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Quantum chemical study by Density Functional Theory (DFT) of some benzodiazepine derivatives

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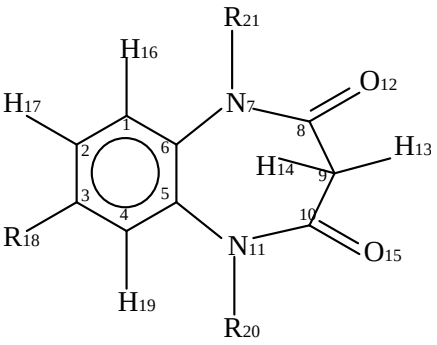
Abstract
Geometries and properties depending on the electron density for some benzodiazepine derivatives are optimized and obtained by RHF/STO-3G quantum calculations. The results indicate a strong polarization between carbonyl and phenyl ring which determines to a great extent the expected reactivity. Electrostatic potentials, atomic charges and dipole moments permit qualitative predictions about the reactivity of these derivatives.

Keywords: *Benzodiazepine, RHF/STO-3G, Geometrical parameters, Atomic charge, Electron density, Electrostatic potential, Dipole moments.*

1. Introduction
Density functional theory (DFT) has become very popular in recent years. This is justified based on the pragmatic observation that it is less computationally intensive than other methods with similar accuracy. This theory has been developed more recently than other ab initio methods. Because of this, there are classes of problems not yet explored with this theory, making it all the more crucial to test the accuracy of the method before applying it to unknown systems [1]. The most fundamental difference between DFT and MO theory must never be forgotten: DFT optimizes an electron density while MO theory optimizes a wave function. So, to determine a particular molecular property using DFT, we need to know how that property depends on the density, while to determine the same property using a wave function, we need to know the correct quantum mechanical operator [2]. The 1,5-benzodiazepin-2,4-dione is a none planar molecule composed of a phenyl ring linked with a seven numbered heterocycle (compound **1** in Fig. 1). We were interested by the molecular properties of these compounds since several publications recently indicated that some benzodiazepine derivatives have been studied because of their biological activity as carcinostatic compounds [3, 6] and were highly effective for the relief of anxiety [7-13]. They have a lower potential for addiction than many other drugs that were used earlier and are less likely to cause death or serious, lasting harm when taken in overdoses. There are now several dozen benzodiazepine drugs in clinical use worldwide, although use has become less popular because of side effects, including dependence. The various compounds appear to differ primarily in their pharmacokinetics, that is, the speed with which they are taken up and eliminated by the body, rather than in differences in their clinical effects [14]. This pharmacological interest has motivated the search for methods of synthesis of substituted benzodiazepines [15-20]. Because of this pharmacological interest, and in absence of fundamental spectroscopic data in the literature on these compounds, we considered it useful in this work to discuss some of their molecular properties of potential interest. Recently, the energy and spectroscopic study was made by the Kenitra's group [21-25], these last could explore of advantage the reactivity and the mechanisms implying the part of benzodiazepine in the biological systems like those mentioned above. For this purpose, we studied molecular properties obtained in quantum calculations for the five compounds

represented in figure 1, i.e., benzodiazepine **1** itself as well as its four derivatives: the 3-chloro-benzodiazepine **2**, the 3-methyl-benzodiazepine **3**, the 7-methyle-benzodiazepine **4** and the 7,11-dimethylbenzodiazepine **5**.



Compound	R_{18}	R_{20}	R_{21}
1	H_{18}	H_{20}	H_{21}
2	Cl_{18}	H_{20}	H_{21}
3	$Me(C_{18}H_{22}H_{23}H_{24})$	H_{20}	H_{21}
4	H_{18}	H_{20}	$Me(C_{21}H_{22}H_{23}H_{24})$
5	H_{18}	$Me(C_{20}H_{22}H_{23}H_{24})$	$Me(C_{21}H_{25}H_{26}H_{27})$

Fig.1. General formula for benzodiazepine derivatives.

