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Research Article

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Hydrogen bonding sites in benzimidazolyl-chalcones molecules: An *ab initio* and DFT investigation

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ABSTRACT

In this work, we are interested in the geometrical, energetical and spectroscopic characterization of hydrogen bonding interactions in the family of benzimidazolyl-chalcones(BZC) substituted molecules. The BZC exhibit wide ranges of properties, and particularly, show important nematicidal activity properties. Four molecules from the family of BZC, with various activity, have been selected for this work, including (2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (BZC-1, LC_{100}= 0,002 μg/ml), (2E)-1-(1H-benzimidazol-2-yl)-3-(4-bromophenyl)prop-2-en-1-one (BZC-2, LC_{100}= 424,5 mcg/ml), (2E)-1-(1H-benzimidazol-2-yl)-3-(4-fluorophenyl) prop-2-en-1-one (BZC-3, LC_{100} =12,0 μg/ml), and(2E)-1-(1H-benzimidazol-2-yl)-3-(2-furyl) prop-2-en-1-one (BZC-4, LC_{100}= 2,87 μg/ml). The activity measuring is based on the lethal concentration for one hundred larvae (LC_{100})population. The geometrical, energetical and spectroscopic parameters of hydrogen bonds on each heteroatom (named H bond complexes) of these molecules have been determined by quantum chemical methods, particularly at HF/6-311+G(d,p) and MPW1PW91/6-311+G(d,p)theories levels. Choosing Hartree-Fock (HF) and Density Functional Theory methods(DFT/MPW1PW91) allowed accuracy results with relatively less time consuming. Furthermore. Taking into account basis set superposition error(BSSE), gives a quantitative results. Finally, sp^{2}nitrogen atom has been identified as the preferential hydrogen bonding site in the four studied benzimidazolyl-chalcones, even if carbonyl oxygen cannot be neglected.

Keywords: Benzimidazolyl-Chalcone, nematocides, quantum chemistry, Hydrogen bonding, BSSE.

INTRODUCTION

Nematodes (worm from hearth, freshwater or sea) are responsible for most of human parasitic diseases[1.2]. Nematodes are also known as the main cause of gastro-intestinal infections of small ruminants as well as loss and reduction in productivity of the livestock [3.4]. The development of an "ideal" anthelmintic seems to be possible with the benzimidazoles, imidazothiazoles, tetrahydropyrimidines and organophosphate compounds. Such an anthelmintic should possess a broad spectrum of action, a high degree of efficiency, a good safety margin and a flexibility of use. Till date, researches have led to synthesize several hundreds of compounds. A few have been selected for their effective anthelmintic activity at broad spectrum, and among them, the benzimidazolyl-chalcones (BZC) kernel.

