the ribosome have also been performed. (Sanbonmatsu and Joseph, 2003) And mean free energy generated from the secondary structure of RNA sequences of varying length and composition has been studied to show that some nucleotide sequences found in biologically active organisms do relate to the free energy of their structures. Recently, a theoretical model based on similarity for studying RNA base pairings has been built up to analysis both Waston–Crik and non-Waston–Crick pairings. And some theoretical considerations concerning the capability of the genetic code to repair dangerous mutations contribute to the ongoing debate (Patrizia et al,.1996). The impact of base-pair interactions to the RNA folding and biological functions is quite prevalent. Codon–anticodon interactions are involved in the discrimination between the correct and incorrect aminoacyl-tRNAs. Hydrogen bonding, steric fit, and base-pair stability may be the main aspects that influence the whole process [14].

Water is the natural medium of all biological reactions, participating in different processes involving the living cell. Particularly, several structural features that are necessary for the biological functions of nucleic acids, such as DNA double helix formation or RNA folding and nucleic acids base pairing, are dependent on their interactions with surrounding water .The hydration of nucleic acids is controlled by the interaction of water molecules with various hydrophilic sites such as phosphates, bases and sugars.

Water is a highly polar molecule which can be simultaneously an acceptor and a donor of H-bond via the interactions occurring through its oxygen or hydrogen atoms, respectively, with the nucleic acid constituents.

Computational methods allow for the visualization of large amounts of structural data and the generation of related conformations for statistical and dynamic analyses. The application of these methods to systems of biological interest has advanced tremendously in recent years to encompass models that describe local conformational effects with

great precision: such as quantum mechanical (QM) studies of the effect of substituent modifications, methods that perform statistical energy-guided conformational searches

such as energy minimization, Monte Carlo (MC) and molecular dynamics (MD) simulations, and algorithms that aim to describe the collective structural constraints

that influence macromolecular tertiary structure, folding pathways and the energetics of supercoiling.

Theoretical backgrounds

The most common type of ab-initio calculation is called Hartree-Fock calculation (abbreviated HF), in which the primary approximation is called the mean field approximation. This means that the coulombic electron-electron repulsion is not explicitly taken into account, however, its average effect is included in the calculation [15].

In the density functional theory (DFT), electron correlation is introduced through the Kohn and Sham method [16, 17], based on the combinations of some density functional (exchange, correlation).In the present work, the hybrid functional Beck's three parameters (B3) [18] combined with the gradient corrected correlation functional of Lee-Yang-Parr [19] also denoted B3LYP is used.

Computational methods

The studies of Hydrations of nucleobases were a subject of numerous theoretical studies using Monte-Carlo, molecular dynamics, and quantum-chemical approaches within the

continuum model. Such information may by obtain only within the super molecules approach using high level *ab initio* methods. Also so far, no theoretical study has been done on pairing behaviors of these bases. Thus by this study we intend to propose the first detailed mechanism and investigate the effects of solvent surrounding them on changing of succession of amino acids.

A quantum mechanical (QM) calculation was performed to verify the nature of the minimum state of the stationary points reached after geometry optimization. The geometries of the AAA, UUU, AAG and UUC have been optimized by *ab initio* and DFT calculations using the standard STO-3G, 3 -21 G, 6-31Gand 6-31G* basis sets, in Hartree-Fock (HF) and B3LYP levels. The calculations have been performed by using the Gaussian 03 suite of program.

RESULTS AND DISCUSSION

Nucleic acid bases contain a row of N and N-H groups, which provide a range of possible hydrogen-bonded with water molecules. In all of these the water molecule is bonded to AAA, UUU, AAG and UUC triplex sequences hydrogen bond (OH...N or NH...O). Firstly, the complexes were fully optimized with HF and DFT (BLYP and B3LYP) methods at 3-21G, 6-31 G and 6-31 G* basis sets and we have located the minima on the nucleobases potential energy surface.

