



Quantum-Chemical Study of the Coordination of Some Biguanides and their *N*-Deprotonated Derivatives

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Abstract The biguanides [HN=C(NR₁R₂)-NH-C(NR₃R₄)=NH] constitute an important family of molecules used as drugs in the treatment of diabetes. The five nitrogen atoms are potential coordination sites since they each carry a free electron pair. In the state of complexes, the therapeutic properties of the active molecules increase considerably. Recent experiments with Zinc complexes on diabetic animals have been very successful.

The present work deals with the Quantum-Chemical Study of the Coordination of some Biguanides such as biguanide, metformin and butformin. The objective is to determine the most favorable sites for the coordination of these ligands through the analysis of chemical properties that are coordinating indicators: the interatomic bond lengths, the atomic charges, the electrostatic potentials, the structures of boundary orbitals and atomic electrophilic supradelocalisability index.

Calculations were performed by the DFT / B3LYP method in the 6-31G (d, p) database with the Gaussian 09 and 03 softwares and the DCENT-QSAR program.

The sp² nitrogen atoms have proved to be the most favorable coordination sites. Complexes of these ligands with Zn (II) were modeled.

Keywords Coordination compounds, biguanides, anti-diabetic treatments, DFT / B3LYP / 6-31G (d, p) basis set.

1. Introduction

The treatment of non-insulin-dependent diabetes and the medical support of the insulin-dependent diabetes require, in view of the increasingly alarming extent of this disease, more effective and financially accessible drugs.

To date, one of the first and most effective drugs used in this treatment is the metformin molecule (STAGID or GLUCOPHAGE in pharmacy) which is of the biguanide family [1]. In the biguanide carbon skeleton there is five nitrogen atoms. They are potential donors of electronic doublets.

On the other hand, the coordination of the bio-ligands profoundly alters the physiological properties of the metals as well as those of the ligands with an overall improvement in the activity of the ligand taken alone in the pure state or that of the complexing metal the salt [2-6].

Recent experiments with Zinc complexes on animals suffering from diabetes have been very successful [7]. Zinc complexes with biguanides should improve the treatment of this disease.

In this work, we will carry out the QUANTO-CHEMICAL STUDY OF THE COORDINATION OF SOME BIGUANIDES. Our overall goal is to determine which of the five nitrogen atoms the most favorable coordination site in the biguanides is. For this purpose, five coordination indicators (CI) are used: interatomic bond lengths,



atomic charges, electrostatic potentials, boundary orbital structures and electrophilic supredelocalisability indices (ESDI) [8-10].

2. Materials and Methods

As hardware we mainly have used versions 09 and 03 of the Gaussian software and the DCENT-QSAR program for the calculations [8-11]. For the drawings, GaussView 5.08 and Chemdraw were used. The main method used in our work is DFT / B3LYP / 6-31G (d, p). All the work was done at atmospheric pressure and at $T = 25^{\circ}\text{C}$. The present work focused on four biguanide conformers, four metformin conformers and four butformin.

3. Results and Discussion

The optimization of the twelve ligands studying in the present work was made. The geometry, calculated in B3LYP / 6-31G (d, p), of each studied molecule is shown (Figure 1, 2 and 3). The following abbreviations are adopted:

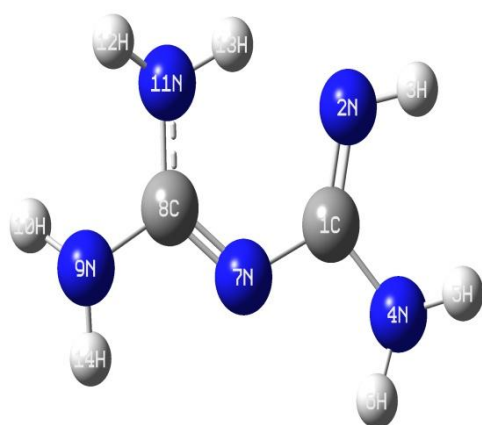
- Cis-1: The biguanide conformer in which the two bonds π are in the cis position relative to each other and with respect to the hydrogen atom carried by the nitrogen atom number 7.
- Cis-2: The biguanide conformer in which the two bonds π are in cis position relative to each other but both trans with respect to the hydrogen atom carried by the nitrogen atom number 7.
- π -t: The biguanide conformer in which the two bonds π are in trans position with respect to each other.
- N-dep.: N-deprotonated
- bgde = biguanide; mtfne = metformin ; btfn = butformin ; t= trans.
- ESDI: Electrophilic superlocalisability indice

It is found that the N-deprotonated form is the most stable tautomer ($\Delta G = -354.130344$ hartrees). This is consistent with the data from the literature [12]. Nevertheless the most commonly encountered in literature are the N-deprotonated forms [13-16]. Among them, the

