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DFT studies of molecular structure, equilibrium constant for keto-enol tautomerism and geometrical isomerism (E-Z) of 2-amino-1-phenylpropan-1-one (Cathinone)

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ABSTRACT

Relative tautomerization energies, dipole moments, entropies, enthalpies and Gibbs free energies and the equilibrium contents for the tautomers of cathinone (2-amino-1-phenypropan-1-one) of the two possible (E and Z) isomers was studied by quantum-chemical calculations, using the B3LYP level of calculation with the 6-311G (d,p) basis set in the gas phase with full geometry optimization. The optimized geometries indicate that these molecules show a distinctly non planar configuration. These calculations have been used to establish the most stable tautomer and calculations showed that, the keto form is the most stable form than other isomers in the gas phase and the (Z) isomer is more stable compared to the corresponding (E) isomer.

Key words: cathinone, density functional theory, keto-enol tautomerisim, geometrical isomerism, equilibrium contents.

INTRODUCTION

Natural cathinones constitute a pharmacologically important family of compounds, related to the ephedrines and amphetamines and well recognized as CNS stimulants. Vegetable cathinones are phenylalkylamine alkaloids naturally present in the khat plant (Catha edulis), an evergreen slow-growing shrub or tree native to Ethiopia and cultivated in East Africa and South West Arabian Peninsula [1]. The main natural cathinones present in the khat are cathinone and cathine. Cathinone, the most abundant and powerful, is a beta-keto analog of amphetamine with a molecular weight of 149.19 g/mol [2]. This molecule, formally named S-(-)-2-amino-1-phenylpropan-1-one, is more labile in the presence of oxygen and it is oxidized and decomposed within a few days of harvesting or if dried .The stored product loses activity rapidly, becoming physiologically inactive after about 36 h. It is for this reason that for maximum power, khat should be picked in the morning and chewed in the afternoon [3]. Like amphetamines, cathinone is central nervous system (CNS) stimulants, but is potency is less. These alkaloids cause the release of catecholamines from pre-synaptic storage sites in the central and peripheral nervous system [4-5]. In addition, this molecule may also have monoamine oxidase inhibition effects [6].

The psychotropic effects of khat start after about 1 h of chewing and they last for approximately 3 h [7]. Peak plasma levels of cathinone are obtained 1.5–3.5 h after the onset of chewing while it is barely detectable after 8 h. First-pass metabolism of cathinone in the liver leads to the formation of norephedrine. Only 2% of cathinone is excreted unmodified in the urine. Cathinone derivatives are nowadays an emerging group of designer drugs, besides synthetic cannabimimetics and pipera-zines. This group contains derivatives of cathinone itself (β-keto amphetamines), β-keto analogues of methylene dioxy amphetamines, and pyrrolidino phenones [8–12]. Clinical data

have shown that cathinone determine an increase in blood pressure and heart rate, euphoria, alertness and psychomotor hyperactivity [13]. Several studies have shown that the chronic use of this plant may produce various harmful effects such as increased incidence of acute coronary vasospasm and myocardial infarction, esophagitis, gastritis, oral keratotic lesions and liver toxicity [14]. Furthermore, insomnia, depression, anorexia, psychosis and impaired working memory have been reported after occasional or chronic use of khat [15]. In particular, khat use can exacerbate psychotic symptoms in people with pre-existing psychosis and precipitate psychotic disorders in vulnerable subjects [16]. Literature data suggest that khat use may induce abuse, tolerance and dependence. Despite khat induced dependence seems to be less likely than amphetamine or cocaine induced dependence, khat alkaloids have the potential to induce addiction disorders. Khat induced tolerance appear to be more rapid than to that of amphetamines and there is a cross-tolerance between amphetamines and cathinone [17-18]. Finally, it was reported a withdrawal syndrome after suspension characterized by insomnia, lack of concentration, craving, nightmares and slight trembling [14].