2. Theoretical methodology

DFT methods were used in this study. These methods have become very popular in recent years because they can reach exactitude similar to other methods (ab initio, QSAR: quantitative structure–activity relationships) in less time and less expensive from the computational point of view. In agreement with the DFT results, energy of the fundamental state of a polyelectronic system can be expressed through the total electronic density, and, in fact, the use of electronic density instead of wave function for calculating the energy constitutes the fundamental base of DFT [26]. Molecular geometries were optimized by using analytical gradients in DFT calculations with the hybrid RHF functional and STO-3G gaussian basis sets. This level of theory is known to provide reliable theoretical results for medium size organic compounds in quantum calculations that include electron correlation at a moderate computational effort [27]. The geometry optimization was performed for compound **1** with symmetry restrictions to keep the regular hexagon structure in phenyl ring. Then, after checking in **2** that the changes in the geometrical parameters of both rings were negligible when the geometry was reoptimized in the presence of a methyl group in R_{18}, only variables concerning R_{18}, R_{20} and R_{21} groups were optimized while keeping frozen both rings in **2**, **3**, **4** and **5**. Although this optimization procedure is obviously approximated, our main interest here is to explore changes produced by the substituent in terms of properties obtained from ρ(r) rather than providing accurate geometries. Insofar as the structures thus obtained provide reliable enough models of the molecules considered, the properties studied are expected not to change noticeably when fully optimized geometries should be used instead. The RHF/STO-3G electron density was obtained in single point calculations at these geometries for subsequent atoms in molecules (AIM) [28, 29] and natural bond orbital (NBO) analyses [30] as well as for the determination of electrostatic potentials [31-33].
The AIM theory developed by Bader and co-workers [28] since the early 1970s has grown into a mature theory firmly rooted in quantum mechanics and currently widely used as a rigorous and elegant tool to extract from ρ(r) a great deal of information of interest in chemistry. The theory has been exposed in depth by Bader and reviewed at an introductory level by Popelier [29], so we present succinctly the particular properties considered here. The NBO analysis put forward by Weinhold and coll [30, 33] uses the one-electron density matrix for defining atomic orbital in the molecular environment and deriving bonds from the ρ(r) between atoms. It applies an orthogonalization scheme to define an orthonormal basis in which the matrix representation of the one-electron matrix is diagonal [33]. The orbitals in this orthonormal set are the natural orbitals and the diagonal elements of the density matrix in this basis are the orbital populations [30, 33]. Summing all the contributions from orbitals belonging to a specific center gives its natural population analysis (NPA) atomic charge. From the abundant literature on the different population schemes for computing atomic

charges in organic molecules, a consensus has been reached in recent years about the superiority of NPA and AIM charges not only due to their firm theoretical grounds but also because of their stability and good performance regarding conformational and structural changes [34, 35]. The DFT calculations to optimize geometries and obtain the electron density as well as the NBO analyses were performed with the GAUSSIAN03 package [36].

3. Results and discussion

The geometrical parameters of the benzodiazepine and its four derivatives obtained after optimization by the method of calculation RHF/STO-3G are collected in table 1 (bond lengths and angles obtained by symmetry were neglected). The phenyl cycle presents the regular hexagonal geometry with standard CC bond length about 1.38Å, while in the heptagonal cycle which contains the two nitrogen atoms, only the $C_5C_6N_7$ and $N_{11}C_5C_6$ bond angles present a value close to that of regular hexagonal (120°), with an CNC angle increased of 3.5° but $N_7C_8C_9$ and $C_9C_{10}N_{11}$ angles decreased of 5°.

Table 1: Geometrical parameters for compounds in Fig.1 optimized at the RHF/STO-3G level of theory (atom numbering refers to Fig.1), Bond lengths in Å, angles in degrees.