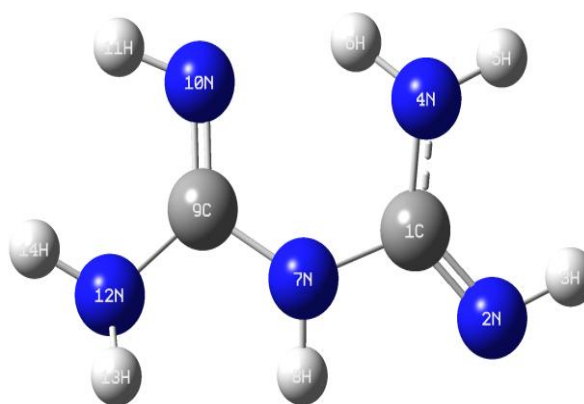
π -transbiguanide conforms to the highest stability ($\Delta G = -354.119436$ hartrees or 1.54×10^{-15} J).

π -cis-1 biguanide ($\Delta G = -354.112472$ hartrees) shows stability comparable to Π -trans biguanide.

The π -cis-2biguanide ($\Delta G = -354.103524$ hartrees) conformer, with relatively less stability, is most frequently found in complex compounds obtained experimentally [12]. All these reasons led to the choice of these four categories of molecules for the present study; these categories are the π -trans, π -cis1, π -cis2 and N-deprotonated tautomers of biguanide, metformin and butformin; this makes twelve ligands in total.



a) N- deprotonated Biguanide ($\Delta G = -354.130344$)



b) π -trans Biguanide ($\Delta G = -354.119436$)



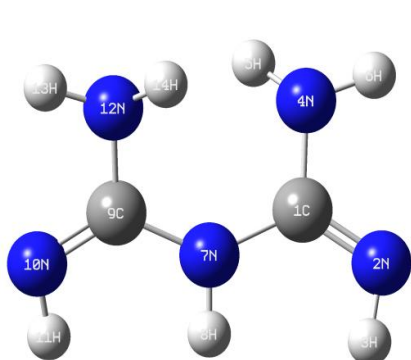
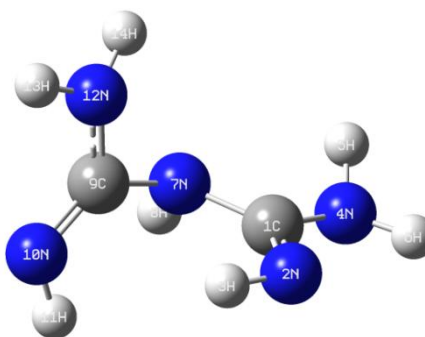
c) π -cis-1-Biguanide ($\Delta G = -354.112472$)d) π -cis-2-Biguanide ($\Delta G = -354.103524$)

Figure 1: The different studied forms of biguanide with their energies in hartrees

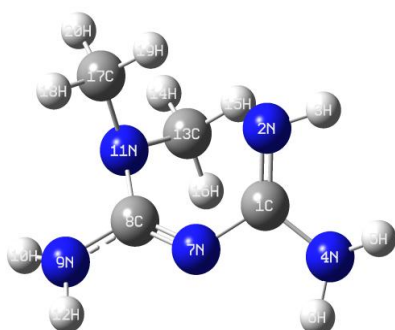
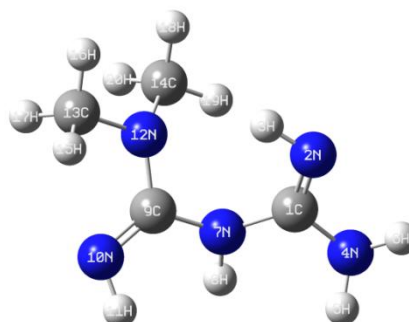
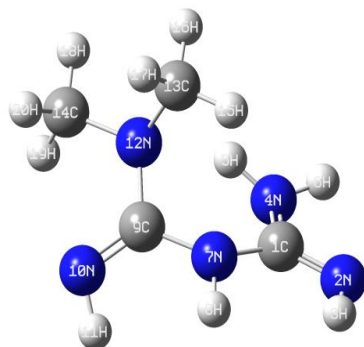
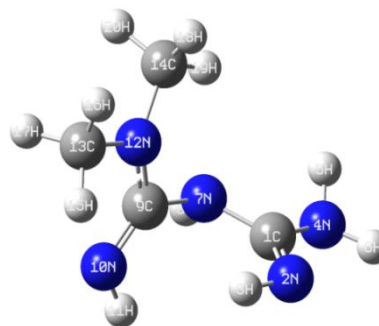
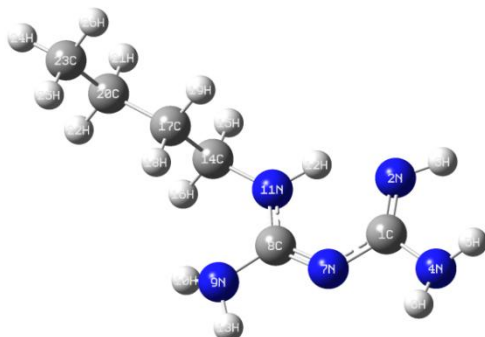
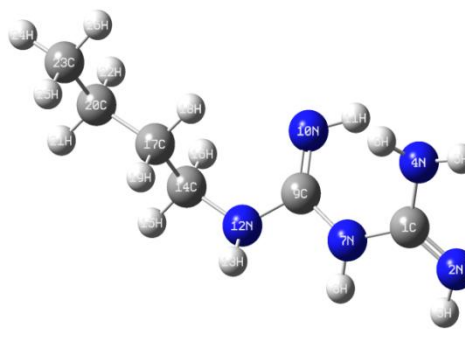
a) *N*-deprotonated Metformin ($\Delta G = -432.677661$)b) π -trans Metformin ($\Delta G = -432.673193$)c) π -cis-1-Metformin ($\Delta G = -432.673850$)d) π -cis-2-Metformin ($\Delta G = -432.670039$)

