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Full Length Research Paper

Thermo-chemical investigation and NBO analysis of some anxileotic as Nano- drugs

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Extensive quantum chemical calculations have been carried out to investigate the thermochemical properties as well as IR vibrational frequencies of different 1,4-benzodiapazine derivatives, namely, lorazepam, temazepam and oxazepam. 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 three different levels of RHF, B3LYP and SVWN theories using 3-21G, 6-311G and 6-311++G 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 thermochemical parameters including thermal energy, entropy, Gibbs free energy and entropy of compounds have been computed and based on these obtained data the structural stabilities of these drugs have been discussed. However, in a series of drugs presented here the natural bond orbital (NBO) analysis has been performed which seemed quite informative to show some important atomic and structural features. This article is expected to be used for general bioinformatics researchers interested in drug design and will also provide update information to those who have been actively pursuing this field of research.**

Key words: 1, 4-Benzodiapazine, IR frequency, thermochemical parameters, natural bond orbital (NBO), *ab initio*.

INTRODUCTION

Benzodiazepines (BDZs) are widespread compounds used for the treatment of mental disorders and are known as anxileotic drugs (Dourlat et al., 2007).
Benzodiazepines and their derivatives are well known to the chemists mainly because of the broad spectrum biological properties exhibited by this class of compounds. Some of these drugs exhibited anti-proliferative properties against some tumor cell lines. This biological feature highlights them as potential anti-cancer agents (Dourlat et al., 2007; Sinha et al., 1999).

Benzodiazepines have been widely used to provide anxiolytic and sedation in various clinical settings since over four decades ago (Zarghi et al., 2005). 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 (Ingman et al., 2004). The chemical structure of 1, 4-benzodiapazine derivatives, namely lorazepam, temazepam and oxazepam have been illustrated in Figure 1.

Many researches have focused on correlating molecular

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Abbreviations: NAO, Natural atomic orbital; **NBO,** natural bond orbital.

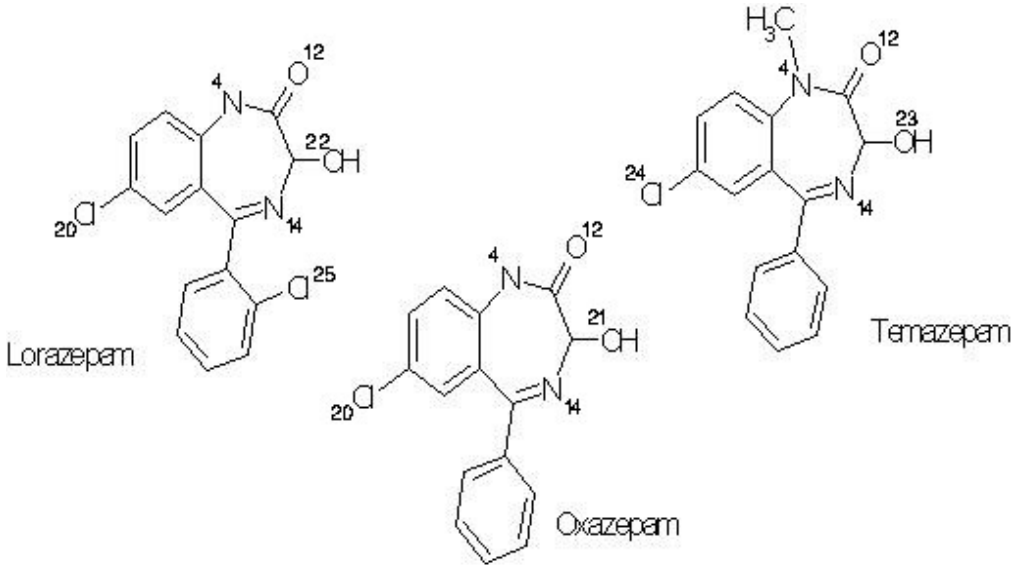

Figure 1. Chemical structures of 1, 4-benzodiapazine derivatives.

structure of these compounds to their pharmacological activity (Sinha et al., 1999). Although the concept of a relationship between the chemical structure of a chemical compound and its biological activity appeared several years ago, prediction of the compound activity on the basis of its structural stability still comes across serious difficulties. 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 (Latosinska, 2005).

The enthalpy relaxation of three amorphous benzodiazepines, diazepam, temazepam and tiazepam has been studied using differential scanning calorimetric for ageing temperatures which were below the glass transition temperature. It was found that the benzodiapazine derivatives exhibited significant molecular mobility until approximately 50 K below the glass transition temperature; below this temperature molecular mobility becomes unimportant with respect to the shelf life stability. Hence, the presented procedure provides the formulation scientist with a tool to set storage conditions for amorphous drugs and glassy pharmaceutical products (Ingman et al., 2004; Mooter et al., 1999).

