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THERMOCHEMICAL INVESTIGATIONS AND VIBRATIONAL SPECTROSCOPIC STUDIES OF1, 4-BENZODIAZEPINES USING AB INITIO AND DFT METHODS

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ABSTRACT: *Extensive quantum chemical calculations have been carried out to investigate the IR vibrational frequencies as well as chemical shifts of different 1, 4-benzodiazepine derivatives, namely, lorazepam (LZ), nitrazepam (NZ) and clonazepam (CZ). Indeed, the obtained theoretical results clarified the interpretation of biological stabilities of these compounds. In order to evaluate and suggest the optimum method and basis set, all considered calculations have been carried out at two different levels of RHF and B3LYP theories using 6-31G(d,p) and 6-311G(d,p) basis sets. In each case, we were focused on finding the optimal quantum chemical model through either fitting these theoretical data with experimental measurements or comparing amongst theoretical data. For IR frequency calculations, the absence of imaginary frequencies indicated the stationary points correspond to minima on the potential energy surfaces. In addition, the isotropic 1H- and 13C- nuclear magnetic shielding constants of these compounds were calculated by employing the direct implementation of the gauge including-atomic-orbital (GIAO) method at the B3LYP density functional theory using 6-311G basis set has been performed which seemed quite informative to show some important atomic and structural features. Global reactivity descriptors such as ionization energy, molecular hardness, electrophilicity, frontier molecular orbital energies and shapes, the condensed Fukui functions, total energies were determined and used to identify the stability and reactivity of 1, 4 benzodiazepines.*
KEYWORDS: *1, 4-Benzodiapazine, IR frequency, chemical shifts, Thermochemical properties, Reactivity descriptors, Ab initio and DFT*

INTRODUCTION

Benzodiazepines (BDZs) are widespread compounds used for the treatment of mental disorders and are known as anxiolytic drugs [1]. Benzodiazepines and their derivatives are well known to the chemists mainly because of the broad spectrum of biological properties exhibited by this class of compounds. Some of these drugs exhibited antiproliferative properties against some tumor cell lines. This biological feature highlights them as potential anticancer agents [1-2].

Benzodiazepines have been widely used to provide anxiolytic and sedation in various clinical settings since over four decades ago [3]. Benzo-diazepine class drugs are extensively used in the pharmacotherapy of anxiety disorders throughout the world. Their well established anxiolytic properties have been entailed by an activation of GABA system, which is the principal inhibitory neurotransmitter system in brain [4]. Conformational and electronic properties of 21 benzodiazepines were calculated by using empirical energy and semiempirical molecular orbital methods [5]. Analysis of thermochemical properties of some anxiolytic drugs were studied by Monajjemi et al., [6]. Vibrational analysis was made on Nitrazepam by Gunasekaran et.al. [7]. The chemical structure of 1, 4-benzodiapazine derivatives, namely lorazepam, nitrazepam and clonazepam have been illustrated in Figure 1.

