ISSN 0036-0244, Russian Journal of Physical Chemistry A, 2008, Vol. 82, No. 13, pp. 2277–2285. © Pleiades Publishing, Ltd., 2008.

PHYSICAL CHEMISTRY OF SOLUTIONS

A Theoretical Thermochemical Study of Solute–Solvent Dielectric Effects in the Displacement of Codon–Anticodon Base Pairs

M. Monajjemi[a], M. H. Razavian[b, c], F. Mollaamin[a, d], F. Naderi[e], and B. Honarparvar[a]

[a] *Islamic Azad University, Tehran, Iran*

[b] *Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran*

[c] *Department of Microbiology, Qom Branch, Islamic Azad University, Qom, Iran*

[d] *Department of Chemistry, Qom Branch, Islamic Azad University, Qom, Iran*

[e] *Department of Chemistry, Islamic Azad University, Shahriar-Shareh Gods Branch, Iran*

e-mail: m_monajjemi@yahoo.com

Received September 24, 2007

Abstract—Quantum-chemical solvent effect theories describe the electronic structure of a molecular subsystem embedded in a solvent or other molecular environment. The solvation of biomolecules is important in molecular biology, since numerous processes involve proteins interacting in changing solvent–solute systems. In this theoretical study, we focus on mRNA–tRNA base pairs as a fundamental step in protein synthesis influenced by hydrogen bonding between two antiparallel trinucleotides, namely, the mRNA codon and tRNA anticodon. We use the mean reaction field theories, which describe electrostatic and polarization interactions between solute and solvent in the AAA, UUU, AAG, and UUC triplex sequences optimized in various solvent media such as water, dimethylsulfoxide, methanol, ethanol, and cyclopean using the self-consistent reaction field model. This process depends on either the reaction potential function of the solvent or charge transfer operators that appear in solute-solvent interaction. Because of codon and anticodon biological criteria, we performed nonempirical quantum-mechanical calculations at the BLYP and B3LYP/3-21G, 6-31G, and 6-31G* levels of theory in the gas phase and five solvents at three temperatures. Finally, to obtain more information, we calculated thermochemical parameters to find that the dielectric constant of solvents plays an important role in the displacement of amino acid sequences on codon–anticodon residues in proteins, which can cause some mutations in humans.

DOI: 10.1134/S0036024408130207

INTRODUCTION

Whereas DNA stores information for protein synthesis and RNA carries information encoded in DNA, most biological activities are catalyzed by proteins, molecules whose accurate synthesis is at the heart of cellular function. Since the linear order of amino acids in each protein determines its structure and function, the mechanism that maintains this order during protein synthesis is a critical option, because any mistake in amino acid protein sequence can cause a mutation and then a disease such as various cancers.

It is known that base pairing is a fundamental step of molecular recognition in the duplex formation of nucleic acids and the processes of transcription and translation [1]. So, during translation in ribosomes, each protein amino acid is specified by a group of three adjacent nucleotide bases, a codon on the messenger RNA (mRNA) strand, which interacts with other three special nucleotide bases in the tRNA molecule, and an anticodon, in a complementary manner according to the Watson–Crick base-pairing rules [2]. The fidelity of transcription and translation is ensured primarily through tRNA recognition events during both amino acylation and codon–anticodon pairing [3, 4], where hydrogen bonds in both of them play a critical role [3].

Consequently, there are numerous experimental [5–27] and computational [13–27] studies concerned with the association of nucleotide base pairs. Computational studies range from gas phase energy minimizations to Monte Carlo and molecular dynamics simulations in solution [22]. But codon–anticodon pairing is not merely a simple process controlled by hydrogen bonding between two antiparallel trinucleotides and influenced by many different physico- and stereochemical factors. For example, the peculiarities of codon–anticodon interaction such as the absence of noncanonical base pairing at the first two positions of the codon [23–26] or the dependence of the mean codon on adjacent codons (codon context effects) [27, 28] cannot be explained by just the internal stability of the codon–anticodon minihelix [29].

There are also a series of indications that various characteristics of solutions in which processes are performed, such as the dielectric constant, are determining

factors. Nucleic acids are highly charged molecular species that interact strongly with their solvent environment [30], and nucleic acids adopt conformations not at all similar to the original Watson and Crick model [30, 31].

Rigid body docking and static models have been used to examine codon and anticodon interactions with each other and in solutions [32]. Smaller scale molecular dynamics simulation studies of cognate codon–anticodon interactions were also performed. There is no doubt that computational methods provide 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 advanced tremendously in recent years to encompass models that describe local conformational effects with great precision. The ability to accurately calculate solvation energies of molecules using molecular simulation methods is an important development in computational chemistry [30]. These methods have wide applicability not only in studies of free energies of solvation, but also in studies of free energies of binding and protein and nucleic acid stability [30]. Knowledge of free energies of solvation of DNA bases would be useful, for example, for understanding the forces involved in protein–nucleic acid interactions and the stability of nucleic acid tertiary structures.

The solvent effect is taken into account using the self-consistent reaction field (SCRF) method [34]. This method is based on the Onsager reaction field theory of electrostatic solvation [35]. In this model, a solvent is treated as a uniform dielectric with a given dielectric constant. A solute is placed into a cavity within the solvent. Various SCRF approaches differ in how they treat the cavity and reaction field [36].