Optimization parameters such as: dipole moments and energies yields molecular geometries in good agreement with experimental values and those previously obtained theoretically.

The results in Table1 show that, with increase of dielectric constant from vacuum to cyclohexane, ethanol, methanol, DMSO and water, the dipole moment of each model increases by different quantum mechanic levels.

A dipole in the molecule will induce a dipole in the medium, and the electric filed applied by the solvent dipole will in turn interact with the molecular dipole, leading to net stabilization. These parameters represent the subtle structural changes of the triplets are not statistically correlated because the distributions of subtle structural changes of different triplets are very different, and the contributions of dedicated structure changes should be analysed individually (Fig.2).The values of calculations in table.1 show that the interactions between water molecules and triplets reduce the energy of the integer system. The only exception is non-bond dispersion energy; it may imply that in aquatic solution, import of polarized water molecules reduces the polarization rates of triplets. The significance levels of parameters reveal the changes of solvent groups are significant.

The effect of solvent on stabilization of triplex bases indicates interesting results and play major roles in their activities. The standard approach of the PCM (by SCRF method) for nucleobases with different basis sets, as is used here appears to be a good first step in the theoretical investigation on the effect of solvent. In this paper, we have presented the solvation of the complexes. The influence of dielectric constant on the standard geometry optimization of AAA,UUU,AAG and UUC triplex sequences in H_2O, C_2H_5OH, CH_3OH and DMSO solvents have investigated. We have shown that relative energies (ΔE) of triplex bases in solution are smaller than gas phase, which is due to interactions in solution is larger than gas phase and it seems for all different sequences that the influence of aquatic solution to mRNA–tRNA triplets is almost the same(Table.1).

The interaction energies of the complexes with increasing dielectric constant of solvent decrease at HF, BLYP and B3LYP methods. The charts of AAA and UUU triplex bases almost are linear but we have not seen this form for AAG and UUC triplex sequences. Also, the non-linear chart in the antisenses sequences(AAG and UUC) at heavy basis set of 6-31 G* turnouts linear(Fig.3).The results obtained from density functional theory are larger than those obtained from Hartree–Fock calculations because correlation energies are considered in DFT method. However, the accuracy of BLYP and B3LYP calculations has been considered as insufficient for base triplets interactions.

Because the increase of dielectric constant in water molecules that are arranged around the hydrophilic part of chain of amino acid, we have found the optimized parameters better than other solvents.

Also, from these calculations we result that the effect of dielectric constant of solvents is important to displacing of amino acids sequences on codon-anticodon residues pairing in proteins and it will be causes some mutations in human body.

Conclusion

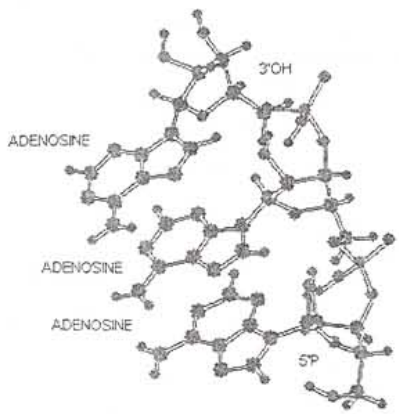
1. For the compound studied, the most important intermolecular interaction between nucleobases and solvent molecules employ different geometrical models in the crystalline structures. These interactions have been approximated by explicitly adding the nearest neighbors into the calculations. Interaction with solvent molecules has caused deformation of the intermolecular geometry of the nucleobases which can be described by assuming the resonance form into the total structure of the bases.

2. The comparison between optimized structures investigates stability of chain amino acids in theoretical levels. We have performed HF and DFT quantum mechanic methods of good quality on the AAA, UUU, AAG and UUC triplex sequences in Water, Ethanol, Methanol, and DMSO solvents with different basis sets.

