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Solvent effects on the relative stability for tautomerism of (*R*)-4-amino-1,2-oxazolidin-3-one(Cycloserine).Ab initio and Density functional theory calculations

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ABSTRACT

Relative tautomerization energies, dipole moments and polarizabilities for the tautomers of (R)-4-amino-1,2-oxazolidin-3-one (Cycloserine) was studied by quantum-chemical calculations, using the HF and DFT(B3LYP) level of theory with the 6-311++G(d,p) basis set in the gas phase and different solvents using SCRF model, with full geometry optimization. Entropies, enthalpies, Gibbs free energies and equilibrium constants for the tautomerization process of cycloserine were calculated. The calculations showed that, the NH tautomer form is the most stable than OH tautomer form in the gas phase and other solvents. Then important molecular parameters and selected IR frequencies results in the gas phase and solvents were extracted. The stability of the tautomers relate to the nature of solvents. In the solution and with increase of polarity; NH isomers were more stable.

Key words: Cycloserine, Ab intio HF, DFT method, Tautomerism, thermodynamic Parameters, equilibrium constant.

INTRODUCTION

D-Cycloserine, a structural analog of D-alanine, is a broad spectrum antibiotic produced by certain strains of *Streptomyces orchidaceus* or *S. garphalus*[1-3]. D-cycloserine (at 100 to 200 µg/ml) inhibits the synthesis of bacterial cell walls (involving peptidoglycan synthesis) by preventing formation of D-alanine from L-alanine and hence the formation of peptide bonds involving D-alanine[3]. D-cycloserine has antibiotic activity *in vitro* against growth phase Gram-negative bacteria including *Escherichia coli* (working concentration of approx. 200 µg/ml)[4], strains of *Staphylococcus aureus*, *Nocardia* species and *Chlamydia*[2], and some mycobacteria including *Mycobacterium tuberculosis*. The minimum inhibitory concentrations (MIC) *in vitro* for *M. tuberculosis* range from 5-20 µg/ml. Studies *in vitro* show no suppression of growth in cultures made in media containing D-alanine which appears to block the antibacterial action of D-cycloserine[2]. Cycloserine is a highly polar general antibiotic which can also be used in the treatment of pulmonary tuberculosis [4]. Until recently it has not been in wide-spread use for the treatment of TB due to its toxicity. With more drug-resistant strains of tuberculosis emerging, cycloserine treatment is becoming more common [5]. Bioequivalency has been demonstrated when cycloserine is administered in different formulations [6]. It also exhibits the ability to increase the levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) [7] as well as inhibit the pyridoxal- 5`-phosphate (PLP) enzyme GABA-aminotransferase [7,8]. The interaction of cycloserine with a number of other PLP enzymes has also been studied [9].

Knowledge of the geometric and electronic structure as well as the relative stability of tautomeric forms provides a basis for understanding biological activity of cycloserine . In addition, knowing how these tautomerisation energies change in different environments can give an insight into the influence of solvent effects on molecular stability. Furthermore, a deeper knowledge of the tautomerism of the cycloserine in different environments is essential to an understanding of the pharmacological properties of this molecule and the design of new derivatives with improved activity. Literature survey reveals that to the best of our knowledge, no ab initio HF/DFT quantum chemical calculations of cycloserine in different solvents have been reported so far. In this study, we have investigated the structural geometries, dipole movements, thermodynamic properties and equilibrium constants of cycloserine molecule theoretically, by performing Ab intio and DFT calculations because of biological and medical importance of title compound.

MATERIALS AND METHODS

COMPUTATIONAL METHODS

Theoretical calculations were carried out at the Hartree–Fock level (HF)[10] and The Becke's three parameter hybrid exchange functional [11] with Lee-Yang-Parr correlation functionals (B3LYP) [12,13] of the density functional theory [14] and 6-311++G (*d*,*p*) basis set were chosen to optimize the structures of the molecules under investigation. All these calculations were carried out on a Pentium V personal computer by means of GAUSSIAN09 program package [15] and for our computations. First, all compound's structures were drawn using Gaussview 5.08 program [16]. Positive values of all the calculated vibrational wave numbers confirmed the geometry to be located at true local minima on the potential energy surface. The stationary structures are confirmed by ascertaining that all ground states have only real frequencies. Thermodynamic quantities were obtained through standard harmonic oscillator-rigidrotator treatments. Until recent years, many theoretical studies with quantum chemical program packages have been carried out without incorporating solvent effects. As calculations are usually carried out with an isolated molecule, which simulates the behavior of the gas phase, information derived from calculations may often show a large discrepancy, when compared to results that mostly come from experiments in solution. Recently, a great deal of effort has been given to overcome this problem [17-19].One quick and popular approach is the SCRF method, in which solvents are treated as a dielectric continuum that interacts with the solute charge distribution[20-21].We have used the SCRF method in our work in an attempt to find the degree and possible origins of relative stability of NH tautomer and OH tautomer in various solvent properties. In this method treats solvents as a dielectric continuum, local interactions with the solvent molecules, and particularly highly polar protic media like water. The tautomers were optimized in all solvents by utilized in the gas phase optimized geometries.