In this paper, we use nonempirical calculations in one of the first detailed studies of triplet structures, geometries, energies, enthalpies, free energies, entropies, atomic charges, dipole moments, and other thermochemical properties with special emphasis on solvent effects on them.

We optimized the geometries of the AAA, UUU, UUC, and AAG triplets in various solvents using the Onsager model at the Hartree–Fock, BLYP, and B3LYP levels of theory and compared our results with those obtained for the gas phase. In addition, the effect of the permittivity of solvents on the stability of these triplets was explored and discussed. The calculations of all systems were performed using the 3-21G, 6-31G, and 6-31G* basis sets.

THEORETICAL

The hydration of nucleobases was a subject of numerous theoretical studies by the Monte-Carlo, molecular dynamics, and quantum-chemical methods within the continuum model. Such information can be obtained only within the supramolecular approach using high-level nonempirical methods. So far, no theoretical study of pairing behaviors of these bases has been done. Thus, in this study, we propose the first detailed mechanism and investigate solvent effects on variation of amino acid sequences.

A Quantum-Mechanical Continuum Solvent Model

The use of the SCRF model in quantum-chemical theory requires that the shape and volume of the solute molecule be defined uniquely for any set of compounds. A number of approaches to calculating these characteristics are known, but no nonempirical methods for their estimation have been developed. However, it can be concluded from the results of model calculations that the simple model assuming a spherical or an ellipsoidal shape of the cavity for the solute molecule is likely satisfactory for comparatively small and rigid molecules. Therefore, this method was selected in our calculations [37, 38].

The Onsager-SCRF code elaborated by Wiberg and co-workers [39, 40] for the Gaussian computational code has been fairly popular in the past years. The Onsager model is the simplest version of the MPE approach. Solvation is described in terms of a dipole moment drawn iteratively from QM calculations of the molecule. The appealing feature of the Onsager-SCRF method was the ability of directly exploiting almost all the computational facilities of the Gaussian package [17].

Following the Onsager model, the interaction energy of a dipole in a solvent is

$$E^{\text{solv}}(t) = -m(t)R(t), \quad (1)$$

where $R(t)$ is the reaction field at time t caused by the surrounding solvent that acts on the dipole of the solute.

The Onsager model describes the system as a molecule with a multipole moment inside a spherical cavity surrounded by a continuous dielectric. In some programs, only the dipole moment is used, and calculations therefore fail for molecules with zero dipole moment. The results obtained using the Onsager model and HF calculations are as a rule qualitatively correct. Accuracy increases significantly with the use of MP2 or hybrid DFT functionals. This is not the most accurate method available, but it is stable and fast. This makes the Onsager model an attractive alternative when PCM calculations fail [41].

The Relation between Structural Stability and Thermodynamic Parameters

A theoretical analysis at the HF, BLYP and B3LYP/3-21, 6-31G, and 6-31G* levels of theory was performed to characterize all the stationary points of the potential energy surface as minima and obtain thermodynamic corrections. Solvation effects were mod-

eled by the Onsager method as implemented in the GAUSSIAN 98 program [17]. The equilibrium free energy of solvation can be divided into smaller contributions corresponding to cavitation, universal solvation effect such as solute-solvent electrostatic, dispersion, and repulsion interactions, and nonuniversal specific interactions, such as intermolecular hydrogen bonding or electron donor–electron acceptor interactions [42],

$$\begin{aligned}\Delta G(\text{solvation}) &= \Delta G(\text{electrostatic}) \\ &+ \Delta G(\text{dispersion}) + \Delta G(\text{repulsion}) \\ &+ \Delta G(\text{cavitation}) + \Delta G(\text{specific}).\end{aligned} \quad (2)$$

Electrostatic solute–solvent interactions are usually introduced into quantum-mechanical calculations by means of the self-consistent reaction field (SCRF) approach.

In the Onsager model, a solute is placed in a spherical cavity immersed in a continuous solvent, and the full classical multipole expansion of the total solute charge distribution is truncated after the dipole term, that is, it only includes solute monopole and dipole interactions with the continuum. Despite the simplicity of the Onsager approach, its applicability was proved for many systems. The advantage of this model is analytic calculations of the solvent reaction field for spherical cavities, which speed up the process and allow geometric optimizations in solution to be performed for compact molecules at a modest computational cost. Although this method includes significant improvements of the Onsager approach, a new problem arises. For the definition of the density surface, an isodensity level that fixes the amount of electron density within the built cavity must be specified. However, a small percentage of charge density extends outside the cavity. This causes serious problems in the dielectric continuum treatment of solvents by affecting the charge inside the cavity.

RESULTS AND DISCUSSION

Recently, much effort has been devoted to the modeling of physicochemical processes in condensed phases and biological environments. The progress in various fields, such as the theory of intermolecular forces, in computer simulation techniques and in solid-state physics methods enabled us to obtain better understanding of many of these important phenomena. It became evident that, at least in certain cases, the influence of intermolecular interactions on the electronic structure of constituents was substantial.

