

Computational and Theoretical Study of Active Species of Bridge Head Isomers of $C_8H_{13}^{+-}$: A DFT Level of Study

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ABSTRACT

The electron density of active Iso-I [Bicyclo (2.2.2) Octane] and Iso-II [Bicyclo (3.2.1) octane] are the fundamental property to reduce the problems in many-body wave functions. The electron density relies on the three spatial coordinates (3N) which can be used to describe the excited states of these molecules. It is difficult to get exact functional of exchange and correlation (except free electrons) of certain physical quantities. The local density approximation (LDA) and local spin density approximation (including electron spin) (LSDA) as well as generalised gradient approximation (to count the non-homogeneity on the exchanges of the true electron density) (GGA) has been used to measure the physical quantity. The theoretical investigations were performed using the Density Functional Theory at B3LYP level of theory at 6-31G* in the Gaussian program.

INTRODUCTION

Prevalence of psychostimulant use is high while abuse of Cocaine compared to other illicit drugs is a growing international public health ^[1]. Cocaine stimulates the central nervous system by blockade of neurotransmitter and induce damage to the cardiovascular systems is widely reported ^[2,3]. Several researches have been involved in understanding the mechanism of action and found that cocaine's additives properties largely depend on its ability to inhibit dopamine ^[4-9]. Although DAT has been a prime focus for the development of medication, still a comprehensive understanding of the mechanism action of cocaine and its tropane analogues at the molecular has been elusive. Studies have reported the synthesis and binding profile of bicyclo [3.2.1] octane core of 3-(biaryl)-8-oxabicyclo [3.2.1]oct-2-ene-2-carboxylic acid methyl esters over the DAT ^[10]. Bicyclo [3.2.1] octane derivatives like 8- azabicyclo [3.2.1] octane are used as a key precursor for the synthesis of medicinally important alkaloids because of its versatile reactivity such as anatoxin-a, epibatidine, epiboxidine 1, pupukeanone and Gibberelline A 12 ^[11].

A series of bicyclo [2.2.2] octane are close structural mimics of the two-key leucine (L690 and L694) is useful in nuclear hormone receptor (NR) and steroid receptor coactivator (SRC) reaction ^[12]. The application of these isomers at these two positions can inhibit the NR-SRC interaction inside the peptide bond. Initially, this is useful for the treatment of cancer ^[12], and bicyclo [3.2.1] octane ring is the ubiquitous skeleton in different big molecules are mainly because of carbo-bicyclo nature with variable functional diversity especially in tri-, tetracyclic, sesqui and diterpenes ^[13]. Several reactions had been performed by using these two molecules as a skeleton structure like 4- substituted bicycle [2.2.2] Octane-1-carboxylic acids ^[13] or 2-carboxylic acids ^[14], bicycle[2.2.2]octane-2,5- dione ^[15], Asymmetric 1,4-bis (ethynyl) bicycle [2.2.2] octane ^[16] etc.

In the present work, we concentrate only on the Bridged-head Rings in the gas phase. Clayden simplifies that bridgehead bicyclic compounds are a bridge of atoms is thrown across from one side of the ring to the other. These compounds are either fully carbocyclic (all carbon) or heterocyclic (having one or more non-carbon atoms), while the characteristics of these rings are always different, even though they appear planar. Due to the geometrical constraint caused by the bridge, no double bonds are formed in most of the bridgehead rings which are known as Bredt's rule ^[17], but with a sufficiently large number of atoms in the ring, this distortions are relaxed and allowing the formations of a double bond at the bridgehead rings ^[18]. The bridgehead rings have two active isomers, where the bridging carbons contain bicyclo [2.2.2] octane and bicyclo [3.2.1] octanes, which are assigned Iso-I and Iso-II respectively. In the present study, *ab initio* density functional theory (DFT) calculations were employed to compare and evaluate the relative stabilities of the active structural isomers through their geometrical parameters, energetic, thermodynamic and thermochemical analysis and compared with the experimental structure.

