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Investigation of Solvent Effect on CUA Codon Mutation: NMR Shielding Study

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ABSTRACT

P53 is one of the gene that has important role in human cell cycle and in the human cancers too. Models of codon substitution make it possible to separate mutational biases in the DNA from selective constraints on the protein, and offer a great advantage over amino acid models for understanding the evolutionary process of proteins and protein-coding DNA sequences. In this work, we investigated about CUA codon in exon5 of p53 that has mutated to CCA codon.

We studied solvent effects on CUA codon by theoretical method, because the most of biological systems studied in solution and solvents have essential role in mutation of genes. Five solvents consist of acetone, ethanol, methanol, DMSO and water are predicated using ab initio method. Also, indirect ($\Delta\sigma$ ind) solvent effects are obtained and NMR shielding tensors (ppm) have been computed with the continuous set of the gauge independent atomic orbital (GIAO) method.

Keywords: P53, CUA; Mutation; Ab initio method; NMR shielding

INTRODUCTION

Most water-immiscible organic solvents are generally toxic to microorganisms. In a nonionizable organic solvent-aqueous two-phase culture, toxicity of an organic solvent is inversely correlated with the log of the partition in n-octanol–water (logPow value) of the solvent. An organic solvent with a low logPow value is generally toxic to most microorganisms [1]. Models of codon substitution make it possible to separate mutational biases in the DNA from selective constraints on the protein, and offer a great advantage over amino acid models for understanding the evolutionary process of proteins and protein-coding DNA sequences [2]. The reason of discussed changes is the H-bonded complexes created by the molecule of solute with this solvent in solution. The chemical shifts of these systems have been calculated. Theoretical calculations predict a significant downfield shift for protons involved in intermolecular N-H...DMSO H-bonds. The influence of the solvent molecules on other nuclei chemical shifts is also reported. The calculations have included Hartree-Fock level of theory [3]. Hydrogen bonding plays a major role in the self-organization and molecular recognition of nucleic acids [4-7]. Naturally occurring nucleosides are found to have some specific functions.

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Modifications of nucleic acids followed by studies of the resulting chemical structures and functional changes contribute to an understanding of their role in various biochemical processes such as catalysis or gene silencing. The structure of every protein, and ultimately in every cellular constituent is the result of the coded information programmed into the nucleic acids. In addition, cells contain many types of nucleotides, which have a wide variety of cellular processes, including metabolic regulation [8].

DNA is also involved in other functions such as DNAzyme in catalysis. It has been reported that there are about 93 post-transcriptionally modified nucleosides found in RNA. These modifications may be found in the nucleobase, sugar, or in the phosphate unit and have long been recognized as characteristics of RNA and have specific functions such as codon recognition [9-18].

COMPUTATIONAL DETAILS

In the present work, we have been optimized CUA codon with three basis sets Sto-3g, 3-21g, 6-31g in the gas phase with the Gausian 03 package [19] at the hartree-fock(HF) level of theory.

The calculations including the intermolecular interactions give semi quantitative information on effects of Hydrogen Bonding (HB) on the principal values of chemical shift tensors. We have studied the influence of acetone, DMSO, ethanol, methanol and water on chemical shielding tensors. There are different methods of salvation. One family of models for systems in solution is referenced to as Self-Consistent Reaction Field (SCRF) method. The simplest SCRF model is the onsager reaction field model. For the simulation of a polar environment, this model was used as implemented in Gaussian 03. In this model the solvent is consider as a uniform dielectric with a given dielectric constant. Indirect ($\Delta\sigma_{ind}$) solvent effects are obtained with a slight modification of the method used by Manalo *et al.* [20-21]

$\Delta\sigma ind=\sigma$ vac (Rs)-σ vac (Rmeth) .

NMR shielding tensors (ppm) have been computed with the continuous set of the gauge independent atomic orbital (GIAO) method [22_25].

RESULT AND DISCUSSION

In figures 1-3, chemical shift anisotropy asymmetry (Etha,η), isotropy (σ iso) and $\Delta\sigma$ are observed for O, N and P atoms in CUA molecule with respect to dielectric constants.