Quantum-chemical solvent effect theories give a self-consistent description of the electronic structure of solutes, which is closely related to the polarizable environment. Such calculations are indispensable for getting insight into the molecular properties and reactivity of condensed phases. This goal is usually achieved by means of a solute–solvent Schrödinger equation corresponding to some simplified representation of the solvent. In particular, the electronic structure of solute molecules can be closely related to the solvent structure and vice versa. This effect can be of key importance, for example, for the understanding of the microscopic mechanism of certain reactions in solutions.

We should note that there is interaction energy between solutes and solvents. Because of this, solute properties that depend on energy and several other factors, such as geometry, vibrational frequencies, total energy, and electronic spectrum, also depend on the solvent. The presence of a solvent, particularly a polar solvent, can also stabilize charge separation within a molecule. This not only changes energy, but also causes electron density shifts and influences associated properties. In reality, this is a result of quantum-mechanical interactions between the solute and solvent, which must be averaged over all possible arrangements of solvent molecules according to the statistical mechanics principles.

The energy of solvation can further be divided into terms that describe the bulk solvent and terms that specify the first solvation shell. The bulk solvent contribution is primarily the result of dielectric shielding of electrostatic charge interactions. In the simplest form, it can be included in electrostatic interactions by means of the dielectric constant ε, as in the Coulomb interaction equation [43]

$$\varepsilon = q_i q_j / \varepsilon r_{ij}. \quad (3)$$

This modification of charge interaction is responsible for electron density shifts allowed by the polarizabilities of the AAA, UUU, AAG, and UUC triplex sequences. There are several effects in the region where a molecule meets its solvent shell. The first one is referred to as cavitation energy, which is the energy required to push aside solvent molecules to produce a cavity for the solute molecule. The second effect is related to forces attracting the solute molecule to the solvent. These are van der Waals, dispersion, and hydrogen bonding interactions. Finally, the solvent molecules in the first shell can rearrange in order to maximize interactions with the solute. The largest amount of hydrogen bonding energy is usually related to solvent rearrangement to the preferred hydrogen bonding orientation. By solving the corresponding electrostatic equations inside and outside the sphere and applying proper boundary conditions, one can find the potential at any point inside the cavity and the total electrostatic energy of the interaction of molecular charge distribution with polarizable medium. In the quantum-chemical application of this theory, this interaction energy is represented by additional molecular Hamiltonian terms corresponding to nuclear–nuclear, nuclear–electronic, and electron–electron contributions. Because of the unavoidable deficiencies of the Onsager model, further insight into the nuclear polarization effects, i.e., geometric optimization in solution, would not yield better results. Therefore, the use of

