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Quantum-Chemical and Solvatochromic analysis of solvent effects on the Electronic Absorption Spectra of Some Benzodiazepine Derivatives

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ABSTRACT

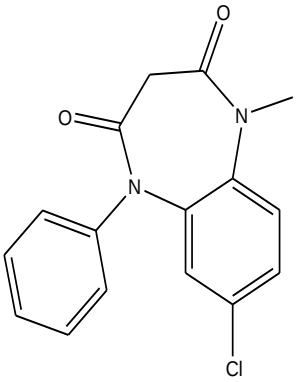
The solvatochromic behaviour of two ketonic derivatives of benzodiazepine namely 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione (Clobazam®) and 5,(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepine-2-one (Clonazepam®) were analysed in some selected solvents of different polarities using UV-Visible spectroscopy and DFT computational techniques. The solute-solvent interactions were evaluated by means of Kamlet-Taft's Linear Solvation Energy Relationship (LSER) concept. The results show that electronic absorption properties of the compounds depend on the solvent polarity and both specific and non-specific interactions between solute and solvent. Also, the spectral properties show satisfactory correlation with solvatochromic parameters (α, β and π). The plot of $\bar{\upsilon}_{max}$ calculated against $\bar{\upsilon}_{max}$ observed in the representative solvents gives a good linear regression value of R^2=0.998.The results of Frontier Orbital calculations showing the differences between HOMO and LUMO of the ground states and various excited states of Clobazam® and Clonazepam® are -5.15eV and -4.20eV respectively and both are in good agreement with the most important transitions observed in the two compounds.

Keywords: Solvatochromic; Benzodiazepine; Linear solvation energy; Frontier orbital calculations; solvent polarity

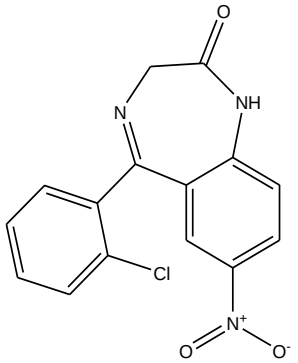
INTRODUCTION

The Benzodiazepines represent one of the most widespread classes of drugs used primarily in the treatment of psychiatric disorders, anxiety and insomnia [1-2]. Some of benzodiazepines are widely used as anti-depressive and sedative drugs and also as anti-epileptic drugs [3-4]. In some cases it can be useful as an adjunct in the treatment of refractory epilepsies or as anti-alcoholic therapy [5-7]. Of the many drugs in this class, only a few are used to treat epilepsy; they include: Clobazam® (namely 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione) and Clonazepam® (5,(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepine-2-one) [8-9]. Clobazam® is a 1, 5-benzodiazepine, which implies that its diazepine ring has nitrogen atoms at the 1 and 5 positions (instead of the usual 1 and 4)[10] as shown in figure 1.

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7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione
(Clobazam®)



5,(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepine-2-one
(Clonazepam®)

Fig. 1. The molecular structures of the investigated benzodiazepine compounds.

The types of biological activity exhibited by a particular drug does not depend only on its chemical/electronic structure but are substantially influenced by the nature and strength of its interactions with the solvent environment. Therefore, the knowledge of these interactions which commonly manifest through the electronic absorption spectra can lead to more accurate predictions of the types and intensities of transitions occurring in the studied drug. The methods that are most frequently applied for this purpose are UV-visible a well as DFT calculations [11-12].

The solvent effects on the electronic spectra known as solvatochromism, is exhibited as changes in absorption band frequencies governed by the physical properties of the solvent such as refractive index, dielectric constant, polarizability, etc. and it is independent of the chemical nature of the solvent [13]. These changes arise from either specific (e.g., hydrogen bonding, proton transfer, intramolecular charge transfer (ICT) or non-specific (dielectric enrichment) interactions with media.

Quantitative assessment of different types of solvent-solute interactions can be interpreted by means of linear solvation energy relationship (LSER) as reported by Kamlet-Taft equation [14-15].

$$\tilde{\upsilon} = \tilde{\upsilon}_o + s\pi^* + b\beta + a\alpha \qquad (1)$$

where π^* is a measure of solvent dipolarity/polarizability which measures the ability of the solvent to stabilize a charge or dipole by virtue of its dielectric effect, α is a measure of the solvent hydrogen bond donor (HBD) acidity, β is a measure of solvent hydrogen bond acceptor (HBA) basicity, $\tilde{\upsilon}_o$ is the regression value of the solute property in reference solvent (cyclohexane or in vacuum), $\tilde{\upsilon}$ is solute property such as wavenumber of maximum absorption in the UV-visible spectrum. The multi-linear regression coefficients *s*, *b* and *a* in Equation (1) measure the relative susceptibilities of the solvent dependent solute property (absorption frequency) to the indicated solvent parameters.