In the literature, we found neither IR data nor NBO calculations for these compounds. On the other hand, the experimental evidence for the existence of those derivatives is sparse and has not been developed (Remko et al., 1999). So the infrared spectroscopic properties and NBO analysis of this species could be of a particular interest.

In current research, structural analogy motivated us to investigate the reliability of RHF, B3LYP and SVWN theory with 3-21G, 6-311G and 6-311++G** 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 thermochemical 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 ($\Delta \upsilon_{IR}$) in terms of experimental IR spectrum have been calculated.

The natural bond orbital (NBO) analysis of the electron density has also been studied to describe the electron occupation in terms of a natural minimal basis which is highly occupied and a natural Rydberg basis that is largely unoccupied.

COMPUTATIONAL DETAILS

The quantum chemical calculations have been performed using Gaussian 98 program (Frisch et al., 1998). 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) (Roothan, 1951; Pople and Nesbet, 1954) and density Functional theory (B3LYP) (Becke, 1993; Lee et al., 1998) and SVWN methods (Vosko et al., 1980) with 3-21G, 6-311G, 6-311++G** basis sets (Frisch et al., 1985). Three 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. Zero point energy corrections scaled

by 0.96 have been added to the final obtained energies. The stationary points found on the molecular potential energy hyper-surfaces were characterized using standard analytical harmonic vibrational analyses (Monajjemi et al., 2008).

For further investigation of the substituent effects, the frequency calculations as well as their corresponding thermochemical parameters including thermal energies, and entropies, Gibbs free energies and entropies of the derivatives of 1,4-benzodiapazine have been performed to find the most stable candidate for anxileotic drug which full fills their structural stability. To evaluate the temperature dependence of thermodynamical parameters, frequency calculations have been carried out at different temperatures, namely, 77 K (the crystallographic temperature), 298 K (room temperature), 310 K (normal body temperature), and, 313 K (the fever temperature) and the graph of entropy values (cal/mol.k) at different temperature has been plotted and analyzed.

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 ($\Delta \upsilon_{IR}$) has been estimated in terms of frequency values taken from experimental IR spectrum (Silverstein et al., 1981) through comparing RHF and B3LYP methods. Also, the plotted graphs of intensities versus frequencies have been analyzed.

Finally, natural bond orbital (NBO) analysis has been carried out to explore the distribution of electrons into atomic and molecular orbitals and thereby derived molecular bonds are then based on these data the graphs of %P orbitals of some nuclei for different bonds of considered drugs have been plotted and analyzed using DFT approach. Also, the ratios of core/charge and valence/charge of some nuclei have been compared and analyzed.

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.

Analysis of thermochemical properties

Calculated Gibbs free energies, enthalpies, entropies of lorazepam, temazepam and oxazepam have been summarized in Table 1. Also, the graph of entropy versus temperature changes has been displayed in Figure 2.

It is 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 thermochemical parameters such as thermal energies, enthalpies and Gibbs free energies of considered drugs at three different RHF, B3LYP and SWVN levels revealed that Temazepam 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:

Temazepam > Oxazepam > Lorazepam

Supposing basis set effect, it is notable that the differences of the thermochemical parameters of lorazepam with the large basis set, that is, 6-311++G** seemed very considerable and also may exhibit the significant instability in compare with temazepam and oxazepam which may confirm the above trend.

For more evidence, it is interesting to mention that the positive value of heat of formation (ΔH_f = 26.838 cal/mol) has been obtained for lorazepam with Hyperchem program (Hyperchem, 1996) which may confirm the less stability of lorazepam. On the other hand, the obtained entropy values (ΔS) with both RHF and B3LYP methods and three 3-21G, 6-311G, and 6-311G++G** basis sets and suggested the same trend as:

Temazepam > Oxazepam > Lorazepam

Although, the observed results of SVWN method seems slightly different with RHF and B3LYP methods. 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 lorazepam differs significantly from temazepam and oxazepam and this fact could confirm the relative structural instability of lorazepam. 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.

Furthermore, the graph of entropies at different temperatures (see Figure 2) exhibited dramatically increasing trend from 77 up to 298 K. Of course such a sharp increase was more significant for temazepam range over the 298 up to 313 K revealed slightly constant trend. So, in 310 K which is the normal body temperature the higher structural stability of all three drugs has been revealed.

Based on Figure 2, it is interesting to notice that, while these considered drugs appeared close on the energetical scale, the predicted entropies of these compounds are substantially different. On the other hand, the thermochemical parameters of considered drugs at different temperatures were quite similar in spite of the large differences in their entropies. It is reasonable to be reminded that the results of B3LYP with the larger basis set (6-311++G**) has provided the most reliable description of the thermochemical properties. Since energy changes obtained with the larger basis set are regular for

Table 1. Thermochemical parameters of anxiolytic drugs obtained at different theoretical levels.