EXPERIMENTAL SECTION

To calculate geometry and thermochemistry of the active bridgehead isomers at the level of DFT by using various basis sets G09 software package [19]. The molecular structures were drawn with GaussView [20] 5.0 graphics interface. The active iso-I and Iso-II isomers of the electron density were considered as stationary systems, here, the total ground state energy of many-electron systems is a function of the density. The values of bond angle, bond length and dihedral angles are taken from the hybrid method with 6-311G+dp [21]. The important structures of Mulliken charges, highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) HOMO-LUMO, electron densities along with their values are obtained as well as the total value of internal energy, heat capacity and entropy are taken from the calculation of optimised frequency.

DFT determines the physical characteristics of all the molecules and is classified broadly into four categories according to the types of functional dependencies viz., local density approximation (LDA), Gradient Corrected (GC) or generalise gradient approximations (GGA) and local spin- density approximation (LSDA) and Hybrid method [22,23]. LDA method assumes the density of all the molecule is uniform throughout the molecule with the formula of. To calculate geometry and thermochemistry of the active bridgehead isomers at the level of DFT by using various basis sets G09 software package [19]. The molecular structures were drawn with GaussView [20] 5.0 graphics interface. The active iso-I and Iso-II isomers of the electron density were considered as stationary systems, here, the total ground state energy of many-electron systems is a function of the density. The values of bond angle, bond length and dihedral angles are taken from the hybrid method with 6-311G+dp [21]. The important structures of Mulliken charges, highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) HOMO-LUMO, electron densities along with their values are obtained as well as the total value of internal energy, heat capacity and entropy are taken from the calculation of optimised frequency.

DFT determines the physical characteristics of all the molecules and is classified broadly into four categories according to the types of functional dependencies viz., local density approximation (LDA), Gradient Corrected (GC) or generalise gradient approximations (GGA) and local spin- density approximation (LSDA) and Hybrid method [22,23]. LDA method assumes the density of all the molecule is uniform throughout the molecule with the formula of:

$$E_{XC}^{LDA}[n] = \int \varepsilon_{xc}(n) n(\vec{r}) d^3 r$$

and when the spinning of electrons is included, we have the LSDA with the mathematical formula of:

$$E_{XC}^{LDA}[n] = \int \varepsilon_{xc}[n_{\uparrow}, n_{\downarrow}](\vec{r}) d^3 r$$

GC or GGA assumes the non-uniformity of the electron density and has the following formula:

$$E_{XC}^{LDA}[n_{\uparrow}, n_{\downarrow}] = \int \varepsilon_{xc}(n_{\uparrow}, n_{\downarrow}, \nabla n_{\uparrow}, \nabla n_{\downarrow})(\vec{r}) d^3 r$$

While the last one is the hybrid methods which attempt to incorporate the more useful feature from the lower calculations like B3LYP/6-311G+dp, the most commonly used methods have been used in this study. DFT calculation is now more appreciated in the quantitatively accurate electronic structure of dynamic electron correlation and static correlation or non- dynamic correlations than wave function theory (WFT).

The frequency calculation predicts all the thermochemical analysis of the system like thermal energy (E), heat capacity (CV) and Entropy (S) is also given in the output. Entropy is used to calculate the Gibbs free energy from enthalpy. The value of the sum of electronic and thermal energies is same as the internal energy denoted as U ($E = E_0 + E_{trans} + E_{rot} + E_{vib} = E_{elect} + E_{therm}$), Enthalpy of the system is also calculated denoted as H ($H = E + pV = E_{elect} + H_{therm}$), and the Gibbs free energy of the system is denoted as G ($G = H - TS = E_{elect} + G_{therm}$).