The use of quantum-chemical calculations to determine the optimal energies, electronic transitions, HOMO and LUMO frontier orbitals, etc. has been widely accepted by the chemistry community as a reliable and effective approach. Therefore, theoretical computation of the spectra of the drugs

under investigation are essential to get a quantitative understanding of the ground and excited state properties and their polarizabilities [12]

In the present study, the effects of solvents on electronic absorption spectral properties of two benzodiazepine derivatives (namely: Clobazam® and Clonazepam®) were investigated in polar protic, non-polar and polar aprotic solvents, and the spectral properties were correlated with solvatochromic parameters in order to evaluate the contribution from HBD, HBA and dipolarity/polarizability to the solute-solvent interaction. Lastly, the optimal energies, electronic transitions, HOMO and LUMO frontier orbitals were calculated theoretically at the DFT/B3LYP/6-31G** level of theory with full geometry optimization.

SPECTOSCOPIC MEASUREMENT AND THEORETICAL METHOD

Clobazam® and Clonazepam® were products of Sigma-Aldrich Chemical Co. and were used without further purification. Methanol, ethanol, 1-butanol, cyclohexane, n-hexane, acetone, acetonitrile, chloroform and DMSO purchased from the British Drug House Ltd. are spectro-quality grade and were used without further purification. The solvent polarity parameter constants are given in Table 2 [14].

Electronic absorption spectra were measured at room temperature using a Schimadzu UV-1650 double beam spectrophotometer coupled with UV-probe® 2.31 version, operated in the wavelength region of 200–500 nm at a concentration range of 10^{-5}-10^{-6} mol dm^{-3}. The quartz cells used were of 1.00 cm in optical path. The other experimental conditions had been described previously [16]

The ground state equilibrium geometries of 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione (Clobazam®) and 5,(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepine-2-one (Clonazepam®) were fully optimized at the DFT level using the B3LYP hybrid functional with the 6-31G(d,p) basis set. The UV absorption energies of the studied drugs were calculated from the optimized geometry in the ground state S_o by TD-DFT/6-31G (d,p) theory method in methanol, ethanol, acetonitrile and DMSO. The frontier molecular orbitals and HOMO-LUMO energy gaps of the optimized structures of these studied drugs were also calculated with the same method. All calculations were performed using Spartan 14 software [17] implemented on an Intel-Core ™ i5-2350 M CPU, 2.30 GHz computer.

RESULTS AND DISCUSSION

Spectral frequency shift

Table 1 shows the values of absorption maxima of both Clobazam® and Clonazepam® in the representative solvents. The electronic absorption spectra of Clobazam show three major absorption bands in methanol, acetonitrile, chloroform and cyclohexane (Figure 2).

The $S_o \rightarrow S_1$ transitions appeared at 34965 cm^{-1} in methanol, 34843 cm^{-1} in acetonitrile, 35211 cm^{-1} in chloroform and 35461 cm^{-1} in cyclohexane. The $S_o \rightarrow S_2$ transitions appeared at 43103 cm^{-1} in methanol, 42918 cm^{-1} in acetonitrile, 43478 cm^{-1} and 43860 cm^{-1} in chloroform and cyclohexane respectively. The $S_o \rightarrow S_3$ transition occurs at 47619 cm^{-1}, 46948 cm^{-1} and 48077 cm^{-1} in methanol, acetonitrile and cyclohexane respectively. Similar trends were observed for the $S_o \rightarrow S_1$ and $S_o \rightarrow S_2$ transitions in the electronic absorption spectra of clonazepam as shown in figure 3

From the spectra, it is evident that the transitions are red-shifted in polar solvents relative to non-polar in agreement with the

Baylis theory of solvent polarization [18-20]. The red shift of the absorption bands due to increased solvent polarities denotes the increased solvent stabilization of the excited state relative to the ground state. This observed trend suggest the presence of $\boldsymbol{\pi \rightarrow \pi^*}$ Intramolecular Charge Transfer (ICT) transition within the benzene ring and the fused diazepine ring. Also, it is possible to suggest that the presence of specific solute-solvent interaction such as intermolecular hydrogen bonding (between the solute and solvent molecules) have contributed to spectral frequency shift.