Drugs	Basis set	Temp. (k)	RHF				B3LYP				SVWN			
			ΔE ×10^{-5} Cal / mol	ΔH ×10^{-5} Cal / mol	ΔG ×10^{-5} Cal /mol	ΔS Cal / mol k	ΔE ×10^{-5} Cal / mol	ΔH ×10^{-5} Cal / mol	ΔG ×10^{-5} Cal / mol	ΔS Cal / mol k	ΔE×10^{-5} Cal / mol	ΔH ×10^{-5} Cal / mol	ΔG×10^{-5} Cal / mol	ΔS Cal / mol k
Temazepam	3-21G	298	-83.094	-83.094	-83.097	121.330	-83.479	-83.479	-83.482	126.510	-83.109	-83.109	-83.112	125.037
	6-311G	298	-83.525	-83.525	-83.529	124.438	-83.919	-83.919	-83.922	126.314	-83.547	-83.547	-83.551	126.674
	6-311++G**	298	-83.552	-83.552	-83.555	131.583	-83.938	-83.938	-83.942	137.339	-83.565	-83.565	-83.569	130.494
		77	-	-	-	-	-83.939	-83.939	-83.942	78.408	-	-	-	-
		310	-	-	-	-	-83.938	-83.938	-83.942	140.109	-	-	-	-
		313	-	-	-	-	-83.938	-83.938	-83.942	140.821	-	-	-	-
Lorazepam	3-21G	298	-10.940	-10.940	-10.932	116.231	-10.973	-10.973	-10.973	121.511	-10.930	-10.930	-10.930	131.169
	6-311G	298	-10.986	-10.987	-10.988	121.410	-11.030	-11.030	-11.030	126.281	-10.987	-10.987	-10.987	131.634
	6-311++G**	298	-76.406	-76.406	-76.410	120.484	-11.031	-11.031	-11.032	137.366	-10.989	-10.989	-10.989	130.159
		77	-	-	-	-	-11.032	-11.032	-11.032	81.096	-	-	-	-
		310	-	-	-	-	-11.031	-11.031	-11.032	137.336	-	-	-	-
		313	-	-	-	-	-11.032	-11.032	-11.032	140.810	-	-	-	-
Oxazepam	3-21G	298	-80.661	-80.661	-80.664	120.524	-81.028	-81.028	-81.032	126.859	-80.671	-80.671	-80.675	119.797
	6-311G	298	-81.080	-81.080	-81.083	117.921	-81.455	-81.455	-81.459	123.565	-81.097	-81.097	-81.100	121.781
	6-311++G**	298	-81.105	-81.105	-81.109	129.382	-81.473	-81.473	-81.477	128.428	-81.114	-81.114	-81.118	128.301
		77	-	-	-	-	-81.474	-81.474	-81.477	76.634	-	-	-	-
		310	-	-	-	-	-81.473	-81.473	-81.477	131.025	-	-	-	-
		313	-	-	-	-	-81.473	-81.473	-81.477	131.681	-	-	-	-

all systems tasted and the conclusions drawn from B3LYP/6-31G (d, p).

Analysis of vibratational 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.

This is a reflection of the underlying atoms interactions within that molecule. The calculations exhibited the higher frequency band (3655 cm^{-1}) corresponds to the asymmetric NH_2 mode. A very strong band at 3092 cm^{-1} is predicted to correspond to the v (OH) mode. Also, an analysis of the frequency values yielded the maximum frequency with 3-21G as a small basis set. To be more specific about basis set effect on the frequency values, we can see the same trend at all three RHF, B3LYP, and SVWN levels of theory as thus:

3-21G > 6-311G++G** > 6-311G

For temazepam and lorazepam of course, the same trend has been obtained using B3LYP and SWVN as well as with RHF for oxazepam.

The relative deviation of IR frequency values can be estimated using the following equation:

$$\Delta \upsilon_{IR} = \frac{\left|\upsilon_{Theo} - \upsilon_{Exp}\right| \times 100}{\upsilon_{Exp}} \quad (1)$$

Where υ_{Theo} is the calculated geometrical parameter, υ_{Exp} the experimental value taken from experimental IR spectrum (Silverstein et al., 1981

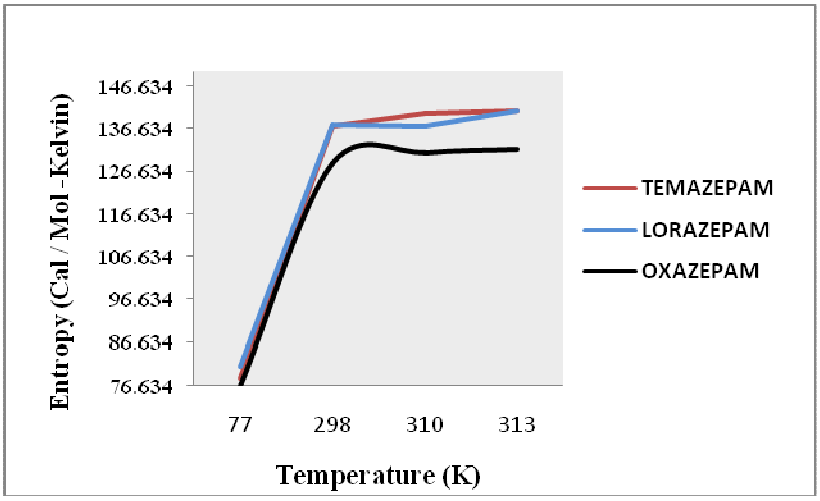

Figure 2. The graph of entropy values of 1, 4-benzodiapazine derivatives at different temperatures.