Compound	Bond length r		Bond angle θ, dihedral τ	
1	r (CC) phenyl cycle	≈ 1.3845	θ (CCC) phenyl cycle	≈ 120.00
	r (CH) phenyl cycle	≈ 1.0824	θ (CCH) phenyl cycle	≈ 120.00
	r (C_5C_6)	1.4044	θ ($C_5C_6N_7$)	120.63
	r (C_6N_7)	1.4381	θ ($C_6N_7C_8$)	123.54
	r (N_7C_8)	1.4332	θ ($N_7C_8C_9$)	115.14
	r (C_8C_9)	1.5437	θ ($N_7C_8O_{12}$)	120.97
	r (C_8O_{12})	1.2179	θ ($C_8C_9C_{10}$)	113.01
	r (C_9H_{13})	1.0863	θ ($C_8C_9H_{13}$)	108.43
	r (N_7H_{21})	1.0233	θ ($C_6N_7H_{21}$)	114.02
			τ ($C_6N_7C_8C_9$)	-18.25
			τ ($C_6N_7C_8O_{12}$)	162.53
			τ ($N_7C_8C_9H_{13}$)	179.95
			τ ($N_7C_8C_9H_{14}$)	61.72
2	r (C_3Cl_{18})	1.7816	θ ($C_2C_3Cl_{18}$)	119.62
3	r (C_3C_{18})	1.5266	θ ($C_2C_3C_{18}$)	120.54
	r ($C_{18}H_{22}$)	1.0851	θ ($C_3C_{18}H_{22}$)	110.90
	r ($C_{18}H_{23}$)	1.0881	θ ($C_3C_{18}H_{23}$)	110.62
			θ ($H_{22}C_{18}H_{23}$)	108.39
			τ ($C_2C_3C_{18}H_{22}$)	170.53
			τ ($C_2C_3C_{18}H_{23}$)	-69.40
4	r (N_7C_{21})	1.4733	θ ($C_6N_7C_{21}$)	118.81
	r ($C_{21}H_{22}$)	1.0887	θ ($N_7C_{21}H_{22}$)	108.36
	r ($C_{21}H_{23}$)	1.0927	θ ($N_7C_{21}H_{23}$)	112.64
			θ ($H_{22}C_{21}H_{23}$)	108.53
			τ ($C_6N_7C_{21}H_{22}$)	158.56
			τ ($C_6N_7C_{21}H_{23}$)	-81.80
5	r (N_7C_{21})	1.4746	θ ($C_6N_7C_{21}$)	118.51
	r ($C_{21}H_{22}$)	1.0888	θ ($N_7C_{21}H_{22}$)	108.42
	r ($C_{21}H_{23}$)	1.0926	θ ($N_7C_{21}H_{23}$)	112.84
			θ ($H_{22}C_{21}H_{23}$)	108.51
			τ ($C_6N_7C_{21}H_{22}$)	160.25
			τ ($C_6N_7C_{21}H_{23}$)	-80.03

Optimization establishes the methyl groups in a new conformation (the dihedrals angles are practically about 60°), but normal deviations of the regular tetrahedron were noted in compound **3**, the methyl groups in compounds **4** and **5** preserve the tetrahedral angles without essential change but with a light increase of 1°. This result is explained in terms of the repulsive effects resulting from the π electronic cloud in the phenyl cycle. A geometrical characteristic which deserves to be mentioned in compounds **4** and **5** relates to the CN bond lengths: then let us notice the distance between the nitrogen and the methyl group (about 1.47Å) is clearly larger than that located in the cycle (1.38 and 1.40Å). These data are in good agreement with those obtained by X-ray diffraction results [37-39]. On table 2, we gather the local electron density of the critical points of connections BCPs (bonds with hydrogen atoms in phenyl cycle were neglected).

Table 2: Local values (a.u.) of electron density ρ_c at BCPs for compounds in Fig.1.

Bond	**1**	**2**	**3**	**4**	**5**
C_1C_2	0.5109	0.5094	0.5143	0.5108	0.5101
C_2C_3	0.5096	0.5089	0.5050	0.5095	0.5100
C_3C_4	0.5109	0.5090	0.5117	0.5107	0.5101
C_3R_{18}	0.3958	0.2443	0.3773	0.3957	0.3958
C_4C_5	0.5082	0.5079	0.5069	0.5083	0.5072
C_5C_6	0.4964	0.4941	0.4986	0.4961	0.4955
C_1C_6	0.5082	0.5084	0.5062	0.5068	0.5073
C_6N_7	0.3605	0.3630	0.3600	0.3634	0.3599
N_7C_8	0.3438	0.3423	0.3442	0.3521	0.3477
N_7R_{21}	0.3454	0.3458	0.3453	0.3355	0.3337
C_8C_9	0.3479	0.3481	0.3478	0.3488	0.3486
C_8O_{12}	0.4432	0.4442	0.4430	0.4414	0.4419
C_9C_{10}	0.3479	0.3482	0.3479	0.3479	0.3486
$C_{10}N_{11}$	0.3438	0.3421	0.3441	0.3387	0.3477
$C_{10}O_{15}$	0.4432	0.4443	0.4430	0.4437	0.4419
$N_{11}C_5$	0.3605	0.3631	0.3606	0.3566	0.3599
$N_{11}R_{20}$	0.3454	0.3459	0.3455	0.3429	0.3337

