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Theoretical investigation of the Cl and CH₃ substitutions effect on structural and energy behavior of benzodiazepine

Abdeslam El Assry · Bouziane Benali ·
Abdelkhalek Boucetta · Denise Mondieig

Abstract In this study, heat energy, atomic charges and dipole moments permit qualitative predictions about the substituent effects by a chlorine or methyl group on the benzodiazepine properties in the ground state. AM1 and MNDO semi-empirical methods of calculation are used to obtain information on the structural and energy properties for some benzodiazepine derivatives.

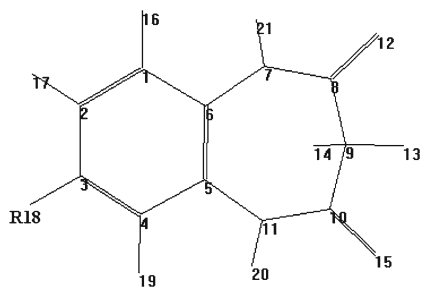
Keywords Benzodiazepine · 3-Chlorobenzodiazepine · 3-Methylbenzodiazepine · AM1 · MNDO · Conformational and energy properties · Dipole moment

Introduction

Benzodiazepine derivatives are known for their therapeutic properties, especially antitumor, anti-AIDS, antihypertensive, anti-inflammatory, analgesic agents, muscle relaxant, etc. [1, 2]. Several studies have been conducted on the chemistry of the benzodiazepine molecule justified by its interest in the field of biology. Indeed, some of its derivatives are known as effective antibacterial agents [3]. They can also be used as therapeutic agents for some diseases [4]. The chemistry of benzodiazepine has been the subject of intense interest, since this compound shows remarkable biological properties [5]. Although a large number of benzodiazepine-based derivatives have been reported in the literature, few crystal structures have been determined [6-9].

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Compound	R ₁₈
1	H ₁₈
2	Cl ₁₈
3	Me (C ₁₈ H ₂₂ H ₂₃ H ₂₄)

Fig. 1 Structure of benzodiazepine and its derivatives

The benzodiazepine molecule is non-planar and composed of a phenyl ring condensed with a seven-membered heterocycle. To our knowledge, little theoretical and experimental studies exist in the literature. This lack of information on structural and energetic properties of these molecules led us to use the semi-quantum methods AM1 and MNDO to develop them. These properties lead to information on some electronic deactivation processes and intramolecular charge transfer. We therefore propose to develop in this paper the structure, formation energy, dipole moment and charge distribution of the benzodiazepine molecule in the ground state. Then, we complete the work with a discussion of the effect of substitution by a chlorine atom or a methyl on the behavior of the structural and energy properties of the base molecule.

The calculation method AM1 (Austin Model 1) [10, 11] is part of the series of DEWAR [11, 12], in which the parameters are optimized to achieve the best agreement with experimental results, using the minimum computation possible time. Its application to other organic molecules has led to excellent results [13, 14]. In the conformational study of isolated benzodiazepine molecules, we adopted the basic geometry of the molecule structure determined in Fig. 1.

Results and discussion

The main parameters obtained by both methods of calculation and experimental results [15], characterizing the structure of the molecule of benzodiazepine in the ground state, are given in Table 1.

It can be seen from Table 1 that the geometry of benzodiazepine given by the AM1 method is very close to that obtained by MNDO calculations. The absolute differences between the lengths calculated by the two methods are less than 0.02 Å.

The geometric parameters of benzodiazepine and its two derivatives are collected in Table 2 (bond lengths and angles obtained by symmetry were neglected). The phenyl cycle presents the regular hexagonal geometry with standard CC bond length of about 1.38 Å, while in the heptagonal cycle which contains the two nitrogen atoms, only the C₅C₆N₇ and N₁₁C₅C₆ bond angles present a value close to that of the regular hexagonal (120°) with an CNC angle increased by 3.5° but the N₇C₈C₉ and C₉C₁₀N₁₁ angles decreased by 5°. Optimization establishes the methyl groups in

Table 1 Bond lengths (Å) and bond angles (°) of the benzodiazepine in its ground state