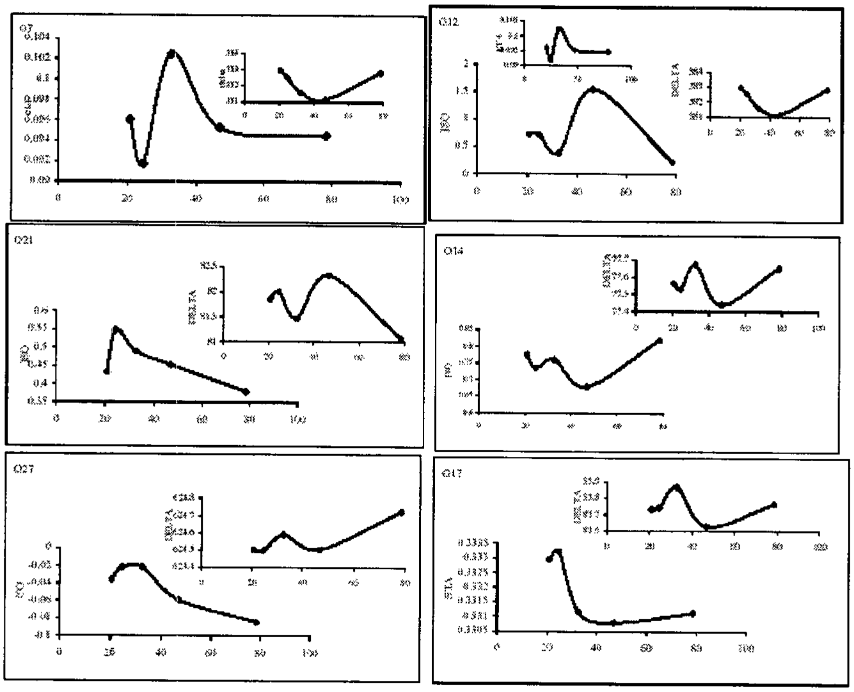
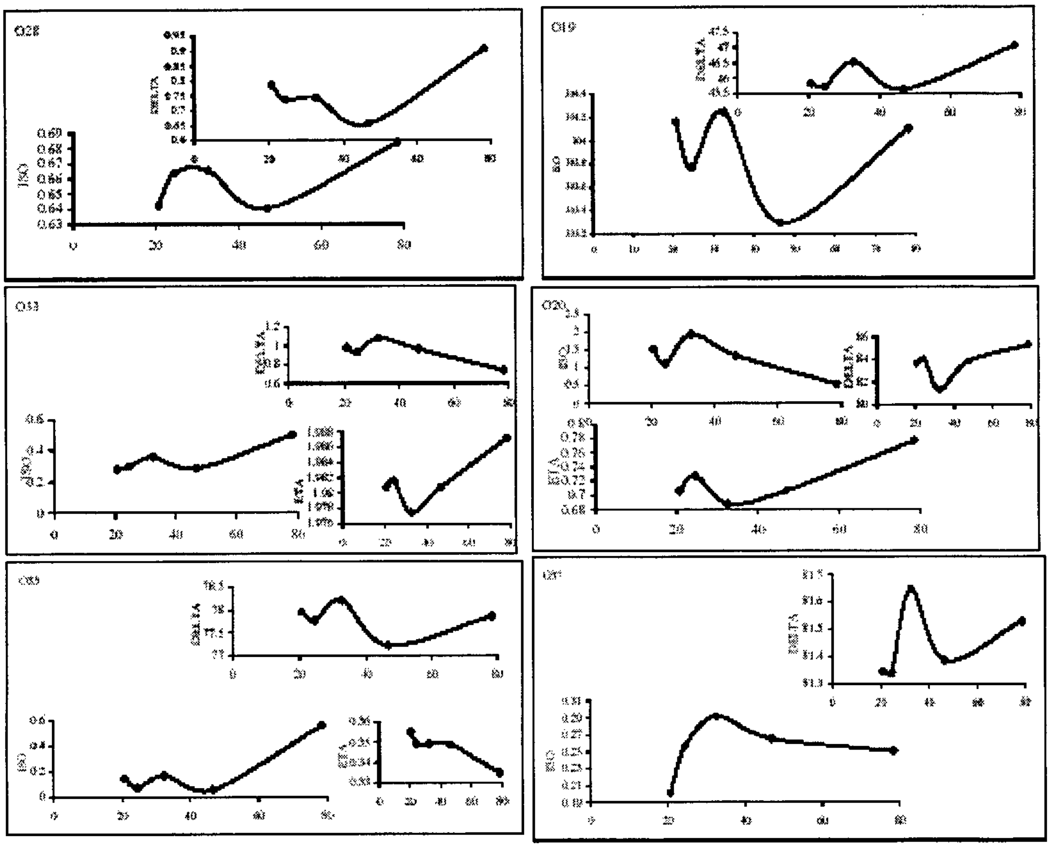


