Computational Study of Frontier Orbitals, Chemical Reactivity and Molecular Electrostatic Potential Surface of Carbamazepine

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ABSTRACT
On the basis of theoretical calculations using density functional theory at 6-31++G(d,p)/B3LYP level in vapour and water phase, frontier orbitals and molecular electrostatic potential surface of carbamazepine molecule have been investigated. On the basis of HOMO-LUMO analysis, global reactivity descriptors viz. chemical potential, electrophilicity power, chemical hardness, softness, electronegativity of the carbamazepine molecule have been evaluated in both the phases. Thermodynamic parameters viz. specific heat, enthalpy and entropy of the title molecule calculated at same level of theory are also reported.

Keywords
Carbamazepine, MEP, DFT, Molecular orbitals

1. INTRODUCTION
Carbamazepine is a medication used to treat epilepsy, seizures and nerve pains such as diabetic neuropathy and trigeminal neuralgia. Its molecular formula is $C_{15}H_{12}N_2O$ and molar mass is 236.269 g/mol. It acts by stabilizing the inactive state of voltage gated sodium channels. It is also a GABA receptor antagonist. The drug has been modeled by Clare et al using Density Functional Theory at B3LYP/6-31G (d,p) level both as a single molecule and a dimer[1]. Carbamazepine polymorphs were also studied by Wojciech et al [2] both experimentally and theoretically. We have employed DFT at 6-31++G(d, p) /B3LYP level[3-6] for the title molecule to investigate frontier orbitals and molecular electrostatic potential surface, global reactivity descriptors and thermodynamic parameters of carbamazepine in vapour and water phase using Gaussian 09 Revision C.01 program package[7].

2. MOLECULAR ELECTROSTATIC POTENTIAL SURFACE
Molecular electrostatic potential (MEP) map of the title molecule was calculated at B3LYP/6-31++G(d,p) level of DFT to study its electron distribution. It provides a visual method to understand the relation between structure and activity of the molecule. It is used to identify electrophilic and nucleophilic sites of a molecule. It is the resultant of energy of interaction of point positive charge with nuclei and electrons of molecule. Negative electrostatic potential corresponds to attraction of proton by concentrated electron density in molecule (red) and positive electrostatic potential corresponds to repulsion of proton by atomic nuclei in the regions of low

electron density (blue). As can be seen from Fig. 1, oxygen atom has maximum electron density as the region around it appears red while for the rest of molecule, difference in electronegativity is not great as indicated by green and yellow color in MEP.

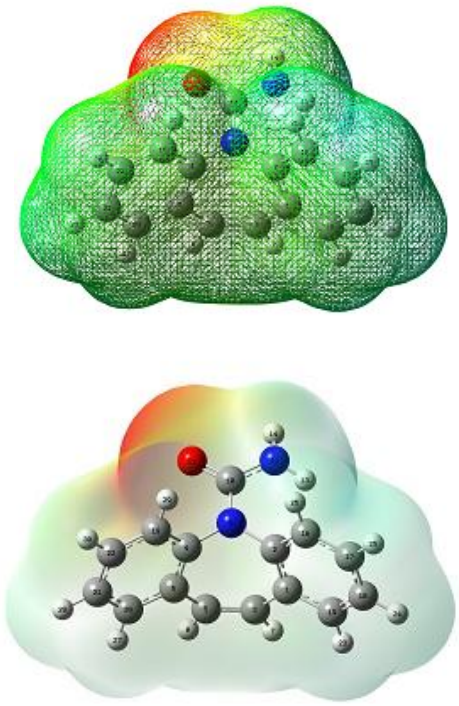


Fig 1: Molecular electrostatic potential surface of carbamazepine

3. FRONTIER ORBITAL ANALYSIS
The main orbitals responsible for the reactivity of a molecule are highest occupied molecular orbital (HOMO) which can donate electrons and the lowest unoccupied molecular orbital (LUMO) which can accept electrons and are called frontier orbitals. The energy difference between HOMO and LUMO is called energy gap. Higher the energy gap of a molecule, more stable the molecule and vice versa. Energies of frontier orbitals and energy gap of carbamazepine calculated in vapour phase and water using 6-31++G(d,p) basis set and B3LYP/DFT theory are listed in Table 1. As can be seen from Table 1, the energy gap in case of carbamazepine in vapour phase is 0.16208 eV while in case of water it comes out to be 0.16381 eV. Thus, a higher energy gap is obtained using water as solvent. This also indicates eventual charge transfer interaction taking place in molecule. The relatively small value of energy gap indicates that electrons can be easily excited with incident radiation of low energy.