Tautomers are structural isomers that are conceptually related by the shift of hydrogen and one or more bonds. Aldehydes and ketones, which have at least one hydrogen atom, are in equilibrium with an isomer called enol, and this type of equilibrium between constitutional isomers is called tautomerism. For the past two decades, there has been considerable interest in studying the tautomerism of heterocyclic compounds to identify the influence of tautomerism on chemical and biological properties of molecules. The phenomenon of tautomerism is related to aromaticity and lone pair– lone pair repulsions. The experimental studies on tautomerism are still a challenging problem in chemistry and molecular biology. Most tautomers are not observed in the experimental studies because of their low concentration. A detailed analysis of the structure and changes in geometrical and energetic parameters caused by the migration of hydrogen atom would enable us to understand the different properties of tautomers. Knowledge of the relative stabilities of tautomeric forms of heterocycles as well as the conversion from one tautomeric form to another is important from the point of view of structural chemistry.

MATERIALS AND METHODS

Computational Methods

The geometries of keto and enol isomers (Z & E) (Scheme1) were completely optimized with the Gaussian 09 program [19], employing the B3LYP functional [20-21] within the scope of density functional theory (DFT) [22] level with the 6–311G (d,p) as triple split valence basis sets in gas phase. All geometries were taken as starting points using HF/3-21G geometry optimizations. These results were reoptimized at Becke's 3-parameter exact exchanges functional (B3) combined with gradient corrected correlation functional of Lee-Yang-Parr (LYP) method [23].For the optimized geometries, the frequencies were obtained from the second derivates of the energy computed using analytically calculated first derivates to establish the stationary points. All optimized structures were checked by analysis of harmonic vibration frequencies. The optimized structures of all investigated molecules are at the stationary points corresponding to local minima without imaginary frequency. The atomic charges have been calculated using Mulliken population analysis.

The transition states were optimized by using Synchronous Transit-Guided Quasi-Newton (STQN) Methods. The STQN method, implemented by H. B. Schlegel and coworkers,[24] uses a quadratic synchronous transit approach to get closer to the quadratic region of the transition state and then uses a quasi-Newton or eigenvector- following algorithm to complete the optimization. Firstly, the structures of every stable configuration were optimized at B3LYP/6-311G (d,p) level. Then the frequencies and zero-point energies (ZPE) of these structures were calculated at the same level. Frequency calculations were performed to distinguish local minima from saddle points; meanwhile, they were also used to confirm the reaction transition states (TS), which were optimized using QST2 method. There was only one imaginary frequency for the transition state, whereas there was no imaginary frequency for stable states.

RESULTS AND DISCUSSION

Geometrical structures

The calculated molecular structures of cathinone isomers scheme and the theoretical geometric structures of isomers of the titled compound are shown in Fig.1 and Fig.2. The optimization studies of the cathinone isomers showed that the molecules belong in a C_1 symmetry point group. The optimized structural parameters (bond lengths, bond angles and dihedral angles) of the titled compound have been obtained at the B3LYP level of theory with a 6-311G (d,p)

basis set are listed in table.1, in accordance with the atom numbering given in Fig 2. To the best of our knowledge, there is no experimental report on the geometry of the titled compound isomers in the literature for comparison. The calculated dihedral angles demonstrate that both the keto and enol tautomers are planar. From the table 1, the almost all bond lengths of (Z)-isomer is less than (E)-isomer. The bond lengths C7-O8 and O8-H17 are in Z-isomer 1.3493, 0.9471 and 1.4099, 0.992 in E-isomer respectively. Similarly the bond lengths C9-N11and N11-H21 are 1.4399, 1.0017 in Z-isomer and 1.4461, 1.0279 in E-isomer respectively. Because Z –isomer, to form intra molecular hydrogen bond. The bond length (C9-H17) is 1.0829, 1.5421, 2.3211, 2.4494 and 2.4126 for keto, TS (Z), enol (Z), TS (E), and enol (E) respectively. This shows clearly the formation of Z and E isomers. As shown in Table 1, there is very good agreement between all the levels of theory for the changes in geometry on going from reactants to the transition state to products.