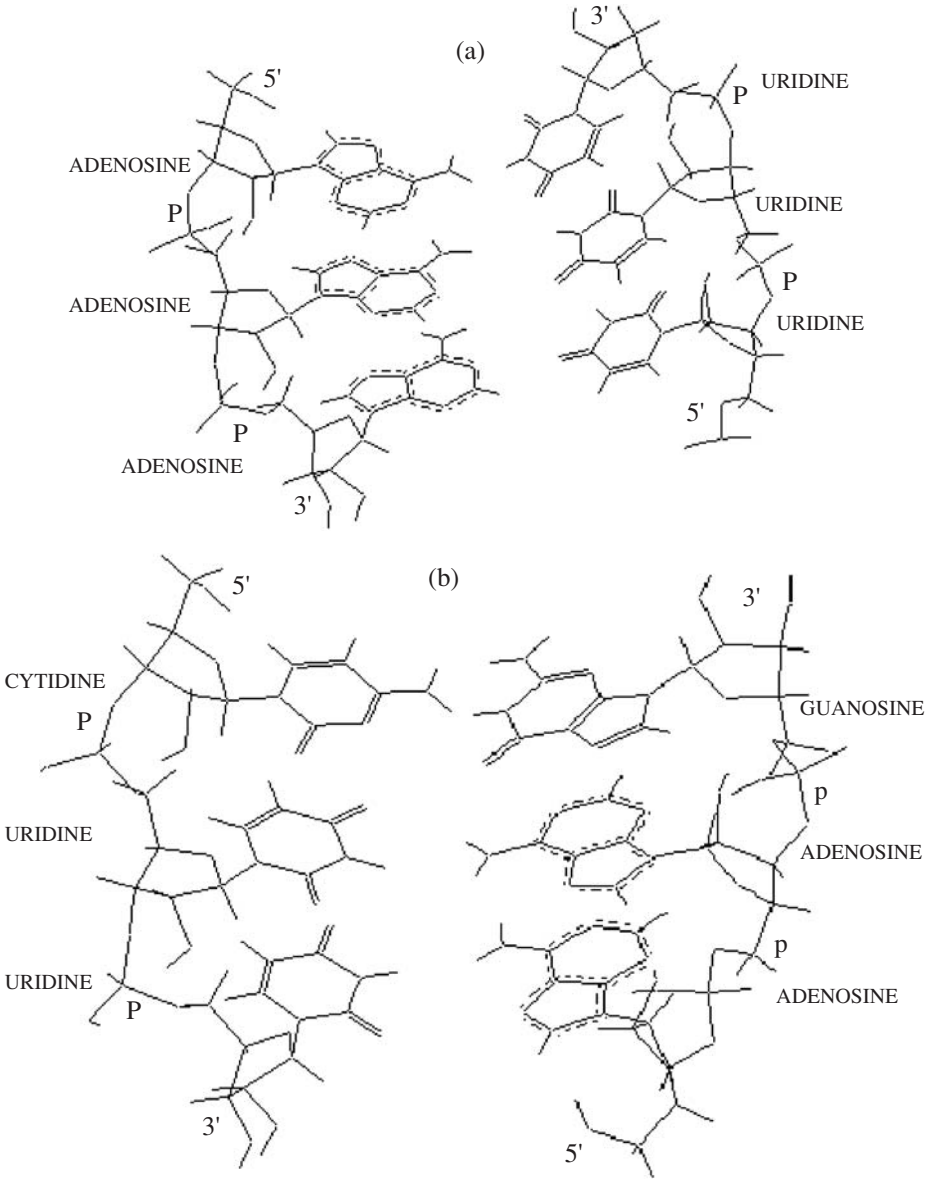

Fig. 1. Optimized structures of (a) AAA-UUU and (b) AAG-UUC triplex sequences with their active centers.

multipole expansions up to infinite order and a more realistic description of the solute cavity are necessary.

Solvent Effects on Relative Stabilities

All triplex sequences were studied in the gas phase ($\varepsilon = 1$) and various solvent media with dielectric constants of water ($\varepsilon = 80$), dimethylsulfoxide ($\varepsilon = 46.7$), methanol ($\varepsilon = 32.63$), ethanol ($\varepsilon = 24.55$), and cyclohexane ($\varepsilon = 2.023$) at 35, 37, and 39°C.

Nucleic acid bases can form various hydrogen bonds with water and the other protonic solvents. In all of them, water is bonded to AAA, UUU, AAG, and UUC triplex sequences by the OH…N or NH…O hydrogen bonds (Fig. 1). First, the complexes were fully optimized by the HF and DFT (BLYP and B3LYP) methods using the 3-21G, 6-31G, and 6-31G* basis sets to obtain minima of the potential energy surfaces of the bases.

The influence of the solvent on the relative stability of triplex sequences was studied by means of the Onsager approach. The results listed in Table 1 reveal that, as the dielectric constant increases in passing from the vacuum to cyclohexane, ethanol, methanol, DMSO, and water, the dipole moment of each solvent increases when different quantum-mechanical levels are used.

The dipole of a molecule induces a dipole in the medium, and the electric filed of the solvent dipole in turn interacts with the molecular dipole, leading to overall stabilization. These parameters represent the

Table 1. Dipole moment (Debye) of AAA, UUU, UUC, and AAG triplex sequences obtained in various solvent media

Solvent (ε)	Sequence	HF			BLYP		B3LYP		
		3-21G	6-31G	6-31G*	3-21G	6-31G	3-21G	6-31G	6-31G*
Vacuum	AAA	40.9237	40.4713	59.2331	–	–	–	–	–
	UUU	15.2868	16.0293	15.2690	16.7047	18.0163	17.5797	18.9040	16.6210
	UUC	16.8035	28.3729	29.0364	18.9039	19.1747	28.4225	28.5565	27.8173
	AAG	13.3232	12.0622	8.5889	11.8733	–	20.6002	20.9178	20.9900
Cyclo-hexane (2.023)	AAA	65.1489	66.0421	64.8689	–	–	63.3546	64.2557	–
	UUU	21.8012	23.2887	20.1126	18.2376	19.8183	19.1567	20.7070	18.2452
	UUC	22.5474	23.1587	31.3776	20.6831	21.0766	21.1167	21.5551	30.3786
	AAG	8.9051	9.0319	9.4007	12.9324	–	7.7720	7.9025	8.2450
Ethanol (24.55)	AAA	69.5254	78.9865	78.0468	–	–	–	–	–
	UUU	24.3433	25.2440	22.7177	20.8330	22.8365	21.7288	23.6885	20.9485
	UUC	35.2009	57.8514	35.1146	23.6523	24.3226	23.9741	24.6818	34.5681
	AAG	26.0378	10.3613	10.7556	14.6379	–	9.0034	9.2329	9.6057
Methanol (32.63)	AAA	73.3946	80.2768	78.4816	–	–	–	–	–
	UUU	24.4898	25.4140	22.7984	20.9145	22.9320	21.8089	23.7822	21.0338
	UUC	35.3862	57.3185	35.2293	23.7455	24.4254	34.8387	35.4717	34.6989
	AAG	26.2731	10.4034	10.7984	14.6903	–	9.0428	9.2760	9.6497
DMSO (46.7)	AAA	77.9591	79.9790	78.8884	–	–	–	–	–
	UUU	24.8802	25.6346	22.8736	20.9903	23.0210	21.8834	23.8695	21.1133
	UUC	25.4117	26.3158	35.3359	23.8322	24.5211	34.9504	35.5931	34.8176
	AAG	15.8840	15.9317	10.8383	14.7391	–	9.0796	9.3161	9.6907
Water (78.39)	AAA	31.8664	83.1767	79.2766	–	–	–	–	–
	UUU	24.7558	25.7244	22.9451	21.0626	23.1058	21.9545	23.9527	21.1891
	UUC	36.0207	30.8165	35.4374	23.9149	24.6123	24.2249	24.9588	34.9366
	AAG	26.7052	10.4799	10.8763	14.7855	–	9.1147	9.3545	9.7299

subtle structural changes of the triplets, which are not statistically correlated, because the distributions of subtle structural changes of different triplets are very different, and the contributions of these structural changes should be analyzed individually.