Table 1. Calculated energies of frontier orbitals of carbamazepine calculated with 6-31++G(d,p)/B3LYP level of DFT in vapour phase and in water.

Orbital	Energy (eV) Vapour	Energy (eV) Water
HOMO	-0.22594	-0.22868
LUMO	-0.06386	-0.06487
Energy gap	0.16208	0.16381
HOMO -1	-0.24606	-0.25277
LUMO +1	-0.03477	-0.03492
Homo-1-Lumo+1 gap	0.21129	0.21785

HOMO, LUMO, HOMO-1 and LUMO+1 in vapour phase and water are pictorially represented in Fig.2. Green and red color in the plots denotes negative and positive phase respectively. LUMO is largely distributed over benzene rings and azepine while HOMO is somewhat distributed over carboxamide group along with the benzene rings and azepine. It can be seen from the figure that charge density is shifting from one portion of the molecule to the other. Consequently, the transition from HOMO to LUMO implies transfer of electrons from carboxamide group to the benzene rings and azepine of molecule. It can also be seen from Fig. 2 that positive and negative regions in frontier orbitals of carbamazepine in vapour phase and water differ slightly from each other.

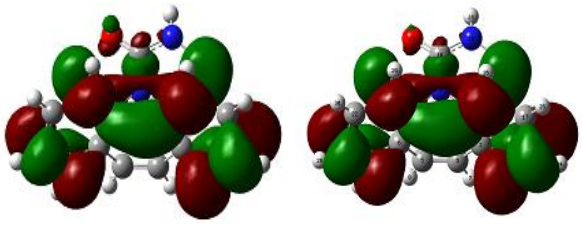
4. CHEMICAL REACTIVITY

Chemical potential μ and chemical hardness η of a molecule can be described in terms of ionisation energy and electron affinity which by using Koopman's theorem[8] can be replaced by energies of HOMO and LUMO by the following equations :

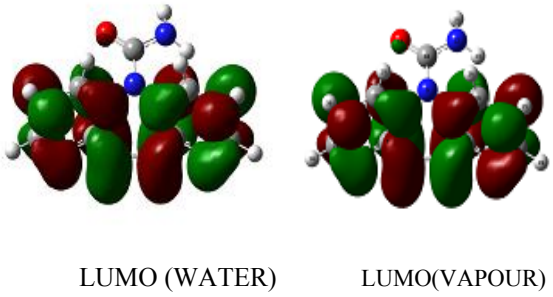
$$\mu = -\frac{1}{2}(E_{HOMO} + E_{LUMO}) = -\chi \quad (1)$$

$$\eta = \frac{1}{2}(E_{LUMO} - E_{HOMO}) \quad (2)$$

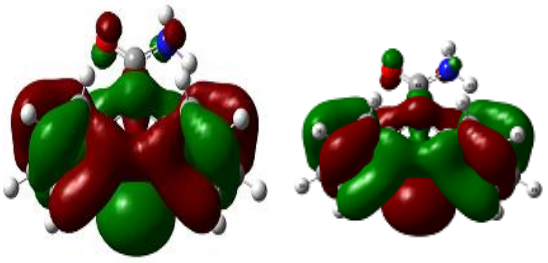
Both the above parameters along with electronegativity χ are important descriptors of reactivity of a molecule. The former one represents pattern of charge transfer in ground state of molecule while latter one is related with its stability. The values of these parameters calculated for title molecule in vapour phase and water using 6-31++ G(d,p) /B3LYP level of DFT are listed in Table 2. Global electrophilicity index ω [9] which indicates the stabilization in energy when the system acquires additional electronic charge from environment ΔN_{max} ($-\frac{\mu}{\eta}$) is defined in terms of chemical potential and chemical hardness as