Figure 2: The different forms studied of metformin with their energies in hartrees

a) *N*-deprotonated butformin ($\Delta G = -511.286901$)b) π -trans butformin ($\Delta G = -511.269486$)

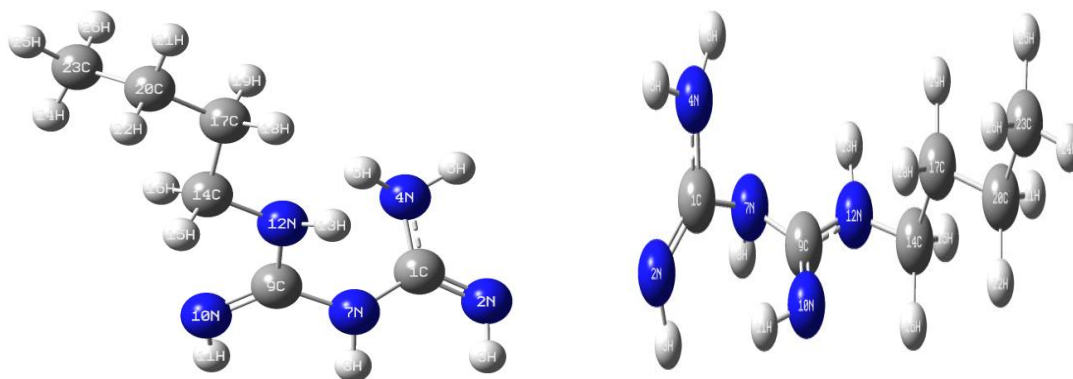
c) π -cis1-butformin ($\Delta G = -511.266451$)d) π -cis2-butformin ($\Delta G = -511.262062$)

Figure 3: The different studied forms of butformin with their energies in hartrees

3.1. Study of ligands

3.1.1. Analysis of geometric parameters

Table 1: Some geometric parameters of N-deprotonated forms of biguanides

Parameters	Bgde-N-dep	Mtfne-N-dep	Btne-N-dep	Standard values [13]
Distances (Å)				
C ¹ =N ²	1.30	1.29	1.30	1.27
C ¹ -N ⁴	1.39	1.39	1.39	1.47
C ¹ -N ⁷	1.38	1.39	1.38	1.47
N ⁷ =C ⁸	1.31	1.29	1.32	1.47
C ⁸ -N ⁹	1.38	1.37	1.38	1.27
C ⁸ -N ¹¹	1.36	1.42	1.35	1.47

Table 2: Some geometric parameters of π -Cis-1 forms of biguanides

Parameters	π -cis1-Bgde	π -cis1-Mtfne	π -cis1-Btfne	Standard values [13]
Distances (Å)				
C ¹ =N ²	1.28	1.28	1.28	1.27
C ¹ -N ⁴	1.39	1.38	1.40	1.47
C ¹ -N ⁷	1.41	1.42	1.40	1.47
N ⁷ -C ⁹	1.41	1.41	1.42	1.47
C ⁹ =N ¹⁰	1.28	1.28	1.28	1.27
C ⁹ -N ¹²	1.39	1.41	1.37	1.47

Table 3: Some geometric parameters of π -Cis-2 forms of biguanides

Parameters	π -cis2-Bgde	π -cis2-Mtfne	π -cis2-Btfne	Standard values [13]
Distances (Å)				
C ¹ =N ²	1.27	1.28	1.28	1.27
C ¹ -N ⁴	1.39	1.39	1.37	1.47
C ¹ -N ⁷	1.43	1.42	1.43	1.47
C ⁹ -N ⁷	1.44	1.44	1.45	1.47
C ⁹ =N ¹⁰	1.28	1.29	1.28	1.27
C ⁹ -N ¹²	1.37	1.37	1.37	1.47