Multiple Linear Regression Analysis

The correlation of the spectroscopic data was evaluated by means of Kamlet –Taft's expression (equation 1) and solvatochromic parameters constants α, β and π* using Linear Solvation Energy Relationship (LSER). The solvent polarity parameter constants [14] are shown in Table 2. The fitted regression values of coefficients $\bar{\upsilon}_o$, *s*, *b*, and *a* at the 95% confidence level are presented in Table 3. The degree of success of equation (1) is shown in figure 3 by means of plot of $\bar{\upsilon}_{max}$ calculated against $\bar{\upsilon}_{max}$ observed in the representative solvents (R^2=0.998). From the data presented in Table 3, the negative signs in the values of coefficient *s* and *b* show the significant roles play by solvent dipolarity/polarizability and hydrogen-bond acceptor (HBA) basicity respectively in the bathochromic shift of the two investigated compounds. This suggests the stabilization of the electronic excited state relative to the ground state. Normally, the bathochromic shift happens when the dipole moment of the probe (Clobazam and clonazepam in the present case) increases during the electronic transition (i.e. the ground state dipole moment μ_g < excited state dipole moment μ_e), and the excited state is formed in a solvent cage of already partly oriented solvent molecules [18, 21].

Table 1. Absorption maxima of the investigated compounds in the selected representative solvents

Compounds and Electronic transitions	**methanol**		**cyclohexane**		**acetonitrile**		**chloroform**	
	$\bar{\nu}_{max}\,(cm^{-1})$	ε_{max} (x10^3) M^{-1} cm^{-1}	$\bar{\nu}_{max}\,(cm^{-1})$	ε_{max}(x10^3) $M^{-1}cm^{-1}$	$\bar{\nu}_{max}\,(cm^{-1})$	ε_{max} (x10^3) M^{-1} cm^{-1}	$\bar{\nu}_{max}\,(cm^{-1})$	ε_{max} (x10^3) $M^{-1}cm^{-1}$
Clobazam								
$S_0 \rightarrow S_1$	34965	1620	35461	978	34843	1800	35211	985
$S_0 \rightarrow S_2$	43103	4167	43860	2565	42918	5100	43478	2565
$S_0 \rightarrow S_3$	47619	3167	48077	1932	46948	3840	-----	----
Clonazepam $S_0 \rightarrow S_1$	32467	1210	32895	1155	32258	1250	32680	1165
$S_0 \rightarrow S_2$	40650	590	41322	549	40323	630	40984	552

Table 2. solvent polarity parameters [14]

Solvents	π*	β	α
Methanol	0.60	0.66	0.98
Ethanol	0.54	0.75	0.86
1-Butanol	0.47	0.84	0.84
n-Hexane	-0.11	0	0
Cyclohexane	0	0	0
Chloroform	0.53	0.10	0.20
Acetone	0.62	0.48	0.08
Acetonitrile	0.66	0.40	0.19
DMSO	1	0.76	0

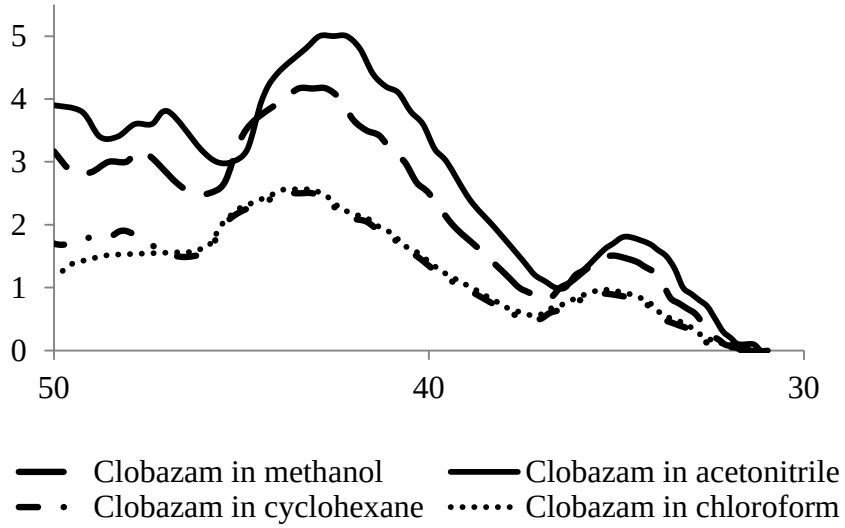


Fig. 2. UV-visible absorption spectra of Clobazam® in the representative solvents.