Table 2. The relative deviation of IR frequency values in terms of frequency values taken from experimental IR spectrum with RHF and B3LYP methods.

Drugs	Bond types	u^{Exp} (cm^{-1})	$\Delta \upsilon_{IR} = \frac{\lvert \upsilon_{Theo} - \upsilon_{Exp} \rvert \times 100}{\upsilon_{Exp}}$	
			RHF	B3LYP
	C = O	1670 - 1720	4.1	3.9
	C - O	1050 - 1150	4.5	0.4
	C - N	1080 - 1360	31.03	2.9
Lorazepam	C = N	2210 - 2260	21.2	10.47
	O - H	3200 - 3600	7.3	0.4
	C - Cl (1)	600 - 800	2.3	1.9
	C - Cl (2)	600 - 800	2.5	1.8
	C = O	1670 - 1720	5.6	1.3
	C - O	1050 - 1150	5.7	0.005
Oxazepam	C - N	1080 - 1360	30.41	2.8
	C = N	2210 - 2260	25.6	10.49
	O - H	3200 - 3600	9.7	7.3
	C - Cl	600 - 800	7.2	1.3
	C = O	1670 - 1720	1.5	1.005
	C - O	1050 - 1150	0.4	0.1
Temazepam	C - N	1080 - 1360	1.6	0.07
	C = N	2210 - 2260	23.04	11.84
	O - H	3200 - 3600	7.3	0.3
	C - Cl	600 - 800	1.4	0.3

and Δu_{IR} the relative error of a given value in percent (Braeuer et al., 2000).

Suppose Equation 1 , the relative deviation of frequency values in terms of frequencies taken from experimental IR spectrum using RHF and B3LYP methods has been listed in Table 2. Based on the reported results, we can clearly see the less values of relative frequency deviation with B3LYP method in compare with RHF. So, we can

Table 3. NBO analysis displaying the form and occupancy of the complete set of NAOs with B3LYP method.