Table 4: Quelques géométries des formes π -tranbiguanides

Parameters	π -tbgde	π -tmtfne	π -tbtfn	Values standards [13]
Distances (Å)				
C ¹ =N ²	1.28	1.28	1.28	1.27
C ¹ -N ⁴	1.37	1.37	1.37	1.47
C ¹ -N ⁷	1.42	1.42	1.42	1.47
N ⁷ -C ⁹	1.40	1.41	1.41	1.47
C ⁹ =N ¹⁰	1.28	1.28	1.28	1.27
C ⁹ -N ¹²	1.40	1.40	1.39	1.47

From the analysis of bond lengths of the three N-déprotonated biguanide conformers (π -transbiguanide, π -cis-1biguanide et π -cis-2biguanide) one noticed that liaisons C¹-N⁴, C¹-N⁷, N⁷-C⁹ et C⁹-N¹² are about 1.40 Å ; these lengths are between the C = N double bond (1.27 Å) and the C-N single bond (1.47) [13]. This situation shows that the free electron pairs of N⁴, N⁷, N⁹ et N¹² conjugate with π electron pair of the C⁹N¹⁰ (N⁷ and N¹²) or of the C¹N² (N⁷ et N⁴) bonds. Since these pairs are thus delocalized, they aren't available for coordination with a metal; it is the same for the respective conformers of metformin and butformin. This analysis is then favorable to the coordination through the nitrogen atom of the C¹=N² and C⁹=N¹⁰ bonds since the free electron pairs of these N are localized; the lengths of these bonds are about 1.270 Å, standard of C=N bonds [13].

In the N-deprotonated tautomers, all electronic pairs of N atoms, except N², conjugate with CN bonds ; the greatest delocalization is observed at the level of N¹¹ (in biguanide and butformin) or N⁹ (in metformin), evidenced by the value of the length of C⁸N¹¹⁽⁹⁾ (about de 1,35 Å). This is consistent with the literature data ¹³. These N atoms are therefore not favorable for this reason to coordination; coordination through N² is then the most favorable.

3.1.2. Analysis of atomic charges

The nitrogen atoms N², N⁴, N¹⁰ and N¹² carry the highest electron densities in absolute values. It should be noted that the N⁴ and N¹² atoms carry, each, two positively charged hydrogen atoms; N⁴ and N¹² are therefore at a disadvantage compared to N² and N¹⁰ which, therefore, constitute the most favorable coordination sites from the atomic NBO charge point of view.

Table 5: Atomic NBO charges of biguanide, metformin and butformin

Atoms	Biguanide			Metformine			Butformine		
	π -tbgde	Π -cis1-bgde	π -cis2-bgde	π -tmtfne	π -cis1-mtfne	π -cis2-mtfne	π -tbtfn	Π -cis1-btfne	π -cis2-btfne
C ¹	0.600	0.603	0.594	0.500	0.758	0.597	0.602	0.601	0.590
N ²	-0.779	-0.772	-0.754	-0.78	-0.853	-0.762	-0.782	0.765	-0.753
N ⁴	-0.877	-0.896	-0.884	-0.879	-0.946	-0.887	-0.879	-0.904	-0.857
N ⁷	-0.715	-0.700	-0.771	-0.719	-0.781	-0.764	-0.719	-0.702	-0.778
C ⁹	0.598	0.603	0.584	0.605	0.755	0.593	0.606	0.612	0.598
N ¹⁰	-0.749	-0.772	-0.745	-0.743	-0.812	-0.760	-0.755	-0.792	-0.764
N ¹²	-0.908	-0.896	-0.853	-0.515	-0.618	-0.458	-0.699	-0.682	-0.664
C ¹³	-	-	-	-0.482	-0.426	-0.481	-	-	-
C ¹⁴	-	-	-	-0.480	-0.415	-0.476	-0.286	-0.261	-0.264
C ¹⁷	-	-	-	-	-	-	-0.474	-0.472	-0.478
C ²⁰	-	-	-	-	-	-	-0.462	-0.464	-0.463
C ²³	-	-	-	-	-	-	-0.691	-0.683	-0.683

Table 6: NBO charges of N-deprotonated tautomers of biguanides

Atoms	Bgde N-dep	Mtfne N-dep	Btfne N-dep
N ²	-0,855	-0.878	-0.865
N ⁴	-0,869	-0.798	-0.871
N ⁷	-0,675	-0.624	-0.683
N ¹¹	-0,871	-0.835	-0.866
N ⁹⁽¹⁰⁾	-0,866	-0.550	-0.665
C ¹	0.611	0.596	0.612
C ⁸⁽⁹⁾	0.558	0.666	0.665



3.1.3. Analysis of electrostatic potentials

Tables 7 and 8 show the electrostatic potentials of nitrogen atoms contained in the studied molecules.