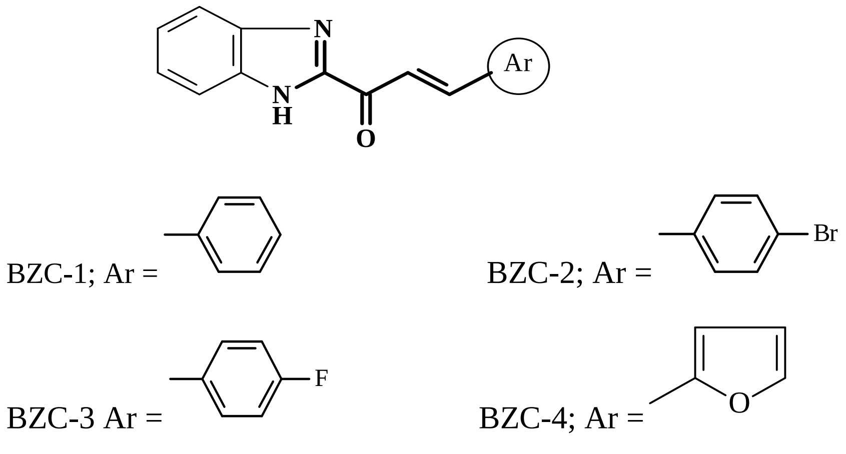

Figure 1: Structure of benzimidazolyl-chalcones studied

Molecules shown in figure 1have been synthesized by OUATTARA *and al.* [5]. The BZC derivatives have considerable pharmacological interest due to their therapeutic virtues. Several studies have demonstrated that the derivatives of benzimidazolyl are antihistaminic [6], antifungal [7], antiallergic[8], antibacterial [9-11] and antiviral [12]. These therapeutic properties could be related to the molecules' conformation of molecules and the interactions they can establish with other molecules. The hydrogen bonding (H bond) is of very importance in the matter cohesion [13]. In fact, the hydrogen bonding is one of the most important intermolecular interactions involved in supramolecular chemistry, protein-ligand [14]interactions and crystals engineering [15.16].Generally, molecules are polyfunctional, i.e these molecules contain several heteroatoms capable to receive H bond. Therefore, it is important to be able to characterize the H bonding preferential(s) site(s). There is very little work devoted to competition study between different sites within the same molecular structure. The first attempts to determine the H bond accepting power in different organic compounds are due to Etter and Reutzel [17]. More recently, studies on the competition between nitrogen and oxygen atoms [18-21] or amino nitrogen and nitrile nitrogen atoms [22] in different molecular structures have been reported. All the research works carried out specifically with the BZ Care focused only on the synthesis and the activity research. By implementing quantum chemistry methods, this work mainly focuses the determination of some chemical and physical properties of the BZC molecules, including the geometrical and energetical parameters of hydrogen bonding established on the different heteroatoms.

EXPERIMENTAL SECTION

2.Materials and methods of calculation

2.1. The calculation level

Geometry optimization of the monomers and H bond complexes, with a water molecule as a probe, as well as the calculations of the vibration frequencies have been carried out using the Gaussian 03software [23], in blank, at the HF/6-311+G(d, p)andMPW1PW91/6-311+G(d,p) theories levels. The choice of split-valence and triple-d zeta basis set is justified by the need of sufficiently extended levels. Diffuse and polarization functions are important, whenever the matter is intermolecular interactions. Each of the H bond complexes has been fully optimized, with a calculation of frequencies to the same levels of theories. Subsequently, a single point calculation has been carried out on each complex after optimization, at the two levels of theories mentioned above, using the keyword$counterpoise = 2$in order to obtain the BSSE.

2.2. Geometry optimization

The BZC kernel contains three heteroatoms and, all are prone to establish one H bond. Thus, three hydrogen bonds complexes have been constructed for each molecule using water molecule as hydrogen bond donor (HBD). The characteristic parameters of an H bond are shown in figure 2.

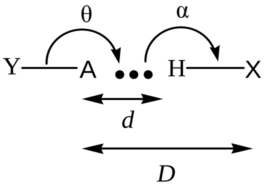

Figure 2: Geometrical parameters d, D, θ, α describing an H bond

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The optimal approach distances between the hydrogen bond acceptor HBA(atom A) and the hydrogen atom will correspond to the minimum electronic energy of the complex formed between the water and the site. Thus, the minimum average distances obtained for eithersp^2 or sp^{3}nitrogen atoms is 1.8 Å. This distance equals2.15 Åfor the oxygen atom. These different lengths correspond to the lengths of H bond as initial parameters in the optimization process. The linearity angle O-H $\cdots$ N/O (α) of the interactions is initialized at 180°. These are the optimal parameters available for a strong H bond[14]. However, the measured angles related to the direction(θ) of interactions have been defined and fixed(figure 3) to the average angles of 109° and 120° respectively for the sp^2 and sp^{3}nitrogen atoms, and 120° for the carbonyl oxygen.