Bond lengths	MNDO	AM1	Exp	Bond angles	MNDO	AM1	Exp
C ₁ C ₂	1.364	1.3870	1.367	C ₆ C ₁ C ₂	121.05	121.18	120.9
C ₂ C ₃	1.377	1.3947	1.403	C ₁ C ₂ C ₃	119.96	120.095	119.6
C ₃ C ₄	1.363	1.3873	1.367	C ₂ C ₃ C ₄	119.96	120.092	119.6
C ₄ C ₅	1.393	1.4142	1.391	C ₃ C ₄ C ₅	121.05	121.185	120.9
C ₅ C ₆	1.395	1.4266	1.384	C ₄ C ₅ C ₆	118.58	118.713	119.5
C ₆ N ₇	1.384	1.4045	1.417	C ₅ C ₆ C ₇	122.51	122.64	122.3
N ₇ C ₈	1.356	1.3870	1.339	C ₆ N ₇ C ₈	125.30	125.438	126.0
C ₈ C ₉	1.473	1.5092	1.490	N ₇ C ₈ C ₉	119.39	119.525	117.2
C ₉ C ₁₀	1.472	1.5094	1.490	C ₈ C ₉ C ₁₀	111.61	111.742	109.4
C ₁₀ N ₁₁	1.359	1.3857	1.339	C ₉ C ₁₀ N ₁₁	119.28	125.697	117.2
N ₁₁ C ₅	1.384	1.4040	1.417	C ₁₀ N ₁₁ C ₅	125.56	122.643	126.0
C ₁ C ₆	1.393	1.4144	1.391	N ₁₁ C ₅ C ₆	122.51	118.668	122.3
C ₈ O ₁₂	1.224	1.2441	1.239	N ₇ C ₈ O ₁₂	118.53	118.668	122.0
C ₁₀ O ₁₅	1.224	1.2442	1.239	C ₉ C ₁₀ O ₁₅	121.77	121.907	121.8

a new conformation (the dihedral angles are practically about 60°), but normal deviations of the regular tetrahedron were noted in compound **3**. This result is explained in terms of the repulsive effects resulting from the π electronic cloud in the phenyl cycle. These values are comparable to those obtained for some similar molecules such as azulene, the benzimidazolones, and their derivatives [14, 16].

We examine later the distribution of the electronic charge distribution in the two cycles of benzodiazepine and its derivatives. The contour maps in Fig. 2 and the values compiled in Table 3 are obtained using the AM1 method.

We note by the analysis of this table that the carbonyl carbons C₈ and C₁₀ present the most important positive values, which are of approximately +0.31e. That is due to their proximity, at the same time, 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, while C₉ carbon presents an important negative value about -0.16e, whereas carbons C₅ and C₆ separated 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 N₇ and N₁₁ atoms. Consequently, other carbons of phenyl have negative charges producing in their turn the polarized CH bonds. The effect of substituents 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 the phenyl cycle. Indeed, the polarization in the C₃R₁₈ bond disappears and carbons at the ortho and para positions lose and gain electronic charges. Thus, C₂ and C₄ carbons become less negative by losing 0.0061e and 0.0054e in compound **2** and more negative by gaining 0.0076e and 0.0069e in compound **3**, while C₆ carbon becomes more positive with 0.0052e in compound **2** and less positive with 0.0047e in compound **3**. The carbon atoms at the meta

Table 2 Geometric parameters calculated for the benzodiazepine molecule and its derivatives.(the atom numbers refer to Fig. 1)