Table 7: Electrostatic potentials ESP (in a.u.) of nitrogen atoms of N-protonated tautomers

Atoms	Biguanide			Metformine			Butformine		
	π -tbgde	π -cis bgde1	π -cbgde2	π -t mtfne	π -cis mtfne1	π -cis mtfne2	π -tbtfn	π -cis btfn1	π -cis btfn2
N ²	-18.409	-18.4	-18.404	-18.411	-18.405	-18.407	-18.412	-18.396	-18.397
N ⁴	-18.341	18.331	-18.337	-18.342	-18.347	-18.338	-18.343	-18.325	-18.333
N ⁷	-18.305	-18.300	-18.323	-18.311	-18.305	-18.324	-18.311	-18.305	-18.329
N ¹⁰	-18.386	-18.4	-18.394	-18.392	-18.387	-18.399	-18.394	-18.408	-18.406
N ¹²	-18.321	-18.331	-18.329	-18.314	-18.320	-18.317	-18.321	-18.334	-18.332

Table 8: ESP (a.u.) of nitrogen atoms of N-deprotonated tautomers

Atoms	Bgde N-dep	Mtfne N-dep	Btfn N-dep.
N ²	-18,386	-18.420	-18.42
N ⁴	-18,359	-18.35	-18.357
N ⁷	-18,377	-18.392	-18.41
N ⁹	-18,364	-18.332	-18.337
N ¹¹	-18,332	-18.349	-18.345
C ¹	-14.660	-14.659	-14.665
C ²	-14.636	-14.638	-14.640

The analysis of the electrostatic potentials values recorded in atomic units (a.u.) in the table 7 shows that the N² and N¹⁰ nitrogen atoms of the N-protonated tautomers carry the most negative potential values. Then they are the most favored coordination sites if you consider this CI.

The table 8 records some PES of the N-deprotonated forms of the biguanides molecules studied in this work. Here, the more favorable nitrogen atoms are, in descending order, N², N⁷ and N¹².

3.1.4. Analysis of atomic indices of electrophilic superdelocalisability

The atomic electrophilic superdelocalisability indice expresses the ability of the atom to attract an electrophilic center. The table 9 summarizes the different atomic values.

Table 9: Electrophilic superdelocalisability indices of Nitrogen atoms

Atoms	Atomic electrophilic superdelocalisability indices of ligands											
	Biguanide				Métformine				Butformine			
	Bgde N-dep	π -cis1-bgde	Cis2-bgde	Tbgde	Mtfne N-dep.	π -cis1-mtfne	π -cis2-mtfne	Tmtfn	Btfn N-dep.	π -cis1-btfn	π -cis2-btfn	Tbtfn
N2	-16.492	-15.391	-15.422	-16.460	-17.332	-15.985	-15.985	-15.716	-16.735	-15.163	-15.074	-15.332
N4	-13.372	-12.455	-12.714	-13.151	-13.629	-12.836	-12.836	-12.776	-13.548	-12.256	-12.535	-13.359
N7	-15.622	-11.688	-12.370	-11.961	-15.748	-11.966	-11.966	-12.015	-16.035	-11.868	-12.557	-11.964
N10 (N9)	-12.671	-15.390	-14.928	-15.130	-12.715	-14.952	-14.951	-15.182	-12.747	-15.980	-15.578	-17.020
N12 (N11)	-12.949	-12.453	-12.408	-12.265	-12.402	-12.204	-12.204	-12.361	-12.916	-12.757	-12.669	-12.949

This table shows that N² and N¹⁰ atoms carry the most negative electrophilic superdelocalisability indice in the N-protonated molecules.

In the N-deprotonated molecules, N² and N⁷ carry the most negative electrophilic superdelocalisability indice with prominence of N².

3.1.5. Analysis of the boundary orbitals

The analysis of the frontier orbitals from the values recorded in Table 10 shows that, in the biguanide, the highest occupied molecular orbital (HOMO) is located more in the nitrogen atom N²; in metformin and in butformin the HOMO is found more in N², N⁴ and N¹⁰. This means that the metal-ligand orbital recovery is more favorable at the level of these atoms.



Table 10: HOMO, HOMO -1 of the studied ligands and LUMO, LUMO +1 of ZnCl₂

Orbitals	Biguanide			Metformine		
	Energy (eV)	Dominant atomic orbitals	Coefficient	Energy (eV)	Dominant atomic orbitals	Coefficient
HOMO -1	-0,252	N ⁴ (pz)	0,46	-0,241	N ¹⁰ (pz)	0,53
HOMO	-0,223	N ² (pz)	0,72	-0,221	N ² (pz), N ⁴ (pz)	0,52 ; 0,46
Favorable site		N ²			N ² , N ⁴ , N ¹⁰	
	Butformine			ZnCl ₂		
	Energy (eV)	Dominant atomic orbitals	Coefficient	Energy (eV)	Dominant atomic orbitals	Coefficient
HOMO -1	-0,246	N ¹⁰ (pz)	0,56	-	-	-
HOMO	-0,211	N ² (pz), N ⁴ (pz)	0,68 ; 0,55	-	-	-
LUMO	0,0234	N ² (pz), N ¹⁰ (pz)	0,54 ; 0,63	-2,31	Zn(s)	2,01
LUMO+1	0,0604	N ¹⁰ (pz)	0,45	-0,79	Zn (p y)	1,43
Favorable site		N ² , N ⁴ , N ¹⁰			Zn	