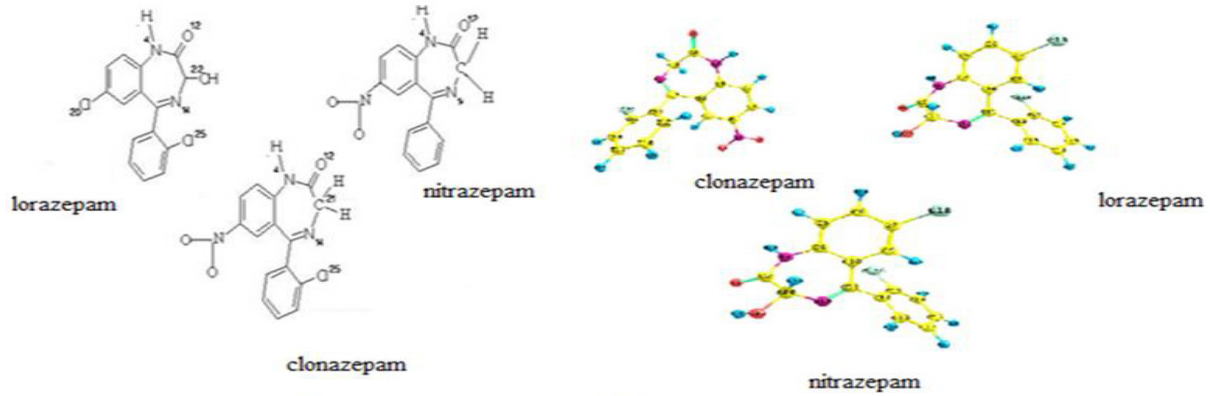

Figure 1. Chemical structure and optimized structure (shown in 3d) of 1, 4-benzodiapazine derivatives

*Moreover, it was understood that the chemical structure of a compound and its physical and chemical properties has significant influence on its activity both therapeutic and toxicity. In the literature, we found neither IR data nor chemical shift calculations for these compounds. On the other hand, the experimental evidence for the existence of those derivatives is sparse and has not been developed [8]. So the infrared spectroscopic properties and chemical shift analysis of this species could be of a particular interest. In current research, structural analogy motivated us to investigate the reliability of RHF and B3LYP theory with 6-31G (d, p) and 6-311G (d, p) basis sets in predicting the structural properties of these compounds. For this purpose, the IR spectral frequencies as well as their corresponding intensities and also their thermo chemical features related to their structural stabilities have been analyzed. To accomplish this goal, we were hopeful to be able to convey the message that normal frequency analysis is basically sufficient for understanding the stability and accuracy of quantum chemical model. In order to confirm our obtained theoretical data the plotted graphs of frequencies versus intensities and then obtained relative deviation of IR frequency values (**Δν** IR) in terms of experimental IR spectrum have been calculated. 1H and 13C chemical shifts were calculated which gives a number of relevant parameters (shielding tensors, coupling constants either through bonds or through space, quadrapole interactions) are tensor quantities that contain a richness of information concerning details of the electronic structure and three dimensional structure of the molecule.*

EXPERIMENTAL

The title compounds were purchased from Sigma-Aldrich chemical company, USA with more than 98% purity and were used as such without further purification to record Fourier transform infrared (FTIR) spectrum in the region 4000 – 400cm^{-1} at an accuracy of ± 4cm^{-1} on a bruker model IFS 66V spectrophotometer using the KBr pellet technique. The FT-Raman spectrum of TMHQ was recorded using 1064 nm line of Nd: YAG laser of 200mW in the region100-3500 cm^{-1} on the BRUCKER IFS-66 V spectrophotometer equipped with FRA 106 Raman module. The observed FTIR and FT Raman spectrum of the title compounds are shown in Figure 2.