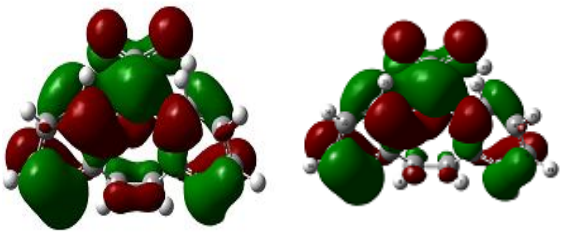
LUMO+ 1(WATER) LUMO+ 1(VAPOUR)



LUMO (WATER) LUMO(VAPOUR)



HOMO(WATER) HOMO(VAPOUR)



HOMO-1(WATER) HOMO-1(VAPOUR)

Fig 2: Molecular orbitals of carbamazepine calculated with 6-31++G(d,p)/B3LYP/DFT in vapour phase and in water.

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

Both the above reactivity descriptors are also listed in Table 2 along with the value of softness σ which is also related with stability of molecule and is defined as:

$$\sigma = \frac{1}{2\eta} \quad (4)$$

Table 2. Global reactivity descriptors of carbamzepine calculated with 6-31++G(d,p)/B3LYP level of DFT in vapour phase and in water

Parameter	Value (eV) Vapour	Value (eV) Water
χ	0.1449	0.146775
μ	-0.1449	-0.146775
η	0.08104	0.081905

σ	6.169412055	6.1046334168
ω	0.1295410291	0.1315115109
ΔN_{max}	1.788005923	1.7920151395

In the context of QSAR, the values of these global reactivity descriptors are of great interest in studying drug receptor interaction. Here we can see from Table 2, electrophilicity index increases as we go from vapour to water phase. Also, hardness comes out to be more in case of carbamazepine molecule in water which indicates carbamazepine molecule is more stable in water.

5. THERMODYNAMIC PARAMETERS

Thermodynamic study of carbamazepine molecule considering it to be at a temperature of 298.15 K and 1 atm pressure was carried out both in vapour and water phase using same level of DFT. The calculated thermodynamic parameters viz. heat capacity, entropy, enthalpy, zero point vibrational energy, rotational constants and rotational temperatures are listed in Table 3.

Table 3. Thermodynamic parameters of carbamazepine in vapour and water phase using 6-31++G(d,p)/B3LYP/DFT

Thermodynamic Parameter	Value/Vapour	Value/Water
Enthalpy (kcal/mol)	157.629	157.505
Specific heat (cal/molK)	56.775	56.867
Entropy (cal/molK)	116.947	116.793
Zero point vibrational energy (kcal/mol)	148.91871	148.77498
Rotational temperature (K)	0.3326 0.01764 0.01475	0.03322 0.01755 0.01502
Rotational constant(GHz)	0.69307 0.36746 0.30724	0.69212 0.36566 0.31287

As can be seen from Table 3, in case of carbamazepine molecule as we go from vapour to water phase using same level of DFT, enthalpy and entropy decreases by small amount while specific heat increases. The above listed thermodynamic parameters can be used to acquire more information of carbamazepine molecule.

6. CONCLUSIONS

In the present work, molecular electrostatic potential and frontier orbitals of carbamazepine molecule in vapour and water phase were studied. From MEP, we came to know the electrophilic sites of the molecule. These sites give information about the possible regions for inter and intramolecular hydrogen bonding. Analysis of frontier orbitals were also carried out and higher energy gap is obtained using water as solvent as compared to vapour phase. The HOMO-LUMO energy gap explains the eventual charge transfer within the molecule. The global reactivity descriptors of the title molecule were calculated along with the thermodynamic parameters. This study will help in correlating the biological properties of the title molecule with its structure and studying drug receptor interaction.

7. REFERENCES

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