Fig.1. σiso, $\Delta\sigma$ and η values for O atoms vs. dielectric constant (all horizontal axis are dielectric constants).



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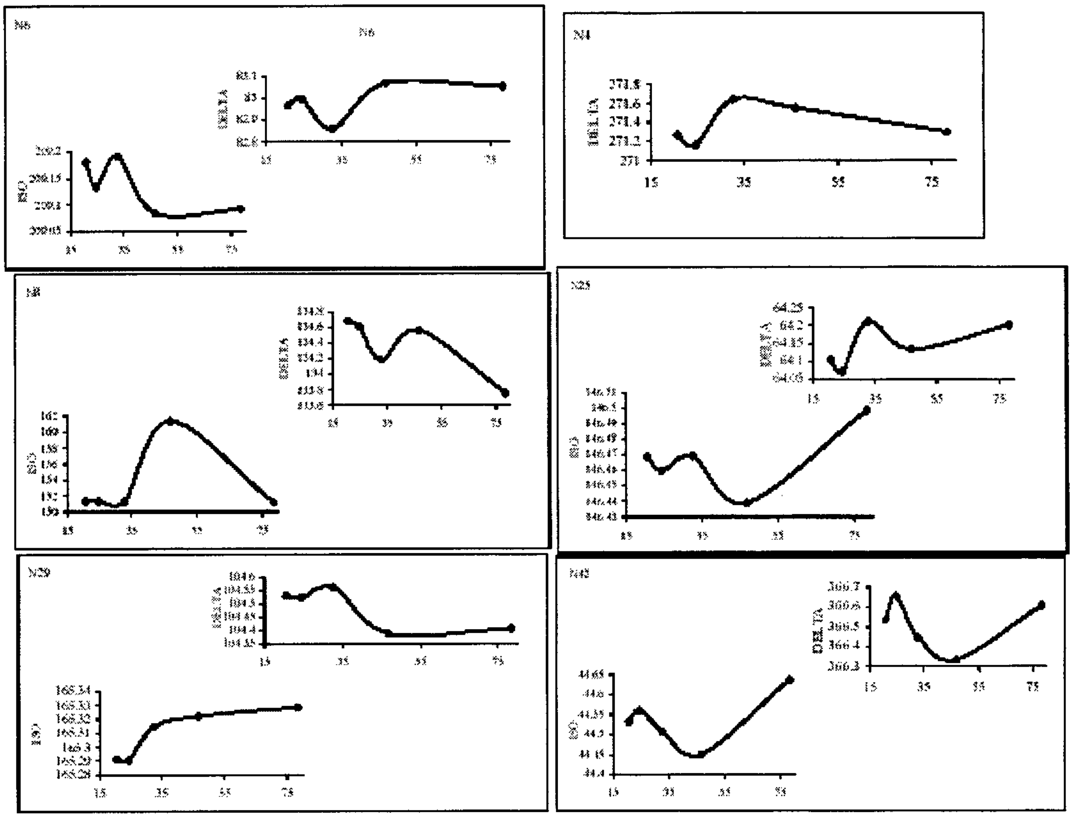