3.1.6. Summary Analysis

Table 11 summarizes the results of previous analyzes. It appears that coordination through N² nitrogen atom is favored by 100% of the coordination indicators in forms of biguanide, metformin and butformin. N¹⁰ atom too is very favored in N-protonated forms (80 % in N-protonated forms of biguanide, 100% in N-protonated forms of metformin and butformin). In the N-deprotonated conformers, N⁷ atom is favored by 40% of the CI, taking thus the second place after N². The N-deprotonated biguanide don't shows any coordination possibility via N¹⁰ atom. It is therefore concluded that N2 and N10 are probably the most favorable coordination sites in biguanides. This is in accordance with the literature ¹². As for the deprotonated forms of the biguanides, N² and N⁷ prove to be favorable to coordination.

Table 11: Recapitulative analysis

Species	Biguanide				Metformine				Butformine			
	N-dep	π -trans	π -cis1	π -cis2	N-dep	π -trans	π -cis1	π -cis2	N-dep	π -trans	π -cis1	π -cis2
Bond lengths	N ²	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ²	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ²	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰
Atomic charges	N ²	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ²	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ²	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰
PES	N ² , N ⁷	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ⁷	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ⁷	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰
ESDI	N ² , N ⁷	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ⁷	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ⁷	N ² , N ¹⁰	N ² , N ¹⁰	N ² , N ¹⁰
HOMO and HOMO-1	N ²	N ²	N ²	N ²	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰	N ² , N ⁴ , N ¹⁰
% of favorables CI	N ² (100), N ⁷ (40)	N ² (100), N ¹⁰ (80)	N ² (100), N ¹⁰ (80)	N ² (100), N ¹⁰ (80)	N ² (100), N ⁴ (20), N ¹⁰ (20), N ⁷ (40)	N ² (100), N ⁴ (20), N ¹⁰ (20)	N ² (100), N ⁴ (20), N ¹⁰ (20)	N ² (100), N ⁴ (20), N ¹⁰ (20)	N ² (100), N ⁴ (20), N ¹⁰ (20), N ⁷ (40)	N ² (100), N ⁴ (20), N ¹⁰ (20)	N ² (100), N ⁴ (20), N ¹⁰ (20)	N ² (100), N ⁴ (20), N ¹⁰ (20)

The ligands study is thus carried out; it is now appropriate to simulate corresponding complexes in order to verify the results of the study. This is the second part of the present investigative work.

3.2. The complexation modeling

3.2.1. Modeling

The modeling of the complexes of each ligand with zinc (II) has been considered. This element was brought by zinc chloride. The ZnCl₂ molecule was placed at a distance of about 2.5Å from each type of nitrogen atom. These

systems were optimized and complexes were formed according to the structures shown on figure 4 and the Zn-N bond length values (about 2. Å) shown in tables 12, 13¹⁷⁻²⁰. In the case of each π -cis-2 conformer, the dihedral $N^2C^1N^7N^{10}$ was kept constant during optimization until formation of the Zn-N² and Zn-N¹⁰ bonds; this twist angle was then relaxed and the system was optimized again. This precaution was useful because, being considerably unstable, this conformer would be transformed into a more stable conformer during the complexation process. The tables 12 and 13 gather the calculated interatomic distances Zn-N of the complexes.

Except the $ZnCl_2(\text{Metformine N-dep.})_2$ complex where Zinc atom was coordinated through N⁷ nitrogen atom, the coordination in all complexes has obtained via N² atom; this confirms the forecast made from analysis of the calculated CI. In the π -cis-2 conformers, the coordination occurred via N² and N¹⁰ giving some chelates according to the previous results.

bgde = biguanide; mtfne = metformin ; btfn = butformin ; t = trans.