RESULTS AND DISCUSSION

Relative stabilities

Structures and numbering of cycloserine is depicted in Fig. 1 and the results of energy comparisons of two tautomers in the gas phase and different solvents are given in Table 1.The predicted relative stability of NH and OH tautomers show the NH tautomer is more stable than OH tautomer in gas phase and also different solvents. The gas phase relative energy is more comparison of other solvents and the relative energies are increasing with increasing of dielectric constants of solvents at both methods of levels. The relative energy difference between OH and NH form in gas phase and other solvents were found 5-10 kcal mol^{-1}. The order of relative stabilities are Gas > Benzene > Acetone > Methnol > water. Comparing the energies of HF with those of DFT as a whole, the former are higher side than the later, because of in which the instantaneous Columbic electron–electron repulsion is not specifically taken into account and only its average effect is included in the calculation and it is well known that the DFT (B3LYP) method adequately takes into account electron correlation contribution and/or electron lone paris.

Geometric parameters

The optimized parameters of all structures are listed in Table 2. Important aspects of molecular structure can be observed in Table 2. The N2-C1 bond length, reported in the first row of table, lies in the range of 1.38–1.36 Å in NH tautomer and N2=C1 bond length is 1.25-1.28 Å in OH tautomer for all solvents at both level of theory. The C1=O6 bond length, lies in the range of 1.18-1.22 Å in NH tautomer and C1-O6 bond length, lies in the range of 1.32-1.34 Å for all solvents. Next six rows of Table 2 consist of C2-O3, C4-O3, C4-C5, C5-N7, N2-H8 and O6-H11bond lengths.

Four important vibrational frequencies of both NH and OH tautomers are listed in Table 3, for all solvents. In the first and second row, N2-H8 and C1=O6 frequencies (these frequencies only exists in tautomer NH) and Next two rows of Table 3, consists of O6-H11and C1=N2 frequencies (these frequency only exists in tautomer OH. After the stationary points were located, vibration frequencies were calculated in order to ascertain that the structures found corresponds to minima on the potential energy surface. Based on the vibrational analysis, the changes of the thermodynamic properties: Change in free energy ΔG, change in enthalpy ΔH, change in entropy ΔS, as well as the equilibrium constant (K) were theoretically determined from the results of electronic, vibrational and electronic components using the HF and DFT/6-311++G (d,p) level of calculation.

Thermodynamic properties and Equilibrium constants.

The calculated tautomeric enthalpies, Gibbs free energies, and entropies for the tautomerization process in vapor and different solvents are shown in Table 4. Thermodynamic results showed that tautomersim process is non spontaneous because of the positive value of the free energy change (ΔG) and therefore NH tautomer is more stable than OH tautomer. The positive value of enthalpy change (ΔH) indicates that the tautomersim process is endothermic process.

The tautomeric equilibrium between tautomers a and b is described as

$$a \underset{}{\overset{K_T}{\rightleftharpoons}} b \qquad (1)$$

Equilibrium constants for each species were calculated by using the following equation

$$K_T = \text{Exp}(-\Delta G/RT) \qquad (2)$$

Where K_T is the tautomeric equilibrium constant between the tautomers, the gas constant R is 1.987 x10^{-3} kcal mol, and the temperature T is 298.15 K. The quantity ΔG stands for the difference in the Gibbs energies of the individual tautomers. The value of the equilibrium constant K which represent the expected ratio of NH tautomer to the OH tautomer has been found to be of a value less than 10^{-7} at room temperatures (Table 2). This indicates the predominance of the NH form of cycloserine at temperatures in all solvents. Table 4 contained the equilibrium constants (pK_T)values in different solvents .All pK_T values in gas phase and the solvents were positive and this confirmed the fact that NH tautomer is most stable.