Bond lengths r(Å)	Angle $\theta(^{\circ})$, $\tau(^{\circ})$
1	
r(CC) \approx 1.38	θ (CCC) \approx 120.00
r(CH) \approx 1.08	θ (CCH) \approx 120.00
r(C ₅ C ₆) 1.39	θ (C ₅ C ₆ N ₇) 120.63
r(C ₆ N ₇) 1.402	θ (C ₆ N ₇ C ₈) 123.54
r(N ₇ C ₈) 1.401	θ (N ₇ C ₈ C ₉) 115.24
r(C ₈ C ₉) 1.523	θ (N ₇ C ₈ O ₁₂) 120.87
r(C ₈ O ₁₂) 1.217	θ (C ₈ C ₉ C ₁₀) 113.04
r(C ₉ H ₁₃) 1.086	θ (C ₈ C ₉ H ₁₃) 108.42
r(N ₇ H ₂₁) 1.023	θ (C ₆ N ₇ H ₂₁) 114.04
	τ (C ₆ N ₇ C ₈ C ₉) 18.25
	τ (C ₆ N ₇ C ₈ O ₁₂) 162.53
	τ (N ₇ C ₈ C ₉ H ₁₃) 179.95
	τ (N ₇ C ₈ C ₉ H ₁₄) 61.72
2	
r(C ₃ Cl ₁₈) 1.781	θ (C ₂ C ₃ C ₄) 120.436
	θ (C ₂ C ₃ Cl ₁₈) 119.601
3	
r(C ₃ C ₁₈) 1.526	θ (C ₂ C ₃ C ₁₈) 120.524
r(C ₁₈ H ₂₂) 1.085	θ (C ₃ C ₁₈ H ₂₂) 110.903
	θ (H ₂₂ C ₁₈ H ₂₃) 108.396
	τ (C ₂ C ₃ C ₁₈ H ₂₂) 170.53
	τ (C ₂ C ₃ C ₁₈ H ₂₃) 69.40

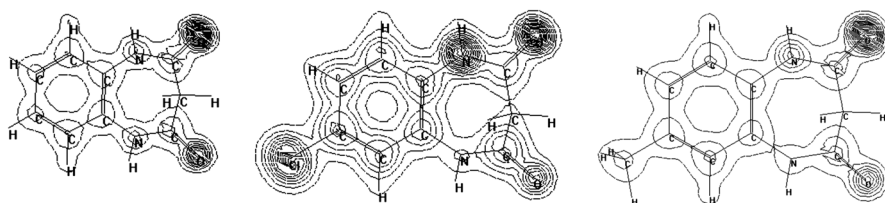


Fig.-2 Contour maps using AM1 of atomic charges in the plane of the two cycles of compounds 1–3

position lose electronic charge; C₁ carbon becomes less negative with 0.0066e in compound 2 and 0.0011e in compound 3 and finally C₅ more positive with 0.0085e in compound 2 and only 0.0007e in compound 3. The atoms in the heptagonal heterocyclic remain primarily unchanged when R₁₈ = CH₃ whereas they undergo a slight loss of electronic charge when R₁₈ = Cl. This table also shows that the net charge of the carbons in positions 2 and 3 is greater than that of other carbon atoms;

Table 3 Atomic charges calculated for the compounds (**1-3**) (the atom numbers refer to Fig. 1)

Atom	1	2	3
C ₁	0.073	0.066	0.071
C ₂	0.062	0.056	0.069
C ₃	0.062	0.046	0.016
C ₄	0.073	0.067	0.079
C ₅	0.095	0.103	0.096
C ₆	0.095	0.100	0.090
N ₇	0.353	0.352	0.353
C ₈	0.307	0.309	0.307
C ₉	0.157	0.157	0.157
C ₁₀	0.307	0.309	0.307
N ₁₁	0.353	0.352	0.353
O ₁₂	0.255	0.249	0.256
H ₁₃	0.096	0.099	0.096
H ₁₄	0.083	0.084	0.083
O ₁₅	0.255	0.249	0.256
H ₁₆	0.065	0.074	0.064
H ₁₇	0.068	0.089	0.064
R ₁₈	0.068	0.149	0.184
H ₁₉	0.065	0.085	0.061
H ₂₀	0.196	0.200	0.195
H ₂₁	0.196	0.199	0.195
H ₂₂			0.066
H ₂₃			0.070
H ₂₄			0.068

this may explain the high reactivity of benzodiazepine in these positions by preferential substitution at this level. The value of the corresponding angle is estimated at 121° for the most stable conformation of benzodiazepine to the ground state. However, our results assume that this is the angle at the N₇ of benzodiazepine which most influences its energy properties by participation in the lone pair of the nitrogen atom; this angle is estimated at 123°.