The values listed in Table 2 show that interactions between water molecules and triplets reduce the energy of the whole system (ΔE). The only exception is nonbonding dispersion energy; this may imply that, in aqueous solutions, the import of polarized water molecules reduces the rate of triplet polarization. The significance levels of the parameters reveal that solvent group changes are significant.

The effect of solvents on the stabilization of the triplex is of interest; it plays a major role in their activities. The standard Onsager approach (the SCRF method) to nucleic bases with different basis sets, as is used here, appears to be a good first step in theoretical investigations of solvent effects. In this paper, we studied the solvation of the complexes. The influence of the dielectric constant on the standard geometry of AAA, UUU, AAG, and UUC triplex sequences in H_2O, DMSO, CH_3OH, C_2H_5OH, and C_6H_{12} was studied. We found that the relative energies (ΔE) of triplex bases in solution are smaller than in the gas phase, because interactions in solution are stronger than in the gas phase. For all the sequences, the influence of water on mRNA–tRNA triplets is almost the same (Table 2).

The interaction energies of the complexes decrease as the dielectric constant of solvents increases according to HF, BLYP, and B3LYP calculations. The results obtained at the HF/6-31G* level are more negative than those of density functional calculations because these methods differently take correlation energy into account (Table 2). However, BLYP and B3LYP calculations can be considered fairly accurate.

As regards the high dielectric constant of water molecules surrounding the hydrophilic part of amino acid chains, we optimized these parameters much better than for the other solvents.

Table 2. Relative thermochemical parameters (energy ΔE, enthalpy ΔH, and Gibbs free energy ΔG, cal/mol, and thermal coefficient ΔC_V and entropy ΔS, cal/(mol K), of AAA, UUU, AAG, and UUC triplex sequences obtained in water using different methods and basis sets

Sequence	Basis Set	T, °C	HF					BLYP					B3LYP				
			$-\Delta E$	$-\Delta H$	$-\Delta G$	$-\Delta C_V \times 10^3$	$-\Delta S \times 10^3$	$-\Delta E$	$-\Delta H$	$-\Delta G$	$-\Delta C_V \times 10^3$	$-\Delta S \times 10^3$	$-\Delta E$	$-\Delta H$	$-\Delta G$	$-\Delta C_V \times 10^3$	$-\Delta S \times 10^3$
AAA	3-21G	35	119.2	119.2	106.7	11	893	0	0	4265.1	0	0	0.6	0	4248.8	0	0
		37	119.2	119.2	106.7	10	893	0	0.6	4393.7	0	1	0	0	4248.2	0	0
		39	119.2	119.2	106.7	10	893	0.6	0.6	4393.7	0	1	0	0	4247.6	0	1
	6-31G	35	0.6	0	262.9	2	0	449.9	449.3	62.1	1968	15105	453.7	453	61.5	1974	15066
		37	0.6	0	264.8	1	0	453.7	453.7	31.4	1968	15118	457.4	456.8	30.8	1974	15080
		39	0	0	266.1	0	0	457.5	457.5	0	1968	15132	461.2	461.2	0	1974	15092
	6-31G*	35	42	21.4	0.6	6	987	–	–	–	–	–	–	–	–	–	–
		37	42	42	0.6	5	986	–	–	–	–	–	–	–	–	–	–
		39	21.4	21.4	0	5	987	–	–	–	–	–	–	–	–	–	–
UUU	3-21G	35	348.3	348.3	375.2	83	52	–	–	–	–	–	147.5	0	133.7	24	48
		37	349.5	348.9	374	84	55	–	–	–	–	–	146.9	0.6	133.1	24	47
		39	350.1	349.5	372.1	83	58	–	–	–	–	–	146.9	0	132.4	24	46
	6-31G	35	0	0	3.1	0	131	–	–	–	–	–	0	146.9	1.3	24	1
		37	1.2	0.6	1.9	1	133	–	–	–	–	–	0	146.9	0.7	24	0
		39	1.9	1.3	0	1	135	–	–	–	–	–	0	146.9	0	24	0
	6-31G*	35	999	998.4	1042.3	29	0	–	–	–	–	–	355.8	208.9	328.2	0	93
		37	999.6	999	1040.4	29	3	–	–	–	–	–	355.2	208.3	327	0	93
		39	1000.2	999.6	1039.1	29	6	–	–	–	–	–	354.6	207.7	326.3	1	93
AAG	3-21G	35	57.1	56.5	60.9	0	462	70.9	71.5	85.9	1	0	64.6	64.6	123	0	
		37	56.5	56.5	60.9	0	461	71.5	71.5	85.9	0	1	64.4	64.6	123.7	0	199
		39	57.1	57.1	60.9	0	461	70.9	70.9	86.6	1	1	64.6	64.6	124.9	1	199
	6-31G	35	0	0	0	1	475	0	0	0	4	49	0.6	0.6	0	5	391
		37	9.4	8.8	9.4	1	474	0	0	0	4	48	0	0	0	6	391
		39	8.8	8.2	9.4	1	474	0	0	0	5	48	0	0	0	6	390
	6-31G*	35	87.2	86.6	232.8	1	0	–	–	–	–	–	32	32.6	20.1	5	428
		37	86.6	87.2	234.1	1	0	–	–	–	–	–	32.6	32	20.7	6	428
		39	87.2	87.2	235.3	3	0	–	–	–	–	–	32	32	20.7	6	428
UUC	3-21G	35	87.3	87.3	82.3	8	13	0.6	0	0	0	0	504.5	505.1	49	1987	16270
		37	87.3	87.3	82.3	8	13	0.6	0	0.7	0	1	504.5	505.1	49.6	1968	16270
		39	87.3	87.3	82.9	8	13	0	0	0	0	1	504.5	505.1	49.6	1986	16270
	6-31G	35	197.7	197.7	91.7	9	343	109.2	109.8	99.2	2	34	7.5	8.1	4555.1	0	25
		37	197.1	197.7	91	8	342	109.8	109.2	98.5	2	34	3.2	4.4	4587.7	1	13
		39	197.7	197.7	89.9	8	343	109.2	109.2	99.2	3	34	0	0	4620.3	0	0
	6-31G*	35	0.7	0	0	0	1	–	–	–	–	–	447.4	448	0	1994	16243
		37	0.7	0	0	0	1	–	–	–	–	–	447.4	448	0	1995	16243