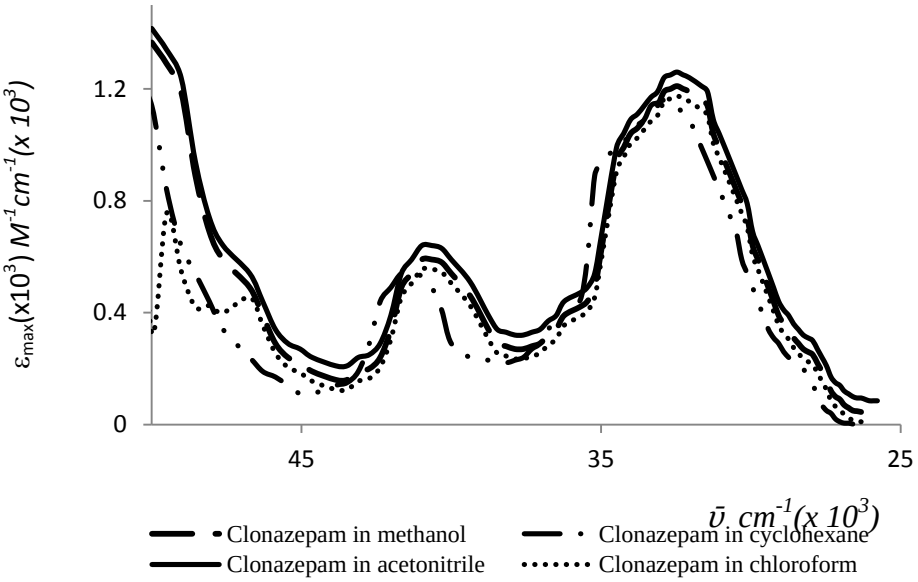


Fig. 3. UV-visible absorption spectra of Clonazepam® in the representative solvents.

The observed red shift in the absorption bands might be the resultant effects of (i) the probable extension of conjugation or induced electron redistribution due to presence of electron lone pairs the nitro group at the C8 of diazepine ring, oxygen lone pair on the carbonyl C2 of the diazepine rings (in clonazepam) and carbonyl oxygen C2 and C4 (in Clobazam). (ii) The specific solute-solvent interaction caused by intermolecular hydrogen bonding between the solvent molecules and the –O or probably –N group. The absorption maxima underwent a hypsochromic shift with increasing solvent hydrogen bond donor (HBD) acidity (i.e. *a* coefficient is positive), this is due to the hydrogen bond formation between protic solvents and carbonyl group in the diazepine ring. The results presented in Table 3 show that the absolute value of *s* coefficient is greater than those of *a* and *b* coefficients which implies that the solvent dipolarity/polarizability plays a more important role in the solvatochromism than hydrogen bonding interactions. Furthermore, the percentage contribution of solvatochromic parameter presented in Table 4 corroborates the importance of solvent dipolar/ polarizability to the solvatochromism of the compounds in this study. The hydrogen bonding acceptor basicity also plays dominant while hydrogen bonding donor acidity exerts little or no influence on the solvatochromism. Similar situations were reported in the literature. [11, 15, 22].

Quantum-chemical analysis

The optimized structures of Clobazam® and of Clonazepam® at B3LYP/6-31G** basis set are shown in Figure 5. Figure 6 shows the corresponding electronic transfers that occur between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the investigated compounds in gas phase. In the HOMO of Clobazam®, the electrons are delocalized all over the entire rings in the compound leaving out only C9, whereas the delocalization of electrons in the LUMO of Clobazam®, cover the entire diazepine rings leaving out the phenyl substituent. Also, the electrons in the HOMO of Clonazepam® are delocalized mainly on chlorophenyl substituent and some atoms (i.e. O1 and N2) of the diazepine ring. In the LUMO of Clonazepam®, the electrons are delocalized on the nitrophenyl substituent of the diazepine ring and some atoms (i.e N1 and O1) of the seven member ring. From the result of the frontier molecular orbital of the investigated compounds presented in Table 5, it is evident the main molecular orbitals responsible for this transition are HOMO-LUMO with a $\pi \rightarrow \pi^*$ character [18, 23-24].