The relations of the thermochemical energy of the calculation system obtained from the Gaussian 09 software and the formulae obtained from experimental are shown below:

- (1) Thermal correction to Energy ($E_{therm} = ZPE + E_{trans} + E_{rot} + E_{vib}$),
- (2) Thermal correction to Enthalpy ($H_{therm} = E_{therm} + pV$),
- (3) Thermal correction to Gibbs free energy ($G_{therm} = H_{therm} - TS$),
- (4) Sum of electronic and zero-point Energies ($E_0 = E_{elect} + ZPE$),
- (5) Sum of electronic and thermal Energies ($E = E_0 + E_{trans} + E_{rot} + E_{vib} = E_{elect} + E_{therm}$),
- (6) Sum of electronic and thermal Enthalpies ($H = E + pV = E_{elect} + H_{therm}$),
- (7) Sum of electronic and thermal Free Energies ($G = H - TS = E_{elect} + G_{therm}$).

RESULTS AND DISCUSSION

Optimized Geometry

The optimized structure was obtained by the density functional theory calculation (DFT). The active isomers investigated as shown in **Tables 1 and 2** are Iso-I and Iso-II were optimized while the molecular geometries of inactive isomers of Iso-I and Iso-II are in good agreement with the experimental values of bond length (C-C=1.54 Å to 1.56 Å, C-H=1.09 Å), Bond Angle (C-C-C=101 to 112.09) and dihedral angle (C-C-C-C=0.00 ± 71.47). Iso-I (H₂) have two carbon atoms at the bridgehead, but the removal of hydrogen caused bond breaking between HG, AB and EF because of the distortion and repulsion of the LHS and RHS of the ring, one hydrogen is removed from carbon C (**Figure 1**). One hydrogen is also removed from carbon H (**Figure 1b**). Iso-II (H₁) has one carbon atom at the bridged - connecting from one side of the ring molecule to the other with the asymmetric cyclic ring and the bond between carbon C and D is broken, and the double bond is formed between C and H, unlike inactive isomers.

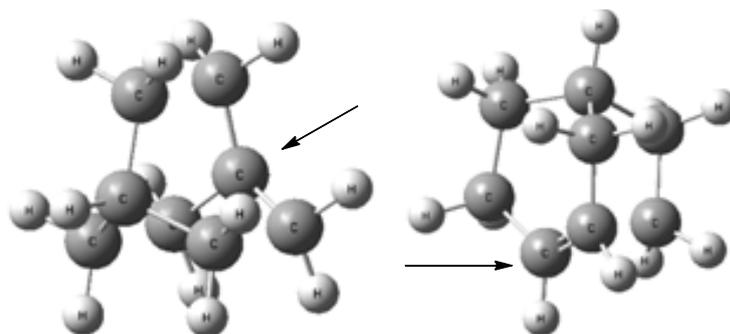


Figure 1. Showing removal of hydrogen from Iso-I (H₂) and Iso-II (H₁).

Bridgehead Rings

There is a removal of cationic hydrogen from the stable hydrocarbons to form unstable isomers, but we are looking for the most predominant hydrogen environment for the most convenient reactions.

Bicyclo (2.2.2) octane (Iso-I)

Here, we have the two hydrogen environments, one hydrogen is removed from the corner carbons and the other is from the centre or common carbons and they are called H₁ and H₂ respectively. In Iso-I, H₂ is more predominant, and the order of stability is H₂>H₁ (**Figure 2**).

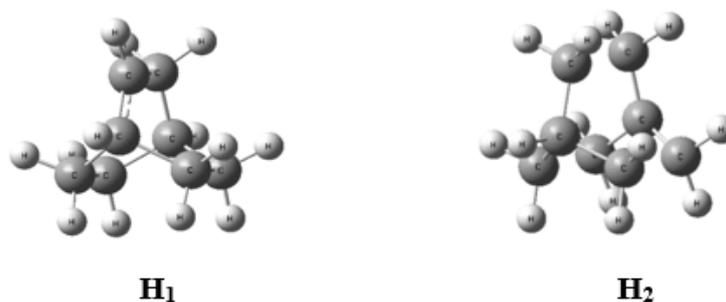


Figure 2. Geometrical Analysis of Selected Isomers of C₈H₁₃⁺.