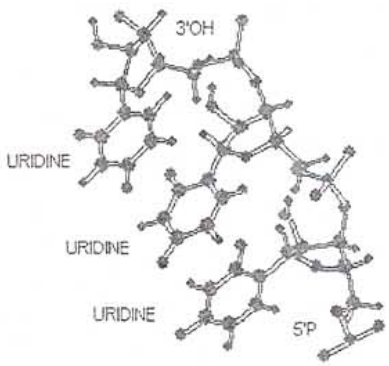
Based on the obtained results and stabilized structures, we conclude that it may be dielectric constant effect of solvents have been caused to displacing of amino acids sequences on codon-anticodon residues pairing in proteins and it will be indicates some changes in biological ambient.

3. Based on the analysis of the physico-chemical properties of mRNA and tRNA, Jean Lehmann (2000) pointed out that nature of the codon–anticodon interaction can explain the volume of the corresponding amino acids. Peptide bond formation may exist between two successive amino acids during translation. And the nature of codon–anticodon may be sufficient to explain the origin of comparison the energies of mRNA and tRNA triplets in vacuum, and those in aquatic solution show significant differences.

4.Presence of active centers in base triplex may be important in the recognition code mechanism involving tRNA .we are now working towards an ab initio confirmation. The calculated group-group bond indices and molecular valences agree with these features. The change of nucleotide in codon-anticodon shows complexity which may lead to different biological functions. As a matter of fact, the energies can provide some valuable information for binding stabilities of pairing in proteins and it will be causes some mutations in human body.



(a)



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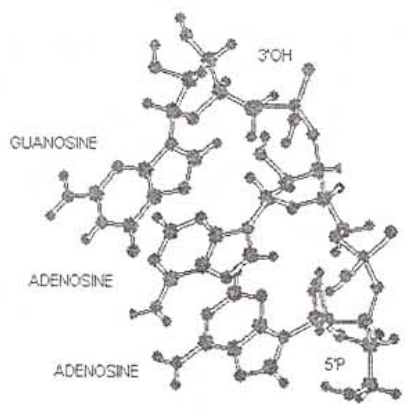
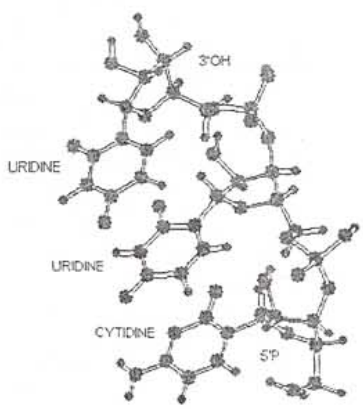


(c)

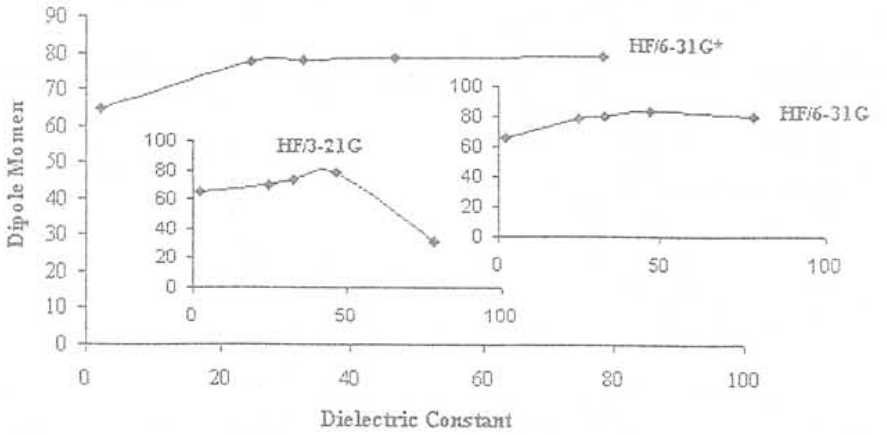


(d)