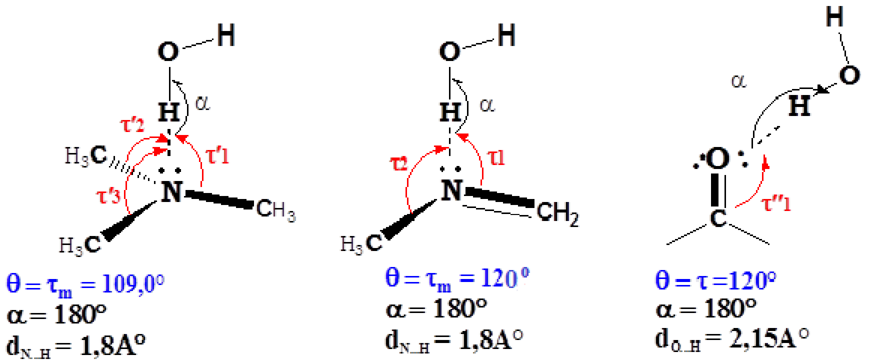


Figure 3: Definition of linearity and direction angles describing the interactions on the hydrogen bonding sites

2.3. Energetical parameters

Internal energy variation,ΔE^0, at 0 K, between hydrogen bonding complex and monomers can be calculated according equation (1).

$$Y - A + H - X \longrightarrow Y - A \ldots H - X$$
$$\Delta E^0 = E^0(Y - A \ldots H - X) - [E^0(Y - A) + E^0(H - X)] \qquad (1)$$

This energy is the sum of the electronic, rotational, translational and vibrational contributions given in equation (2):

$$E = E_{électronique} + E_{rotation} + E_{translation} + E_{vibration} \; (2)$$

Geometry optimization of both complexes and free molecules provides the electronic contribution to the interaction energy (containing nuclear repulsion energies).In ideal gas approximation, rotational and translational contributions are given according equation (3):

$$\Delta E_{translation} = \Delta E_{rotation} = -\frac{3}{2}RT \qquad (3)$$

ZPVE (Zero Point Vibrational Energy) contribution, i.e. lowest vibrational level energy, due to 3N-6 normal vibrational modes (3N-5 for the linear molecules), each with frequencyV_i,up to N kernels at 0 K, is defined according equation (4):

$$ZPVE = \frac{1}{2}R \sum_i^{3N-6} \frac{h\nu_i}{k} \qquad (4)$$

To obtain the corresponding energy at 298.15 K, it is necessary to take into account the extra energy due to vibrational levels population during temperature rising from 0 to 298.15 K. Thus, equation (4)becomes equation (5):

$$E_{vib.therm.} = R \sum_i^{3N-6} \frac{h\nu_i/k}{e^{(h\nu_i/298K)} - 1} \qquad (5)$$

As a result, internal energy variation at 298.15 K is given by equation (6):

$$\Delta E_{298}^0 = \Delta E_{él} + \Delta ZPVE + \Delta E_{vib.therm.} - 3RT \; (6)$$

Enthalpy variation and free enthalpy variation, at 298.15 K, are given respectively by equations (7) and (8):

$$\Delta H_{298}^{0} = \Delta E_{298}^{0} - RT \qquad (7)$$

$$\Delta G_{298}^{0} = \Delta H_{298}^{0} - T.\Delta S_{298}^{0} \qquad (8)$$

Where

$$\Delta S_{298}^{0} = \Delta S_{trans}^{0} + \Delta S_{rot}^{0} + \Delta S_{vib}^{0} (9)$$

When calculating energy according equation (1), one must take into account the basis set superposition error (BSSE). In this work, the BSSE has been corrected according to the counterpoise method proposed by Boys and Bernardi[24] in order to eliminate or decrease the BSSE. For a complex molecule A····B formed by two fragments A and B in interaction according to equation (10), the corrected interaction energy can be obtained following equation (11):

$$A + B \longrightarrow A \ldots B \ (10)$$

$$\Delta E^{CP}(AB) = \Delta E^{0}\,(AB) + \delta^{BSSE}(AB) \qquad (11)$$

The term $\delta^{BSSE}(AB)$is the BSSE, and$\Delta E^{0}\,(AB)$gives the non-corrected interaction energy.