The values of $\rho_c = \rho(r_c)$ can be used to control the increase or the decrease relating to the charge accumulation due to the presence of a substituent when $V_c = V(r_c)$ includes the effect of core and giving thus an evaluation of the final electrostatic balance. The general characteristics of the various values in table 2 are similar to the covalent bonds [28, 29]. The values of ρ_c obtained are between 0.2 and 0.5 a.u.. To be able to discuss the particular and distinctive characteristics rising from table 2, let us initially analyze the heptagonal cycle: NC bonds with methyl groups R_{20} and R_{21} in compounds **4** and **5** are qualitatively different from NC bonds in the cycle. Indeed, the electron density is approximately 10% lower in the above mentioned case. Concerning the six numbered rings, it is interesting to mention that the local properties of the BCPs can constitute a means of an extreme sensitivity to analyze the bonds. The condensed cycle in the benzodiazepine **1** forces CC bonds in phenyl to be grouped in four categories: (i) $C_1C_2 = C_3C_4$, (ii) C_2C_3, (iii) $C_1C_6 = C_4C_5$ and (iv) C_5C_6, this same remarks is met in compound **5**, and thus symmetry is carried out. CC bonds show successively the low values of ρ_c in this order with a clear difference between C_5C_6 and the remainder of the bonds. The lack of symmetry produced by the presence of a substituent in R_{18} in compounds **2** and **3** makes the six CC bonds different; this structural behaviour influences primarily the electronic properties. The only exception lies in substitution by a chlorine atom which returns the values of ρ_c in C_2C_3, identical C_3C_4. This result is the consequence of the proximity of R_{18} to segment $C_3C_4C_5$ of the aromatic nucleus. On the contrary, the existence of a Chlorine atom in compound **2** compete the N_7 and N_{11} atoms by producing important electrostatic potentials on the level of the bonds close to position 3. As for C_3R_{18} bond, while compounds **1**, **4** and **5** exhibit features typical character of C-H bonds [28], whereas in compound **3**, C_3C_{18} single bond presents low values of ρ_c. The large C_3Cl_{18} bond length in compound **2** along with the electronegative character of chlorine makes this single bond to exhibit the lowest values of ρ_c in table 2. Table 3 gathers the values of electrostatic potential for each atom of the studied molecules.

Table 3: Local values (a.u) of electrostatic potential V_c for each atom for compounds in Fig.1.

Atom	**1**	**2**	**3**	**4**	**5**
C_1	-14.53695	-14.51440	-14.53898	-14.53890	-14.54014
C_2	-14.53834	-14.51021	-14.54579	-14.53981	-14.53999
C_3	-14.53834	-14.46507	-14.53085	-14.53827	-14.53999
C_4	-14.53695	-14.50943	-14.54423	-14.53800	-14.54015
C_5	-14.48511	-14.46195	-14.48755	-14.48808	-14.49100
C_6	-14.48512	-14.46497	-14.49018	-14.48799	-14.49102
N_7	-18.06529	-18.05203	-18.06763	-18.06407	-18.06745
C_8	-14.41402	-14.40326	-14.41597	-14.42071	-14.42319
C_9	-14.49696	-14.48704	-14.49853	-14.50011	-14.50347
C_{10}	-14.41402	-14.40312	-14.41545	-14.41635	-14.42318
N_{11}	-18.06527	-18.05155	-18.06684	-18.06852	-18.06743
O_{12}	-22.04692	-22.03449	-22.04929	-22.05888	-22.05679
H_{13}	-1.11956	-1.10994	-1.12110	-1.12224	-1.12539
H_{14}	-1.10737	-1.09765	-1.10894	-1.10999	-1.11283
O_{15}	-22.04696	-22.03421	-22.04879	-22.04461	-22.05682
H_{16}	-1.12271	-1.10310	-1.12478	-1.12523	-1.12578
H_{17}	-1.12879	-1.10109	-1.13395	-1.13013	-1.13029
R_{18}	-1.12879	-63.32383	-14.52020	-1.12867	-1.13029
H_{19}	-1.12271	-1.09558	-1.12789	-1.12322	-1.12578
R_{20}	-1.04620	-1.03309	-1.04769	-1.04934	-14.48472
R_{21}	-1.04621	-1.03354	-1.04839	-14.48376	-14.48472

One can note like side effect, that the presence of methyl groups in compounds **4** and **5** involves a light increase of V_c in the heptagonal cycle (compare the five values of C_5, C_6, C_8, C_9 and C_{10} atoms). The changes induced in this cycle by the substituent in R_{18} are less important. However, the presence of a chlorine atom in compound **2** generates a considerable reduction in V_c in the C_5, N_{11}, C_{10} and O_{15} atoms. Table 4 gathers the general model given by NPA atomic charges of the benzodiazepine and its four derived.