Bicyclo (3.2.1) octane (Iso-II)

We have four hydrogen environments, and the order of stability are H₁>H₂>H₄>H₃ respectively. The Hartree energies of H₁ and H₂ are almost similar, and their difference is 1.87 Kcals/mol. However, H₃ and H₄ are a little different, and their values are 6.83 and 5.16 Kcals/mol respectively (**Figure 3**).

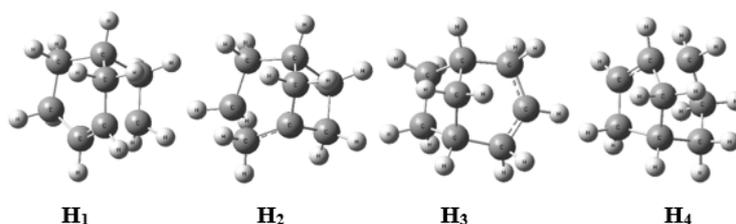


Figure 3. Geometrical Analysis of Selected Isomers of C₈H₁₃⁺.

Bridgehead

In Iso-I, here, the bond length of the non-bonded carbons on the three corners AB, EF and GH are similar, i.e., 1.63 Å, though one hydrogen is removed from the common (or centred) carbon, the symmetrical nature is still conserved. As we see from the bond length of the three corners, this isomer is divided into two parts. On one side of the isomer (A-D-E-H), we have the similar bond length of 1.53 Å between these carbons -AD, DE and DH. On the other side of B-C-G-F, all the bond lengths (BC, CF and CG) are same, i.e., 1.45 Å. Iso-I is exactly symmetrical when viewed at the centre of C and D. The distance between the carbons and hydrogens are 1.08, but the centre carbon D-H is 1.09 (Figure 4a).

In Iso-II, there is a removal of hydrogen from cyclohexane ring, and there is a bond breaking and formations of double bonds. The bond length of AB and BE are surprisingly same, i.e., 1.54 Å, and the bond length of CA and GH are also similar, i.e., 1.50 Å. The other similar bond length is found between DE and BF, and the length of the bond are 1.53 Å each. The bond length of the broken bond lies between C and D, i.e., 1.86 Å (1.5 Å normals) and the new double bond is seen between C and H (1.39 Å). The distance of the non-binding carbon and their bond lengths of BC and FH are 2.41 Å and 2.55 Å respectively. The distance between carbon and Hydrogen at carbon B-H is 1.09 Å, and all the rest of the carbon and hydrogens are 1.08 Å (Figure 4b).

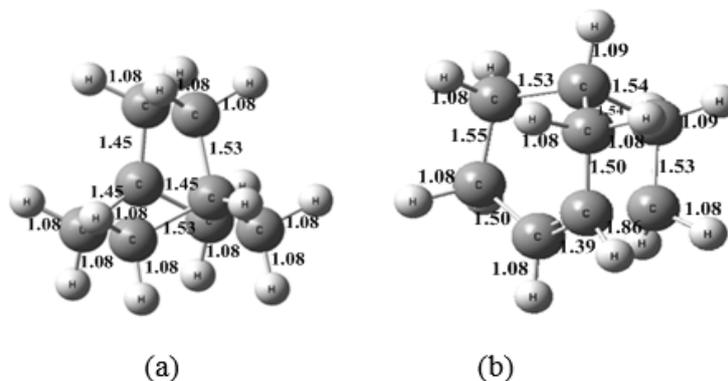


Figure 4a. (a) Bond length of Iso-I (H₂), 4b (b) Bond length of Iso-II (H₁).

Iso-I, as we know that the bond length of this isomer is broken on three points, i.e., AB, EF, and GH. But their symmetrical property can be proved from the bond angle. Here the bond angle of ABC, CFE and CGH are $\angle 98.92$ while the bond angle of BCF, GCB and FCG are $\angle 117.74$, and this clearly shows there is a slight variation in the bond angle because of the removal of one hydrogen from the common carbon 'C'. In contrast, we have a common value of $\angle 109.22$ from the bond angle of EDH, ADE and ADH while DHG and EDH are $\angle 109.51$, which shows both yields very similar results. The entire bond angle follows the real nature of sp^[12] (Figure 5a).