Atomic charge distribution

The knowledge of the charge distributions is essential for the interpretation of molecular properties. The atomic charges for all the atoms of the title compound calculated by DFT method in gas phase are presented in Table 2. As seen from this table, the oxygen atom O8 have negative atomic charges with values as –0.301425, -0.131058, -0.122878, 0.135289 and – 0.148133 units and N11 have negative atomic chares with values as -0.046888,-0.055183,-0.097555,-0.055078 and -0.050663 units for keto, TS(Z), enol (Z), TS(E) and enol (E) respectively. Besides the oxygen and nitrogen atoms some carbon atoms like C4, C6 in keto, and TS(Z), C2,C4,C6,and C9 in enol (Z) isomer and C2,C4,C3,and C6 in TS(E) and C2,C3,C4,and C6 in enol(E) isomer have negative charge values than the other carbon atoms in two isomers. This data of the charge distribution of atoms suggests that the two isomers (Z&E) are different.

Thermodynamic parameters and kinetic parameters

Thermodynamic properties such as: the enthalpy, the Gibbs free energy and the entropy were given according to the formulas [25]

$$H = E + RT \quad (1)$$

$$G = H - TS \quad (2)$$

E is the thermal energy
H is the enthalpy
G is the Gibbs free energy

In order to determine the kinetic parameters of the transformations, we calculated their tautomeric equilibrium constants by using the following relations [24].

$$K_T = \exp(-\Delta G/RT) \quad (3)$$

Where K_T is the equilibrium constant between the tautomers, the gas constant is R is 1.987×10^{-3} kcal.mol^{-3} and the temperature T is 298.15K. The quantity ΔG is the difference between the Gibbs free energies of the given tautomer with respect to stable one. The pK_T values of the studied molecules were calculated by the following equation [25]:

$$pK_T = - \log K_T \quad (4)$$

Calculated total energies (a.u), zero-point vibrational energies (ZPVE) (kcal mol^{-1}), thermal Enthalpy (H) (a.u), thermal free energy (G) (a.u), dipole moment (μ)(debye) enthalpy change (ΔH^0), free energy change (ΔG^0), entropy change (ΔS^0) equilibrium constants (Keq) and pK_T for various tautomers of keto, Enol(Z),and Enol(E) of cathinone for DFT/6-311G (d,p)level presented in table 3 and 4. It was found that (Table.2) cathinone is more stable than other isomers (Z & E), as the energy of the of keto form of cathnione is less than the energy of other enol forms of cathinone (Z & E).As it takes less energy for a compound to it an equilibrium state. Comparison the energies of the Z-isomer and the E–isomer, enol (Z) isomer is less energy than the energy of enol (E) isomer, i.e enol(Z) isomer is more stable than enol(E) isomer.

we can also calculated the equilibrium distribution of the two at room temperature using the formula[26]:

$N_{keto}/N_{enol} = \exp [(-1060)(E_{keto}- E_{keto})$ (5)

Where N_i the number of molecules in a tautomer i, and E is the energy of the tautomer in au. Using this formula we get the equilibrium constant for Keto to enol (Z) is 1.5 x 10^2 and keto to enol (E) is 6.64x 10^4. This is number of keto formed with respect to one enol, which clearly shows that enol (Z) isomer formed and stable.

Thermodynamic calculations of Δ*H* of the isodesmic reaction for keto-enol (Z) are 3.6439 kcal/mol and keto-enol (E) is 7.0067 kcal/mol. This explains the shift in equilibrium to the keto side. It can be seen that the Δ*G* (Table 4) for the keto-enol (Z) system show that 1.4225 kcal/mol, and more positive for keto-enol (E) system shows that 4.2620 kcal/mol, which means that the reaction is non spontaneous and more stable form is enol (Z) isomer. This is explaining the intramolecular hydrogen bond generates a five member ring [27] in enol (Z) isomer. Intramolecular H-bonding is between O8-H17 donor and N11 acceptor of the enol (Z) isomer, but in case of the enol (E) no intramolecular hydrogen bond generate.