Drugs	Bond	B3LYP/3-21G	B3LYP/6-311G	B3LYP/6-311++G**
Lorazepam	σ_{C1-N4}	0.6209 ($sp^{2.80}$) C + 0.7839 ($sp^{1.73}$) N	0.6219 ($sp^{2.69}$) C + 0.7831 ($sp^{1.64}$) N	0.6210 ($sp^{2.69}$) C + 0.7838 ($sp^{1.65}$) N
	$\sigma_{C8-N14}(1)$	0.6376 ($sp^{2.14}$) C + 0.7703 ($sp^{1.40}$) N	0.6422 ($sp^{2.04}$) C + 0.7665 ($sp^{1.39}$) N	0.6411 ($sp^{2.02}$) C + 0.7674 ($sp^{1.37}$) N
	$\sigma_{C8-N14}(2)$	0.6793 ($sp^{99.99}$) C + 0.7339 ($sp^{99.99}$) N	0.6637 ($sp^{99.99}$) C + 0.7480 ($sp^{99.99}$) N	0.6592 ($sp^{99.99}$) C + 0.7519 ($sp^{99.99}$) N
	$\sigma_{C13-N14}$	0.6346 ($sp^{3.26}$) C + 0.7728 ($sp^{2.58}$) N	0.6400 ($sp^{2.92}$) C + 0.7684 ($sp^{2.66}$) N	0.6367 ($sp^{2.92}$) C + 0.7711 ($sp^{2.63}$) N
	σ_{N4-C7}	0.7998 ($sp^{1.72}$) C + 0.6003 ($sp^{2.19}$) N	0.7928 ($sp^{1.76}$) C + 0.6095 ($sp^{2.13}$) N	0.7968 ($sp^{1.73}$) C + 0.6042 ($sp^{2.15}$) N
	$\sigma_{C7-O12}(1)$	0.5851 ($sp^{2.16}$) C + 0.8110 ($sp^{1.43}$) N	0.5921 ($sp^{2.05}$) C + 0.8058 ($sp^{1.53}$) N	0.5884 ($sp^{2.04}$) C + 0.8086 ($sp^{1.40}$) N
	$\sigma_{C7-O12}(2)$	0.5817 ($sp^{99.99}$) C + 0.8134 ($sp^{99.99}$) N	0.5581 ($sp^{99.99}$) C + 0.8298 ($sp^{99.99}$) N	0.5478 ($sp^{99.99}$) C + 0.8366 ($sp^{99.99}$) N
	$\sigma_{C13-O22}$	0.5935 ($sp^{3.54}$) C + 0.8048 ($sp^{2.32}$) N	0.5900 ($sp^{3.31}$) C + 0.8074 ($sp^{2.26}$) N	0.5854 ($sp^{3.30}$) C + 0.8108 ($sp^{2.16}$) N
	$\sigma_{C11-Cl20}$	0.6824 ($sp^{3.32}$) C + 0.7310 ($sp^{5.29}$) N	0.6721 ($sp^{3.49}$) C + 0.7405 ($sp^{4.92}$) N	0.6734 ($sp^{3.47}$) C + 0.7393 ($sp^{4.44}$) N
	$\sigma_{C18-Cl25}$	0.6824 ($sp^{3.39}$) C + 0.7310 ($sp^{5.29}$) N	0.6720 ($sp^{3.56}$) C + 0.7405 ($sp^{4.88}$) N	0.6737 ($sp^{3.53}$) C + 0.7390 ($sp^{4.42}$) N
Temazepam	σ_{C1-N4}	0.6211 ($sp^{2.81}$) C + 0.7838 ($sp^{1.75}$) N	0.6220 ($sp^{2.70}$) C + 0.7830 ($sp^{1.65}$) N	0.6225 ($sp^{2.71}$) C + 0.7826 ($sp^{1.69}$) N
	$\sigma_{C8-N14}(1)$	0.6374 ($sp^{2.18}$) C + 0.7705 ($sp^{1.43}$) N	0.6423 ($sp^{2.08}$) C + 0.7665 ($sp^{1.41}$) N	0.6225 ($sp^{2.71}$) C + 0.7826 ($sp^{1.69}$) N
	$\sigma_{C8-N14}(2)$	0.6690 ($sp^{1.00}$) C + 0.7432 ($sp^{99.99}$) N	0.6530 ($sp^{99.99}$) C + 0.7574 ($sp^{99.99}$) N	0.6497 ($sp^{99.99}$) C + 0.7602 ($sp^{99.99}$) N
	$\sigma_{C13-N14}$	0.6348 ($sp^{3.22}$) C + 0.7726 ($sp^{2.51}$) N	0.6402 ($sp^{2.88}$) C + 0.7682 ($sp^{2.58}$) N	0.6364 ($sp^{2.91}$) C + 0.7714 ($sp^{2.55}$) N
	σ_{N4-C7}	0.7996 ($sp^{1.73}$) C + 0.6006 ($sp^{2.18}$) N	0.7926 ($sp^{1.77}$) C + 0.6098 ($sp^{2.13}$) N	0.7958 ($sp^{1.74}$) C + 0.6055 ($sp^{2.15}$) N
	$\sigma_{C7-O12}(1)$	0.5849 ($sp^{2.16}$) C + 0.8111 ($sp^{1.42}$) N	0.5919 ($sp^{2.05}$) C + 0.8060 ($sp^{1.53}$) N	0.5873 ($sp^{2.02}$) C + 0.8094 ($sp^{1.27}$) N
	$\sigma_{C7-O12}(2)$	0.5805 ($sp^{99.99}$) C + 0.8142 ($sp^{99.99}$) N	0.5569 ($sp^{99.99}$) C + 0.8306 ($sp^{99.99}$) N	0.5506 ($sp^{99.99}$) C + 0.8348 ($sp^{99.99}$) N
	$\sigma_{C13-O21}$	0.5933 ($sp^{3.57}$) C + 0.8050 ($sp^{2.33}$) N	0.5894 ($sp^{3.34}$) C + 0.8079 ($sp^{2.26}$) N	0.5841 ($sp^{3.30}$) C + 0.8117 ($sp^{2.00}$) N
	$\sigma_{C11-Cl20}$	0.6820 ($sp^{3.33}$) C + 0.7313 ($sp^{5.29}$) N	0.6716 ($sp^{3.51}$) C + 0.7409 ($sp^{4.91}$) N	0.6735 ($sp^{3.46}$) C + 0.7392 ($sp^{4.29}$) N
Oxazepam	σ_{C1-N4}	0.6187 ($sp^{2.81}$) C + 0.7857 ($sp^{1.79}$) N	0.6214 ($sp^{2.68}$) C + 0.7835 ($sp^{1.67}$) N	0.6203 ($sp^{2.69}$) C + 0.7844 ($sp^{1.69}$) N
	$\sigma_{C8-N14}(1)$	0.6324 ($sp^{2.12}$) C + 0.7746 ($sp^{1.28}$) N	0.6398 ($sp^{2.00}$) C + 0.7686 ($sp^{1.28}$) N	0.6379 ($sp^{1.98}$) C + 0.7701 ($sp^{1.27}$) N
	$\sigma_{C8-N14}(2)$	0.6563 ($sp^{1.00}$) C + 0.7545 ($sp^{99.99}$) N	0.6397 ($sp^{99.99}$) C + 0.7686 ($sp^{99.99}$) N	0.6356 ($sp^{99.99}$) C + 0.7720 ($sp^{99.99}$) N
	$\sigma_{C13-N14}$	0.6268 ($sp^{3.26}$) C + 0.7792 ($sp^{2.35}$) N	0.6363 ($sp^{2.89}$) C + 0.7714 ($sp^{2.47}$) N	0.6310 ($sp^{2.90}$) C + 0.7758 ($sp^{2.44}$) N
	σ_{N4-C7}	0.8044 ($sp^{1.73}$) C + 0.5941 ($sp^{2.20}$) N	0.7945 ($sp^{1.78}$) C + 0.6072 ($sp^{2.14}$) N	0.7999 ($sp^{1.75}$) C + 0.6001 ($sp^{2.16}$) N
	$\sigma_{C7-O12}(1)$	0.5792 ($sp^{2.12}$) C + 0.8152 ($sp^{1.21}$) N	0.5909 ($sp^{1.98}$) C + 0.8067 ($sp^{1.37}$) N	0.5846 ($s^{p1.98}$) C + 0.8113 ($sp^{1.23}$) N
	$\sigma_{C7-O12}(2)$	0.5512 ($sp^{99.99}$) C + 0.8343 ($sp^{99.99}$) N	0.5274 ($sp^{99.99}$) C + 0.8496 ($sp^{99.99}$) N	0.5160 ($sp^{99.99}$) C + 0.8566 ($sp^{99.99}$) N
	$\sigma_{C13-O21}$	0.5844 ($sp^{3.53}$) C + 0.8115 ($sp^{2.00}$) N	0.5866 ($sp^{3.26}$) C + 0.8099 ($sp^{2.06}$) N	0.5795 ($sp^{3.25}$) C + 0.8150 ($sp^{1.97}$) N
	$\sigma_{C11-Cl20}$	0.6848 ($sp^{3.21}$) C + 0.7288 ($sp^{4.71}$) N	0.6718 ($sp^{3.42}$) C + 0.7408 ($sp^{4.34}$) N	0.6733 ($sp^{3.38}$) C + 0.7394 ($sp^{4.02}$) N