From the absorption spectra presented in Figure 7, it is shown that contrary to the experimental results, the absorption spectra obtained from B3LYP/6-31G** theoretical calculations of the investigated compounds show one major absorption band for each of the compounds. Though each of these bands obtained theoretically in the gas phase correspond to the major absorption bands observed in the solvent media, they are blue shifted compared to the major bands in solvent media as shown in Table 5. Since the electronic spectrum of a substance in solution or condensed state undergoes modifications relative to its spectrum in the vapour phase, these modifications arise due to various interactions (both specific and non-specific) induced by solvents [18, 22, 25]. The hypsochromic shift and presence of one major absorption band observed in the spectra of the compounds calculated in the gas phase compare to the spectra of the solvated compounds are resultant effects of the solvent spectra frequency shift and

solvent perturbation of electronic intensity respectively [16, 27].

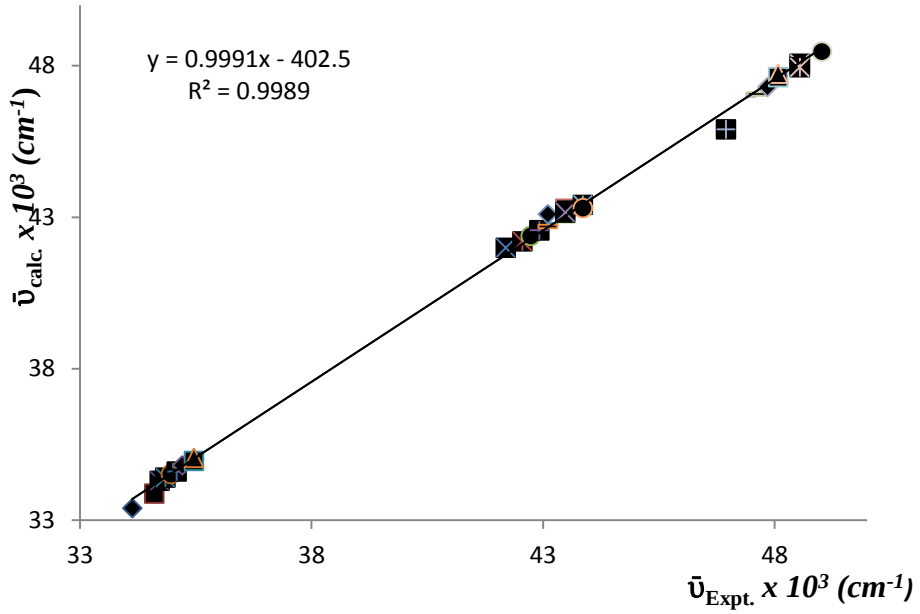


Fig. 4. The plot of ῡ observed against ῡ calculated from equation 1 for Clobazam® in the representative solvents.

Table 3. Regression fits to the solvatochromic parameter

Compounds and Electronic transitions	$\bar{\upsilon}_o$ x10³ (cm⁻¹)	s x10³ (cm⁻¹)	b x10³ (cm⁻¹)	a x10³ (cm⁻¹)	R^2	n
Clobazam $S_0 \rightarrow S_1$	35.442 (±0.064)	-3.122 (±0.620)	-2.138 (±0.12)	0.226 (±0.102)	0.99	10
$S_0 \rightarrow S_2$	43.368 (±0.055)	-5.265 (±0.972)	-4.694 (±0.148)	0.396 (±0.193)	0.96	10
$S_0 \rightarrow S_3$	46.689 (±0.019)	-4.864 (±0.771)	-4.043 (±0.125)	0.128 (±0.141)	0.96	9
Clonazepam $S_0 \rightarrow S_1$	32.573 (±0.033)	-5.618 (±0.837)	-2.775 (±0.216)	0.854 (±0.098)	0.99	10
$S_0 \rightarrow S_2$	40.824 (±0.025)	-2.334 (±0.418)	-2.130 (±0.198)	0.698 (±0.107)	0.97	10