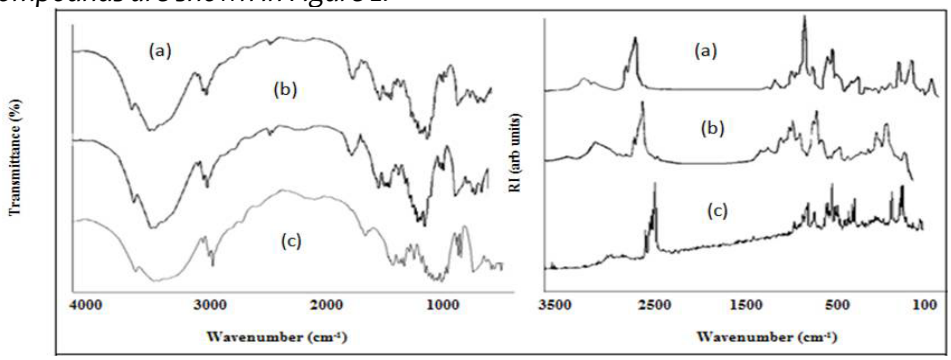

Figure 2. FT-IR and FT-Raman spectra of a) CZ, b) NZ, c) LZ

The quantum chemical calculations have been performed using Gaussian 03W program [9]. Full geometry optimizations and frequency calculations of the fundamental vibrational frequencies of all possible 1,4-benzodiapazine derivatives have been carried out employing Hartree-Fock (RHF) [10-11]and density Functional theory (B3LYP) [12-13]with 6-31G(d,p) basis sets [14]. Two different quantum chemical methods have been chosen due to the hydrogen bonding network governed in considered drugs and the satisfactory experimental correlations with the IR spectral frequencies. The absence of imaginary values of frequencies on the calculated vibrational spectrum conforms that the structure deduced corresponds to minimum energy. The assignments of the calculated frequencies are aided by the animation option of chemcraft program. The DFT values were found to be in good agreement with the experimental values after scaling the vibrational frequencies in comparison to the RHF values. Zero point energy corrections scaled by 0.96 have been added to the final obtained energies. For further investigation of the substituent effects, the frequency calculations as well as their corresponding thermo chemical parameters including thermal energies, and enthalpies, Gibbs free energies and entropies of the derivatives of 1,4-benzodiapazine have been performed to find the most stable candidate for anxiolytic drug which full fills their structural stability.

*Moreover, to evaluate the applicability of different ab initio methods and basis set effect on the range of frequency variations, the relative deviation of frequency values (**Δν** IR) has been estimated in terms of frequency values taken from experimental IR spectrum through comparing RHF and B3LYP methods is given in Table 1. Also, the plotted graphs of intensities versus frequencies shown in figure 3 have been analyzed. In order to investigate the performance and vibrational frequencies for the title compounds correlation coefficients between calculated harmonic and observed fundamental vibrational frequencies for HF and B3LYP method were also calculated. The small difference between the experimental and calculated vibrational modes is observed. This discrepancy can come from the*

formation of intermolecular hydrogen bonding. Also we note that the experimental results belong to the solid phase and the theoretical calculations belong to the gaseous phase. The frequency values computed at B3LYP level contains known systematic error. Therefore, linearity between the experimental and calculated vibrational frequency can be estimated by plotting the calculated values against experimental frequency (shown in figure 3). Certain values obtained between the two methods, are strongly underestimated. If the variations are omitted, B3LYP calculations provide good linearity between the calculated and experimental frequencies (Cc for HF is around 0.91 and for B3LYP is around 0.99). Finally, 1H and 13C chemical shifts has been carried out to explore the information about the structure and some dynamic properties of a sample subjected to a static magnetic field were calculated with GIAO method using corresponding TMS shielding calculated at the B3LYP/6-311G level.

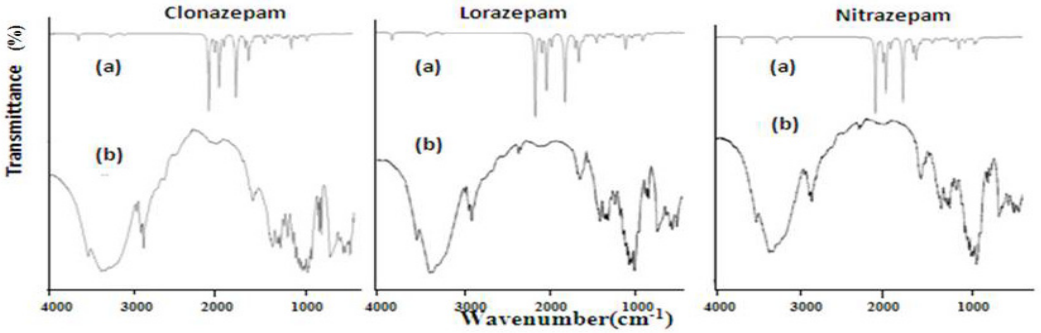

Figure 3. Comparison of computed (a) and observed (b), FTIR spectra of CZ, LZ and NZ

Table 1. Relative deviation of IR frequency values in terms of frequency values taken from Experimental IR spectrum with RHF and B3LYP methods.