Dipole movements and Molecular polarizability

The dipole moment (μ) is an important tool which can be used to show the charge distribution in a molecule, and it is one of the properties often used to rationalize the structure of many chemical systems [22]. Thus, by comparing the calculated dipole moment values from table 2, for the optimized structures of the NH and OH tautomers, a strong evidence for the existence of the cycloserine molecule in the NH form rather than the OH form can be supported. The dipole movements were found different in different solvents because of the solvents has different dielectric constants and the order of dipole movements are Gas > Benzene > Acetone > Methnol > water.

We have investigated the effect of solvents on molecular polarizability of cycloserine using Gaussian 09W. In this study, the computation of molecular polarizability of cycloserine with different solvents reported. Here, α is a second rank tensor property called the dipole polarizability and mean polarizability ⟨α⟩ are evaluated using

$$\langle\alpha\rangle = 1/3(\alpha xx + \alpha yy + \alpha zz) \qquad (3)$$

The polarizability calculations carried out for different basis sets of cycloserine are summarized in table 4. As seen from the figure 3, polarizability was observed for different solvents, the polarizability increases with increase dielectric constant of solvents and Acetone, methanol and water the polarizability increase is small comparison of Benzene and gas. The polarizabilities of OH tautomer are higher than the NH tautomer in all solvents.

Table 1. Total energies (a.u) and relative energies (kcal/mol) of cycloserine tautomers for HF and DFT(B3LYP)methods at level of 6-311++G in the gas phase and in different solvents.**

Tautomer	HF/6-311++G(d,p)				
	Gas(ε=1)	Benzene(ε=2.2)	Acetone(ε=21.0)	Methnol(ε=33)	Water(ε=78.4)
NH	-375.75745411	-375.76524118	-375.77468712	-375.77527563	-375.77587584
OH	-375.74525708	-375.75326384	-375.76270330	-375.76327686	-375.76385923
E2-E1	9.339364837	7.515851516	7.519917755	7.529298968	7.540493673
DFT/6-311++G(d,p)					
NH	-377.93062560	-377.94153499	-377.94637828	-377.94692842	-377.94748971
OH	-377.92215090	-377.92972505	-377.93794068	-377.93846293	-377.93899347
E2-E1	5.31795476	7.410849544	5.294674157	5.312175397	5.331471314

Table. 2: Selected molecular parameters of optimized structure of cycloserine tautomers HF and DFT(B3LYP)methods at level of 6-311++G basis set in the gas phase and in different solvents.**

HF/6-311++G(d,p)										
Bond length	GAS		Benzene(ε=2.2)		Acetone(ε=21.0)		Methnol(ε=33)		Water(ε=78.4)	
	NH	OH	NH	OH	NH	OH	NH	OH	NH	OH
C1-N2	1.38	1.25	1.37	1.25	1.36	1.25	1.36	1.25	1.36	1.25
C1=O6	1.18	-	1.19	-	1.19	-	1.19	-	1.19	-
C1-O6	-	1.32	-	1.32	-	1.32	-	1.32	-	1.32
C2-O3	1.39	1.39	1.39	1.39	1.39	1.40	1.39	1.40	1.39	1.40
C4-O3	1.41	1.41	1.41	1.41	1.42	1.42	1.42	1.42	1.42	1.42
C4-C5	1.53	1.53	1.53	1.53	1.53	1.53	1.53	1.53	1.53	1.53
C5-N7	1.44	1.45	1.44	1.44	1.44	1.44	1.44	1.44	1.44	1.44
N2-H8	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
O6-H11	-	0.95	-	0.95	-	0.95	-	0.95	-	0.95
DFT/6-311++G(d,p)										
C1-N2	1.38	1.27	1.37	1.28	1.37	1.28	1.37	1.28	1.37	1.28
C1=O6	1.21	-	1.22	-	1.22	-	1.22	-	1.22	-
C1-O6	-	1.34	-	1.33	-	1.34	-	1.33	-	1.33
C2-O3	1.43	1.43	1.43	1.41	1.42	1.44	1.42	1.44	1.42	1.44
C4-O3	1.44	1.44	1.44	1.43	1.45	1.45	1.45	1.45	1.45	1.45
C4-C5	1.54	1.53	1.53	1.53	1.54	1.53	1.54	1.53	1.54	1.53
C5-N7	1.44	1.46	1.45	1.44	1.45	1.45	1.45	1.43	1.45	1.45
N2-H8	1.01	-	1.01	-	1.01	-	1.01	-	1.01	-
O6-H11	-	0.97	-	0.98	-	0.98	-	0.98	-	0.98