In Iso-II, we have a different number of bond angles ranges between 123.46 to 69.64, and the distance between carbon C and D are broken. Inside cyclohexane $\angle BAC$ and $\angle BFG$ are $\angle 105.02$ and $\angle 111.15$. $\angle ACH$ and $\angle FGH$ are $\angle 120.13$ and $\angle 113.52$. $\angle GHC$ and $\angle FBA$ are $\angle 123.46$ and $\angle 109.37$. Outside the cyclohexane, we have $\angle BED$, i.e., $\angle 107.13$. (Figure 5b).

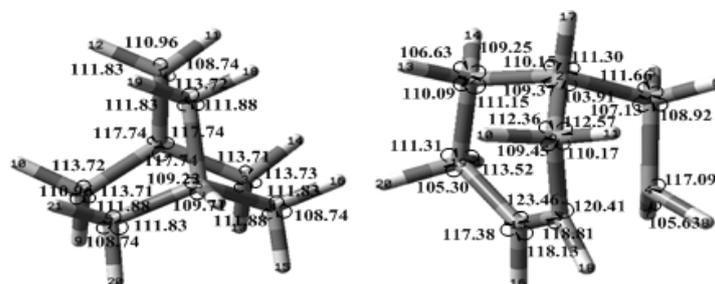


Figure 5a. (a) Bond Angle of Iso-I (H₂), (b) Bond Angle of Iso-II (H₁).

Iso-I have a symmetrical arrangement which can be proved from the dihedral angle in DABC, DEFC and DHGC, we have the same value of 0.37, in ABCF and HGCB, and we have the same value of 75.52. But in FEDA and BADH, the dihedral value is -59.94, and in ABCG and EFCB, we have 75.05 respectively (Figure 6a). In Iso-II, there is no same value of the dihedral angle, in BCDE (10.71) and BCHF (17.91) (Figure 6b). Similarly, in ABFG and ACHG, we have -59.45 and -5.92 respectively. All the details are given in Table 1.

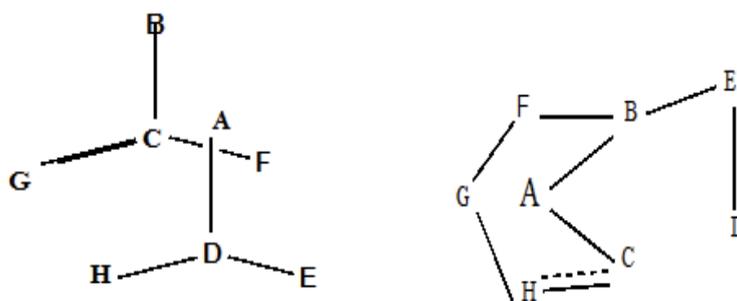


Figure 6a. (a) Dihedral angle of Iso-I (H_2), (b) Dihedral angle of Iso-II (H_1).

Table 1. The optimized geometrical parameters for active **Iso-I** and **Iso-II** showing the bond lengths (Å), bond angles (\angle) and the Dihedral Angles (φ) obtained from the calculated values in 6-311G+**.

