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Theoretical Study of the Solvent Effect on the Stability Energies of Pyrazole and Pyrazoline

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ABSTRACT

Using the Density Functional Theory (DFT) level by means of 3-21G, 6-31G and 6-31+G (d) basis sets, the structural optimization of isolated Pyrazole and Pyrazoline was done in the gas phase. Then, the calculation about the solvent effect on the stability energies of Pyrazole and Pyrazoline was performed for the ten solvents using PCM model method at B3LYP/6-31+G(d) and then the dielectric effects of the surrounding and the solvent effects on the stability energies of Pyrazole and Pyrazoline molecules were discussed.

Keywords: Heterocyclic compounds, Pyrazole, Pyrazoline, Solvent effects, PCM model, B3LYP-calculations.

INTRODUCTION

Heterocyclic compounds are well known for their wide range of biological applications out of which Pyrazole and Pyrazoline occupy unque position due to dominant applications [1-2]. Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon and two nitrogen atoms in adjacent positions and to the unsubstituted parent compound. Being so composed and having pharmacological at effect on humans, they are classified as alkaloids although they are not known to occur in nature. Pyrazols are produced synthetically through the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation. Pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranclulizing, muscle relaxing, psychoanalepic, anticonvulsant, monoamineoxidase, inhibiting, antidiabetic and antibacterial activities. There is no data for the solubility of Pyrazole in organic solvents in the data base perform the experiment. Pyrazoline is a five membered heterocyclic having two adjacent nitrogen atoms within the ring. It has only one double bond in the ring. Pyrazolines are known to possess antimicrobial, antitubercular, antiviral, anti HIV, molluscicidal and cerebroprotective properties etc. One of the important applications of Pyrazoline is the use of Pyrazolines as a fluorescent brightening agent. They can absorb light of 300-400 nm and emit blue fluorescence. Pyrazolines are also acting as whole transporting meterial in OELD (organic electroluminescent device) because of formation of p-n conjugated system due to

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one of the nitrogen atom. Pyrazolines have variety of methods for its synthesis but one of the popular methods is of Fischer and knoevenagel i.e. the reaction of α, β - unsaturated ketons with phenylhydrazine in acetic acid under refluxing condition. However depending on the reactivity of molecules and need of the chemist they have synthesized the Pyrazolines under different solvent media & acidic or basic conditions. Such a glamour history prompted us to synthesize Pyrazolines as an urgent need which can possess biological and medicinal importance. Numerous Pyrazoline derivaties have been found to possess considerable biological activitieswhich stimulated the research activity in the field. They have several prominent effects, such as antimicrobial, antimycobacterial, antifungal, antiamoebic, anti-inflammatory, analgesic, antidepressant and anticancer activities. They also possess some potent receptor selective biological activity like Nitric oxide synthase (NOS) inhibitor and cannabinoid (CB1) receptor antagonists activity 4,5- dihydro-1 Hpyrazolines seems tobe the most frequently studied Pyrazoline type compounds. As a result a large number of such Pyrazolines using different synthetic methods for their preparation have been described in the chemistry literature [3-6].

The Gaussian 03, program is suite for, which is induded the popular electronic structure the necessary modules for performing calculations in a solvated environment using the continuum models approximations [12]. Among such models, the polarizable continuum model (PCM) is one of the most widely used methods since it meets a good compromise between accuracy and computation time. Never the less, Gaussian programs may not be the best option for performing such calculations, but it still can be very useful when used properly[12]. In particular PCM model program does not provide any information on the solvent structure. In addition, the size and shape of cavity have no rigorous definitions. However, there are also several important adventages [12]. First, one can select a designed level of quantum mechanical theory from a wide range of ab initio molecular orbital (MO) and density functional theory (DFT) levels that are sufficiently accurate for modeling bond breaking and forming processes. Second, the reaction coordinate is uniquely defined because solvent effects from the continuum medium are effectively included in the solute Hamiltonian and do not increase the dimensionality of the system. Although these self-consistent reaction field studies provide useful insight, their accuracy is often questionable due to the uncertainty in the cavity size and shape for variable geometry of the reacting system [12].

