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Theoretical Study of the Absorption Spectra of Tolperisone

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ABSTRACT

Density functional theory (DFT) and Time dependent density functional theory (TDDFT) calculations have been carried out to study the electronic structure and the UV absorption spectra of Tolperisone. The UV spectra have been investigated with inclusion of solvent effect. The B3LYP functional with cc-pVDZ basis sets have been used for geometry optimization and also to compute absorption energies. The solvent effects have been included using the polarizable continuum model (PCM). The vertical absorption energies both in gas phase and in polar solvents such as water, methanol and ethanol were computed. The absorption maximum both in gas phase and in polar solvents is discussed in terms of electrostatic interaction energy, oscillator strength and dipole moment.

Keywords: DFT; TDDFT; cc-pVDZ; PCM; Tolperisone.

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INTRODUCTION

Tolperisone (TOL) is chemically 2-methyl-1-(4-methylphenyl)-3-(1-piperidyl) propan-1-one with a molecular formula $C_{16}H_{23}NO$ and molecular weight of 245.36 gm/mol. It is a centrally acting muscle relaxant drug that is mainly used for treating muscle spasticity of neurological origin and painful muscle spasms due to rheumatologic conditions. Besides being an effective antispastic agent,[1,2] TOL also has analgesic activity in rodents[3] and in humans.[4] It possesses relatively few side effects in humans.[5] Literature survey reveals UV spectrophotometry[6] methods for determination of TOL with other drugs in combination.

The density functional theory (DFT)[7] with B3LYP[8,9] functional combined with cc-pVDZ[10-12] basis sets are most usefull to optimize the geometries of molecules. The Time-Dependent Density Functional Theory (TDDFT)[13-15] has been used to simulate the electronic absorption spectra of free molecules. The calculated excitation energies are well agreed with experimental data for various compounds. Moreover, the inclusion of solvent effect *via* a PCM[16-19] model tends to change the excitation energies, due to a stabilization of the lowest unoccupied molecular orbitals (LUMO). Thus, the location of the first absorption band and the energy of the highest occupied molecular orbitals (HOMO) were used as parameters to evaluate the absorption maximum (λ_{max}). The absorption maximum is one of the important parameter of the UV spectrophotometric methods in pharmaceutical formulations especially in quantitative estimation.[20-25]

In this work, the absorption maxima of TOL both in gas phase and in polar solvents such as ethanol, methanol and water are computed using the DFT/TDDFT method.

Computational Details

TOL was modeled using Avogadro.[26] The ground state geometry was optimized using DFT/B3LYP hybrid functional with cc-pVDZ basis sets. The effect of the solvents (ethanol, methanol and water) were added using the polarizable continuum model (PCM) of solvation. The optimized geometries are utilized to get the frontier orbitals and to carry out the time dependent density functional theory (TDDFT) studies. λ_{max} of TOL is calculated at the level of TDDFT/cc-pVDZ. All calculations are performed using GAMESS-US software suit.[27,28] Molecular orbitals were plotted using wxMacMolPlt[29] and UV spectra were plotted using Gabedit.[30]

RESULTS AND DISCUSSION

The optimized structure of the TOL has non-planar geometries, as can be seen in Figure 1.

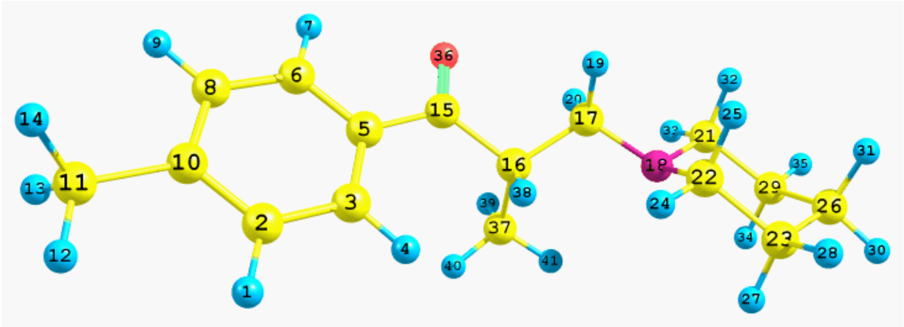

Figure 1. Optimized structure of TOL, Yellow-C, Cyan-H, Red-O and Magneta-N.