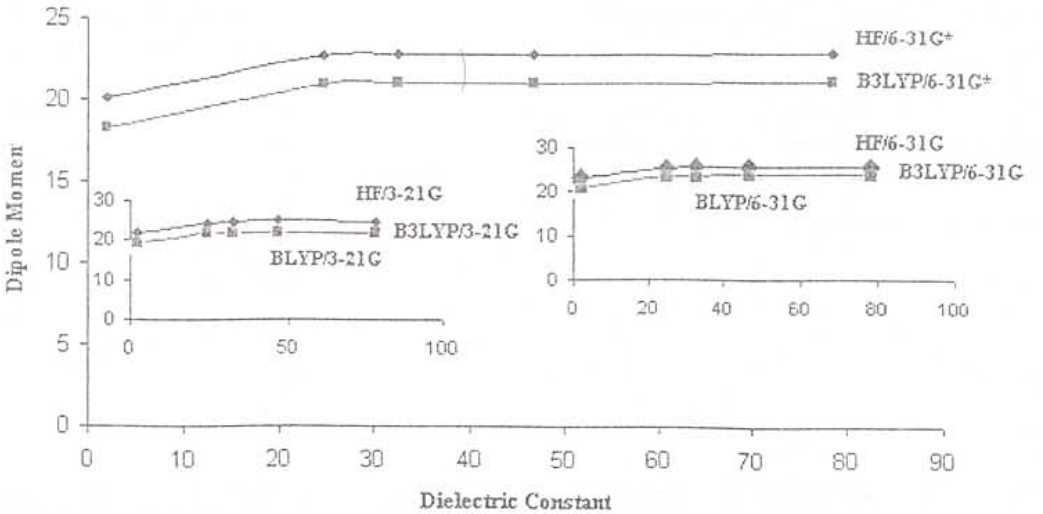
Fig.1. geometry optimization of (a)AAA. (b)UUU,(c) AAG and (d)UUC triplex sequences by showing of active centers.

Table 1. Values of dipole moment and relative energy in AAA, UUU, UUC and AAG triplex sequences in HF and DFT (BLYP and B3LYP) methods at various ambient.