The solvent effect is taken into account *via* the self-consistent reaction field (SCRF) method. The solute is placed in to a cavity within the solvent. SCRF approaches differ in how they define the cavity and the reaction field. Properties measured in low-pressure gases and those derived from measurements in the liquid phase differ as molecular interactions perturb the intrinsic polarizabilities, in the so-called solvent effect [7-8]. A dielectric continuum model with the solvated molecule placed in a spherical cavity and surrounded by a linear, homogeneous, polarizable dielectric medium was employed for the description of the condensed phase. The system (usually indicated as a solute) is described as a quantum mechanical charge distribution within a volume, the so-called solute cavity, modeled on the molecular shape of the solute and the environment (or the solvent) as a continuum dielectric. The

solute polarizes the dielectric and dielectric polarization in turn generates an electrostatic field at the solute which modifies the original charge distribution [9-11].

In this study, the structural optimizations of the two heterocyclic compounds Pyrazole and Pyrazoline were investigated. The optimization results of the isolated Pyrazole and Pyrazoline molecules in the gas phase, at the DFT level by means of 3-21G, 6-31G and 6-31+G(d) basis sets have also been carried out. The calculations about the solvent effects on the stability of Pyrazole and Pyrazoline were performed for ten solvents [(Water 1, DMSO 2, Acetonitrile 3, Methanol 4, Ethanol 5, Dichloroethane 6, Dichloromethane 7, Aniline 8, Dietheleter 9, and Heptane 10)] using PCM model method at B3LYP/6-31+G(d) and then the dielectric effects of surrounding were analyzed.

COMPUTATIONAL METHODS

Geometries

All calculations for the optimization of Pyrazole and Pyrazoline and solvent effects were done with the Gaussian 03 [14], ab initio packages at the Density Functional Theory (B3LYP) level of theory. Three basis sets were used 3-21G, 6-31G and 6-31+ G (d). At first, the geometry of Pyrazole and Pyrazoline were full optimized at the B3LYP/ 3-21G, 6-31G and 6-31+ G (d) levels of theory in the gas phase.

Solvent Model

Polarized Continuum Model (PCM) was used respect to ten solvents including: (water 1, DMSO 2, acetonitrile 3, methanol 4, ethanol 5, dichloroethane 6, dichloromethane 7, aniline 8, diethylether 9, and heptane 10). First, the molecular geometries were obtained by B3LYP/6-31+ G (d) level of optimization for Pyrazole and Pyrazoline in the gas phase. Then each of them was separately placed in each of ten solvents and the results were comparaed with each other and gaseous phase.

RESULTS AND DISCUSSION

The geometry optimization of Pyrazole and Pyrazoline molecules was chosen as the starting step in the gas phase. The Pyrazole and Pyrazoline were found to be stable in the optimized gas phase at B3LYP/ 3-21G, 6-31G and 6-31+ G (d) level. The results are summarized in Table1.

In accordance with the obtained results, the minimum energies were related to the basis set 6-31+ G (d) level. Therefore, here the basis set 6-31+ G (d) was selected for the calculations.

A quantum-mechanical analysis of the solvent effect on the stability of Pyrazole and Pyrazoline molecules are presented in Table2. The stability energies are identified by: $\Delta E= E_{solute}- E_{gaseous\ phase}$. The stability energies ΔE (in kcal mol^{-1}) for Pyrazole and Pyrazoline as a function of dielectric constant, ε, of considerd solvents are gathered in Table 2. The values were obtained by using B3LYP/6-31+ G (d) method. The results show that the stability of Pyrazole and Pyrazoline reduce by decreasing the polarisability of the solvents. The most stability is observed for water with ε = 78.39 and the lowest one is for heptane with ε=1.92.

Regular alterations were observed concerning energy *versus* dielectric constant. With increasing of the dielectric constant of the solvents the stability,of Pyrazole and Pyrazoline molecules were increased (Fig .1). The figure 1 showes the plot of the stability energies ΔE (in kcal mol^{-1}) of Pyrazole and Pyrazoline versus the dielectric, ε, of the ten solvents (**1-10**).