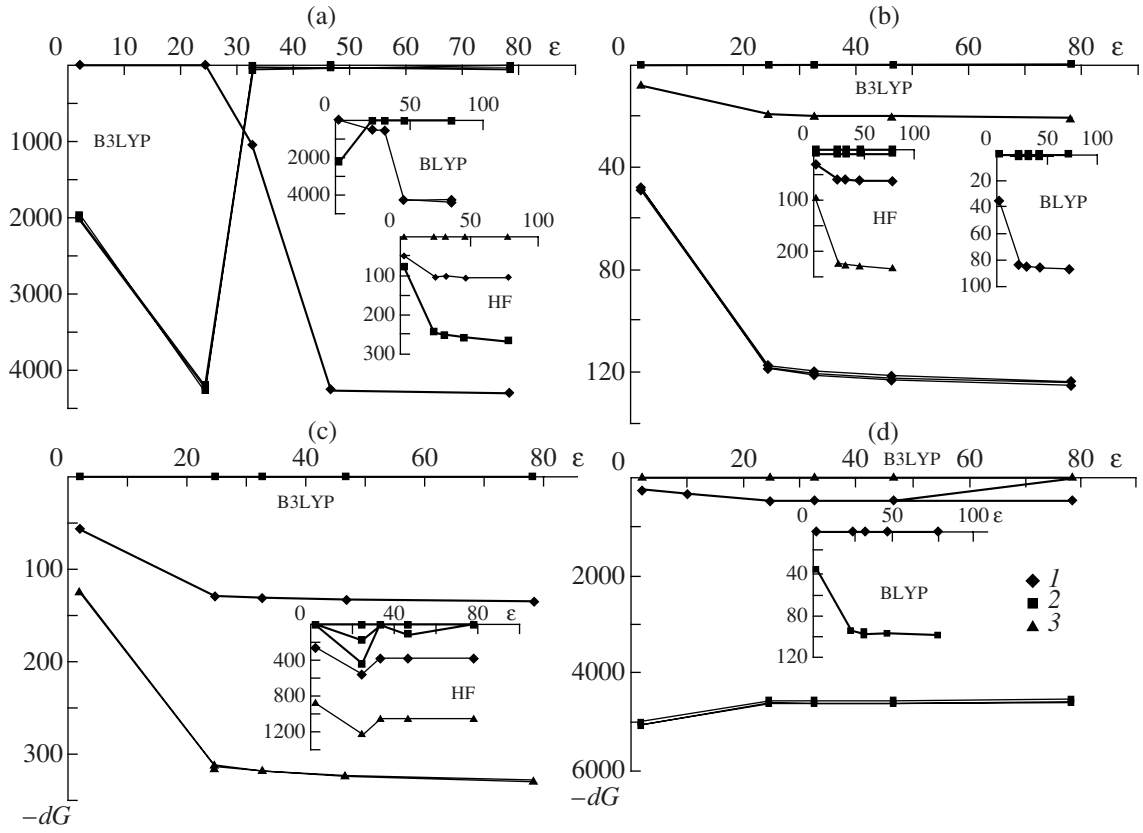

Fig. 2. Comparison of the free energies (cal/mol) of (a) AAA, (b) AAG, (c) UUU, and (d) UUC triplex sequences versus dielectric constants obtained using the HF and DFT (BLYP and B3LYP) methods and different basis sets at three temperatures (35, 37 and 39°C); basis sets: (*1*) 3-21 G, (*2*) 6-31 G, and (*3*) 6-31 G*.