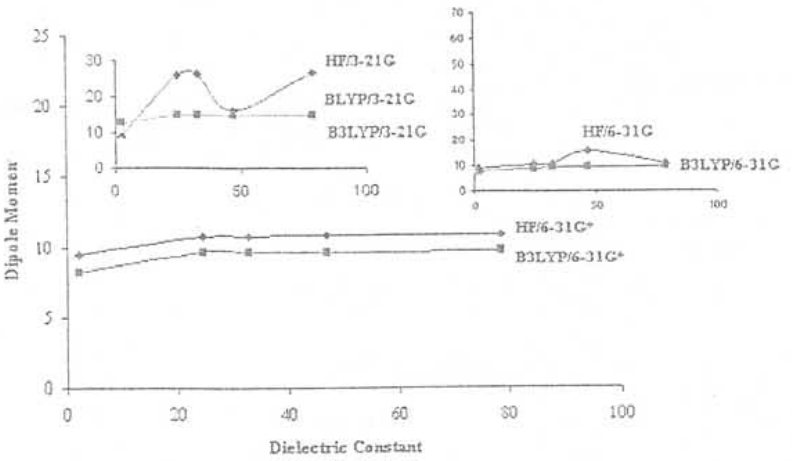
Solvent (dielectric)	SEQUENCE	PARAMETER	HF			BLYP			B3LYP		
			3-21g	6-31g	6-31g*	3-21g	6-31g	6-31g*	3-21g	6-31g	6-31g*
vaccum	AAA	dipole	40.9237	40.4713	59.2331	----------	----------	----------	----------	----------	----------
	UUU	dipole	15.2868	16.0293	15.2690	16.7047	18.0163	----------	17.5797	18.9040	16.6210
	UUC	dipole	16.8035	28.3729	29.0364	18.9039	19.1747	----------	28.4225	28.5565	27.8173
	AAG	dipole	13.3232	12.0622	8.5889	11.8733	----------	----------	20.6002	20.9178	20.9900
CYCLOHEXANE (2.023)	AAA	dipole	65.1489	66.0421	64.8689	----------	----------	----------	63.3546	64.2557	--------
		ΔH	42.2118	16.3571	-37.9633	----------	----------	----------	--------	--------	--------
	UUU	dipole	21.8012	23.2887	20.1126	18.2376	19.8183	----------	19.1567	20.7070	18.2452
		ΔH	61.7028	67.8810	91.0885	-3.0847	-3.6391	----------	-3.3811	-3.9392	-3.0257
	UUC	dipole	22.5474	23.1587	31.3776	20.6831	21.0766	----------	21.1167	21.5551	30.3786
		ΔH	105.3939	108.8373	-7.9729	-3.4210	-3.5143	----------	-41.4283	29.6597	-7.2388
	AAG	dipole	8.9051	9.0319	9.4007	12.9324	----------	----------	7.7720	7.9025	8.2450
		ΔH	103.0987	127.9694	-0.6939	-1.3479	----------	----------	41.9057	37.6429	43.8202
ETHANOL (24.55)	AAA	dipole	69.5254	78.9865	78.0468	----------	----------	----------	----------	----------	----------
		ΔH	-37.1962	-51.5244	-99.6934	----------	----------	----------	----------	----------	----------
	UUU	dipole	24.3433	25.2440	22.7177	20.8330	22.8365	----------	21.7288	23.6885	20.9485
		ΔH	-7.0165	-10.2888	84.9459	-8.1924	-9.7175	----------	-8.9770	-10.5334	-8.1638
	UUC	dipole	35.2009	57.8514	35.1146	23.6523	24.3226	----------	23.9741	24.6818	34.5681
		ΔH	-5.0962	-33.9797	-20.6555	-9.0521	-9.4513	----------	35.6009	23.5358	-19.3269
	AAG	dipole	26.0378	10.3613	10.7556	14.6379	----------	----------	9.0034	9.2329	9.6057
		ΔH	-6.9671	126.8873	-1.8954	-3.4907	----------	----------	41.0966	36.7993	42.9046
METHANOL (32.63)	AAA	dipole	73.3946	80.2768	78.4816	----------	----------	----------	----------	----------	----------
		ΔH	-63.5098	-53.6347	-10.17295	----------	----------	----------	----------	----------	----------
	UUU	dipole	24.4898	25.4140	22.7984	20.9145	22.9320	----------	21.8089	23.7822	21.0338
		ΔH	-7.2354	-10.5244	84.7557	-8.3524	-9.9101	----------	-9.1510	-10.7432	-8.3256
	UUC	dipole	35.3862	57.3185	35.2293	23.7455	24.4254	----------	34.8387	35.4717	34.6989
		ΔH	-5.6232	-36.6538	-21.0445	-9.2287	-9.6148	----------	-20.2282	-20.6920	-19.7040
	AAG	dipole	26.2731	10.4034	10.7984	14.6903	----------	----------	9.0428	9.2760	9.6497
		ΔH	-7.1833	126.8532	-1.91124	-3.5608	----------	----------	41.0709	36.7723	42.8753
DMSO (46.7)	AAA	dipole	77.9591	79.9790	78.8884	----------	----------	----------	----------	----------	----------
		ΔH	-22.9531	51.4121	-103.6395	----------	----------	----------	----------	----------	----------
	UUU	dipole	24.8802	25.6346	22.8736	20.9903	23.0210	----------	21.8834	23.8695	21.1133
		ΔH	-3.5374	-10.1222	84.5787	-8.5014	-10.0897	----------	-9.313	-10.9330	-8.4754
	UUC	dipole	25.4117	26.3158	35.3359	23.8322	24.5211	----------	34.9504	35.5931	34.8176
		ΔH	98.4519	101.4534	-21.4063	-9.3932	-9.8004	----------	-20.5820	-21.0589	-20.1913
	AAG	dipole	15.8840	15.9317	10.8383	14.7391	----------	----------	9.0796	9.3161	9.6907
		ΔH	-4.4315	19.0952	-1.9009	-3.6268	----------	----------	41.0469	36.7471	42.8477
WATER (78.39)	AAA	dipole	31.8664	83.1767	79.2766	----------	----------	----------	----------	----------	----------
		ΔH	-17.5337	-62.9385	-1054584	----------	----------	----------	----------	----------	----------
	UUU	dipole	24.7558	25.7244	22.9451	21.0626	23.1058	----------	21.9545	23.9527	21.1891
		ΔH	-7.6356	-10.9563	84.4102	-8.6433	-10.2594	----------	-9.4672	-11.1165	-8.6199
	UUC	dipole	36.0207	30.8165	35.4374	23.9149	24.6123	----------	24.2249	24.9588	34.9366
		ΔH	-6.3440	-7.3945	-21.7504	-9.5498	-10.0225	----------	35.0899	22.9938	-20.3895
	AAG	dipole	26.7052	10.4799	10.8763	14.7855	----------	----------	9.1147	9.3545	9.7299
		ΔH	-7.5819	126.7913	-1.9272	-3.6879	----------	----------	41.0240	413.2238	42.8215