2.4. Spectroscopic parameters

The spectroscopic descriptors are generally considered as H bond scale. An H bond causes an elongation of the X-H bond formed between the donor atom X and the hydrogen atom H. This leads to the reduction of a few hundreds of cm^{-1}of the stretch vibration wave-number as well as a significant increase in the intensity. However their implementation refers to the vibrational spectroscopy, where the displacement of elongation's frequency$\Delta\nu(X - H)$of the donor of H bond during the complexation process, is measured. When$\Delta\nu\ (X - H)$is negative, the shift of the frequency is in the red for the complex, whereas when$\Delta\nu(X - H)$is positive, the shift of the frequency is in the blue. The displacements$\Delta\nu(O - H)$have been calculated by using the symmetric vibrators of H_2O "free", and in the complex. At HF/6-311+G(d,p) and MPW1PW91/6-311+G(d,p) levels, frequencies of vibrator$\nu_s(\mathrm{O-H})_{\mathrm{free}}$equal respectively, 4140,47 cm^{-1}and 3884,43 cm^{-1}. The theoretical frequency displacements$\Delta\nu(O - H)$were calculatedaccording relations (12) and (13) below:

$$\Delta\upsilon_1(\mathrm{O-H}) = \nu_s(\mathrm{O-H})_{\mathrm{free}} - \mathrm{v}\big(\mathrm{O-H}\ldots\mathrm{N_{sp2}}\big)_{\mathrm{complex}} \qquad (12)$$

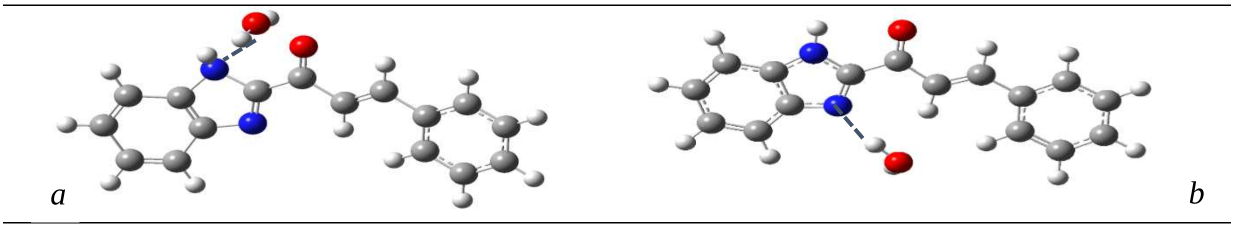
$$\Delta\upsilon_2(\mathrm{O-H}) = \nu_s(\mathrm{O-H})_{\mathrm{free}} - \mathrm{v}\big(\mathrm{O-H}\ldots\mathrm{O_{carbonyl}}\big)_{\mathrm{complex}} \ (13)$$