Solvent Effects on Thermochemical Parameters

The thermochemical data presented in this section are useful for the understanding of codon–anticodon pairing in mRNA and tRNA biomolecular triplets. There are some theoretical considerations concerning the ability of the genetic code to affect mutations in biological systems. Codon–anticodon interactions are involved in the discrimination between the correct and incorrect mRNA and tRNA. Hydrogen bonding, steric fit, and base-pair stability can be the main aspects that influence the whole process according to our calculation results.

The standard enthalpies (ΔH), entropies (ΔS), and free energies (ΔG) of these compounds were obtained by theoretical methods using the GAUSSIAN 98 package (Table 2). We found that there was some difference between these functions obtained by the HF and B3LYP methods. A study of hydrogen bonding between AAA, UUU, AAG, and UUC triplex sequences and H_2O, DMSO, CH_3OH, C_2H_5OH, and C_6H_{12} was performed for optimized structures in solution at 35, 37, and 39°C (see Table 2).The best results in various solvent media were obtained at the HF level of theory.

Free energy variations in terms of dielectric constant at two levels of theory and three temperatures obtained using three basis sets are plotted in Fig. 2 in terms of the dielectric constant. We see that the HF optimization is in close agreement with the experimental data, whereas DFT (BLYP and B3LYP) calculations are somewhat nonlinear. We also observe that, as the dielectric constant changes from cyclohexane ($\varepsilon = 2.023$) to polar water ($\varepsilon = 80$) at 35, 37, and 39°C, the stabilization energy decreases for all basis sets at all theoretical levels (Fig. 2).

Table 2 and Fig. 2 show that the free energies of interactions (ΔG) of AAA, UUU, AAG, and UUC triplex sequence base pairs in solution are more negative than in the gas phase; that is, interactions in solution are stronger than in the gas phase.

Experimental measurements of the heats, entropies, and free energies of formation are required to resolve discrepancies between the predictions of the different nonempirical methods employed here and to obtain reliable thermochemical data on some of the AAA, UUU, AAG, and UUC triplex sequences in various media at different temperatures that remain unstudied. However, the methods used here give sufficiently accurate thermochemical parameters for constructing a self-

consistent preliminary database for models of codon–anticodon pairing in mRNA and tRNA triplets. These models can be used to identify the most crucial species, for which additional experimental and theoretical studies can be performed. Future computational chemistry work can extend these thermochemical predictions to reaction paths for the formation of H-bonds in other biological structures.

These results show that the strongly bonded DNA and RNA chains can affect replication with subsequent mutations or cell termination. Furthermore, this study provides thermochemical data needed for the construction and prediction of detailed models of useful and dangerous mutations under practical and experimental conditions by the Watson–Crick mechanism in hydrogen bonding of these compounds in biological systems in the future.

CONCLUSIONS

Several conclusions can be drawn. Based on our results, we conclude that these interactions were approximated by explicitly adding the nearest neighbors into the calculations. The most important intermolecular interactions between nucleic bases and solvent molecules were described using different structural models. Interaction of solvent molecules distorted the intermolecular geometry of the nucleic bases; this can be described by resonance forms of the total structure of the bases.

Some of the species considered were previously neglected or assumed to be unimportant for codon–anticodon pairs in mRNA and tRNA triplets. On the basis of the results of our calculations, we found that, among various modern quantum mechanical methods, the Hartree–Fock method was the most popular to date.

The results of the quantum-chemical modeling of the AAA, UUU, AAG, and UUC triplex sequences with Onsager reaction field calculations were obtained using the polarizable dielectric model. They are indicative of a possible mutagenic mechanism of these compounds. All systems were optimized by the Hartree–Fock, BLYP, and B3LYP methods. In all cases, the steady-state nature (minimum of the potential energy surface) of the optimized complexes has been confirmed through the investigation of theoretical levels. This will allow the most important reactions and the most important species to be identified for the compounds in question.

We can conclude that, for the hydrogen bonded systems studied in this work, the ab initio method gives similar or even better results than density functional calculations. Nucleotide variations in codon–anticodon pairs show complexity which can lead to different biological functions. As a matter of fact, the energies and thermochemical parameters can provide valuable information about binding stabilities of base pairs in proteins with possible various mutations in humans.