Dipole Momen
Dielectric Constant
HF/6-31G*
HF/6-31G
HF/3-21G

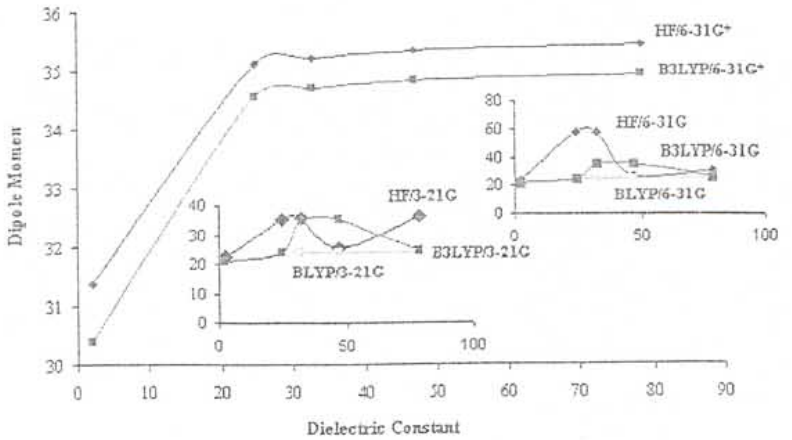
(a)


Dipole Momen
Dielectric Constant
HF/6-31G*
B3LYP/6-31G*
HF/6-31G
B3LYP/6-31G
BLYP/6-31G
HF/3-21G
B3LYP/3-21G
BLYP/3-21G

(b)

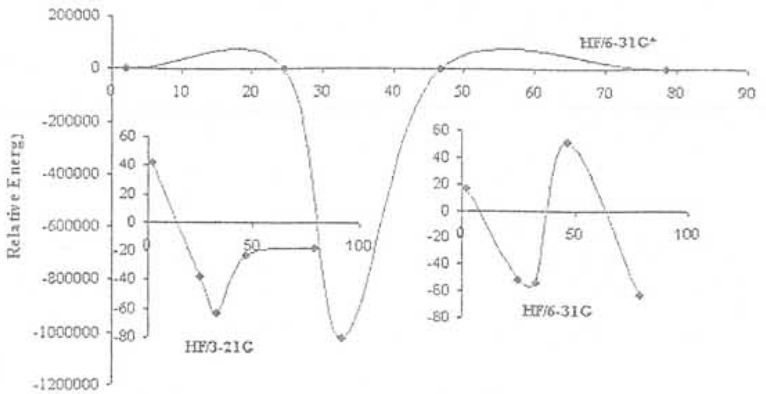


(c)