Table 1: Optimized parameters Calculated bond lengths in (Å) and bond Angles (^{0})and Dihedral angles (^{0}) of Cathinone for Keto, (Z)-isomer ,(E)- isomer and their TS structures ,using B3LYP/6-311G (d,p) .

Bond length	Keto	Z-Isomer		E-Isomer		Bond length	Keto	Z-Isomer		E-Isomer	
		TS	Enol	TS	Enol			TS	Enol	TS	Enol
C1-C2	1.3813	1.3883	1.3858	1.3906	1.386	C7-O8	1.1914	1.3	1.3493	1.3884	1.4099
C1-C6	1.3923	1.4059	1.388	1.4038	1.386	C7-C9	1.5388	1.4529	1.3296	1.3511	1.3245
C1-H12	1.073	1.0825	1.0745	1.0825	1.122	C9-C10	1.5301	1.513	1.5043	1.5098	1.54
C2-C3	1.386	1.3957	1.3828	1.3939	1.386	C9-N11	1.4515	1.4746	1.4399	1.4167	1.446
C2-H13	1.0751	1.0839	1.0755	1.0846	1.122	C9-H17	1.0829	1.542	2.3211	2.4494	2.4126
C3-C4	1.3832	1.3949	1.3863	1.3933	1.3861	C10-H18	1.0849	1.0943	1.0888	1.0965	1.122
C3-H14	1.0754	1.0843	1.0755	1.0841	1.122	C10-H19	1.085	1.1004	1.0807	1.0918	1.122
C4-C5	1.385	1.3895	1.3819	1.3918	1.386	C10-H20	1.0837	1.0936	1.0895	1.0951	1.122
C4-H15	1.0751	1.0838	1.0755	1.0846	1.122	N11-H21	0.9974	1.0166	1.0017	1.0143	1.0279
C5-C6	1.3901	1.4043	1.3917	1.4042	1.3861	N11-H22	0.9996	1.0108	1.0012	1.0108	1.028
C5-H16	1.0722	1.0819	1.074	1.0838	1.122	O8-H17	2.3573	1.2313	0.9471	0.9616	0.992
C6-C7	1.5089	1.4619	1.4874	1.4792	1.54						
Bond angles (^{0})											
Bond angle	Keto	TS	Enol	TS	Enol	Bond angle	Keto	TS	Enol	TS	Enol
(C2,C1,C6)	120.7479	120.2855	120.5877	120.8579	120.0002	(C6,C7,C9)	122.7361	133.0466	126.8871	126.3639	120.0017
(C2,C1,H12)	120.5723	121.1166	119.6584	120.3227	120.0008	(O8,C7,C9)	118.177	107.8329	121.1637	122.6058	119.9951
(C6,C1,H12)	118.6797	118.5979	119.7453	118.8183	119.9965	(C7,C9,C10)	111.9215	121.8469	126.7557	122.8788	120.0017
(C1,C2,C3)	120.015	119.9591	120.1521	120.4302	120.0002	(C7,C9,N11)	116.3073	114.6173	115.7883	123.7252	119.9955
(C1,C2,H13)	119.856	119.998	119.6928	119.5921	120.0008	(C7,C9,H17)	102.6677	64.8575	53.1314	51.7943	54.9629
(C3,C2,H13)	120.1282	120.0409	120.1525	119.9775	119.9965	(C10,C9,N11)	110.9751	111.6918	117.4194	113.1863	120.0003
(C2,C3,C4)	119.8206	120.2426	119.6327	119.352	120.0016	(C10,C9,H17)	107.1235	140.0653	175.5151	71.7332	65.0395
(C2,C3,H14)	120.1351	119.8945	120.1935	120.3534	119.999	(N11,C9,H17)	106.9818	96.3485	62.7353	166.3422	174.953
(C4,C3,H14)	120.0438	119.8626	120.1712	120.2898	119.9969	(C9,C10,H18)	110.5458	112.1482	109.5816	111.9907	109.503
(C3,C4,C5)	120.0632	120.0013	120.2001	120.3057	119.9982	(C9,C10,H19)	112.648	113.1703	112.763	109.3447	109.4984
(C3,C4,H15)	120.1898	120.0673	120.0559	120.0713	119.9985	(C9,C10,H20)	108.8499	108.9255	111.3536	113.567	109.5015
(C5,C4,H15)	119.7469	119.9307	119.7431	119.6135	120.0008	(H18,C10,H19)	108.0242	108.4653	107.7356	108.2082	109.4983
(C4,C5,C6)	120.6467	120.2416	120.5474	120.9229	119.9982	(H18,C10,H20)	108.794	107.6491	106.8954	106.954	109.3296
(C4,C5,H16)	118.4022	120.0862	120.16	119.4916	120.0008	(H19,C10,H20)	107.8791	106.1733	108.2786	106.502	109.4965
(C6,C5,H16)	120.9353	119.6707	119.2923	119.5588	119.9985	(C9,N11,H21)	113.2286	112.9392	111.3537	113.3954	120.004
(C1,C6,C5)	118.6983	119.2661	118.859	118.0997	120.0016	(C9,N11,H22)	111.6494	114.5799	111.2641	113.7039	119.9958
(C1,C6,C7)	117.1129	119.5903	121.9855	119.6597	119.999	(H21,N11,H22)	107.8481	108.3585	107.2097	109.9012	119.9978
(C5,C6,C7)	124.1681	121.0915	119.118	122.1833	119.9969	(C7,O8,H17)	61.2109	78.8168	106.7022	109.2209	109.5041
(C6,C7,O8)	119.0682	119.0999	111.9336	110.9363	120.0007						