REFERENCES

1. A. Pohorille, L. R. Pratt, S. K. Burt, and R. D. MacElroy, J. Biomol. Struct. Dyn. **1**, 1257 (1984); A. Pohorille, S. K. Burt, and R. D. MacElroy, J. Am. Chem. Soc. **106**, 402 (1984).
2. A. Rich, M. Nomara, A. Qtsstres, and P. Lengyel, *Ribosomes* (Cold Spring Harbor, New York, 1974), pp. 871–884.
3. B. Pullman, P. Claverie, and J. Caillet, Proc. Natl. Acad. Sci. U.S.A. **55**, 904 (1966).
4. D. Smith and M. Yarus, Proc. Natl. Acad. Sci. U.S.A. **86**, 439 (1989).
5. E. J. Murgola, Experientia **46**, 1134–1141 (1990).
6. H. Iwahashi and Y. Kyogoku, J. Am. Chem. Soc. **99**, 7761 (1977); M. Watanabe, H. Sugeta, et al., Eur. J. Biochem. **117**, 553 (1981); H. Iwahashi, H. Sugeta, and Y. Kyogoku, Biochemistry **21**, 631 (1982).
7. I. K. Yanson, A. B. Teplitsky, and L. F. Sukhodub, Biopolymers **18**, 1149 (1979).
8. I. V. Lim and C. Venclovas, FEBS Lett. **313** (2), 133 (1992).
9. J. T. Egan, S. Nir, R. Rein, and R. D. MacElroy, Int. J. Quantum Chem., Quantum Biol. Symp. **5**, 433 (1987).
10. D. C. Karakauer and V. A. Jansen, J. Theor. Biol. **218**, 97 (2002).
11. K. H. Buckingham, Experiential **46**, 1126 (1990).
12. K. Y. Sanbonmatsu and S. Joseph, J. Mol. Biol. **328**, 33 (2003).
13. L. D. Williams, Buchwald, and B. R. Shaw, Biopolymers **26**, 591 (1987).
14. L. Pauling, *The Chemical Bond: A Brief Introduction to Modern Structural Chemistry* (Cornell University Press, Ithaca, 1987).
15. M. Aida, J. Comput. Chem. **9**, 362 (1988).
16. M. James, Ogle, and V. Ramakrishna, Ann. Rev. Biochem. **20**, 129 (2005).
17. M. J. Frisch, G. W. Trucks, H. B. Schlegel, et al., *Gaussian 98, Revision A.7* (Gaussian, Inc., Pittsburgh, PA, 1998).
18. M. Kato, K. Nihikawa, M. Untani, et al., J. Biochem. **107**, 242 (1990).
19. M. Monajjemi and B. Chahkandi, J. Mol. Struct. (THEOCHEM) **714**, 43 (2004).
20. M. Monajjemi, S. Ketabi, M. Hashemian Zadeh, and A. Amiri, Biochemistry (Moscow) **71** (Suppl. 1), 1 (2006).
21. N. G. Williams, L. D. Williams, and B. R. Shaw, J. Am. Chem. Soc. **111**, 7208 (1989).
22. P. Cieplak and P. A. Kollman, J. Am. Chem. Soc. **110**, 3734 (1988); L. X. Dang and P. A. Kollman, J. Am. Chem. Soc. **112**, 503 (1990).
23. P. Hobza and C. Sandorfy, J. Am. Chem. Soc. **109**, 1302 (1987).
24. R. A. Newmark and C. R. Cantor, J. Am. Chem. Soc. **90**, 5010 (1968).
25. R. Giege, M. Sissler, and C. Florentz, Nucleic Acids Res. **26**, 5017 (1998).
26. S. B. Petersen and J. J. Led, J. Am. Chem. Soc. **103**, 5308 (1981).

27. S. Louise-May, P. Auffinger, E. Westhoff, et al., J. Chem. Phys. **55**, 117 (1981).
28. S. Kawahara and T. Uchimaru, J. Mol. Struct. (THEOCHEM) **588**, 29 (2002).
29. S. Miertus and J. Tomasi, J. Chem. Phys. **65**, 239 (1982).
30. V. I. Vanloads, A. S. Spirm, R. Brimaeomb, et al., Nucleic Acids Res. **20**, 2627 (1992).
31. V. I. Danilov, I. S. Tolokh, V. I. Poltev, and G. G. Malenkov, FEBS Lett. **167**, 245 (1984); V. I. Danilov, I. S. Tolokh, and V. I. Poltev, FEBS Lett. **171**, 325 (1984); V. I. Danilov and I. S. Tolokh, FEBS Lett. **173**, 347 (1984).
32. Y. Kyogoku, R. C. Lord, and A. Rich, Proc. Natl. Acad. Sci. U.S.A. **57**, 250 (1967).
33. Y. Kyogoku, R. C. Lord, and A. Rich, Biochem. Biophys. Acta **179**, 10 (1969).
34. Y. L. Wang, J. Bao, Y. Sun, and J. Yang, J. Theor. Biol. **238**, 85 (2006).
35. Z. G. Kudritskaya and V. I. Danilov, J. Theor. Biol. **59**, 303 (1976); J. Langlet, P. Claverie, F. Caron, and J. C. Boeuve, Int. J. Quantum Chem. **19**, 299 (1981).
36. V. I. Lira and A. S. Spirin, J. Mol. Biol. **188**, 565 (1986).
37. J. G. Kirkwood, J. Chem. Phys. **7**, 911 (1939).
38. L. Onsager, J. Am. Chem. Soc. **58**, 1486 (1936).
39. M. A. Wong, M. J. Frisch, and K. B. Wiberg, J. Am. Chem. Soc. **113**, 4776 (1991).
40. M. A. Wong, M. J. Frisch, and K. B. Wiberg, J. Am. Chem. Soc. **114**, 523 (1992).
41. J. Tomasi, B. Mennucci, and R. Cammi, Chem. Rev. **105**, 2999 (2005).
42. P. V. R. Schleyer, *Encyclopedia of Computational Chemistry* (Wiley, Chichester, 1998), Vol. 4, pp. 2547–2574.
43. D. C. Young, *Solvation Computational Chemistry: A Practical Guide for Applying Techniques to Real-World Problems* (Wiley, New York, 2001).