Obviously, the manitade of ΔE is increase by increasing the dielectric constant, ε, of the solvents.

Table 1. Absolute calculated results of the conformational energies (E(kcal mol^{-1})) of Pyrazole and Pyrazoline obtained by geometry optimization at basis set 6-31+G(d), 6-31G and 3-21G levels

Basis set	**E(kcal mol^{-1})**	
	Pyrazole	Pyrazoline
3-21G	-141151.688	-141895.092
6-31G	-141892.713	-142637.435
6-31+G(d)	-141948.219	-142692.014

Table 2. The solvent effect on the stability energies of Pyrazole and Pyrazoline as a function of dielectric constant by using B3LYP/6-31+ G (d) method

		- ΔE(kcal mol^{-1})	
Solvents (1-10)	**ε**	**Pyrazole**	**Pyrazoline**
Water(**1**)	78.39	10.509	8.198
DMSO(**2**)	46.70	10.326	7.978
Acetonitrile(**3**)	36.64	10.213	7.948
Methanol(**4**)	32.63	10.152	7.854
Ethanol(**5**)	24.55	9.952	7.687
Dichloroethane(**6**)	10.36	8.934	6.948
Dichloromethane(**7**)	8.93	8.674	5.901
Aniline(**8**)	6.89	8.123	4.263
Dietheleter(**9**)	4.34	6.843	3.695
Heptanes(**10**)	1.92	3.508	2.690

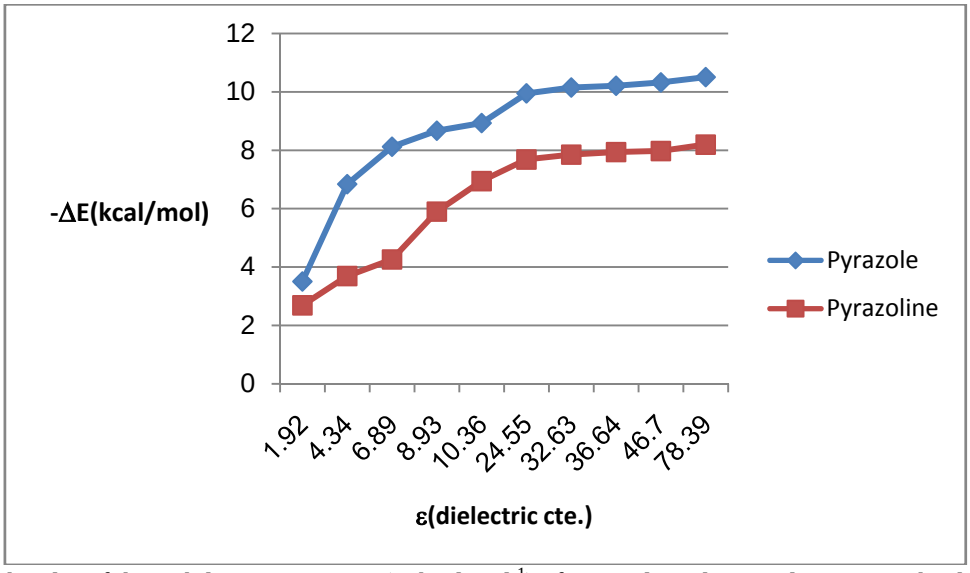

Fig.1. The plot of the stability energies ΔE (in kcal mol^{-1}) of Pyrazole and Pyrazoline versus the dielectric constant, ε, of the solvents.

CONCLUSIONS

Two regions of dielectric constant values were identified (1<ε<10) and (10<ε<80). As it was expected, by increasing the dielectric constant of the solvents the stability energies of Pyrazole and Pyrazoline were increased. By using the plot of the calculated energies and dielectric constant of Pyrazole and Pyrazoline we have reached to interesting results. We have proposed an empirical

communication between effect of the solvent and to the unsubstituted parent compound.

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