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Inductive Effect of Bioactive Intermolecular Hydrogen Bonding Complex of 1,2,4,5 –Tetrazine and Inorganic Acid by NMR and QTAIM

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Abstract

In this paper, NMR and QTAIM analysis for three substituted of T2SA complex was investigated in the gas and four solvents at DFT level. Intermolecular O–H…N hydrogen bonds between 1,2,4,5-Tetrazine and Sulphurous acids enhance the stability of complex.1,2,4,5-Tetrazine is a highly reactive diene for [4+2] inverse-Diels–Alder cycloaddition processes and an excellent precursor to attain the pyridazine ring. 1,2,4,5-Tetrazines have been very widely utilized for the highly effective synthesis of natural products, bioactive compounds and ligands. The comparison between the donor and attractive group on hydrogen bonding intermolecular systems is discussed. The deshielding effects on hydrogen nucleus of this compound in solvents are referred to intermolecular hydrogen bonds which are controlled by dielectric constants. Dielectric constant increased the hydrogen atoms are deshielded, in the DMSO and water, the changes is small, because in theses polarity of solvent is very high. When donor group is substituted in this complex electron density is increased. The QTAIM results show that in the DMSO and water, the changes is small, because in theses polarity of solvent is very high. The NMR and QTAIM results are harmonious together in all cases. All calculations were performed using B3LYP method and 6-311++G** basis set in GAUSSIAN09W and AIM2000 programs.

Keywords: *Hydrogen bonding, NMR study, QTAIM analysis, DFT, Intermolecular complex, Bioactive Complex.*

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Introduction

Hydrogen bonding plays an important role in stabilizing some molecular structures and in constructing molecular assemblies [1, 2]. It has been found that a lot of physical and chemical phenomena are closely related to the intermolecular weak interactions including hydrogen bond [3-5]. Many natural and artificial supramolecules are formed through intermolecular forces such as hydrogen bonding, vanderwaals forces, and hydrophobic interactions [6]. Inorganic compound can be introduced as ligand for organic in the intermolecular complex .

As it is well known, Nuclear Magnetic Resonance (NMR) chemical shifts (δ) are closely relevant to understanding the electronic structure in a molecule [7-9]. An intra- or intermolecular hydrogen bonding will result in a decrease in diamagnetic shielding around the hydrogen nucleus. Ab initio/NMR calculations provide increasing support for NMR spectroscopy in analytical chemistry. Theoretical calculation of NMR has become an indispensable aid in the investigation of molecular structure and accurate assignment of NMR spectra of compounds. Because 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. Many of NMR observables are resulted from anisotropic chemical shielding interaction between the nuclear spin and its environment. Solid-state NMR spectroscopy is a powerful technique to study various types of hydrogen bonding properties [10, 11]. Gauge Including Atomic Orbital (GIAO) is a method for revocation the arbitrary of the choice of origin and form (gauge) of the vector potential used to introduce the magnetic field in the Hamiltonian when calculating chemical shielding and chemical shift tensor. An exponential term containing the vector potential is included with each atomic orbital. Two different solvation models are available in Gaussian– Polarized Continuum Model (PCM) and the Onsager solvation model. Both these methods calculate the energy of a molecule by placing the solute in a cavity and applying a dielectric through it [12, 13]. The PCM procedure, one of the most widely used continuum dielectric methods is applied to study the solvent effects on electronic structures. When using the PCM model and the DFT-based model, potential curves for electron emission can be obtained for all possible directions [14-17].

Bader’s Quantum Theory of Atoms in Molecules (QTAIM) [28, 29] was applied to characterize the π-interaction in the investigated complexes. The QTAIM is based on the analysis of electronic density and identifies interaction or chemical bond as a bond critical point (BCP) and also corresponding bond paths (BP). Many researchers have been applied to carry chemical bond strength and nature in chemical systems, By QTAIM analysis [18-25]. We investigated three complex; 1,2,4,5-Tetrazine- Sulphurous Acid (1:2) (H.T2SA), 3,6- Fluoro1,2,4,5-Tetrazine-Sulphurous Acid (1:2) (F.T2SA) and 3,6-Methyl 1,2,4,5-Tetrazine- Sulphurous Acid (1:2) (Me.T2SA) Complex by NMR tools and QTAIM analysis (Figure 1.).T2SA complex is a type of the intermolecular complex between one aromatic compound and two sulphurous acid that stabilized by hydrogen bonds. T2SA complex is highly sensitive to environmental effects such as dielectric constant. We will report the NMR shielding for T2SA Complex in gas and four solvents with the dielectric constant ranging from 1.00 to 78.39.