Table 1 list the various angles of piperidyl ring which confirms the chair conformation. Plane of the benzene ring C2,C3,C5,C6,C8,C10 is twisted by 177.29° from N18. Figure 2 displays the HOMO and LUMO, both shows π-character. LUMO are localized on C2,C5,C8,C10,C15,C16 and O36, where as HOMO are localized on C2,C3,C6 and C8. This is desirable and leads to the intra-molecular charge separation upon excitation (push-pull effect). The dipole moment of the free TOL molecule is 2.746 Debye and it increased to threefold in the exited state. The interaction energy between TOL with solvent molecules (second column of Table 2) is negative in all solvents. The excited state dipole moment of TOL molecule and the total dipole moment of the system are increased (third and fourth column of Table 2). The change in electronic charge distribution between HOMO and LUMO is also indicative of a large dipole moment and is the possible reason for the increase in oscillator strength (fourth column of Table 3) for the HOMO → LUMO transition in polar solvents. The large dipole moment of TOL molecule in the excited state is additionally stabilised by polar solvent molecules that leads to the decrease in the excitation energy and the corresponding red shift of the spectral maximum.

Table 1. Angles formed in piperidyl ring

Sl. No	Atoms	Angle(°)
1	n18-c21-c29	111.27
2	n18-c22-c23	111.47
3	c21-c29-c26	111.00
4	c22-c23-c26	110.85
5	c23-c26-c29	110.08

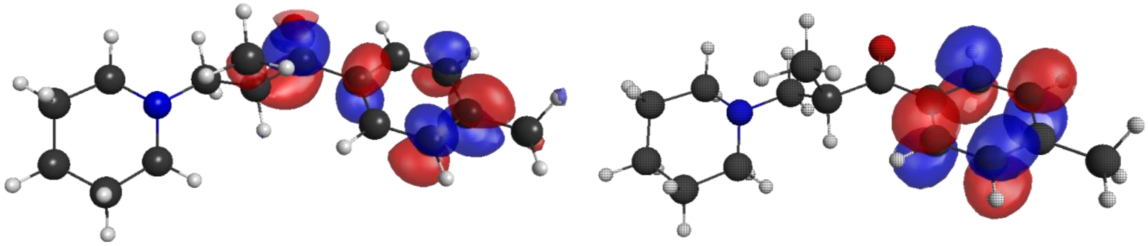

Figure 2. The Molecular orbitals of TOL. LUMO (top) and HOMO (bottom).

Table 2. Electrostatic interaction energy, ground state and excited state dipole moments (D and D*) of TOL molecule in isolated state and in polar solvents, and total dipole moment (D_T and D_T*) of solvated system.

Isolated state/ Solvent	Electrostatic interaction energy (kCal/mol)	Ground state		Excited state	
		D (Debye)	D_T (Debye)	D* (Debye)	D_T* (Debye)
Isolated state		2.746		9.806	
Water	-5.15	3.999	0.187	20.134	20.968
Methanol	-5.01	3.966	0.232	19.992	20.800
Ethanol	-4.94	3.946	0.261	19.910	20.705

The computational UV absorption spectra of TOL in gas phase and in polar solvents are shown in the Figure 3. Spectra show a similar profile in all phases; they present intense bands in polar solvents than in gas phase. The spectra show absorption energies corresponding to the λ_{max} of 349.15, 348.96 and 348.76 nm in water, methanol and ethanol, respectively. In isolated state, the spectrum presents the absorption peak at 342.50 nm. It can also be observed that the λ_{max} is nearly equal in polar solvents. (Table 3 and Figure 3.).

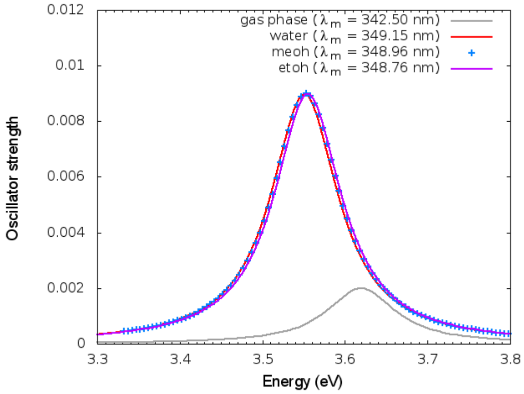

Figure 3. Calculated UV absorption spectra of TOL.

Table 3. λ_{max} corresponding to TDDFT absorption energy (E) and oscillator strength (*f*) of TOL.

Isolated state/ Solvent	λ_{max} (nm)	E (eV)	*f*
Isolated state	342.50	3.620	0.002
Water	349.15	3.551	0.009
Methanol	348.96	3.553	0.009
Ethanol	348.76	3.555	0.009

CONCLUSIONS

In this study UV absorption energy of TOL in isolated state and in polar solvents has been carried out using DFT/TDDFT *via* the PCM model for solvation. From the results, some parameters such as excitation energy, oscillator strength, electrostatic interaction energy, dipole moment of TOL have been chosen to evaluate λ_{max}. Absorption energy calculation shows red shift of λ_{max} in the presence of polar solvents. The absorption intensity of TOL molecule in gas phase is considerably lesser as compared with the absorption intensities in polar solvents. It has been observed that the λ_{max} found to be nearly equal in ethanol, methanol and water.

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