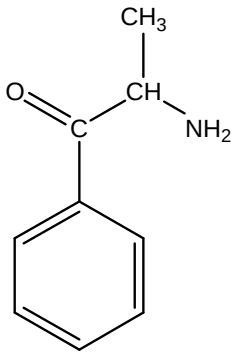
The ratio of the two tautomers is described by the equilibrium constant K_T, (Eq.3). The computed absolute values of $K_T >> 1$ show a large preference for the keto tautomer relative to the enol one (Table 4). In the vapor state, the highest stability is exhibited by the keto tautomer of cathinone. However, the absolute value of K_T strongly depends on the accuracy of the evaluation of the free energy. Table 4 contained the pK_T of the equilibrium constants calculated from the relation (4). Some pK_T were low or high; that determinate the privileged direction of equilibrium. If the pK_T was high, equilibrium moved from right towards the left and when it was low, equilibrium moved from left towards the right. By taking account of all these directions of displacement, we obtained the Keto –

enol (Z) isomer is 1.0428 and Keto – enol (E) 3.1244, which proved to be the enol (Z) is more stable, which explain, intramolecular hydrogen bond generates a five ring member ring. The intramolecular hydrogen bonding is between O8-H17 donor and N11 acceptor of the enol (Z) isomer, but in case of the enol (E) no intramolecular hydrogen bond generate.

The magnitude of the dipole moment is strongly related to the tautomeric stability. The calculated dipole moments of the studied tautomers are listed in Tables 3. The dipole moment values for keto, enol (Z) and enol (E) are 3.0197, 2.3517 and 1.6852 respectively at the B3LYP level. In the gas phase, the highest value of dipole moment is found in case of keto while the lowest dipolar one is enol(E) .The dipole moment order in gas phase is keto > enol(Z) > enol(E).