Table 4: NPA atomic charges for compounds in Fig.1 (atom numbering refers to Fig.1)

Atom	**1**	**2**	**3**	**4**	**5**
C_1	-0.0730	-0.0664	-0.0719	-0.0714	-0.0735
C_2	-0.0622	-0.0561	-0.0698	-0.0636	-0.0627
C_3	-0.0622	0.0462	0.0162	-0.0614	-0.0627
C_4	-0.0730	-0.0676	-0.0799	-0.0745	-0.0735
C_5	0.0953	0.1038	0.0960	0.0926	0.0938
C_6	0.0952	0.1004	0.0905	0.0953	0.0937
N_7	-0.3535	-0.3525	-0.3537	-0.2957	-0.2947
C_8	0.3077	0.3090	0.3074	0.3068	0.3040
C_9	-0.1579	-0.1578	-0.1578	-0.1579	-0.1580
C_{10}	0.3077	0.3093	0.3076	0.3048	0.3040
N_{11}	-0.3536	-0.3522	-0.3537	-0.3517	-0.2947
O_{12}	-0.2552	-0.2499	-0.2564	-0.2643	-0.2621
H_{13}	0.0965	0.0994	0.0960	0.0956	0.0945
H_{14}	0.0832	0.0841	0.0830	0.0831	0.0826
O_{15}	-0.2553	-0.2492	-0.2561	-0.2534	-0.2621
H_{16}	0.0653	0.0743	0.0646	0.0702	0.0697
H_{17}	0.0686	0.0890	0.0644	0.0679	0.0678
R_{18}	0.0686	-0.1498	-0.1842	0.0687	0.0678
H_{19}	0.0653	0.0853	0.0611	0.0647	0.0697
R_{20}	0.1962	0.2007	0.1959	0.1924	-0.0788
R_{21}	0.1962	0.1996	0.1955	-0.0778	-0.0788

We note by the analysis of this table that carbonyl carbons C_8 and C_{10} present the most important positive values, which are of approximately +0.31e. That is due to their simultaneous proximity with the two oxygen atoms and the two nitrogen atoms. Indeed, these last four atoms present high negative charges about -0.25e and -0.35e, as well as C_9 carbon presents an important negative value about -0.16e whereas carbons C_5 and C_6 separating by the two cycles of the molecule are positively charged. This charge which is of approximately +0.10e is due to their bond with the two nitrogen N_7 and N_{11} atoms. Consequently, other carbons of phenyl have negative charges producing in their turn of the polarized CH bonds. The effect of substituent on these electron populations can be summarized as follows: The chlorine in compound **2** and the methyl group in compound **3** substituted respectively at position 3 do not cause the same qualitatively changes on the level of carbon atoms on phenyl cycle. Indeed, the polarization in C_3R_{18} bond disappears and carbons at Ortho and Para positions lose and gain electronic charges. Thus, C_2 and C_4 carbons become less negative by losing 0.0061 and 0.0054e in compound **2** and more negative by gaining 0.0076 and 0.0069e in compound **3**, while C_6 carbon becomes more positive of 0.0052e in compound **2** and less positive of 0.0047e in compound **3**. The carbon atoms at Meta position lose electronic charge; C_1 carbon becomes less negative of 0.0066e in compound **2** and 0.0011e in compound **3** and finally C_5 more positive of 0.0085e in compound **2** and only of 0.0007e in compound **3**. The atoms in the heptagonal heterocyclic remain primarily unchanged when R_{18}=CH_3 whereas it undergo a light loss electronic charge when R_{18}=Cl. This loss is noticed particularly on the level of the two atoms of oxygen whose negative charges decrease by 0.0053 and 0.0061e. Compounds **4** and **5** present in a clear way the most important atomic charge variations; in compound **4**, the methyl group related to the nitrogen atom makes decrease the negative charge of this atom of approximately 0.06e while the carbonyl group becomes more polarized by gaining 0.0009e in favour of C_8 carbon and 0.0091e of the O_{12} atom. In the compound **5**, a methyl group related to the nitrogen atom makes decrease the negative charge of this atom of approximately 0.06e while a carbonyl group becomes more polarized by gaining 0.0037e in favour of C_8 and C_{10} carbons and 0.0069e of the O_{12} and O_{15} atoms. These changes affect phenyl with small proportions and this according to the distance of the carbon atoms. Thus, the positive charges of divided carbons C_5=C_6 decrease by 0.0015e, the negative charges of C_1=C_4 increase 0.0005e and those of C_2=C_3 are more negative of 0.0005e.