realize the point that the obtained frequency values with B3LYP were closer to the experimental data taken from IR spectrum. Therefore, we may conclude that density functional method is good enough to reproduce the right trend exploration of electronic structure of biochemical systems. Hence, a fairly good correlation to the experimental values enables a unique scaling factor to be introduced analogously to the routine procedure for theoretical vibrational spectra.

NBO analysis

The concept of natural atomic orbital (NAO) and natural bond orbital (NBO) analysis which is useful for distributing electrons into atomic and molecular orbitals used for the one-electron density matrix for defining the shape of the atomic orbitals in the molecular environment and then derive molecular bonds from electron density between atoms (Jensen, 2007). The NAOs will normally resemble the pure atomic orbitals and may be divided into a “natural minimal basis” corresponding to the occupied atomic orbitals for the isolated atom, and a remaining set of natural “Rydberg” orbitals based on the magnitude of the occupation numbers. The minimal set of NAOs will normally be strongly occupied, while the Rydberg NAO usually will be weakly occupied. There are as many NAOs as the size of the atomic basis set and the number of Rydberg NAOs thus increases as the basis set is enlarged (Jensen, 2007).

The results of NBO analysis using B3LYP method have been reported in Table 3. Also, the variation of %P orbitals of some nuclei against different bonds of considered drugs through has been displayed in Figure 3. In Figure 3, we have observed two sharp picks in which the percentage of P orbitals were maximum. It is important to notice that one of the two picks belonged to the double bond of $C_8 = N_{14}$ involved in seven-membered ring of