Table 3: Selected frequencies (in cm^{-1}) of cycloserine tautomers HF and DFT(B3LYP) methods at level of 6-311++G basis set in the gas phase and in different solvents.**

HF/6-311++G(d,p)										
Bond	Gas(ε=1)		Benzene(ε=2.2)		Acetone(ε=21.0)		Methnol(ε=33)		Water(ε=78.4)	
	NH	OH	NH	OH	NH	OH	NH	OH	NH	OH
N2-H8	3839	-	3833		3828		3829	-	3829	-
C1=O6	2016	-	1983		1940		1937	-	1934	-
O6-H11	-	4107	-	4088	-	4067	-	4066	-	4065
C1=N2	-	1947	-	1936	-	1921	-	1920	-	1919
DFT/6-311++G(d,p)										
N2-H8	3599	-	3599	-	3596	-	3597	-	3596	-
C1=O6	1813	-	1772	-	1751	-	1748	-	1747	-
O6-H11	-	3685	-	3660	-	3631	-	3629	-	3629
C1=N2	-	1734	-	1730	-	1723	-	1723	-	1722

Table 4: Thermodynamic properties of change in free energy (ΔG), change in enthalpy (ΔH),(K cal/mol) and change in entropy (ΔS) (cal/mol) of cycloserine tautomers for HF and DFT(B3LYP) methods at level of 6-311++G basis set in the gas phase and in different solvents.**

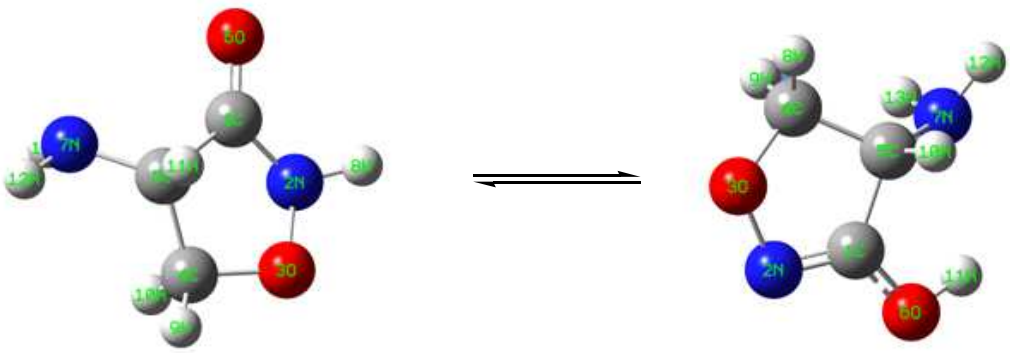
Solvent	HF				DFT			
	ΔH	ΔG	ΔS	p^{K}_{T}	ΔH	ΔG	ΔS	p^{K}_{T}
Gas	7.769	8.010	-0.811	6.41	5.363	5.735	-1.257	4.59
Bemzene	7.544	7.587	-0.145	6.07	7.50	7.834	-1.118	6.27
Acetone	7.496	7.471	0.082	5.98	5.223	5.444	-0.737	4.36
Methanol	7.506	7.492	0.046	5.99	5.233	5.451	-0.727	4.36
Water	7.517	8.018	0.016	6.42	5.247	5.457	-0.707	4.37

Table.5: Calculated dipole moments (Debye) of cycloserine tautomers for HF and DFT(B3LYP) methods at level of 6-311++G basis set in the gas phase and in different solvents.**

HF/6-311++G(d,p)					
Tautomer	Gas(ε=1)	Benzene(ε=2.2)	Acetone(ε=21.0)	Methnol(ε=33)	Water(ε=78.4)
NH	3.9147	4.5328	5.3289	5.3813	5.4344
OH	6.2198	6.9200	7.7422	7.7923	7.8438
DFT/6-311++G(d,p)					
NH	3.6769	1.9160	5.2243	5.2843	5.3421
OH	6.0501	6.8096	7.7162	7.7923	7.8250

Table.6: Polarizabilities of cycloserine tautomers for HF and DFT(B3LYP) methods at level of 6-311++G basis set in the gas phase and in different solvents.**