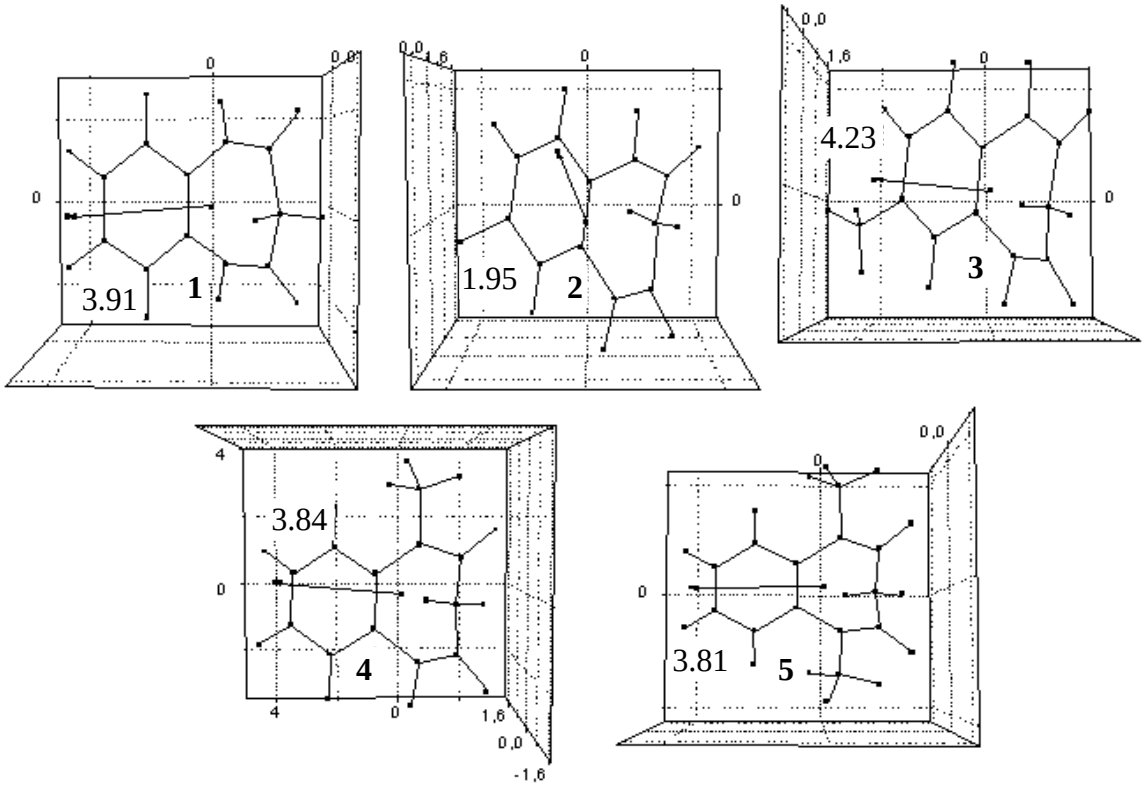


Fig. 2. Dipole moments μ (Debye units) in a three-dimensional representation, computed at the RHF/STO-3G level of theory for benzodiazepine derivatives in Fig. 1. μ Vectors are referred to the standard orientation of every molecule, i.e. the nuclear charge center for the molecule is at the origin of coordinates.

In view of these results, the picture of benzodiazepine derivatives displayed by NPA charges is one of a polarization between the leading carbonyl groups flanked by nitrogen atoms on the one side and the phenyl ring on the other side. Hence, the role played by substituent in R_{18} should be conditioned by this polarization which could explain why chlorine in **2** and methyl in **3** happen to behave apparently alike.
To confirm this result, we determined the dipole moment vectors in a three-dimensional representation of the benzodiazepine and its four derivatives (fig. 2). Dipole moment μ vectors computed at the RHF/STO-3G level displayed in figure 2 lend further support to this image. The dipole moment for **1** (3.91 D) is increased when more carbons are added away from carbonyl in **3** (4.23 D) with a weak orientation (+9°) and decreased when they are symmetrically placed in its immediate neighbourhood in **5** (3.81 D) and even effect at summer noted in the compound **4** (3.84 D) with a small orientation (-12°). However, the variations of μ in these two cases is considerably smaller than that found in **2** where the presence of electronegative chlorine in the opposite side with respect to carbonyl not only reduces dramatically the dipole moment (1.95 D) but also changes the vector orientation with large angle (-69°) (Fig. 2). The information provided by NPA charges as well as this change with regard to μ are in agreement with the known weak resonance effect of chlorine, already known [40, 41], as compared with its inductive effect.