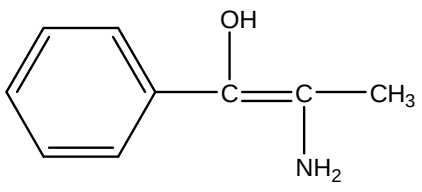
Table 2: Mulliken charges with hydrogens summed into heavy atoms of Cathinone for Keto, (Z)- isomer ,(E)- isomer and their TS structures ,using DFT B3LYP/6-311G(d,p)level.

Atom	Keto	Z-isomer		E-isomer	
		TS	Enol	TS	Enol
C1	0.087602	0.105196	0.028514	0.061041	0.045297
C2	0.010368	0.010935	-0.004999	-0.001905	-0.003914
C3	0.027034	0.038525	0.007010	0.002647	-0.001021
C4	-0.001985	-0.001320	-0.001420	-0.001921	-0.004912
C5	0.026989	0.090451	0.063449	-0.010254	0.004136
C6	-0.140693	-0.183592	-0.075572	-0.071532	-0.070207
C7	0.253697	0.364442	0.212233	0.145391	0.134526
O8	-0.301425	-0.131058	-0.122878	-0.135289	-0.148133
C9	0.008204	-0.293111	-0.096655	0.007191	0.040330
C10	0.077095	0.054717	0.087873	0.059709	0.054561
N11	-0.046888	-0.055183	-0.097555	-0.055078	-0.050663



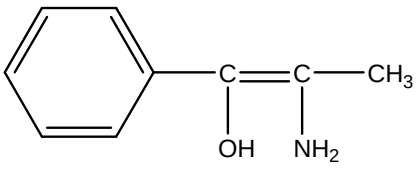
2-amino-1-phenylpropan-1-one (cathinone)

Keto isomer



(E)-isomer

(*E*)-2-amino-1-phenylprop-1-en-1-ol



(Z)- isomer

(*Z*)-2-amino-1-phenylprop-1-en-1-ol

Fig.1. The scheme for the keto and enol tautomerism and geometrical isomerism (E-Z) of Cathinone