Drugs	Bond types	Infrared Range	FTIR (cm^{-1})	FTRaman (cm^{-1})	RHF	B3LYP	$\Delta IR=\lvert\nu_{Theo}-\nu_{Exp}\rvert X \frac{100}{\nu_{Exp}}$	
							RHF	B3LYP
Clonazepam	C=O	1645-1730	1682vw	1680w	1713	1709	1.84	1.60
	C=N	1600-1800	1620w	1601w	1654	1578	2.09	-2.59
	C-N	1382–1266	1275m	1277vw	1377	1299	8	1.88
	C-Cl	600-800	798m	790w	792	802	-0.75	0.50
	C-No_2 (asym)	1570-1485	1535vw	1536vw	1652	1545	7.62	0.65
	C-No_2 (sym)	1370-1320	1359m	--	1418	1328	4.34	-2.28
	N-H	3500-3600	3425w	3425vw	3523	3437	2.86	0.35
	CH_2 (asym)	3000±50	2950w	2978vs	3104	2960	5.22	0.33
	CH_2 (sym)	2965±30	2957w	--	3090	2950	4.49	-0.23
Nitrazepam	C=O	1645-1730	1682vw	1680w	1732	1616	2.97	-3.80
	C=N	1600-1800	1620w	1601w	1698	1602	4.81	-1.11
	C-N	1382–1266	1280m	1277vw	1401	1339	9.45	3.85
	C-No_2 (asym)	1570-1485	1530vw	1544vw	1609	1546	5.16	1.04
	C-No_2 (sym)	1370-1320	1359m	--	1461	1360	7.5	0.07
	N-H	3500-3600	3427w	3425vw	3505	3448	2.27	0.61
	CH_2 (asym)	3000±50	2978w	2978vs	3043	3057	2.18	2.65
	CH_2 (sym)	2965±30	2917w	--	2885	2871	-1.09	-1.57
Lorazepam	C=O	1645-1730	1682vw	1680w	1807	1730	7.43	2.85
	C=N	1600-1800	1620w	1601w	1734	1610	7.03	-0.6
	C-N	1382–1266	1280m	1277vw	1261	1263	-1.48	-1.09
	C-Cl	600-800	718m	720m	746	710	3.89	-1.11
	N-H	3500-3600	3450w	3445vw	3513	3458	1.83	0.37
	C-Cl	600-800	790m	--	818	790	3.54	0

RESULTS AND DISCUSSION

Our investigation have been based on quantum chemical calculations to make shorten the long way from drug design via synthesis and clinical trials to the final approval of the drug for chemotherapy. In the structure of nitrazepam, lorazepam and clonazepam seven membered heterocycle which is having two nitrogen and three double bonds named diazepine fused with benzene ring having a NO_2 group at

the fifth position of the ring for nitrazepam and clonazepam, lorazepam chlorine atom is attached there and a phenyl ring which lies approximately perpendicular to each other.

ANALYSIS OF THERMO CHEMICAL PROPERTIES

Calculated Gibbs free energies, enthalpies, entropies of lorazepam, clonazepam and nitrazepam have been summarized in Table 2.

Table 2. Thermo chemical properties of 1, 4 benzodiazepine derivatives obtained at different theoretical levels

Basis set	T (K)	Lorazepam				Nitrazepam				Clonazepam			
		ΔEx10^{-5} Cal/mol	ΔHx10^{-5} Cal/mol	ΔGx10^{-5} Cal/mol	ΔS Cal/mol K	ΔEx10^{-5} Cal/mol	ΔHx10^{-5} Cal/mol	ΔGx10^{-5} Cal/mol	ΔS Cal/mol K	ΔEx10^{-5} Cal/mol	ΔHx10^{-5} Cal/mol	ΔGx10^{-5} Cal/mol	ΔS Cal/mol K
HF/ 6-31G	298	-10.98	-10.98	-11.37	130.93	-6.03	-6.03	-6.41	126.28	-8.91	-8.91	-9.31	134.58
B3LYP/ 6-31G	298	-11.02	-11.02	-11.43	135.14	-6.07	-6.07	-5.68	130.36	-8.95	-8.95	-9.36	138.41
B3LYP/ 6-311G	298	-11.03	-11.03	-11.43	135.28	-	-	-	-	-8.95	-8.95	-9.37	139.39