Conclusion

The first high level theoretical study performed at RHF/STO-3G quantum calculations is presented for five benzodiazepine derivatives of potential interest in the chemical reactivity of related compounds. The analysis of various molecular properties depending on the DFT electron density shows a number of essential features worth to consider in further studies on the chemistry of these molecules. The most relevant one is the strong enhancement of polarization of carbonyl group due to the presence of two neighbouring nitrogen atoms and one condensed phenyl ring. This molecular arrangement is thus expected to increase considerably the reactivity of carbonyl in benzodiazepine derivatives. As a consequence, carbons in phenyl ring not shared by both rings are also polarized and display a negative character which permits viewing the molecule as a system displaying a polarization between the strong negative end of carbonyl and the weak negative domain of phenyl at the opposite side. This is reflected into the value and orientation of the computed dipole moments whose variation under the presence of the different substituent can be understood from this polarization point of view.
As for the role played by the substituent explored, methyl and chlorine at position 3 exhibit inductive effects much more important in the case of chlorine. This atom happens to heavily distort the electrostatic potential around phenyl on one side and reduce dramatically the molecular dipole moment on the other side, which agrees with the above viewpoint of competing polarization with carbonyl. Methyl groups at positions 7 and 11 provoke the greatest local changes directly affecting carbonyl charges and the electrostatic potential in neighbouring regions. These methyls not only enhance the large negative potential channels but also give place to two additional negative narrow domains near nitrogens. Despite these large changes on the electrostatic behavior, they happen to have a relatively minor effect on the molecular dipole moment.
As anticipated on the basis of this discussion, one could temptatively predict that the molecular reactivity of benzodiazepine **1** should change with the presence of substituent as follows. The behavior of compound **3** is expected to be very similar to **1**. Compound **2** should react in a manner qualitatively distinct to **1**, showing slightly different molecular interactions because of the smaller magnitude and modified spatial orientation of dipole moment as well as the large distortion of the electrostatic potential around phenyl. Compound **5** should react in the same qualitative manner than **1** but showing enhanced features because of the strong polarization of carbonyl atoms and the changes in the negative domain of electrostatic potential, heavily focused and increased.

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References

1. David Young C. (ed.), *Computational Chemistry*: A Practical Guide for Applying Techniques to Real-World Problems, Chap. 5 (Wiley, New York, 2001), p.42. ISBNs: 0-471-22065-5
2. Crame J.C. (ed.), *Essentials of Computational Chemistry*, Theories and Models, Chap. 8, 2nd edn. (Wiley, New York) (2004) 271
3. Di Braccio M., Grossi G., Roma G., Vargiu L., Mura M. and Elena Marongiu M., *Eur. J. Med. Chem.*, 36, 11-12 (2001) 935-949
4. Kiec-Kononowicz K., Karolak-Wojciechowska J., Müller C. E., Schumacher B., PeKala E. and Szymanska E., *J. Med. Chem.*, 36 (5) (2001) 407-419
5. Crupi V., Majolino D., Mondello M. R., Migliardo P., Venuti V., *J. Pharm. Biomed. Anal.*, 29 (6) (2002) 1149-1152