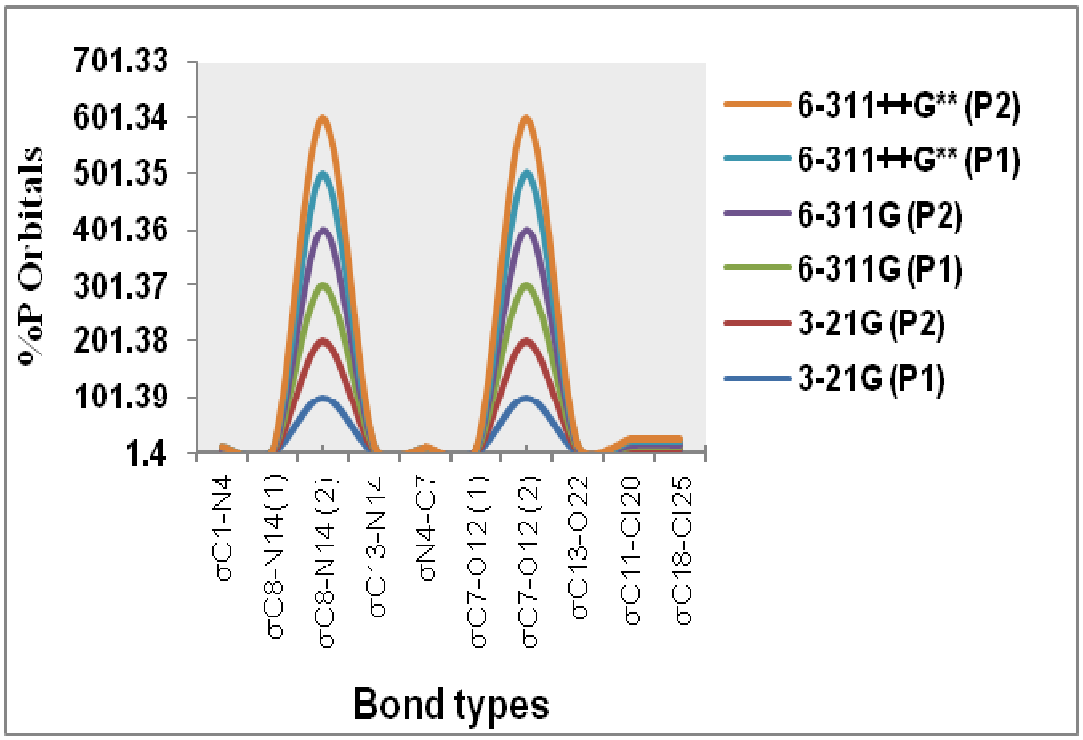

Figure 3. The graph of %P orbitals of some nuclei involved in different bonds of 1, 4-benzodiapazine derivatives.

drugs and the other one has been identified for $C_7 = O_{12}$ bond.

Interestingly, using all consider quantum chemical methods for lorazepam, oxazepam and temazepam this maximum value of P orbital has been obtained with the large basis set, that is, 6-311++G** which reflected its high accuracy amongst considered basis sets.

According to the calculated ratios of core/charge and valence/charge of some nuclei reported in Table 4, we have clearly understood that the more improved and accurate method we have used the more negative values of these quantities have been yielded. Therefore, we realize that the more negative values of core/charge and valence/charge may bring structural stability of whole molecule. This trend has been
repeatedly observed with all employed basis sets.

Another striking fact can be understood from Table 4 is that the core/charge and valence/charge values of Cl_{20} atom of lorazepam, temazepam and oxazepam exhibited considerable differences. Also, the most negative values were corresponded to these atoms of all three considered drugs which may reveal that this atom hold stable bond in all three drugs.

Furthermore, if we compare the core/charge as well as the valence/charge values of two nitrogen atoms (N_4 and N_{14}) of lorazepam, temazepam and oxazepam, it could be observed that the core/charge and valence/charge values of N_{14} which is involved in C = N of six-membered ring is more negative and then we can conclude that the reactivity of this atom is less than N_4 atom in all mentioned drugs.

CONCLUSIONS

The procedures discussed in this study place much emphasis on the importance of electronic structure calculations of thermochemical and NBO parameters as well as IR frequency analysis of some anxileotic drugs. To illustrate the impact of electron correlation and basis set effects on the predicted thermochemical and NBO parameters of considered drugs, we have employed there different theoretical methods including Hartee-Fock (RHF), density functional theory (B3LYP) and SVWN methods with 3-21G, 6-311G, 6-311++G** basis sets to study the substituent effects of 1, 4-benzodiapazine derivatives as well as bioactivity caused by their structural stabilities and corresponding thermochemical parameters.

It has been found out that DFT calculations reproduce well the mentioned parameters. The larger 6-311++G** basis set is much more recommended, because it gives slightly better results then does the other employed cases. The activity and stability as well as vibratational frequencies of the drug are strongly affected under thermochemical properties at the specific temperature.

Table 4. NBO analysis displaying the ratio of Core / Charge and Valence / Charge of some atoms involved in drug´s structures at three theoretical models.