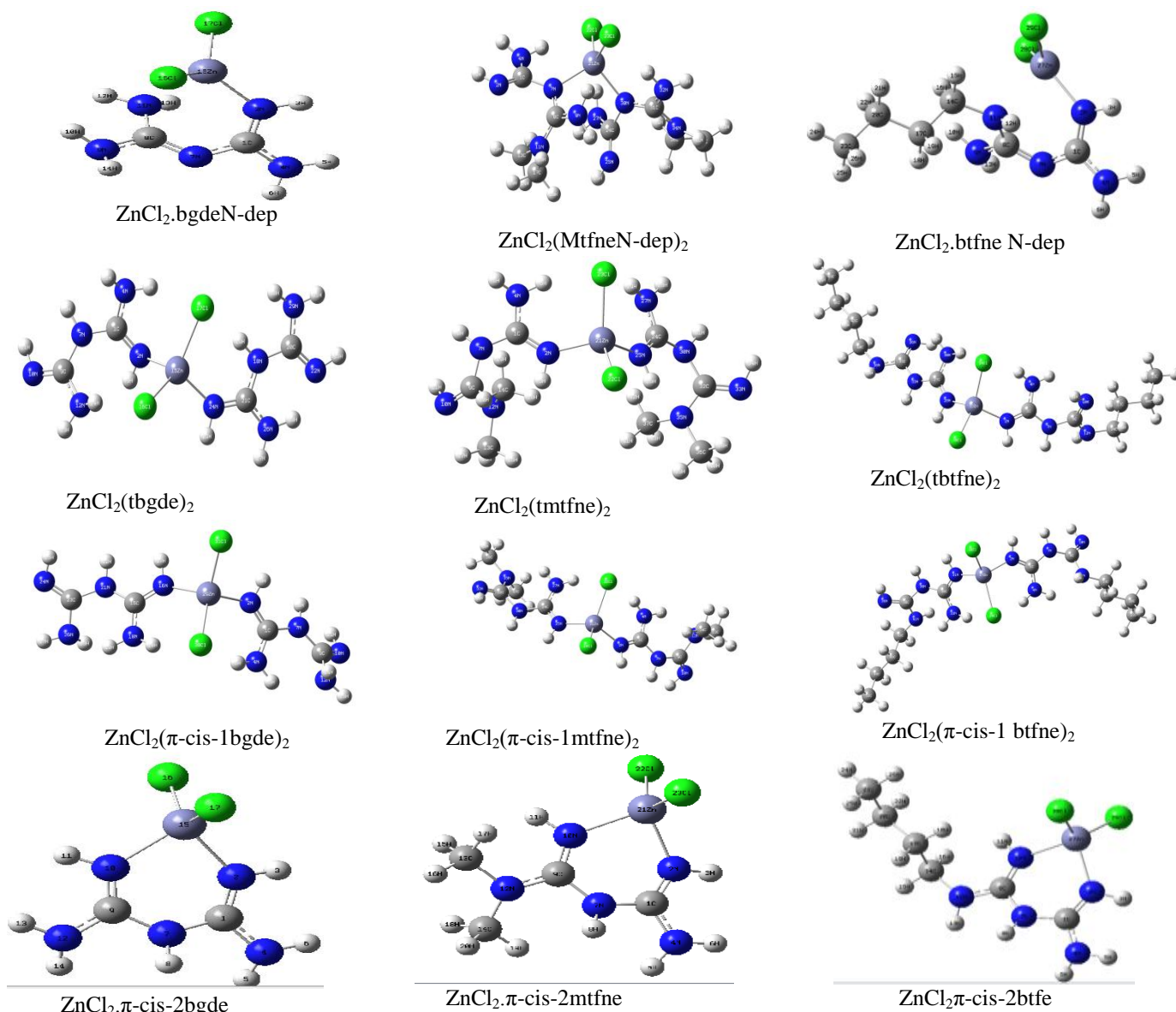


Figure 4: Obtained complexes



Table 12: Interatomic distances Zn-N of complexes with one ligand

Complexes	Zn-N ²	Zn-N ⁴	Zn-N ⁷	Zn-N ¹⁰	Zn-N ¹²
ZnCl ₂ .BgndeN-dep	2,00	4,25	3,27	3,86	2,32
ZnCl ₂ .BtfneN-dep	1,99	4,23	3,26	3,86	2,35
ZnCl ₂ .cis2-Bgnde	2,07	4,34	3,35	2,07	4,33
ZnCl ₂ .cis2-Mtfne	2,06	4,30	3,31	2,05	4,32
ZnCl ₂ .cis2-Btfne	2,06	4,32	3,32	2,05	4,30

Table 13: Interatomic distances Zn-N of complexes with two ligands

Complexes	Ligand 1					Ligand 2				
	ZnN ²	ZnN ⁴	ZnN ⁷	ZnN ¹⁰	ZnN ¹²	ZnN ²⁴	ZnN ²⁵	ZnN ¹⁸	ZnN ²²	ZnN ²⁹
ZnCl ₂ (tbgnde) ₂	2.02	3.38	4.11	5.93	4.06	1.99	4.28	3.29	5.59	5.07
ZnCl ₂ (tmtfne) ₂	2.01	3.47	4.31	6.03	4.58	2.00	3.39	4.33	5.99	4.78
ZnCl ₂ (tbutfne) ₂	2.01	3.41	4.31	6.00	6.59	2.01	3.45	4.30	6.11	6.52
ZnCl ₂ (cis1-bgnde) ₂	2.01	3.43	4.31	6.61	5.88	2.01	3.44	4.31	6.59	5.98
ZnCl ₂ (cis1-mtfne) ₂	2.01	3.43	4.31	6.59	5.95	2.01	3.43	4.31	6.42	6.06
ZnCl ₂ (cis1-btfne) ₂	2.01	3.42	4.31	6.63	5.91	2.01	3.44	4.31	6.54	6.01
ZnCl ₂ (mtfne-N-dep) ₂	4.20	3.26	2.03	3.08	4.08	3.87	3.19	2.06	3.30	4.33

3.2.2. Energetic study of the obtained complexes

The values of coordination Gibbs energies and enthalpies which are shown in table 14 are all negative, suggesting that the coordination process of biguanide and its derivatives studied in the present work with zinc chloride is spontaneous and exothermic.

