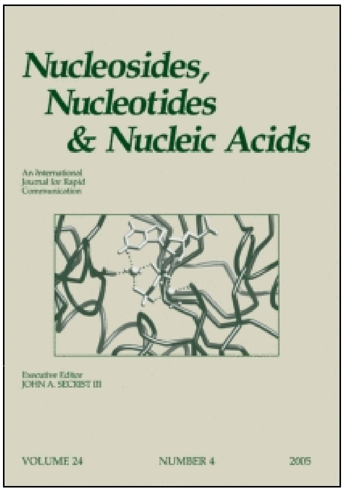

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Design of fMet-tRNA and Calculation of its Bonding Properties by Quantum Mechanics

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DESIGN OF fMet-tRNA AND CALCULATION OF ITS BONDING PROPERTIES BY QUANTUM MECHANICS

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□ *It is generally accepted that initiation of protein synthesis in* Escherichia coli *starts with formylmethionine, directed by the codons of AUG or GUG. In one case, reinitiating on the mRNA of amber mutants of UUG is used as the initiation codon. Early studies indeed showed that the triplets AUG, GUG, and UUG are the most effective in stimulating fMet-tRNA binding to ribosomes in vitro. We study the bonding properties of fMet-tRNA. The structure was optimized at the Hartree-Fock (HF) level of theory. We performed nonempirical quantum mechanical calculations at the HF and BLYP and B3LYP/3-21G, 6-31G, and 6-31G* levels of theory in the gas phase and water solvent at temperature of 310 K. Finally, we employed the density functional theory (DFT) and HF to calculate nuclear magnetic resonance spectra and infrared spectra.*

Keywords Formyl methionine-tRNA (fMet-tRNA); Hartree-Fock (HF); density functional theory (DFT)

INTRODUCTION

Protein synthesis proceeds by transfer of the growing polypeptide chain from the tRNA bound to the ribosomal P site to the incoming aminoacyl-tRNA in the adjacent A site. After translocation of the ribosome in the 30 direction of the mRNA, by the action of elongation factor G, the A site again becomes empty and the next codon exposed so that a new aminoacyl-tRNA ternary complex can be selected.[1] The tRNA binding sites are located at the interface between the ribosomal subunits, with the decoding center (DC) on the small subunit[2] and the peptidyl transfers center (PTC) on the large subunit.[3] Synthetic polynucleotide containing AUG and/or GUG codons as well as natural mRNA have been used extensively in order to elucidate the mechanism of initiation of protein synthesis.[4]

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In all these studies, it has been assumed that binding of fMet-tRNA to ribosomes is the polynucleotide. In bacteria, the start codon AUG is recognized by fMet-tRNA. This tRNA does not recognize internal AUG codons. (Authors may be contacted for graphical support of the data.) Initiation of protein biosynthesis requires the correct positioning of charged initiator tRNA, fMet-tRNA in the ribosomal P-site of the mRNA-programmed 70S ribosomes.[5–9]

The rapid development of molecular biology in recent years has been mirrored by the rapid development of computer hardware and software. This improvement leaded to the development of sophisticated computational techniques and a wide range of computer simulations involving such methods among the areas. It is well known that fMet-tRNA is the pharmacological target of many of the drugs currently in clinical use or in advanced clinical trials. Therefore, the implication throughout this article has been profound is the modeling of fMet-tRNA structure and function, the chemical behavior of fMet- tRNA within drug design, as well as the understanding at a molecular level of the role of solvents in biotechnological applications.[10,11]

Regarding most of the systems studied experimentally are in solution, the formulation of satisfactory theoretical models for solvated systems has been the object of continuously increasing interest. Therefore, ab initio calculation of nuclear magnetic shielding has become an essential aid in the investigation of solvent effects on the structural stability and accurate theoretical nuclear magnetic resonance (NMR) data of compounds.[12,13]

It is well know that the effect of solvent molecules on fMet-tRNA plays an important role in the chemical behavior of fMet-tRNA. Nuclear magnetic resonance is based on the quantum mechanical property of nuclei.[14] The chemical shielding refers to the phenomenon which associated with the secondary magnetic field created by the induced motions of the electrons that surrounding the nuclei when in the presence of an applied magnetic field. The energy of a magnetic moment μ, in a magnetic field, B, is as follow:

$$E = -\mu \cdot (1 - \sigma)\, B, \tag{1}$$

where the shielding σ is the differential resonance shift due to the induced motion of the electrons.[15] In general, the electron distribution around a nucleus in a molecule is more spherically symmetric. Therefore, the size of electron current around the field, and hence the size of the shielding, will depend on the orientation of the molecule within the applied field B_0.[16]