Drugs	Atoms	Basis set	RHF		B3LYP		SVWN	
			Core / Charge	Valence / Charge	Core / Charge	Valence / Charge	Core / Charge	Valence / Charge
Lorazepam	N_4	3-21G	-2.669	-7.670	-3.160	-8.899	-3.341	-9.353
		6-311G	-2.892	-8.215	-3.318	-9.283	-3.398	-9.484
		6-311++G**	-2.841	-8.079	-3.231	-9.061	-3.300	-9.235
	N_{14}	3-21G	-4.423	-12.049	-5.249	-14.114	-6.563	-17.398
		6-311G	-4.398	-11.972	-5.000	-13.474	-5.350	-14.347
		6-311++G**	-4.141	-11.310	-4.758	-12.853	-5.176	-13.896
	O_{12}	3-21G	-3.192	-10.576	-3.840	-12.516	-4.420	-14.260
		6-311G	-3.007	-10.011	-3.429	-11.279	-3.543	-11.622
		6-311++G**	-2.888	-9.645	-3.310	-10.914	-3.457	-11.355
	O_{22}	3-21G	-2.743	-9.227	-3.019	-10.055	-3.126	-10.375
		6-311G	-2.751	-9.247	-2.871	-9.605	-2.876	-9.623
		6-311++G**	-2.693	-9.066	-2.815	-9.431	-2.829	-9.477
	Cl_{20}	3-21G	2.222	1.552	5.160	3.596	-80.708	-56.538
		6-311G	-48.495	-34.003	36.495	25.508	-88.026	-61.616
		6-311++G**	-54.913	-38.416	29.239	20.403	-83.123	-58.166
	Cl_{25}	3-21G	2.941	2.054	4.156	2.895	-78.123	-54.636
		6-311G	-45.227	-31.721	12.515	87.413	-15.128	-10.590
		6-311++G**	-57.173	-39.999	97.939	68.280	-15.723	-10.993
Temazepam	N_4	3-21G	-3.326	-9.311	-4.265	-11.659	-4.848	-13.117
		6-311G	-3.611	-10.012	-4.427	-12.053	-5.024	-13.547
		6-311++G**	-3.474	-9.663	-4.240	-11.581	-4.766	-12.895
	N_{14}	3-21G	-3.735	-10.330	-4.422	-12.048	-4.692	-12.723
		6-311G	-3.713	-10.264	-4.221	-11.533	-4.409	-12.001
		6-311++G**	-3.570	-9.891	-4.111	-11.245	-4.295	-11.704
	O_{12}	3-21G	-3.221	-10.663	-3.880	-12.639	-4.229	-13.686
		6-311G	-3.023	-10.063	-3.460	-11.374	-3.655	-11.959
		6-311++G**	-2.906	-9.698	-3.344	-11.015	-3.560	-11.661
	O_{23}	3-21G	-2.705	-9.113	-3.002	-10.002	-3.067	-10.198
		6-311G	-2.641	-8.917	-2.759	-9.271	-2.787	-9.354
		6-311++G**	-2.606	-8.806	-2.726	-9.166	-2.755	-9.252
	Cl_{24}	3-21G	-17.093	-11.954	12.468	87.049	27.730	19.280
		6-311G	-31.745	-22.293	-10.788	-75.527	50.760	35.388
		6-311++G**	-36.750	-25.743	-13.908	-9.720	45.723	31.816
Oxazepam	N_4	3-21G	-2.667	-7.667	-3.158	-8.894	-3.357	-9.393
		6-311G	-2.892	-8.212	-3.317	-9.279	-3.511	-9.766
		6-311++G**	-2.840	-8.076	-3.239	-9.078	-3.344	-9.343
	N_{14}	3-21G	-4.074	-11.179	-4.848	-13.113	-5.212	-14.022
		6-311G	-4.050	-11.102	-4.625	-12.537	-4.931	-13.301
		6-311++G**	-3.864	-10.620	-4.455	-12.098	-4.750	-12.833
	O_{12}	3-21G	-3.185	-10.553	-3.831	-12.491	-4.128	-13.383
		6-311G	-2.996	-9.980	-3.417	-11.243	-3.584	-11.743
		6-311++G**	-2.880	-9.622	-3.360	-11.059	-3.595	-11.764
	O_{21}	3-21G	-2.729	-9.184	-2.999	-9.994	-3.050	-10.146
		6-311G	-2.733	-9.192	-2.849	-9.541	-2.876	-9.621
		6-311++G**	-2.678	-9.020	-2.824	-9.457	-2.858	-9.559
	Cl_{20}	3-21G	32.361	22.601	56.591	39.454	20.742	14.395
		6-311G	-44.741	-31.379	12.345	86.310	31.065	21.619
		6-311++G**	-50.682	-35.465	20.964	14.624	40.848	28.416

So, out of the many desired drug physico-chemical parameters that is relate to the structural stability and then their optimal bioactivity, we have considered here a subset of thermochemical properties that have to be fulfilled in many biological systems. In other words, through thermochemical calculations it must be guaranteed that anxileotic drugs are active under some thermochemical conditions that is, at body or any critical temperatures. Moreover, IR spectra of all three drugs similar but show small differences. A through 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 the theoretical spectra, which allowed us to validate the computational approach presented in this study. Clearly, high structural stability associated with a broad spectrum of chemical activity is the most important prerequisite for low toxicity of the drug and seems sufficient to guarantee biological activity under suitable thermochemical condition. Hence, we are willing to explain this point later.

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