The search for the most stable geometrical conformations of benzodiazepine and its two derivatives, namely 3-chlorobenzodiazepine and 3-methylbenzodiazepine, to the ground state is achieved by varying the angle $\alpha(\text{C}_6\text{N}_7\text{C}_8)$ located at the endocyclic nitrogen atom N₇ between 119° and 131° (Fig. 3). This molecule is not flat but is symmetric, the variation of the intracyclic angle $\beta(\text{C}_5\text{N}_{11}\text{C}_{10})$ at N₁₁ gives the same results. The curve shows that the most stable conformation of benzodiazepine has a formation energy of about 47.758 kcal/mol with an endocyclic angle α of 125°.

Figure 3 also shows that the benzodiazepine molecule is the most stable of the three compounds having an energy of 47,758 kcal/mol in the ground state. For a

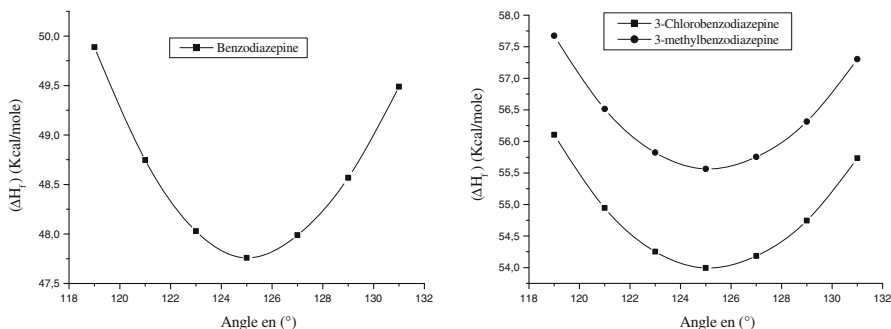


Fig. 3 Variation of the formation energy of benzodiazepine and two of its derivatives in the function of the intracyclic angle (in degrees)

general optimization of the structural parameters of the molecule, the AM1 gives a formation energy of the most stable conformation of 3-chlorobenzodiazepine of the order of 53,953 kcal/mol and of 3-methylbenzodiazepine of the order of 55,613 kcal/mol. In the absence of an experimental result and for comparison we have simply to check with the calculation method MNDO. The results obtained by the two methods are quite comparable.

Figure. 4 shows the dipole moment variation of benzodiazepine and its two derivatives in the ground state in the function of the angle α . The dipole moment value corresponding to the most stable conformation of compounds **1**, **2** and **3** are, respectively, 5.33, 4.14, and 5.73 Debye. A similar variation of the dipole moment was observed in the case of benzodiazepine in the function of the intracyclic angle β ($C_5N_{11}C_{10}$) located at the nitrogen atom to N_{11} .

The variation of the dipole moment (μ) as a function of the angle (α) differs from one compound to another. Indeed, this law is linear, increasing in the case of 3-chlorobenzodiazepine and decreasing in the case of 3-methylbenzodiazepine. In the case of benzodiazepine, the resulting curve actually represents the sum of the two curves obtained for its derivatives. This result appears quite logical because of the antagonistic effect of Cl and CH_3 substitutions on the charge distribution of benzodiazepine.

To confirm this result, we determined the dipole moment vectors in a three-dimensional representation of the benzodiazepine and its two derivatives isolated by the calculating method AM1. Figure 5 illustrates the results obtained; the vector dipole moment μ was compared with standard guidelines for each molecule in which the center of nuclear charge is the origin of coordinates.