S No	Isomers	Bond Length (Å)	Bond Angle (\angle)	Dihedral Angle (φ)
1.		All C-H =1.08 Except D-H=1.09	C-C-C	C-C-C-C
		C-C		
		AB=1.63 EF=1.63 GH=1.63 CD=2.37 AD=1.53 DE=1.53 DH=1.53 BC=1.45 CF=1.45 CG=1.45	ABC=98.92 CFE=98.92 CGH=98.92 BCF=117.74 GCB=117.74 FCG=117.74 EDH=109.22 DHG=109.51 DEF= 109.51 ADH= 109.22 ADE= 109.22	DABC=0.37 DEFC=0.37 DHGC=0.37 ABCF=-75.52 FEDA=- 59.94 HGCB=-75.52 ABCG=75.05 BADH=-59.94 BADE=59.45 EFCB=75.05
2.		All C-H =1.08 Except B-H=1.09	C-C-C	C-C-C-C
		C-C		
		AB=1.54 CA= 1.50 DE=1.53 BE=1.54 CD= 1.86 BF=1.53 CH=1.39 FG=1.55 GH= 1.50 BC=2.41 FH=2.55	BAC=105.02 BED=107.13 CDE=101.00 EBA=103.91 DCA=99.64 EBF=110.55 DCH=69.64 ACH= 120.13 ABF=109.37 FGH=113.52 BFG=111.15 CHG =123.46	BCDE=10.71 BCHF=-17.91 EDCA=-12.60 DEBA=40.91 EBF=63.69 DCHG=-95.42 ABFG=-59.45 ACHG=-5.92 CHGF=15.79 BFGH=17.18 FBAC=67.20 HCAB=-35.00

Table 2. Hartree fock energy and their relative energies of Bridge Head Isomer at the level of B3LYP/6-31Gd, 6-31Gdp, 6-311Gd, 6-311G+dp.

Bridge Head		6-31Gd	R.E	6-31Gdp	R.E	6-311Gd	R.E	6-311G+dp	R.E
			Kcals/mol		Kcals/mol		Kcals/mol		Kcals/mol
1)Bicyclo(2.2.2) Octane (Iso-I)	H_2	-312.3887926	-0.66	-312.4069047	-0.31	-312.4460272	-0.11	-312.463722	0.038
2)Bicyclo(3.2.1) Octane (Iso-II)	H_1	-312.3877427	0	-312.4064165	0	-312.4458469	0	-312.463782	0

The Heat of Formations

These two isomers are not similar in their spatial arrangement, but their energies are nearly identical, and the Hartree calculation is done with the different basis set (B3LYP/6-31Gd, 6-31Gdp, 6-311Gd and 6-311G+dp). Iso- II has a higher value in the highest level of calculation B3LYP/ 6-311G+dp, and their energy difference is 0.038 Kcals/mol with Iso-I. But in all the rest of basis sets, Iso-I has a higher value than Iso-II. When we looked at their arrangement, even though the three bond angles are broken, Iso-I has a symmetrical arrangement as we observe from the geometry it is supposed to be more stable and higher in every corner, in contrast at the highest level, we could able to observe the more stable value of Iso-II. In Iso-II, there is a bond between carbon C and D and double is formed between C and H. The main reason of higher stability of Iso- II may be due to the preservation of cyclohexane, and there will be delocalization of electrons between carbons C-H-G.

Thermochemical Analysis

The thermochemical value of Iso-I and Iso-II are compared by using the thermal energy (E_{tot}), heat capacity (C_{tot}) and entropy (S_{tot}) calculated for the total value of translational, rotational, vibrational and electronics.

The total thermal energy (E_{tot}) of Iso-I and Iso-II are same in electronic, translational and rotational but differed in vibrational and their difference is 0.142 Kcals/mol which means the movement or interactions of all the particles in Iso-I is higher than Iso-II as shown in **Tables 3 and 4**. The amount of energy required to raise the temperature of Iso-II is higher than Iso-I by 0.117 Cals/Mol. The entropy of Iso- II is also higher by 2.768 cal/mol, which indicates that there is more disorder or randomness of the systems at a constant temperature in Iso-II.

The internal energy (E or U) is the total energy of the closed system, and it is the potential energy of the system as a whole due to an external force, excluding the energy of motion (Kinetic energy of the system). The change in internal energy is $\Delta U = q$ (Heat added to the system) $\pm w$ (Plus sign indicates work done on the system and minus sign indicates work done by the system). In these two isomers, Iso-II has higher internal energy than Iso-I, with the value of -195945.400 Kcals/mol and -195945.579 Kcals/mol respectively while their energy difference is -0.179 Kcals/mol. Here the value of q and w are negative as the energy leaves the systems so that the total energy of the system is decreased.