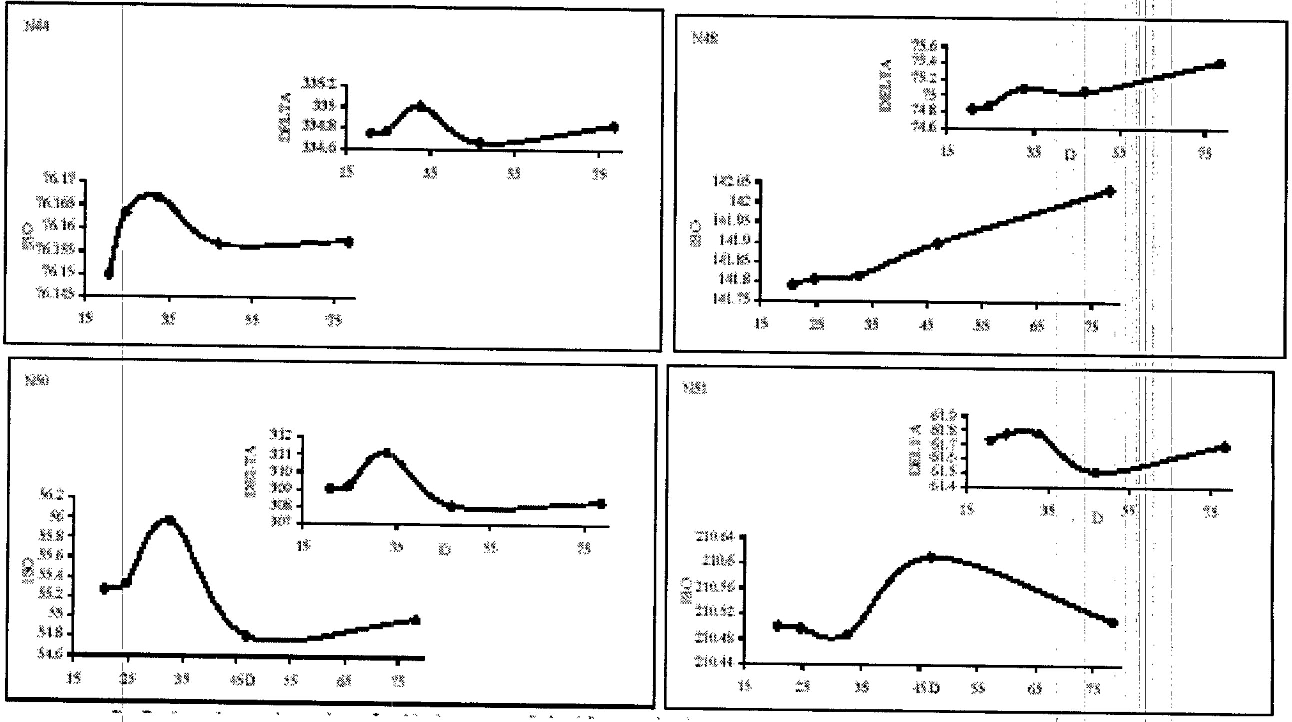

Fig.2. σiso, Δσ and η values for N atoms vs. dielectric constant

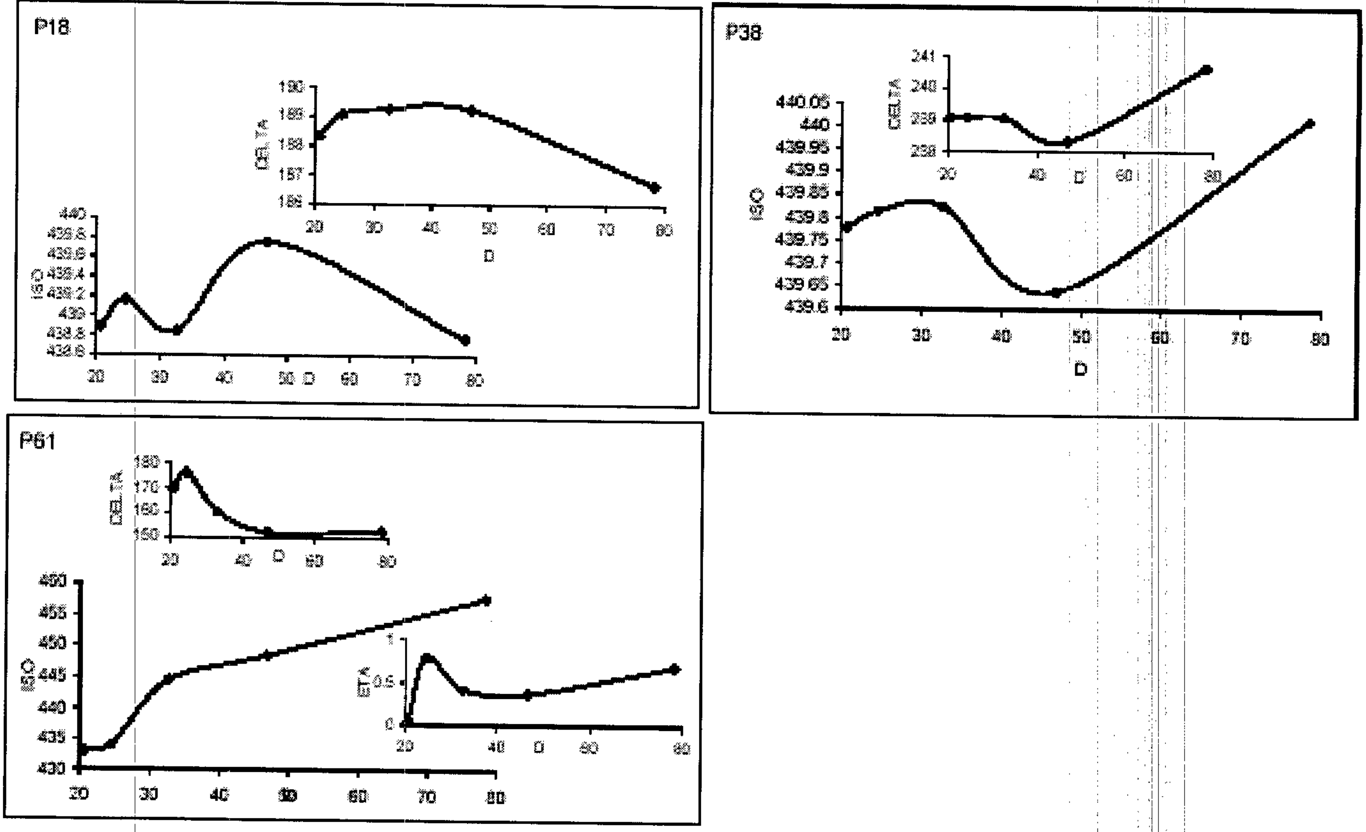

Fig.3. σiso, Δσ and η values for p atoms vs. dielectric constant

In the basis of the above diagrams, tables 1-3 list maximum and minimum of the σiso, $\Delta\sigma$ and η values for O, N and P atoms in different dielectric constants.

Table1.σ_{iso}, $\Delta\sigma$, η for O atoms

	η		$\Delta\sigma$		σiso	
No.O atom	Max	min	Max	Min	Max	Min
O7	32.63	24.55	78.39	46.8	24.55	78.39
O12	32.63	24.55	78.39	46.8	46.8	32.63
O14	78.39	46.8	32.63	46.8	78.39	46.8
O17	24.55	46.8	32.63	46.8	46.8	20.7
O19	46.8	32.63	78.39	46.8	32.63	46.8
O20	78.39	32.63	78.39	32.63	32.63	78.39
O21	46.8	78.39	46.8	24.55	24.55	78.39
O27	20.7	32.63	78.39	24.55	32.63	78.39
O28	78.39	46.8	78.39	46.8	46.8	78.39
O33	78.39	32.63	32.63	78.39	78.39	20.7
O35	20.7	78.39	32.63	46.8	78.39	46.8
O37	46.8	24.55	32.63	24.55	32.63	20.7

Table 2. σ_{iso}, $\Delta\sigma$, η for N atoms

	η		$\Delta\sigma$		σiso	
No.N atom	Max	min	Max	Min	Max	Min
N4	20.7	78.39	32.63	24.55	78.39	46.8
N6	78.39	32.63	46.8	32.63	32.63	46.8
N8	78.39	32.63	20.7	78.39	46.8	78.39
N25	24.55	78.39	32.63	24.55	78.39	46.8
N29	46.8	32.63	32.63	46.8	78.39	24.55
N42	46.8	24.5	24.55	46.8	78.39	46.8
N44	32.63	46.8	32.63	46.8	32.63	20.7
N48	20.7	78.39	78.39	20.7	78.39	20.7
N50	78.39	32.63	32.63	46.8	32.63	46.8
N51	46.8	32.63	32.63	46.8	46.8	32.63