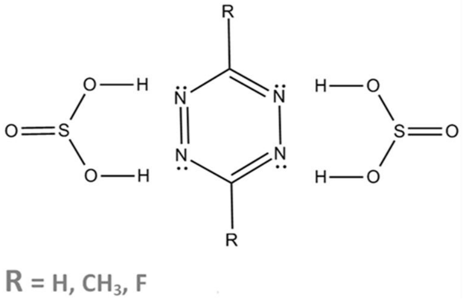

Figure 1. Schematic of T2SA Complex.

Theoretical

All calculations were carried out with the GAUSSIAN09W program [26]. Geometry optimizations in the gas and solvent phases for all components and complex were performed at the DFT level with B3LYP functional and 6-311++G** basis set. The NMR absolute shielding constants were calculated with the GIAO. The calculated magnetic shielding were converted into the chemical shifts by noting that the calculated the ^{1}H absolute shielding in tetramethylsilane (TMS). All PCM calculations in this report have been performed using this formalism as implemented in GAUSSIAN09W.AIM2000 package [27] has been employed to obtain bond properties.

Results and discussion

The equilibrium structure obtained respectively hydrogen bond calculation in the B3LYP/6-311++G** is shown in Figure 2. The formation of intermolecular hydrogen bonds, withN(2), N(12), N(13) and N(4) as donors, in the T2SA and support the behavior of the H(2), H(4), H(12) and H(13), as acceptors. These optimized structures were used to calculate the isotropic shielding constants and QTAIM analysis. This compound is able to form four intermolecular hydrogen bonds. The standard approach of the PCM, as is used here, appears to be a good first step in the theoretical investigation of the effect of solvent on nuclear magnetic shielding. In the first instance, irregular variations were observed concerning relative energy versus dielectric constant.

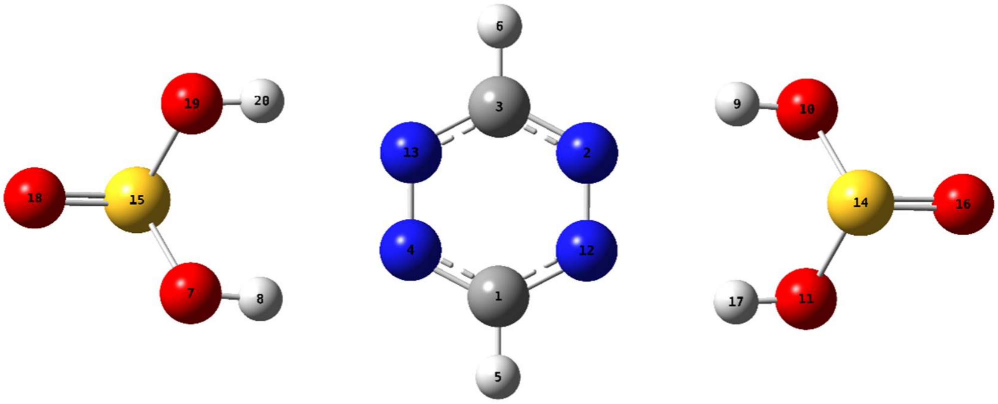

Figure 2. Equilibrium structure of T2SA complex in the B3LYP/6-311++G**.

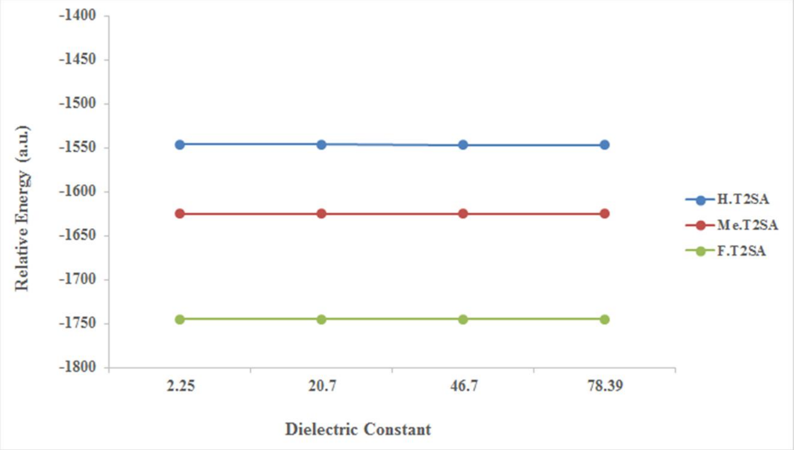

Figure 3. Linear dependence of T2SA Energy to Dielectric Constant(□□ for solvents.