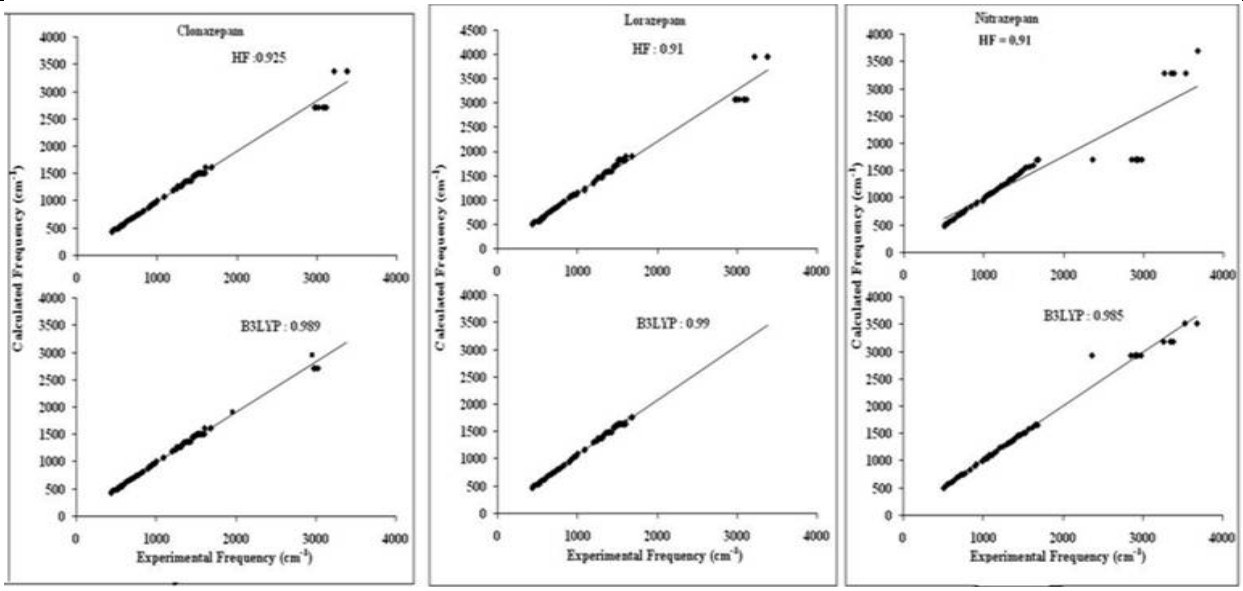

Figure 4. Calculated against experimental frequency of CZ, LZ and NZ

It seems that intermolecular interactions such as hydrogen bonding network stabilize certain chemical compounds. The interference of such a strong interaction depends on the electronegativites of the hydrogen bond donor and acceptor atoms and the distance between them. The reported thermo chemical parameters such as thermal energies, enthalpies and Gibbs free energies of considered drugs at two different RHF and B3LYP levels revealed that Lorazepam has the most negative energy value and then has the most structural stability amongst other 1, 4-benzodiapazine derivatives. So, as a whole, the order of stability obtained is thus:

Lorazepam > Clonazepam > Nitrazepam

Supposing basis set effect, it is notable that the differences of the thermo chemical parameters of lorazepam with the large basis set, that is, 6-311G (d, p) seemed very considerable and also may exhibit the significant stability to compare with clonazepam and nitrazepam which may confirm the above trend. For more evidence, it is interesting to mention that the positive value of heat of formation (ΔHf = 26.838 cal/mol) has been obtained for lorazepam with Hyperchem program [15, 16] which may confirm the less stability of lorazepam. On the other hand, the obtained entropy values (ΔS) with both RHF and B3LYP methods and two 6-31G and 6-311G basis sets and suggested the same trend as:

Lorazepam > Clonazepam > Nitrazepam

In spite of this observed computational contradictory, we can clearly see that the least stability is corresponded to lorazepam and the energy, enthalpy and Gibbs free energy value of Nitrazepam differs

significantly from clonazepam and Lorazepam and this fact could confirm the relative structural instability of Nitrazepam. As a result, our obtained theoretical data the conjugated configuration with the most negative energy or positive entropy values strongest hydrogen bond has been found to be the most stable one. It is reasonable to be reminded that the results of B3LYP with the larger basis set (6-311G (d, p) has provided the most reliable description of the thermo chemical properties. Since energy changes obtained with the larger basis set are regular for all systems tasted and the conclusions drawn from B3LYP/6-31G (d, p).

ANALYSIS OF VIBRATIONAL FREQUENCIES

Vibratational frequency calculations, in general, are generally separated into two tasks:
(1) The calculations of the vibrational modes and frequencies.
(2) The calculations of the corresponding thermochemical parameters.

The vibrational analysis of 1, 4 benzodiazepines was performed on the basis of the characteristic vibrations of carbonyl, hydroxyl, nitro and phenyl ring modes. Theoretical calculations were performed using density functional theory (HF and B3LYP) with 6-31G (d, p) basis set. The title molecules are non-planar and belong to C_1 point group. For C_1 symmetry there would not be any relevant distribution. In our study we have followed two different scaling factors. HF/6-31G (d, p): 0.9181 and B3LYP/6-31G (d, p): 0.9608 [17].The relative deviation of IR frequency values can be estimated using the following equation:

$$\Delta\nu_{IR} = \frac{\left|\nu_{Theo} - \nu_{Exp}\right| \text{ x } 100}{\nu_{Exp}} \qquad (1)$$

OTHER MOLECULAR PROPERTIES

We focus on the HOMO and LUMO energies in order to determine if correlations with interesting molecular/atomic properties and chemical quantities exist. In simple molecular orbital theory approaches, the HOMO energy (ε_{HOMO}) is related to the IP by Koopmanns' theorem and the LUMO energy (ε_{LUMO}) has been used to estimate the electron affinity (EA). The higher HOMO energy corresponds to the more reactive molecule in the reactions with electrophiles, while lower LUMO energy is essential for molecular reactions with nucleophiles [18]. If $-\varepsilon_{HOMO} \approx$ IP and $-\varepsilon_{LUMO} \approx$ EA, then the average value of the HOMO and LUMO energies is related to the electro negativity (φ) defined by Mulliken [19] with φ= IP + EA/2. In addition, the HOMO-LUMO gap is related to the hardness (η) [20]

$$\eta = \varepsilon_{LUMO} - \varepsilon_{LUMO}/2 \qquad (2)$$

In the past the hardness has been associated with the stability of chemical system [21]. This finding reported as the principle of maximum hardness formulated by Parr and Pearson [22-25]: a rule that "molecules arrange themselves to be as hard as possible". Essentially, as Pearson [50] stated in, hardness measures the resistance to change in the electron distribution in a molecule. The hardness and aromaticity show same relationship. In a number of studies shown [26] that a small HOMO-LUMO gap has been associated with antiaromaticity, and vice versa the larger the HOMO-LUMO energy gap is associated with aromaticity.