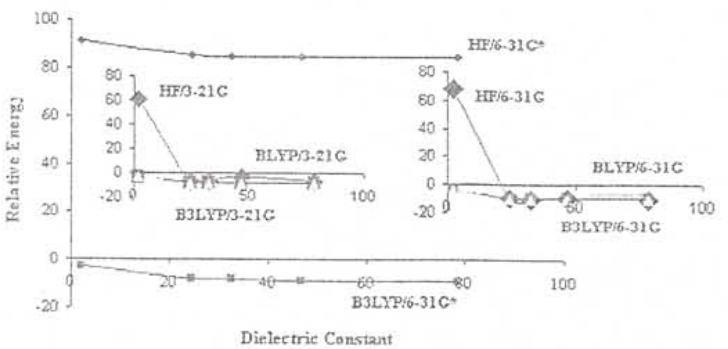


(d)

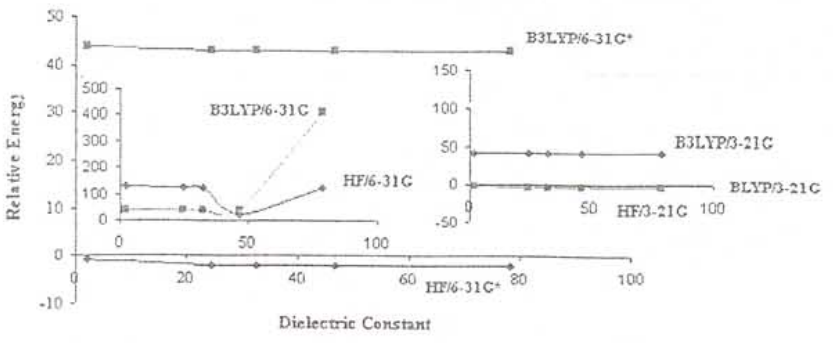
Fig.2. Comparison of the dipole moment (debye) (a)AAA, (b)UUU,(c) AAG and (d)UUC triplex sequences versus dielectric constant obtained from HF and DFT (BLYP and B3LYP) methods at differe basis sets .


HF/6-31C*
HF/3-21C
HF/6-31C
Relative Energy
Dielectric Constant

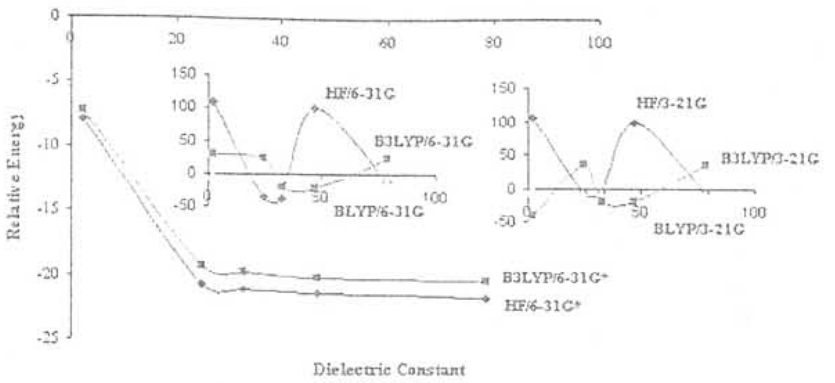
(a)


HF/6-31C*
HF/3-21C
HF/6-31C
BLYP/3-21C
BLYP/6-31C
B3LYP/3-21C
B3LYP/6-31C
B3LYP/6-31C*
Relative Energy
Dielectric Constant

(b)


B3LYP/6-31C*
B3LYP/6-31C
HF/6-31C
B3LYP/3-21C
BLYP/3-21C
HF/3-21C
HF/6-31C*
Relative Energy
Dielectric Constant

(c)



(d)

Fig.3. Variation of relative energy(kcal/mol) (a)AAA, (b)UUU,(c) AAG and (d)UUC triplex sequences versus dielectric constant obtained from HF and DFT (BLYP and B3LYP) methods at different basis sets .

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