It is well observed that energy values increase linearly with decrease in dielectric constants in the former case while future investigations are required to explain the latter. The plotting the relative energy versus dielectric constant (ε) presented in Figure 3. Overall in the NMR study, when nucleus becomes more deshield, values should be much greater (more positive). Dielectric constant is an important factor regarding shielding or deshielding nucleus. In the gas phase, Methyl is donor group and strengthens hydrogen bond that realizable by nucleolus de shielding, also Fluorine is attractive group and to be shield nucleus (see Table 1.), because donor groups increased resonance in the aromatic system and nitrogen atom is more negative.

Table 1. Solvent Effects on nucleus shielding of T2SA complexes (ppm).

Phase	ε	Substitutions	H (8)	H (9)	H (17)	H (20)	H (avg)
Gas	1.00	H.T2SA	6.397	6.405	6.420	6.429	**6.413**
		Me.T2SA	6.878	6.882	6.924	6.929	**6.903**
		F.T2SA	5.713	5.719	5.702	5.707	**5.710**
Benzene	2.25	H.T2SA	7.697	7.744	7.769	7.765	**7.744**
		Me.T2SA	8.159	8.141	8.128	8.170	**8.150**
		F.T2SA	6.890	6.923	6.862	6.903	**6.895**
Acetone	20.70	H.T2SA	8.905	8.908	8.916	8.920	**8.912**
		Me.T2SA	9.264	9.262	9.232	9.232	**9.247**
		F.T2SA	7.859	7.839	7.854	7.832	**7.846**
DMSO	46.70	H.T2SA	9.015	9.016	9.028	9.029	**9.022**
		Me.T2SA	9.373	9.370	9.333	9.334	**9.352**
		F.T2SA	7.946	7.930	7.940	7.922	**7.934**
Water	78.39	H.T2SA	9.037	9.038	9.051	9.052	**9.044**
		Me.T2SA	9.389	9.386	9.349	9.350	**9.368**
		F.T2SA	7.967	7.950	7.961	7.942	**7.955**

If the dielectric constant increased and the electron density around nucleus by the solvent is low, the nucleus becomes more deshield. Because geometrical symmetry of the substituent, comes from shift values close together to all four of hydrogen under similar condition, so we reports average value of the 1H chemical shielding. We plotted 1H chemical shielding versus dielectric constant in the Figure 4. Dielectric constant increases, the hydrogen atoms are deshield and transported HNMR peak to the higher fields. In the DMSO and water, the changes is small, because in theses polarity of solvent is very high (see Figure 4.).

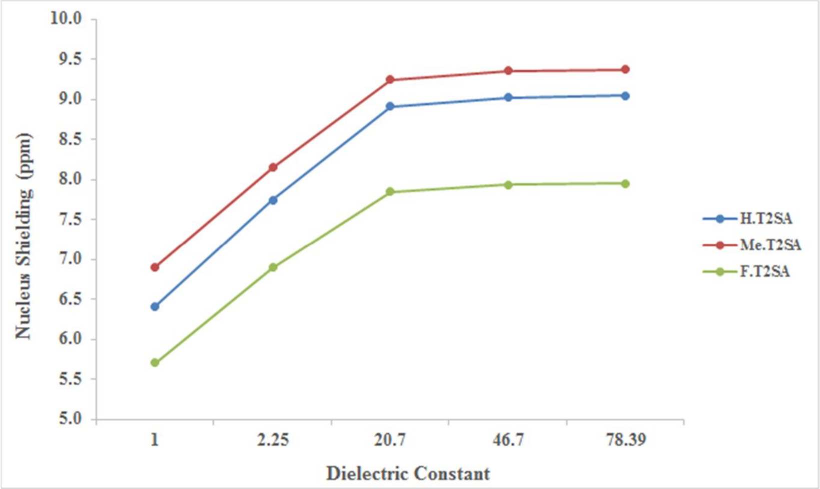

Figure 4. Dependence of ^{1}H chemical shielding (ppm) to Dielectric Constant(ε).