Table 3. σ_{iso}, $\Delta\sigma$, η for P atoms

	η		$\Delta\sigma$		σiso	
No.P atom	Max	min	Max	Min	Max	Min
P18	78.39	32.63	32.63	78.39	46.8	78.39
P38	24.55	32.63	78.39	46.8	78.39	46.8
P61	24.55	20.7	24.55	46.8	78.6	20.7

As regards to table 1-3, it is observed that NMR shielding values often have the maximum in 78.39 and 32.65 dielectric constants and minimum has occurred at 46.8 dielectric constant value, so we conclude that H bonding is the most important reason for this behavior that causes deshielding. In table 4, it is seen that total atomic charges are not related to dielectric constant essentially but indirect solvent effect increases with increasing dielectric constants. These values are related to optimized structure in solvents that NMR shielding has obtained in vacuum and this trend indicates that interactions between solute and solvent molecules is the most important factor and geometry of the solute molecule is not very effective.

Table 4. Values of charges and σind versus dielectric constants

solvent	O7 a	b	O14		O19	
20.7	-0.334	-0.7356	0.0396	-0.3054	0.3927	-0.4332
32.63	-0.891	-0.7356	0.0264	-0.3055	0.4751	-0.4331
46.8	-0.9	-0.7356	-0.0565	-0.3053	-0.4812	-0.4331
78.39	-0.969	-0.7357	0.0863	-0.3054	0.3319	-0.4332
	O21		O27		O33	
20.7	-0.1168	-0.8339	-0.0137	-0.6579	-0.021	-0.6478
32.63	-0.06	-0.8338	0.0002	-0.6578	0.058	-0.6478
46.8	-0.961	-0.8338	-0.03697	-0.6577	-0.0129	-0.6478
78.39	-0.1713	-0.8339	-0.0621	-0.6577	0.2027	-0.6478
	N4		N8		N29	
20.7	0.0808	-0.8547	0.0325	1.0357	0.0006	-1.0596
32.63	0.1093	-0.8547	-0.0638	-1.0357	0.024	-1.0595
46.8	-0.0995	-0.8546	10.0113	-1.0358	0.0316	-1.0595
78.39	0.2469	-0.8546	-0.1395	-1.0357	0.0377	-1.0596
	N44		N50		N51	
20.7	0.01329	-0.8397	-0.0639	-0.8365	0.0035	-0.2032
32.63	0.0033	-0.8397	0.6375	-0.8364	0.0085	-0.2032
46.8	-0.0066	-0.8398	-0.527	-0.8364	0.1134	-0.2031
78.39	-0.0058	-0.8397	-0.346	-0.8365	0.0143	-0.2032
	P18		P38		P61	
20.7	-0.2886	2.0575	-0.0365	2.07942	-1.065	2.12173
32.63	-0.3235	2.05759	0.0102	2.07943	10.3923	2.2.12169
46.8	-0.5949	2.05754	-0.1741	2.07949	14.4039	2.12173
78.39	-0.3899	2.05764	0.1999	2.07944	23.6078	2.12168

a,b are σ ind and charge, respectively.

Solvent effect plays a very important role in chemistry since most chemical reactions and biological process take place in solutions. The most contentious parameter used in continuum electrostatics calculations of dielectric constant. We present a quantum-chemical analysis of the solvent effect on stability of molecule, dipole moment and atomic charge of some selected atoms of CUA codon. Ab initio calculation of nuclear magnetic shielding has become an indispensable aid in the investigation of molecular structure and accurate assignment of NMR spectra of compounds.

Hydration of CUA codon causes that the stabilization energies to be more negative than no-hydrated compound. Effects of hydrogen bond length on the chemical shielding tensor and orientation of nuclei. It is noteworthy that the small variation in the position of atoms, eventually results in a considerable change in the lengths of the various intermolecular hydrogen bonds, which may probably effect the calculation of NMR shielding tensors.

CONCLUSION

The HF/3-21G, 6-31G levels of theory of ab initio method have been employed for CUA codon to study using Gaussian 03. The linear relation sheep were found between the dielectric constant and stability of the Codon structures and energy and population analysis also, which indicated the suitable condition of the mutation.

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