RESULTS AND DISCUSSION

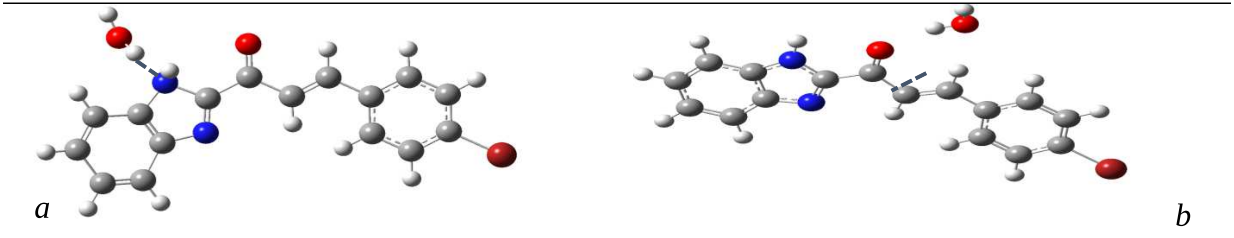
3.1. The optimized geometry

Geometry optimization was not successful on sp^{3}nitrogen atom. It was found that at the end of the optimization, the water molecule representing the probe, has migrated to attach either on the sp^{2}nitrogen atom in the non-substituted moleculesBZC-1 and BZC-4, either on the carbonyl oxygen in the moleculesBZC-2 and BZC-3 (figure 4).

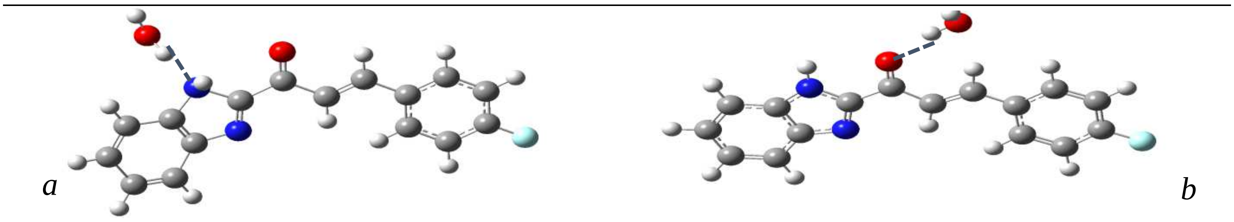
Such observation could be explained for the molecules BZC-1 and BZC-4 by resonance effect in benzimidazolyl-chalcones, showing that the sp^3 free nitrogen lone pair is unavailable. This rather increases the basicity of the sp^2 nitrogen. In the case of molecules where aryl groups is the resultant of the substitution on the phenolic kernel, strong electron attractors, such as bromine in BZC-2 and fluoride in BZC-3, create a resonance effect in the benzene ring enhancing subsequently the basicity strength of the carbonyl oxygen.



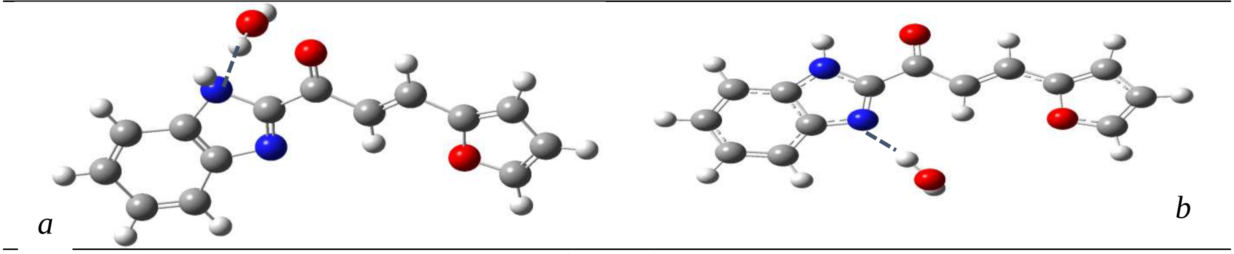
BZC-1: (a) before, (b) after optimization



BZC-2: (a) before, (b) after optimization



BZC-3: (a) before, (b) after optimization



BZC-4: (a) before, (b) after optimization

Figure 4: Geometries of hydrogen complexes on sp^3 nitrogen with benzimidazolyl-chalcone (*a*) before optimization (*b*) after optimization

Table 1: Geometrical parameters of hydrogen bond complexes of BZC on the sp^2 nitrogen and oxygen atoms