Enthalpy is the sum of internal energy and the product of its pressure and volume. It is denoted by H ($H = E + pV$), the change in enthalpy can be defined as the heat evolved or absorbed in a reaction at constant temperature and constant pressure. The enthalpy of Iso-I and Iso-II are -195944.808 Kcals/mol and -195944.987 Kcals/mol respectively and the difference is 0.179 Kcals/mol. The maximum amount of energy that can be converted into useful work is called Gibbs free energy and can be denoted as G ($G = H - TS$). The value of Iso-I and Iso-II are -195968.517 K/mol and -195969.523 K/mol respectively and their difference is -1.006 Kcals/mol.

In Iso-I (H_2), the dipole moment is 0.7215 Debye, while Zero Point vibrational Energy is 507051.4 (Joules/mol)/ 121.18820 (Kcals/mol) and the calculated molecular mass is 109.10173 amu. The total thermal energy correction (E_{tot}), constant volume molar heat capacity (C_{tot}) and dipole moments calculated at the level of B3LYP/6-311G+ dp were given in **Table 3**. The zero-point energies (E°), thermal energies (E), Thermal Enthalpies (H) and thermal free energies (G) values are given in the **Table 5**.

In Iso-II (H_1) the dipole moment is 1.0534 Debye and Zero Point vibrational Energy is 506079.3 (Joules/mol)/ 120.95585 (Kcals/mol). The total thermal energy correction (E_{tot}), constant volume molar heat capacity (C_{tot}) and dipole moments calculated at the level of B3LYP/6-311G+dp are given in **Table 4**. The molecular mass is 109.10173 amu. The zero-point energies (E°), thermal energies (E), thermal enthalpies (H) and thermal free energies (G) values are given in the **Table 5**.

Table 3. The total thermal energy corrections (Etot), Constant volume molar heat capacity (Ctot) and Dipole moment (D) of active Iso-I.

ISO-I	Etot	Ctot	Stot	Dipole moment (Debye)
	(Kcals/mol)	(Kcals/mol)	(Cals/Mol)	
Electronic	0	0	0	
Translational	0.889	2.981	39.978	
Rotational	0.889	2.981	25.312	
Vibrational	123.81	23.026	14.234	
Total	125.588	28.988	79.524	0.7215

Table 4. The total thermal energy corrections (Etot), Constant volume molar heat capacity (Ctot) and Dipole moment (D) of active Iso-II.

ISO-II	E_{tot}	C_{tot}	S_{tot}	Dipole moment (Debye)
	(Kcals/mol)	(Kcals/mol)	(Cals/Mol)	
Electronic	0	0	0	
Translational	0.889	2.981	39.978	
Rotational	0.889	2.981	27.472	2.5627
Vibrational	123.668	23.143	14.843	
Total	125.446	29.105	82.292	

Table 5. Zero point energies (E_0), thermal energies (E), thermal enthalpies (H), thermal free energies (G) and Hartree values which is converted into Kcals/mol.

ISOMER	E_0	E	H	G
Iso- I (H_2)	-312.270596	-312.263586	-312.262642	-312.3004
Iso- II (H_1)	-312.271026	-312.263872	-312.262928	-312.302

CONCLUSION

Several research in the past had developed potential medication for cocaine abuse especially effort has been invested for synthesis and biological evaluation of cocaine compounds. The most widely investigated oxatropanes. In the present study, den-

sity functional theory calculations were employed to investigate the structural characteristics of two active isomers (Iso-I and Iso-II) at B3LYP / 6-311G level. The calculations indicate that Iso-II is more stable than Iso-I, while the most stable isomers confirms the higher internal energy. The quantum chemical calculation offers accurate value of the partition function and related thermodynamic properties. The data related to these isomers may further assist in future studies addressing structural modifications.

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