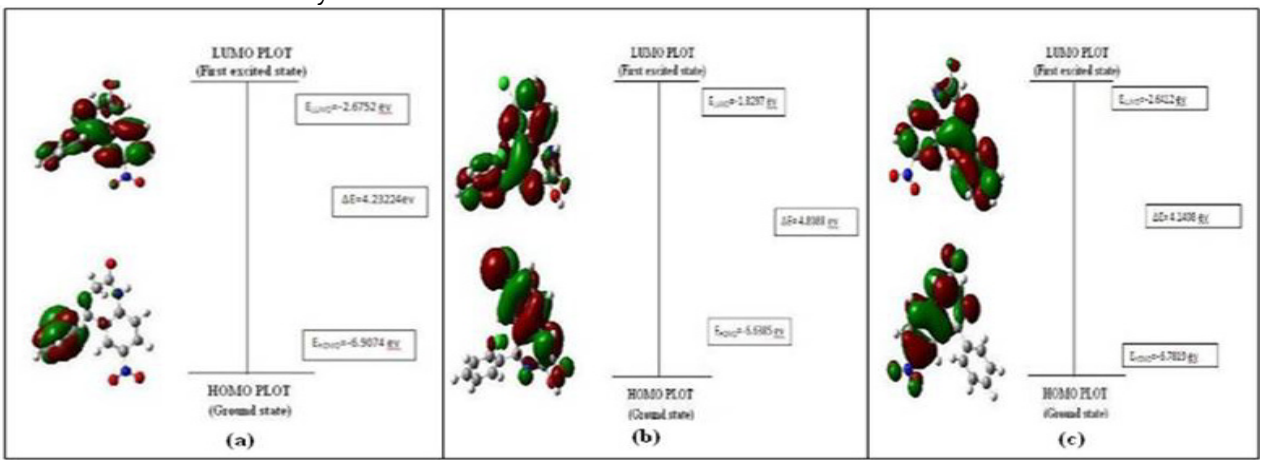

Figure 5. Atomic orbital HOMO – LUMO composition of the molecular orbital for a) Clonazepam, b) Lorazepam and c) Nitrazepam

Moreover Haddon and Fukuhaga[27] showed that a direct relationship exist between the resonance stabilization energies and the HOMO-LUMO gaps in annulenes and demonstrated connection between the thermodynamic stability and kinetic stability (reactivity) of aromatic compounds [28]. They presented the following formula for such relation:

$$RE = (\pi\rho_{rs})^2(\varepsilon_{LUMO}-\varepsilon_{LUMO})/24 \qquad (3)$$

where RE is the resonance energy and ρ_{rs} is the bond order of the r-s bond.

Table 3. Theoretically computed energies (a.u), zero-point vibrational energies (kcal mol^{-1}), rotational constants (GHz), entropies (cal mol^{-1}K^{-1}), dipole moment (D) and heat capacity (kcal mol^{-1} k^{-1}).

Parameters	Clonazepam		Lorazepam		Nitrazepam	
	HF/6-31G(d,p)	B3LYP/6-31G(d,p)	HF/6-31G(d,p)	B3LYP/6-31G(d,p)	HF/6-31G(d,p)	B3LYP/6-31G(d,p)
Total energy	-1420.9003	-1427.4134	-1751.2058	-1757.7389	-962.0053	-967.8186
Zero-point energy	156.69468	144.82485	150.95259	139.96864	162.87018	151.11039
Rotational constants	0.28140	0.28230	0.26995	0.27108	0.33324	0.32933
	0.24331	0.23391	0.26008	0.25565	0.29338	0.28923
	0.16069	0.15462	0.16982	0.16629	0.17194	0.16872
Entropy						
Total	134.580	138.414	130.936	135.147	126.283	130.361
Translational	43.139	43.139	43.185	43.185	42.799	42.799
Rotational	34.634	34.709	34.555	34.588	34.213	34.258
Vibrational	56.807	60.567	53.196	57.374	49.271	53.305
Dipole moment	2.7491	2.5829	3.6570	3.2874	1.2259	1.3876

Unlike thermodynamic stability, which is a (Table 3) unique property of ground state, the kinetic stability (reactivity) measures how fast particular reaction goes. The reactivity depends on energies of reactants, reaction transition states and also intermediates with possibility of various subsequent reactions leading to stable products. This illustrates the difficulties of formulating general quantitative reactivity descriptors based on ground state calculations. On the other hand it is well known that the aromatic compounds undergo electrophilic substitution reactions (aromatic substitution) more easily than they do addition reactions. In other words they exhibit tendency to retain their π-electron delocalized structure herewith resonance stabilization energy unchanged. Accordingly the relationship between the change of resonance energy and reaction activation energy exists and it depends on the reaction type [29]. Since there is connection between resonance energy and HOMO/LUMO energy separation [28-30] the reactivity can be closely related to the hardness and HOMO/LUMO energies.