In Figure 5, shown is a comparison spectrum HNMR, among the three of substitution in the gas phase. It is clearly, an attractive of F group, and donor properties of methyl group.

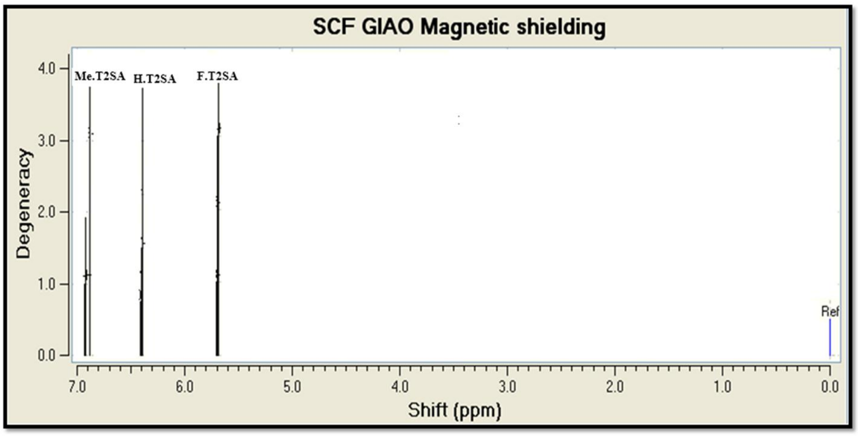

Figure. 5. Comparison of variation of δ (ppm) to the three substitution at gas phase.

The results of QTAIM parameters (in atomic units), are shown in Table 2 and Figure 6. All of forms of the T2SA is able to form four intermolecular hydrogen bonds with hydrogen atoms. From the above analysis (Table 2), in this complex electron density (ρBCP) in the Me.T2SA is greater than F.T2SA and H.T2SA, because methyl group is a weak electron donor and electron density is increased.

Table 2. Solvent Effects on electron density of T2SA complexes (a.u.).

Phase	ε	Substitutions	H (8)	H (9)	H (17)	H (20)	H (avg)
Gas	1.00	H.T2SA	0.0193	0.0194	0.0195	0.0196	**0.0195**
		Me.T2SA	0.0228	0.0229	0.0233	0.0233	**0.0231**
		F.T2SA	0.0149	0.0149	0.0147	0.0148	**0.0148**
Benzene	2.25	H.T2SA	0.0216	0.0219	0.0224	0.0224	**0.0221**
		Me.T2SA	0.0252	0.0253	0.0255	0.0257	**0.0254**
		F.T2SA	0.0157	0.0166	0.0154	0.0164	**0.0160**
Acetone	20.70	H.T2SA	0.0261	0.0262	0.0262	0.0263	**0.0262**
		Me.T2SA	0.0292	0.0291	0.0293	0.0293	**0.0292**
		F.T2SA	0.0191	0.0190	0.0190	0.0189	**0.0190**
DMSO	46.70	H.T2SA	0.0264	0.0265	0.0266	0.0267	**0.0266**
		Me.T2SA	0.0296	0.0295	0.0296	0.0296	**0.0296**
		F.T2SA	0.0193	0.0193	0.0192	0.0192	**0.0193**
Water	78.39	H.T2SA	0.0265	0.0266	0.0266	0.0267	**0.0266**
		Me.T2SA	0.0296	0.0295	0.0296	0.0296	**0.0296**
		F.T2SA	0.0194	0.0193	0.0192	0.0192	**0.0193**

NOTE, NMR study and QTAIM results are the compatible in the T2SA complex, however with a little attention, in the Figure 7, we knew which DMSO and water presented small slope in the chemical shielding and electron density.

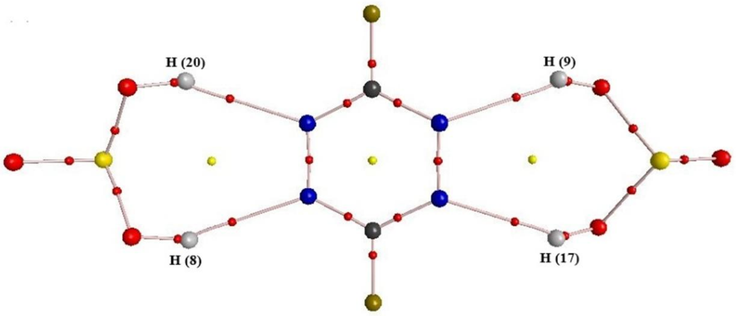

Figure 6. Molecular graph of the F-T2SA complex at the B3LYP/6-311++G** computational level. Red balls indicate the bond critical points.