For chemical shielding (CS) tensor, which describes how the size of shielding varies with molecular orientation, we often use the following convention for the three principal components:

$$\sigma_{11} \leq \sigma_{22} \leq \sigma_{33}. \tag{2}$$

The three values of the shielding tensor are frequently expressed as the isotropic value (σ_{iso}), the anisotropy($\Delta\sigma$), and the asymmetry (η) There quantities are defined as follows:[17]

1. The isotropic value σ_{iso}:

$$\sigma_{iso} = \frac{1}{3}\left(\sigma_{11} + \sigma_{22} + \sigma_{33}\right) \tag{3}$$

2. The anisotropy shielding ($\Delta\sigma$):

$$\Delta\sigma = \sigma_{33} - \frac{1}{2}\left(\sigma_{11} + \sigma_{22}\right) \tag{4}$$

and
3. The asymmetry parameter (η):

$$\eta = \frac{|\sigma_{22} - \sigma_{11}|}{|\sigma_{33} - \sigma_{iso}|}. \tag{5}$$

For further information, relative solvent effects on the NMR parameters can be described as indirect ($\Delta\sigma_{ind}$)solvent effects with a slight modification of the method used by Cammi et al.[18] Instead of deriving ($\Delta\sigma_{ind}$)from the difference of the PCM-optimized shielding and the PCM shielding of the molecule held at the geometry optimized in vacuu, it can be obtained from the shielding calculated in vacuum for a molecule that is geometry-optimized in solution.[18] Thus,

$$\Delta\sigma_{ind} = \sigma_{Vac}\left(R_{sol}\right) - \sigma_{Vac}\left(R_{ref}\right), \tag{6}$$

where $\sigma_{Vac}(R_{sol})$ is the value of the nuclear shielding in vacuum but with the solute geometry optimized in solution. $\sigma_{Vac}(R_{ref})$ corresponding to the parameters for the calculation with reference solvent. In this case, we may suppose that optimization of solute molecule in solvent and performing shielding calculations is similar to shielding calculations in the isolated system.[19]

The self-consistent reaction field (SCRF) method is based on a continuum model with uniform dielectric constant (ε). The simplest SCRF model is the Onsager reaction field model. In this method, the solute occupies a fixed spherical cavity of radius a_0 within the solvent field. A dipole in the molecule will induce a dipole in the medium, and the electric field applied by the solvent dipole will in turn in interact with the molecular dipole leading to net stabilization.

TABLE 1 Calculated relative energy values of adenine + fMet of fMet-tRNA in water phase at HF/6-31G, 6-31G* and B3LYP/6-31G, 6-31G*, and BLYP/6-31G,6-31G* levels in kcal/mol

HF/6-31G	−1479125.239045818
HF/6-31G*	−1479730.347252573
BLYP/6-31G	−1485611.729845542
BLYP/6-31G*	−1486046.241614922
B3LYP/6-31G	−1485919.387832880
B3LYP/6-31G*	−1486383.848709279

COMPUTATIONAL DETAILS

In our current study, extensive quantum mechanical calculations of structure of fMet- tRNA (see Figure 1) and solvent effects on structure of fMet-tRNA and calculations of NMR parameters and infrared (IR) spectra have been performed on a Pentium-4 based system using GAUSSIAN 98 program.[20]

At first, we modeled the fMet-tRNA with Chem office package and then optimized at the Hartree-Fock (HF) level of theory with 3-21G, 3- 21G*,6-31G, and 6-31G* basis sets. After full optimization of fMet- tRNA, we calculated NMR parameters at the levels of BLYP/6-31G,BLYP/6-31G*, B3LYP/6-31G, and B3LYP/6-31G* theory and theoretically explored the solvent effects on structure of fMet-tRNA. All the relative energy values and NMR shielding parameters were calculated supposing gauge-included atomic orbital (GIAO) method[21] and are reported in Tables 1 and 2. Finally, the IR spectra of the structure of fMet-tRNA calculations at the HF level of theory with 3-21G basis sets. Investigation on the properties of fMet-tRNA is important because this structure is the start of protein biosynthesis.

RESULTS AND DISCUSSION

In this article, HF method with 3-21G, 3-21G*,6-31G, and 6-31G* basis sets were usedd for investigating the structure optimization and energy minimization of fMet-tRNA (authors may be contacted for graphical support of the data) have been summarized in Table 3.