So the idea of absolute hardness (half of HOMO/LUMO energies) is commonly used as a criterion of chemical reactivity and stability [30]. As a result Aihira et al [31] proposed index using HOMO-LUMO energy separation multiplied by a number of conjugated atoms and successfully applied this index to measure reactivity of policyclic aromatic hydrocarbons [31]. This index was found to correlate with chemical reactivity of particular aromatic system. Langenaeker [32] proposed the local hardness reactivity descriptor based on global hardness and demonstrated its superiority in predicting intramolecular reactivity for aromatic electrophilic substitution. Roy et al [33] studied the reactivity of some aromatic aldehydes toward acid-catalyzed aromatic exchange reactions with the DFT based reactivity descriptors hardness and local hardness. They interpret the reactivity trends with the trends of aromaticity of aromatic aldehides. They pointed out that in this instance, the aromatic ring influences the reactivity through aromatic π-electron delocalization of positive charge; increasing aromaticity causes the increase of hardness and the decrease of reactivity. So the presented contributions revealed the fact that high aromaticity and hardness are measures of high stability and low reactivity in the particular aromatic systems.

The global electrophilicity index ω was introduced by Parr[33] and calculated using the electronic chemical potential φ and chemical hardness η:

$$\omega = \varphi^2/2\eta \qquad (4)$$

According to the definition this index measures the propensity of a species to accept electrons. Under Domingo et al [34] the high nucleophility and electrophility of heterocycles corresponds to opposite extremes of the scale of global reactivity indexes. A good, more reactive, nucleophile is characterized by a lower value of φ, ω; and conversely a good electrophile is characterized by a (Table 4) high value of φ, ω.

Table 4 .Calculated Ionization Potential (IP), Electron Affinity (EA), Electronegativity (φ), Hardness (η) and Electrophilicity (ω) of 1, 4 benzodiazepines

	Clonazepam		Lorazepam		Nitrazepam	
	HF	B3LYP	HF	B3LYP	HF	B3LYP
E(a.u)	-1420.9	-1427.4	-1751.2	-1757.7	-962.0	-967.8
ΔH-L(ev)	10.7040	4.2322	11.1834	4.8088	10.4697	4.1408
ε_{Homo}(ev)	-9.3956	-6.9074	-9.1192	-6.6385	-9.1371	-6.7819
ε_{LUMO}(ev)	1.3083	-2.6752	2.0643	-1.8297	1.3326	-2.6412
φ(ev)	-4.043	-4.791	-3.527	-4.234	-3.902	-4.711
η(ev)	-5.351	-2.116	-5.591	-2.4044	-5.234	-2.070
ω(ev)	-1.527	-5.423	-1.112	-3.727	-1.454	-5.361

CONCLUSIONS

The HF and DFT calculations carried out using standard 6-31G (d, p) basis set gives a reasonable fit for bands assigned experimentally. The frequencies assigned were performed from FTIR and FTRaman spectrum. A thorough analysis of the most important vibrational frequencies allowed us to assign relative deviation to particular experimental vibrations. It is also interesting to notice a good agreement between the experimental and theoretical spectra, which allowed us to validate the computational approach presented in this study. Calculated Gibbs free energies, enthalpies, entropies obtained with the larger basis set provided the most reliable description.

HF/6-31G (d, p) and B3LYP/6-31G (d, p) calculations were used in this study to compare the performance of both approaches in the interpretation of reactivity descriptors. HF and DFT calculated reactivity descriptors: E, φ, η, ω, Δ H-L, bond length and bond orders show very similar reactivity descriptor values, and yield reasonable agreement with the relevant experiment reactivity results. In general theoretical results are in complete agreement with observed experimental reactivity.

NOMENCLATURE, GREEK SYMBOLS

$\Delta\nu_{IR}$ *Relative deviation of IR frequency*
η *Chemical hardness*
RE Resonance energy
ρ_{rs} *Bond order of the r-s bond.*
ω *Global electrophilicity index*
φ *Electronic chemical potential*

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