The trends of the results for T2SA in the all of phases are similar. By increasing the dielectric constant, values of electron density is increased (Figure 7). In the DMSO and water, the changes are small, because in theses polarity of solvent is very high.

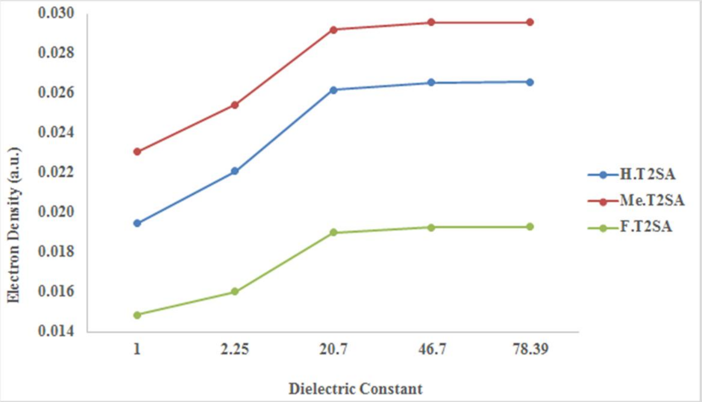

Figure 7. Dependence of electron density (a.u.) to Dielectric Constant(ε).

In the Figure. 8 shows contour maps of hydrogen nucleus shielding and electron density participant in hydrogen bonds at T2SA complex by changing dielectric constant. On the x-axis is the observed dielectric constant, the y-axis is based on 1H chemical shielding (ppm) and z-axis is the observed electron density (a.u.). The main data of this 3D surface exist in Table 1 and Table 2. The contour map shows that trend of electron density after ε = 46.7 (DMSO) is differ, in the three complex. According to the contour map can be understood the electron density value is sensitive to dielectricconstant between benzene (ε = 2.25) and acetone (ε = 20.7), in the F.T2SA.

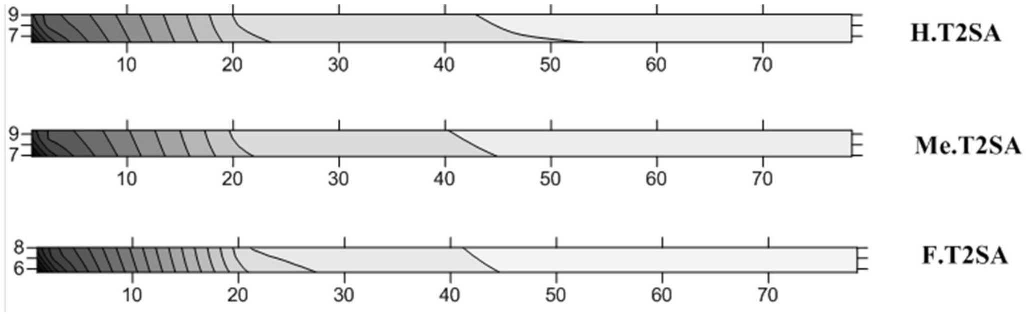

Figure 8. The Contour Map of all compounds in five phases. X-axis: Dielectric Constant, Y-axis: ^{1}H Chemical Shielding (ppm), Z-axis: Electron Density (a.u.).

Conclusion

In this study, chemical shielding tensors of the 1H and QTAIM parameters for three substituted T2SA complex (1:2) were calculated to investigate the influences of the inductive effect of substitution on hydrogen bonding interactions. T2SA to form four intermolecular hydrogen bonds that all hydrogen bonds are similar, because Hydrogen, Fluorine and Methyl groups are symmetric.The deshielding effects on hydrogen nucleus of this compound in solvents are referred to intermolecular hydrogen bonds which are controlled by dielectric constants. When donor group is substituted in this complex electron density (ρBCP) is increased because methyl group is a weak electron donor and electron density is increased.NMR study and QTAIM results are the compatible in the T2SA complex, DMSO and water presented small slope in the chemical shielding and electron density.

Acknowledgements

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