HF/6-311G(d,p)								
Solvent	Tautomer	α_{XX}	α_{XY}	α_{YY}	α_{XZ}	α_{YZ}	α_{ZZ}	<α>
Gas	NH	53.272	-1.023	58.146	-0.627	-0.052	41.170	50.863
	OH	59.918	0.392	53.142	1.247	0.534	41.359	51.473
Benzene	NH	58.571	-1.735	64.279	-0.882	-0.043	45.143	55.998
	OH	66.719	0.545	58.416	1.509	0.677	45.358	56.831
Acetone	NH	64.914	-2.898	71.684	-1.223	-0.012	51.041	62.546
	OH	74.873	0.791	64.888	1.826	0.913	51.373	63.711
Methnol	NH	65.319	-2.998	72.129	-1.246	-0.013	51.452	62.967
	OH	75.372	0.808	65.293	1.845	0.930	51.796	64.154
Water	NH	65.716	-3.083	72.598	-1.268	-0.010	51.878	63.397
	OH	75.880	0.828	65.703	1.866	0.950	52.230	64.604
DFT/6-311G(d,p)								
Gas	NH	63.059	-1.715	65.829	-1.058	0.466	46.091	58.326
	OH	68.157	-0.382	61.650	1.143	0.193	46.026	58.611
Benzene	NH	72.088	2.788	72.139	1.603	0.066	50.366	64.864
	OH	76.706	-0.449	68.294	1.398	0.355	50.641	65.214
Acetone	NH	79.211	-4.970	82.980	-1.989	0.568	57.680	73.290
	OH	87.253	-0.454	76.623	1.709	0.612	57.743	73.873
Methnol	NH	79.773	-5.126	83.578	-2.023	0.574	58.178	73.843
	OH	87.910	-0.451	77.151	1.728	0.630	58.250	74.437
Water	NH	80.343	-5.275	84.201	-2.058	0.578	58.694	74.413
	OH	88.580	-0.443	77.684	1.748	0.653	58.774	75.013



NH Tautomer OH Tautomer

Fig 1. Geometry of the cycloserine optimized tautomers at B3LYP/6-31++G(d, p) in gas phase.

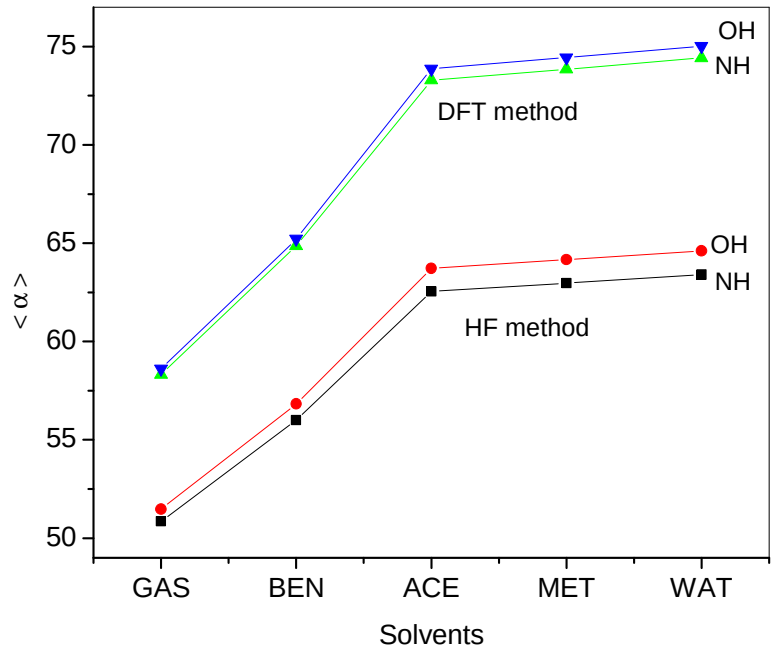


Figure 2. Polarizabilities of cycloserine tautomers for HF and DFT(B3LYP) methods at level of 6-311++G basis set in the gas phase and in different solvents.**

CONCLUSION

In this work, HF and DFT calculation has been applied to study of tautomerism in cycloserine in the gas phase and four solvents. The following points emerge from the present study: 1. The relative energy difference between OH and NH form in gas phase and other solvents were found 5-10 kcal mol^{-1}. The order of relative stabilities are Gas > Benzene > Acetone > Methnol > water. 2. In the solution and with increase of polarity; NH isomers were more stable. With increase of polarity total energy of all compounds were more negative. 3. All pK_T values in gas phase and the solvents were positive and this confirmed the fact that NH tautomer is most stable. 4. The dipole moments of all compounds are affected by solvent with increase of the polarity of solvents the dipole moments of OH and NH tautomers were increased. 5. The polarizability of all compounds are affected by solvent, with increase of the polarity of solvents the polarizability of OH and NH tautomers were increased.

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