	BZC-1		**BZC-2**		**BZC-3**		**BZC-4**	
	N_{sp2}	$O_{carbonyl}$	N_{sp2}	$O_{carbonyl}$	N_{sp2}	$O_{carbonyl}$	N_{sp2}	$O_{carbonyl}$
HF/ 6-311+G(d,p)								
α (°)	169.5	162.5	167.5	160.0	168.1	160.9	171.0	161.4
θ(°)	127.3	138.2	127.3	138.0	127.3	137.9	127.3	138.1
d (Å)	2.14	2.05	2.14	2.06	2.14	2.06	2.13	2.04
D (Å)	2.14	2.05	2.14	2.06	2.14	2.06	2.13	2.04
MPW1PW91/6-311+G(d,p)								
α (°)	170.4	167.5	169.5	166.4	169.8	166.6	178.4	166.7
θ(°)	127.3	133.4	127.3	133.3	127.3	133.3	127.3	132.8
d (Å)	1.92	1.81	1.93	1.88	1.93	1.88	1.91	1.86
D (Å)	1.92	1.88	1.93	1.88	1.93	1.88	1.91	1.86

Linearity angles α on the sp^{2}nitrogenatom vary from167.5 ^{o}to 178.4^{o}and from 160.0^{o}to 167.5^{o}in the case of carbonyl oxygen, from one molecule to another in the two theories levels. It is known that strong H bond is related to flat linearity angle. Concerning the angle of direction, the optimum value for a sp^2 nitrogen should surround 120^o. In fact, the sp^{2}nitrogen atom has a single lone pair giving an average angle of 120^o with each of the two adjacent bonds. Concerning the oxygen, it has two lone pairs forming, each, an angle of 120° with the double bonds. The H bond, a mainly electrostatic bond, trends to be formed in the lone pairs' directions. We have obtained a direction angle value of 127.3^{o}on the sp^{2}nitrogenatom and a variation of 132.8^o to 138.2^o on the carbonyl oxygen from one molecule to another for the two levels. The above considerations show clearly that the H bond is stronger on the sp^{2}nitrogen. This fact can also be justified by the average angle of linearity of 170.5^o more close to 180^{o}than on the carbonyl oxygen which has an average angle of linearity of 164° quite away from 180°. This fact is also consistent with the average angle of direction of 127.3° more closed to the optimum angle, than on the oxygen which has an average angle of 135.6°.Concerning the H bond distances (distance d), in practice, it is considered as effective H bond if the distance d is less than the sum of Van der Waalsradii, taking 1.55 Å and 1.52 Å [25], respectively, for nitrogen and oxygen atoms and 1.0 Å for hydrogen atom[26];meaning that $d \leq 2.65$ Å and $d \leq 2.62$ Å respectively for a contact with the nitrogen and oxygen. It is also known that the shorter the distance d is, the stronger the H bond also is. The calculated average distances d are 2.03 Å on sp^2 nitrogen and 1.95 Å on the carbonyl oxygen and it can be observed that the calculated distances d fulfill the above conditions from a molecule to another in the two levels. But one can notice that the average distance d formed on the nitrogen atom is greater than that formed on oxygen atom. However, the minor differences could find a justification in the fact that the Van der Waals radius of nitrogen atom is naturally greater than that of the oxygen atom. The same analyzes can be made considering distance D between heavy atoms. But, it seems that carbonyl oxygen shows a slightly better H bonding capability.

3.2. Energetical parameters

BSSE corrected parameters are shown in table 2. All these values are expressed in kcal/mol except the entropy, in cal/mol.K.