6. Jadidi K., Aryan R., Mehrdad M., Lügger T., Ekkehardt Hahn F., Weng S., *J. Mol. Struc*., 692 (1-3) (2004) 37-42
7. Cascade E., Kalali A.H., *Psychiatry*, 5 (2008) 21-22
8. Cloos J.M., Ferreira V., *Curr. Opin. Psychiatry.*, 22 (2008) 90-95
9. Marienfeld C.B., Tek E., Diaz E., Shottenfeld R., Chuwarski M., *Psychiatric Quarterly*, 83 (2012) 521-529
10. Paul Y., Tyagi S., Singh B., *Int. J. Pharma and Bio. Sci.*, 2 (2011) 20
11. Rao N.G.R., Ghurghure S.M., Munde M., Hadi A., *Int. J. Pharma and Bio. Sci.*, 2 (2011) 269
12. Gatzonis S.D., Angelopoulos E.K., Dakalopoulou E.G., Chioni A., *Drug. Alcohol. Depend.*, 59(1) (2000) 95-97
13. Nawrocka W., Sztuba B., Wietrzy K., *J. Arch. Pharm. Pharm. Med. Chem*., 334 (2001) 3-10
14. Kalachnik J.E., Hanzel T.E., Sevenich R., Harder S.R., American Journal on Mental Reatardation, 107(5) (2002) 376-410
15. Arshia Parveena, Vishal Patilb A., Mohammad Baseera A., Shaikh kabeer A., *Int. J. Ind. Chem.*, 2(3) (2011) 144-153
16. Hussenether T., Hübner H., Gmeiner P., Troschütz R., *Bioorgan. Med. Chem.*, 12 (10) (2004) 2625-2637
17. De Surya K., Richard Gibbs A., *J. Tetrahedron Lett.*, 46 (11) (2005) 1811-1813
18. Jarikote D. V., Siddiqui S. A., Rajagopal R., Daniel T., Lahoti R. J., Srinivasan K. V., *J. Tetrahedron. Lett.*, 44(9) (2003) 1835-1838
19. Balakrishna M. S., Kaboudin B., *J. Tetrahedron. Lett.*, 42 (6) (2001) 1127-1129
20. Benjaram Reddy M., Pavani Sreekanth M., *J. Tetrahedron. Lett.*, 44 (24) (2003) 4447-4449
21. Benali B., El assyry A., Boucetta A., Lazar Z., Lakhrissi B., Massoui M., and Mondieg D., *J. Spectrosc. Lett.*, 40(6) (2007) 893-901
22. El assyry A., Benali B., Boucetta A., Lazar Z., Lakhrissi B., Massoui M. and Mondieg D., *J. Spectrosc. Lett.*, 42(4) (2009) 203-209
23. El Assyry A., Benali B., Boucetta A., Mondieig D., *Res. Chem. Intermed.*, 40(3) (2014) 1043-1052
24. El Assyry A., Benali B., *Res. Chem. Intermed.*, 40(2) (2014) 627-636
25. El Assyry A., Benali B., Lazar Z., Elblidi K., Lakhrissi B., Massoui M., and Mondieig D., *J. Mol. Liq.*, 128 (2006) 46-49
26. g˘retir C. O¨., Bereket G., *J. Mol. Struct*., 488 (1999) 223-231
27. Soliva R., Orozco M., Luque F.J, *J. Comput. Chem*. 18 (1997) 980-991
28. Bader R.F.W., *Atoms in Molecules*. A Quantum Theory, Clarendon Press, Oxford, (1990)
29. Popelier P., *Atoms in Molecules*. An Introduction, Prentice-Hall, Harlow, (2000)
30. Reed A.E., Curtiss L.A., Weinhold F., *Chem. Rev*., 88 (1988) 899-926
31. Politzer P., Truhlar D.G., (Eds.), *Chemical Applications of Atomic and Molecular Electrostatic Potentials*, Plenum, News York, (1984)
32. Politzer P., Murray J.S., Lipkowitz K.B., Boyd D.B., (Eds.), *Reviews in Computational Chemistry*, VCH, New York, 2 (1991)
33. Reed A.E., Weinstock R.B., Weinhold F., *J. Chem. Phys*. 83 (1985) 735-746
34. Wiberg K.B., Rablen P.R., *J. Comput. Chem*. 14 (1993) 1504-1518
35. Pacios L.F., Gomez P.C., *J. Mol. Struct. (Theochem)* 544 (2001) 237-251
36. Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Montgomery J. A., Jr., Vreven T., Kudin K. N., Burant J. C.,. Millam J. M, Iyengar S. S., Tomasi J., Barone V., Mennucci B., Cossi M., Scalmani G., Rega N., Petersson G. A., Nakatsuji H., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Klene M., Li X., Knox J. E., Hratchian H. P., Cross J. B., Adamo C., Jaramillo J., Gomperts R., Stratmann R. E., Yazyev O., Austin A. J., Cammi R., Pomelli C., Ochterski J. W., Ayala P. Y., Morokuma K., Voth G. A., Salvador P., Dannenberg J. J., Zakrzewski V. G., Dapprich S., Daniels A. D., Strain M. C., Farkas O., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Ortiz J. V., Cui Q., Baboul A. G., Clifford S., Cioslowski J., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Martin R. L., Fox D. J., Keith T., Al- Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Gonzalez C., and Pople J. A., *Gaussian 03 (Revision. B.02), Gaussian, Inc*., Pittsburgh PA, (2003)
37. Mondieig D., Négrier Ph., Léger J. M., Benali B., Lazar Z., El Assyry A., Lakhrissi B., Massoui M., *J. Anal. Sci.*, 21 (2005) 145-146
38. Négrier Ph., Mondieig D., Léger J. M., Benali B., Lazar Z., Boucetta A., El Assyry A., Lakhrissi B., Jermouni C., Massoui M., *J. Anal. Sci*., 22 (2006) 175-176
39. El Assyry A., Benali B., Lakhrissi B., *Mor. J. Chem.*, 1 (1) (2013) 1-10
40. Pacios L. F., Lazar Z., Benali B., *J. Mol. Struct. (Theochem)*, 594 (2002) 89-100
41. Lazar Z., Benali B., Elblidi K., Zenkouar M., Lakhrissi B., Massoui M., Kabouchi B., Cazeau-Dubroca C., *J. Mol. Liq.*, 106/1 (2003) 89-95