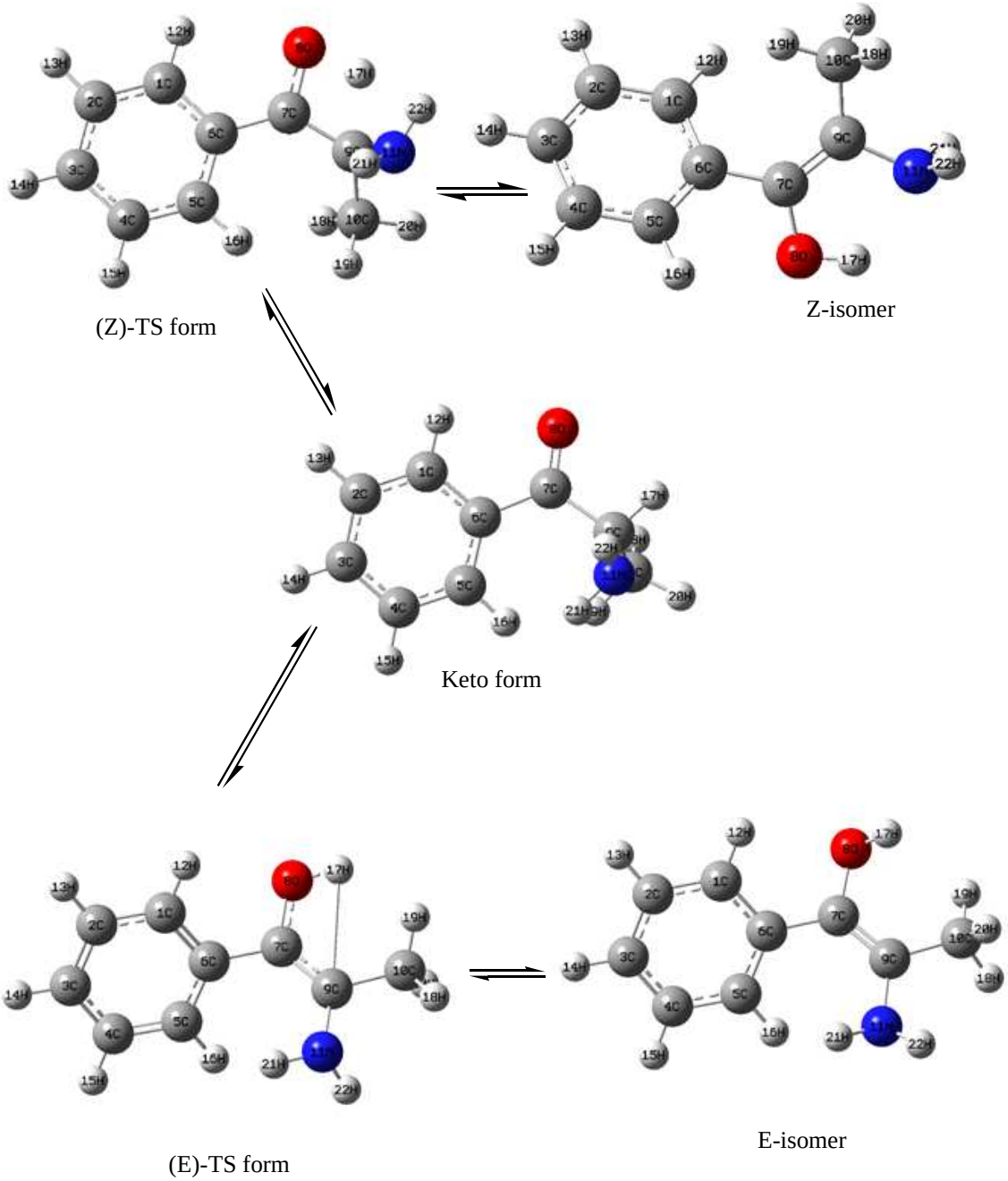


Fig.2. The B3LYP/6-311G (d,p) level of theory , optimized structures of the keto, enol(Z),enol (E) tautomers and their TS structures.

Table 3: Calculated total energies (a.u), zero-point vibrational energies (ZPVE) (kcal mol^{-1}), Thermal Enthalpy (H) (a.u), Thermal Free Energy (G) (a.u), and dipole moment (μ)(debye) for Cathinone for B3LYP/6-311G(d,p)level.

Structure	Total energy	ZPE	H	G	μ
Keto	-479.676515	115.10446	-479.481648	-479.529512	3.0197
Enol(Z)	-479.670430	115.04222	-479.475841	-479.522853	2.3517
TS(Z)	-479.564549	110.73072	-479.376668	-479.424269	3.2114
Enol(E)	-479.664676	114.51107	-479.470482	-479.518328	2.9217
TS(E)	-479.662010	114.22550	-479.468933	-479.515482	1.6852

Table 4: Calculated Enthalpy change (ΔH), Free Energy change (ΔG), Entropy change (ΔS) in equilibrium constants (Keq) and pK_T for Cathinone DFT/6-311G (d,p) level.

	Δ H (kcal/mol)	Δ G (kcal/mol)	Δ S (kcal/mol)	Keq	pK_T
Keto-Enol(Z)	3.643947667	1.422564037	0.007450557	9.060372×10^{-2}	1.042856
Keto-Enol(E)	7.006771077	4.262044524	0.009205858	7.508930×10^{-4}	3.124422

CONCLUSION

The density functional theory (DFT) calculations showed that the keto tautomer is more stable than the enol tautomers (Z&E) in the gas phase, while enol (Z) isomer is more stable than enol (E) isomer. The order of the dipole movements for isomers are Keto > enol (Z) > enol (E). It can be seen that the Δ*G* values for the indicate that the reaction is nonspontaneous and more stable form is enol(Z) isomer, which explain, intramolecular H-bonding is between O8-H17 donor and N11 acceptor of the enol(Z) isomer, but in case of the enol(E) no intramolecular hydrogen bond generate.

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