The dipole moment for **1** (3.91 Debye) is increased when more carbons are added away from carbonyl in **3** (4.23 Debye) with a weak orientation ($+9^\circ$). However, the variation of μ in this case is considerably smaller than that found in **2**, in which the presence of electronegative chlorine in the opposite side with respect to carbonyl not only dramatically reduces the dipole moment (1.95 Debye) but also changes the vector orientation with a large angle (-69°). The information provided by NPA charges as well as this change with regard to μ are in agreement with the already known weak resonance effect of chlorine [16, 17], as compared with its inductive

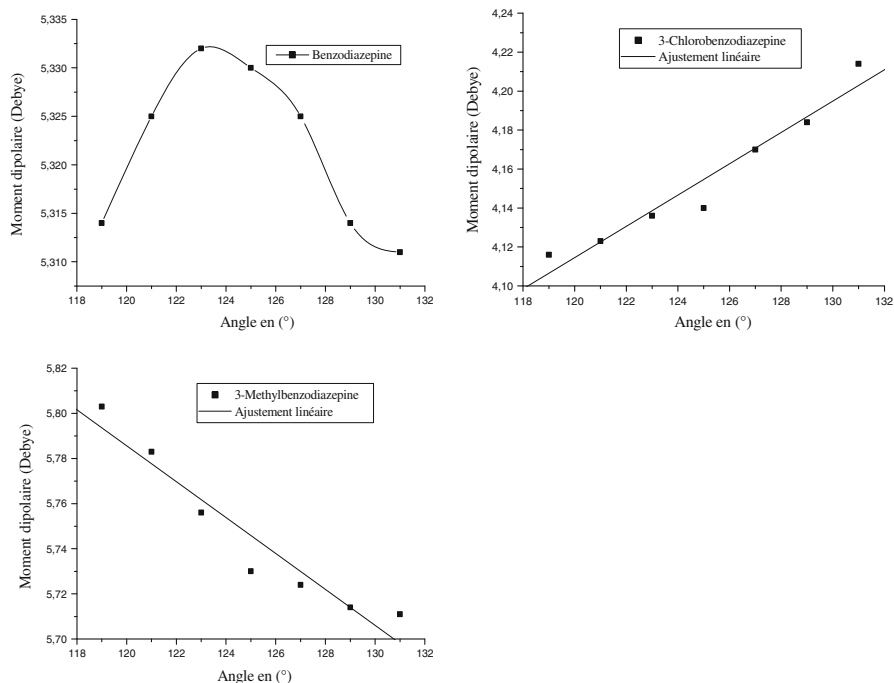


Fig. 4 Variation of the dipole moment of benzodiazepine and two of its derivatives in the function of the intracyclic angle α (in degrees)

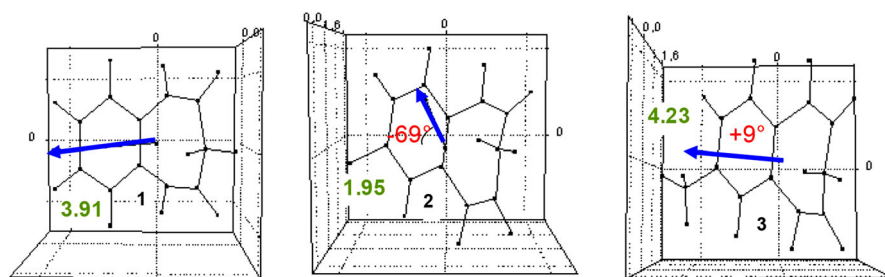


Fig. 5 Vector dipole moment μ (Debye) calculated by the AM1 method for compounds 1-3

effect. Accordingly, we note from this analysis two important effects of substitution on benzodiazepine. The first is that the substitution by a methyl group stabilizes more benzodiazepine and significantly enhances the value of its dipole moment with a small vector orientation. In contrast, if the substitution of the molecule by a chlorine atom decreases the value of its dipole moment, it causes a large change in its orientation vector.