Table 4. Percentage contribution of the solvatochromic effects

Compounds and Electronic transitions	P_{π^*} (%)	P_{β} (%)	Pα (%)
Clobazam			
$S_0 \rightarrow S_1$	56.91	38.97	4.12
$S_0 \rightarrow S_2$	50.85	45.33	3.82
$S_0 \rightarrow S_3$	53.84	44.74	1.42
Clonazepam			
$S_0 \rightarrow S_1$	60.75	30.01	9.24
$S_0 \rightarrow S_2$	45.22	41.26	13.52

Table 5. The calculated energies and HOMO-LUMO energy gap at B3LYP/6-31G* basis sets of optimized structures of the investigated compounds in gas phase

Compounds	$\bar{\nu}_{max}\ (cm^{-1})$	E_{HOMO} (eV)	E_{LUMO} (eV)	$\Delta E_{(H-L)}$ eV)
Clobazam®	41322	-6.21	-1.05	-5.15
Clonazepam®	33875	-6.90	-2.70	- 4.20

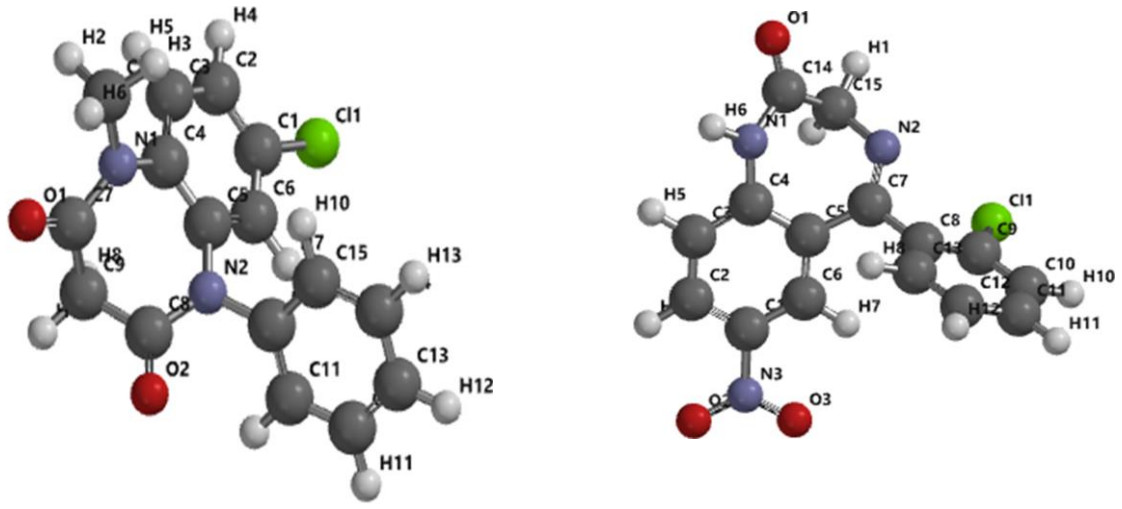


Fig. 5. The optimized structure of Clobazam® and of Clonazepam® at B3LYP/6-31G** basis set.

CONCLUSION

Quantitative treatment of effects of solvent on the Uv-visible absorption spectra of two benzodiazepine-based compounds namely 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione (Clobazam®) and 5,(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepine-2-one (Clonazepam®) were investigated using Kamlet-Taft's expression and quantum-chemical techniques. The results obtained show that the spectral shift are solvent polarity dependent. Electronic transitions in polar solvents were red-shifted in polar relative non-polar solvent. The results also reveal the dominance of solvent dipolarity/polarizability coefficient over the other two solvent parameters (i.e. hydrogen bond acceptor and hydrogen bond donor). The noticeable difference between the experimentally generated absorption spectra and the theoretically calculated the Uv-visible spectra manifested in the number of absorption bands, explanation of which found its root in solvent effects theories.