After full optimization of adenine + fMet of fMet-tRNA, we calculated the IR spectra at the level of HF/3-21G theory (authors may be contacted for graphical support of the data). The HF and density functional theory (DFT) energies are of particular interest because they provide results for interactions appearing in solvent medium considered here, which are in accord with the biological behavior of adenine + fMet of fMet-tRNA. Furthermore, recent research often tend to look at the role of water solvent effect on the stability of adenine + fMet of fMet-tRNA

TABLE 2 Nuclear magnetic resonance parameters of O(12), C (15), and O(19) in adenine + fMet of fMet-tRNA structure in gas phase at the level of BLYP/6-31G, 6-31G*, and B3LYP/6-31G, 6-31G* theory

NMR parameters	BLYP 6-31G	BLYP/6-31G*	B3LYP/6-31G	B3LYP/6-31G*
σ_{iso} **O(12)**	137.7720	213.4672	214.7910	225.2472
$\Delta\sigma$**O(12)**	38.5323	186.7488	184.2246	196.8414
η**O(12)**	1.1287	0.9036	0.9139	0.8898
σ_{iso}**C(15)**	90.6370	87.7807	96.2359	93.0890
$\Delta\sigma$**C(15)**	83.1898	81.1767	87.7043	85.6704
η**C(15)**	1.4031	1.4259	1.3216	1.3554
σ_{iso}**O(19)**	261.0043	267.4912	271.1566	276.9884
$\Delta\sigma$**O(19)**	271.4995	279.1703	278.4712	285.9058
η**O(19)**	0.6205	0.4581	0.9603	0.7469

TABLE 3 Calculated relative energy values of adenine + fMet of fMet-tRNA in gas phase at HF/3-21G, 3-21G*,6-31G, 6-31G*, and B3LYP/3-21G*, 6-31G* levels in kcal/mol

HF/3-21G	−1424241.312526
HF/3-21G*	−1424792.355230
HF/6-31G	−1431418.572420
HF/6-31G*	−1431993.340832
B3LYP/3-21G*	−1478617.977156
B3LYP/6-31G*	−1486398.757155

structure. The detailed results of relative energy values for adenine + fMet of fMet-tRNA structure in water solvent optimized at the HF, B3LYP, and BLYP levels of theory with 6-31G, 6-31G* basis sets are summarized in Table 1.

The gauge including atomic orbital (GIAO) approach was used. The ab initio GIAO calculations of NMR chemical shielding tensors were performed using the DFT method. The chemical shielding tensors were calculated using the GAUSSIAN 98 program. The isotropic chemical shielding (σ_{iso}), asymmetry parameter (η), and anisotropy shielding ($\Delta\sigma$) for O(12), O(19), C(15) atoms (authors may be contacted for graphical support of the data) are summarized in Table 1. O(12), O(19), and C(15) atoms are very important in this structure because they are agent bonding between fMet and tRNA.

CONCLUSION

The results reported in this article indicate that it is possible to measure NMR tensors of various nuclei involving in biological compounds either in gas phase or in the presence of solvent molecules theoretically. Also, we can estimate the stability of biologically relevant super molecular structures according to obtained relative energy values. Several conclusions can be made on the basis of the observed results of the present study, and the theoretical data can provide important insights into the nature of molecular structures in biological systems.

Our main findings from the point of view of Solvent effects can be summarized as follows:

1. Optimization at the HF and DFT levels of theory provides a suitable computational model in terms of calculated NMR parameters and relative energies.
2. Hartree-Fock and DFT calculations provide a fairly clear picture of the adenine + fMet of fMet-tRNA in gas phase and water solvent from both structural and energetic points of view.
3. The largest σ_{iso}value of mentioned nuclei of adenine + fMet of fMet-tRNA structure observed for O(19), whereas the smallest one belongs to C(15). It is interesting to note that the opposite trend has been observed for

asymmetry parameters (η). This usual behavior may be readily understood in accord with biotechnological conceptions.

4. The geometries of adenine + fMet of fMet-tRNA structure at a constant pressure of 1 atmosphere and temperature of 310 K were optimized using the 3-21G basis set, and vibrational frequencies were obtained at the same level. Also in the case of adenine + fMet bonding of fMet-tRNA structure, a carbon bond from adenine organic base and a nitrogen bond from agent NH2, C(25)-N(29) and has the most intense vibration and therefore is the most unstable bond in this structure.
5. By using of IR spectra and NMR spectra results, we understand structural properties of formyl-methionine-tRNA; that is. the IR spectra and NMR spectra results provide a better understanding of formyl-methionine-tRNA structural properties.

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