To examine the substitution effect on the spectral behavior of the molecule in the ground state, we presented the absorption spectrum of benzodiazepine and its derivatives in solution in *n*-hexane and butanol. The spectrum of Fig. 6a, b shows a structure similar to that of the benzodiazepine molecule with a shift to the red of the

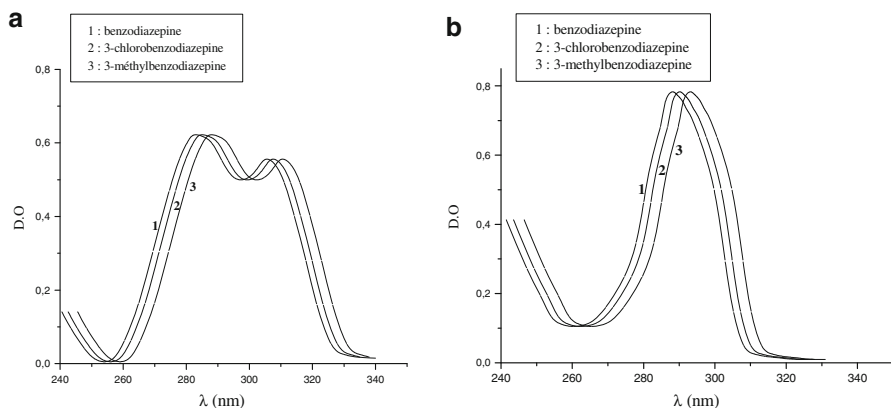


Fig. 6 Substitution effect on the absorption spectrum of benzodiazepine at room temperature, **a** in hexane and **b** in a protic and polar medium (butanol)

Table 4 Calculated and experimental values of energies and oscillator strengths of transitions ($S_0 \rightarrow S_1$) and ($S_0 \rightarrow S_2$) of the isolated compounds **1** **3**

Compounds	Transitions	CNDO/2			Exp E (ev)
		E (ev)	f.o	Log ϵ	
Benzodiazepine	($S_0 \rightarrow S_1$)	3.580	0.0155	3.189	3.278
	($S_0 \rightarrow S_2$)	4.628	0.1944	4.288	4.571
3 Chlorobenzodiazepine	($S_0 \rightarrow S_1$)	3.829	0.0099	2.994	3.514
	($S_0 \rightarrow S_2$)	4.507	0.1873	4.272	4.462
3 Methylbenzodiazepine	($S_0 \rightarrow S_1$)	3.961	0.0682	3.834	3.647
	($S_0 \rightarrow S_2$)	4.274	0.1846	4.266	4.231

maxima of strips by passing chlorine to methyl; this displacement is respectively 316 and 688 cm^{-1} .

This discrepancy is due to the disruption of the electron density of the carbon atom in position 3 following a steric caused by chlorine and methyl; This congestion hinders a charge transfer within the molecule in the inductive effect caused by the substitution; this effect results in a stable molecule in its ground state.

The solvent n-hexane is not capable of forming hydrogen bonds, does not have the same effect on the absorption spectrum of benzodiazepine and its derivatives as does butanol. This then suggests that the observed band in this solvent has an overlap of two bands corresponding to the complex formed by hydrogen bonding between the solute molecules and that of the solvent [18].

Table 4 summarizes the energy values (E) and oscillator strength (f.o) the two first electronic transitions ($S_0 \rightarrow S_1$) and ($S_0 \rightarrow S_2$) calculated for the equilibrium conformation of the isolated benzodiazepine derivatives molecules. These values are compared with experimental results deduced from its absorption spectrum in solution in n-hexane.

Analysis of Table 4 shows that the relative positions of the two first electronic transitions of benzodiazepine and its derivatives, given by calculating CNDO/2, are in good agreement with those observed.

Conclusion

The theoretical study presented in this work focuses on the structural and energy properties of the benzodiazepine molecule and two of its derivatives using the AM1 and MNDO methods for calculations. Analysis of these properties has led to the following observations:

- (i) The geometry of the benzodiazepine and its derivatives have a cycle of a regular hexagon whereas in the cycle heptagonal containing the two nitrogen atoms there is a deviation of angles CNC disrupting the maintenance of this heptagon.
- (ii) Disturbance at the level of the charge distribution of benzodiazepine is substantially on the two carbon atoms separating the two cycles under the effect of the substitution.
- (iii) The dipole moment in the ground state of the benzodiazepine molecule increases by substituting a methyl group with a slight change in the orientation of its vector. In contrast, the substitution of benzodiazepine by chlorine can not only drastically reduce the value of the dipole moment but also change the orientation of its vector with a wide angle.

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