It should be noted that although N-deprotonated isomers of the ligands are the most stable, their complexes are not most stable [12]. Indeed, performing the present investigation, we performed before, the complexes with proportion ZnCl₂/ligand equal 1/1; on this stage only π -cis-2 conformers have formed complexes where Zn(II) coordination number is 4, which gives to this metallic element the tetrahedral structure that is characteristic to it. Moreover these complexes are some chelates. All other conformers have formed complexes with trigonal Zn(II). Therefore, the most stable complexes are those that correspond to the π -cis-2 conformers, which is in concordance with their strong preponderance in the reaction products during the experimental syntheses [14-16].

Table 14: Energy study of the complexation process

	ΔG , eV	ΔG_{coord} , eV	ΔH , eV	ΔH_{coord} , eV	Type de processus
Bgnde-N- déprtné	-9636,13	-	-9635,07	-	-
Mtfne-N- déprtné	-11773,50	-	-11772,20	-	-
Btfne-N- déprtné	-13912,47	-	-13911,02	-	-
π -trans Bgnde	-9635,84	-	-9634,76	-	-
π -trans Mtfne	-11773,21	-	-11771,95	-	-
π -trans Btfne	-13912,00	-	-13910,53	-	-
π -cis1-Bgnde	-9635,65	-	-9634,55	-	-
π -cis1-Mtfne	-11773,21	-	-11771,96	-	-
π -cis1-Btfne	-13911,99	-	-13910,50	-	-
π -cis2-Bgnde	-9635,40	-	-9634,36	-	-
π -cis2-Mtfne	-11773,25	-	-11772,02	-	-
π -cis2-Btfne	-13911,80	-	-13910,27	-	-



ZnCl ₂	-73459,09	-	-73458,28	-	-
ZnCl ₂ .Bgnde-N-depe	-83096,41	-1,20	-83094,92	-1,572	Spontané, exothermique
ZnCl ₂ (mfne-N-dep) ₂	-97007,97	-1,88	-97005,61	-2,93	Spontané, exothermique
ZnCl ₂ .btfne-N-dep	-87372,80	-1,24	-87370,93	-1,63	Spontané, exothermique
ZnCl ₂ (π-tbgnde) ₂	-92732,98	-2,21	-92730,90	-3,1	Spontané, exothermique
ZnCl ₂ (π-tmtfne) ₂	-97008,07	-2,56	-97005,54	-3,36	Spontané, exothermique
ZnCl ₂ . π-tbtfne ₂	-	-2,16	-	-3,01	Spontané, exothermique
	101285,25		101282,35		
ZnCl ₂ . π-cis1-bgnde ₂	-92732,49	-2,10	-92730,40	-3,02	Spontané, exothermique
ZnCl ₂ . π-cis1-mtfne ₂	-97008,04	-2,53	-97005,59	-3,39	Spontané, exothermique
ZnCl ₂ . π-cis1-btfne ₂	-	-2,07	-	-2,99	Spontané, exothermique
	101285,14		101282,27		
ZnCl ₂ . π-cis2-bgnde	-83096,27	-1,78	-83094,75	-2,11	Spontané, exothermique
ZnCl ₂ . π-cis2-btfne	-85234,11	-1,77	-87370,75	-2,10	Spontané, exothermique
ZnCl ₂ . π-cis2-btfne	-87372,67	-1,78	-85232,40	-2,20	Spontané, exothermique

$\Delta G =$ Enthalpie libre des espèces; $\Delta G_{coord} =$ Enthalpie libre de coordination;

$\Delta G_{coord} = \Delta G_{complexe} - (\Delta G_{ligand} + \Delta G_{ZnCl_2})$ ou $\Delta G_{coord} = \Delta G_{complexe} - (2\Delta G_{ligand} + \Delta G_{ZnCl_2})$.

4. Conclusion

The present work focused on the DFT study of the coordination of some biguanides.

The analysis of the coordination indicators namely the geometrical parameters, the atomic charges, the electrostatic potentials, the frontier orbitals and the superlocalisability indices allowed us to show that the coordination of these biguanides is done by the nitrogen atoms in the sp² hybridization state.

Twelve biguanide complexes with Zn (II) were theoretically obtained. The π-cis-2 conformers gave relatively more stable chelates complexes. In these complexes, Zn (II) has the tetrahedral structure where two of the vertices are occupied by two chlorine atoms and the other two by the nitrogen atoms.

All complexation processes have been spontaneous and exothermic.

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