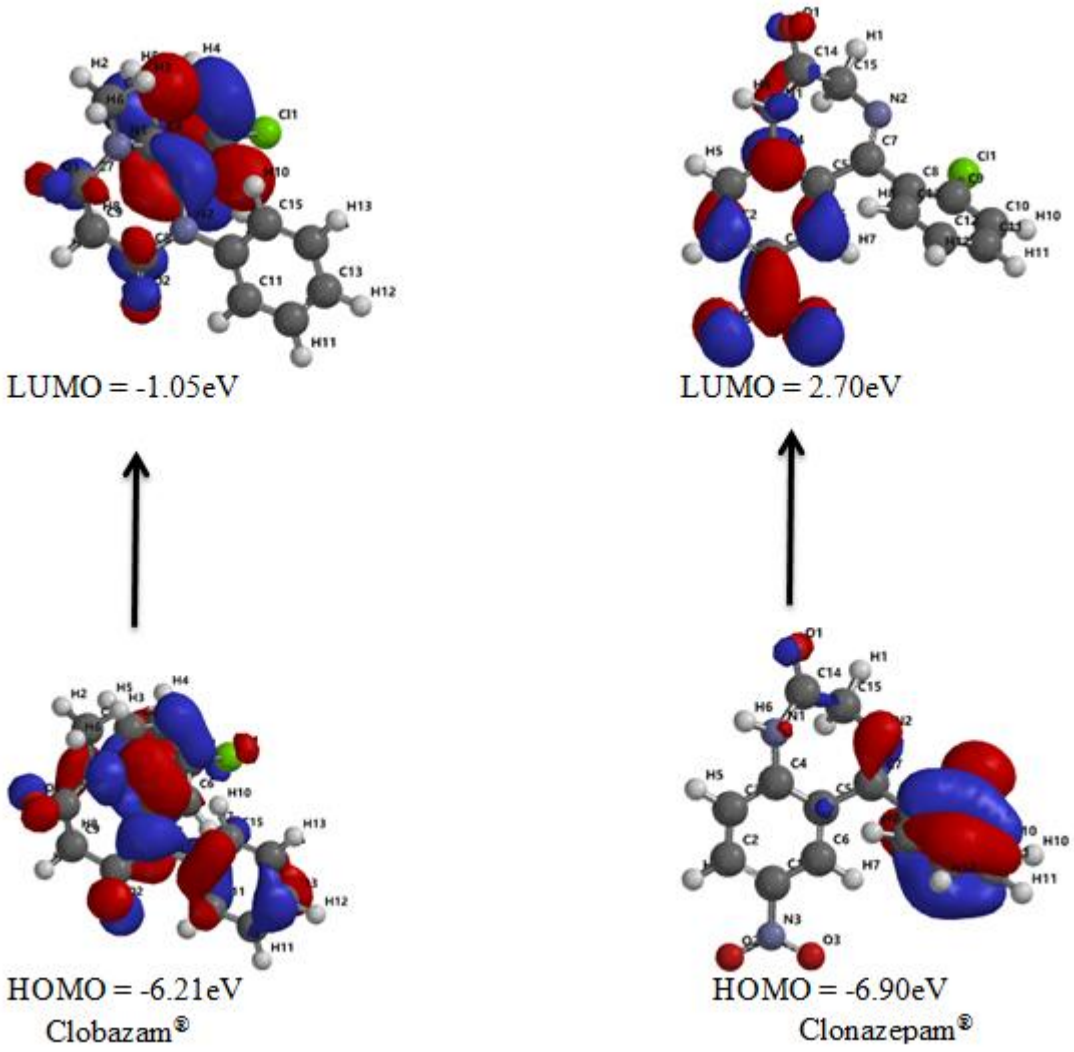


Fig. 6. Calculated frontier HOMO-LUMO energy gaps for Clobazam and clonazepam in gas phase.

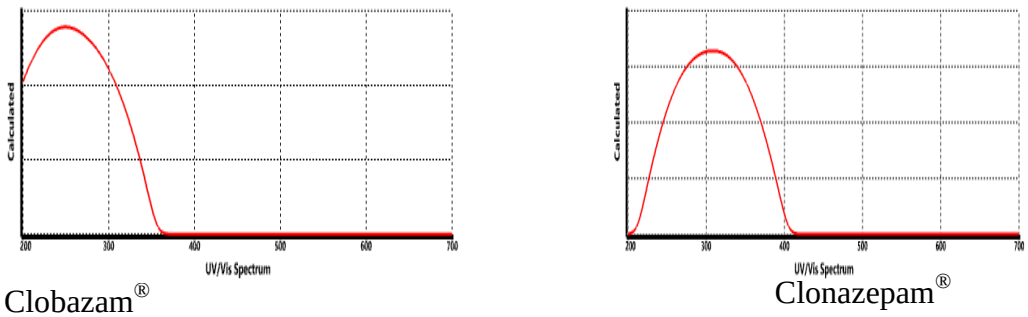


Fig. 7. The Uv-Vis absorption spectra of Clobazam® and Clonazepam® in gas phase using at B3LYP/6-31G** basis set.

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