Tables 2:Energetical parameters for by H bond complexation reactions

	BZC-1		**BZC-2**		**BZC-3**		**BZC-4**	
	N_{sp2}	$O_{carbonyl}$	N_{sp2}	$O_{carbonyl}$	N_{sp2}	$O_{carbonyl}$	N_{sp2}	$O_{carbonyl}$
HF/ 6-311+G (d,p)								
$\boldsymbol{\delta^{BSSE}}$	0.69	0.53	0.73	0.54	0.72	0.53	0.61	0.53
$\Delta_r H_{298}^{\circ}$	-1.38	-1.50	-1.56	-1.60	-1.63	-1.68	-0.62	-1.54
$\Delta_r S_{298}^{\circ}$	-0.02	-0.02	-0.02	-0.02	-0.02	- 0.02	-0.02	-0.02
$\Delta_r G_{298}^{\circ}$	7.10	6.11	6.99	6.04	6.89	5.97	6.49	5.94
MPW1PW91/6 -311+ G (d,p)								
$\boldsymbol{\delta^{BSSE}}$	0.97	0.76	1.00	0.78	1.00	0.78	0.79	0.78
$\Delta_r H_{298}^{\circ}$	-3.25	-2.44	-3.47	-2.53	-3.50	-1.99	-2.40	-2.75
$\Delta_r S_{298}^{\circ}$	-0.03	-0.02	-0.03	-0.02	-0.03	-0.02	-0.02	-0.02
$\Delta_r G_{298}^{\circ}$	5.77	5.79	5.68	5.75	5.58	5.72	5.25	5.61

BSSE values for each level of theory vary show a very little variation, regardless of the complexation site. At the HF/ 6-311+G(d,p), the variation of the BSSE is in the order of0.119kcal/mol and extended from0.61 to 0.73 kcal/mol on N_{sp2}, likelier, we have 0,012kcal/mol and a variationfrom0.532to 0.544kcal/mol on $O_{carbonyl}$. With the level MPW1PW91/6-311+G(d,p), this variation is in the order of 0.218 kcal/mol and extended from 0.791 to 1.009kcal/mol on N_{sp2}whereas it is 0.019kcal/mol and values vary from 0.769 to 0.788kcal/mol on $O_{carbonyl}$. The average value of BSSE at the HF/6-311+G (d,p) is 0.615kcal/mol while at the level MPW1PW91/6-311+G (d, p) it equals 0.862kcal/mol. These average values are almost in the order of the unit magnitude. The overall average for this series of complexes is of0.739kcal/mol. These observations indicate a satisfactory description of H bonds interaction energies in benzimidazolyl-chalcones. Therefore, BSSE can be neglected. Besides, all values of free enthalpies obtained with both HF and MPW1PW91methods, are positive indicating the non-spontaneous complexation process, under the conditions of the study. At the level HF/6-311+G (d,p), the average free enthalpy free is 6.86kJ.mol^{-1}for sp^2 nitrogen and equals 6.01kJ.mol^{-1} on the carbonyl oxygen; whereas atMPW1PW91/6-311+G(d,p) level, theses averages values are respectively 5.57kJ.mol^{-1}and 5.71kJ.mol^{-1}. The free enthalpies averages are respectively6.21 kJ.mol^{-1} and 5.86 kJ.mol^{-1}for sp^2 nitrogen and carbonyl oxygen, regardless the theory level. The difference between these free enthalpies averages enthalpies is of 0.35 kJ.mol^{-1}, slightly in favor of sp^2nitrogen atom. We consider that this difference is too small and one cannot draw a strong conclusion from these values. But again, carbonyl oxygen, due to the lower free enthalpy value, seems to be the major H bonding site. H bonding percentage on each kind of atom can be easily calculated as followed:

$$BZC + H_2O \rightleftarrows N_{sp2} \ldots \mathrm{H-OH} \quad , \quad K_1 (14)$$

with $K_1 = \dfrac{[N_{sp2} \ldots \mathrm{H-OH}]}{[BZC]}$

$$BZC + H_2O \rightleftarrows O_{carbonyle} \ldots \mathrm{H-OH} \quad , \quad K_2 (15)$$

with $K_2 = \dfrac{[O_{carbonyle} \ldots \mathrm{H-OH}]}{[BZC]}$

If it is assumed that$x_N$and x_O respectively correspond to sp^2nitrogenand carbonyl oxygen complexes, then:

$$x_N = \frac{1}{\left[1 + \left(\frac{K_2}{K_1}\right)\right]} (16)$$

$$x_O = 1 - x_N (17)$$

For each complexation reaction, we have :

$$K = exp\left(-\frac{\Delta_r G^0_{298}}{RT}\right)$$

Table 3: Percentages ofsp^2 nitrogen and carbonyl oxygen H bond complexes

	HF/6-311+G (d,p)		MPW1PW91/6 -311+G (d,p)	
	x_N(%)	x_O(%)	x_N(%)	x_O(%)
BZC-1	50.02	49.98	50.00	50.00
BZC-2	50.02	49.98	50.00	50.00
BZC-3	50.02	49.98	50.00	50.00
BZC-4	50.01	49.99	50.01	49.99

It is observed that at level HF/6-311+G(d,p), the averages percentages of H bond for sp^{2}nitrogen and carbonyl oxygen complexes are respectively 50.02% and 49.98% whereas these averages values are both equal to 50.00% at MPW1PW91/6-311+G(d,p) level. The difference between these percentages is not significant and we assume that the two atoms are equally H bond sites.

3.3. The spectroscopic parameters

Table4: Theoretical frequencies variation $\Delta\nu(O-H)$(cm^{-1})

	HF/ 6-311+G(d,p)		MPW1PW91/6 -311+G(d,p)	
	$\Delta\upsilon_1$(OH)	$\Delta\upsilon_2$(OH)	$\Delta\upsilon_1$(OH)	$\Delta\upsilon_2$(OH)
BZC-1	106.83	61.15	417.56	295.82
BZC-2	107.27	58.53	418.36	293.64
BZC-3	109.06	61.67	418.89	297.06
BZC-4	80.97	61.88	381.04	312.44

The review of the values in table4indicates that, the vibrational frequencies of the hydroxyl bond are shifted in the blue. This behavior due to the hydroxyl bond elongation reflects the attraction effect exerted by the HBA, atom A, on hydrogen H. Moreover, it was established that the higher the frequency variation, the stronger is the H bond. Values$\Delta\upsilon_1(O-H)$related to sp^2 nitrogen complexes are always higher than those corresponding to the carbonyl oxygen, $\Delta\upsilon_2(O-H)$. This observation suggests thatsp^2 nitrogen is slightly more predilection site for H bonding.

CONCLUSION

Analysis concerning geometrical, energetically and spectroscopic parameters for hydrogen bonding reaction on the three heteroatoms($N_{sp2}, N_{sp3,}\ O_{sp2}$) in each studied kernel of Benzimidazolyl-Chalcone ((2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one:BZC-1, (2E)-1-(1H-benzimidazol-2-yl)-3-(4-bromophenyl) prop-2-en-1-one: BZC-2, (2E)-1-(1H-benzimidazol-2-yl)-3-(4-fluorophenyl) prop-2-en-1-one:BZC-3 and (2E)-1-(1H-benzimidazol-2-yl)-3-(2-furyl) prop-2-en-1-one: BZC-4) showed that the sp^3 nitrogen can not be H bonding site, being very widely disadvantaged compared to sp^2 nitrogen and the carbonyl oxygen. The latter two atoms are in competition with a slight advantage for the sp^2 nitrogen regarding geometrical parameters. This trend is not confirmed by the values of the free enthalpy variation since H bonding percentages calculated for the two atoms are very close, about 50%. Therefore, we calculated the theoretical frequencies displacements due to complextions on the two atom. The values obtained are always greater on the sp^2 comparatively on carbonyl oxygen. Finally, we can state that sp^2 nitrogen slightly more H bonding site in the family of benzimidazolyl-chalcones, although, carbon oxygen cannot be neglected and is very closed to sp^2 nitrogen. Further calculations should be made in order to undoubtly identify the major H bonding site.

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