DFT Study of the Coordination of N-monochlorosubstituted Derivatives of the N-deprotonated Tautomer of the Biguanide

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Authors' contributions

This work was carried out in collaboration among all authors. Author AF a doctoral student; he initiated the study with his thesis director, performed the calculations, analyzed the results and wrote the first draft. Author KUA is the thesis director of author AF; he followed the progress of the works carried out by author AF. Author KAG helped to analyze the results. Author AGS is the LaCTheSMo director; he gave some advices. All authors read and approved the final manuscript.

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ABSTRACT

Biguanides [HN=C(NR^{1}R^2)-NH-C(NR^{3}R^4)=NH] constitute an important family of molecules used as drugs in the treatment of diabetes. When R^1=R^2=R^3=R^4=H the molecule is named simply "biguanide". The five nitrogen atoms are potential coordination sites. Several experimental works published in literature show that in complex state, therapeutic properties of the active molecules increase considerably. In fact, the chlorine atom, a preferred substitute in pharmacy, improves the effectiveness of these drugs by increasing their activities and also by reducing their side effects. Recent experiments with Zinc complexes on diabetic animals have been very successful.

In the present work a theoretical study of the coordination of N-chlorine derivatives of N-deprotonated tautomer of biguanide has been carried out. The aim is to determine, among the five nitrogen and chlorine atoms, the site most favorable to the coordination of these ligands. This determination is based on some coordination indicators.

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The calculations were performed by the DFT / B3LYP method in the 6-31G (d, p) orbital basis set with the Gaussian 09 and Gaussian 03 software. The DCENT-QSAR program was also used.
The results of the various calculations revealed the imine nitrogen atoms as the most favorable coordination sites in the studied N-chlorosubstituted derivatives of N-deprotonated tautomeric biguanide. Complexes of these ligands with Zn (II) were modelled. The chlorine atom proved unfavorable to coordination.

1. INTRODUCTION

Biguanides $[HN=C(NR^1R^2)-NH-C(NR^3R^4)=NH]$ constitute an important family of molecules used as drugs in the treatment of diabetes. When $R^1=R^2=R^3=R^4=H$ the molecule is named simply "biguanide". The treatment of non-insulin-dependent diabetes and the medical support of the insulin-dependent require, in view of the increasingly alarming extent of this disease [1,2], more effective, varied and financially accessible drugs.

To date, one of the first and most effective drugs used in this treatment contains the metformin molecule (known in the pharmacy under the generic name of Stagid or Glucophage) which is of the biguanide family [3]. The five nitrogen atoms of the biguanides common skeleton are potential sites of coordination. Several experimental works published in the literature have shown that in the complex state, the therapeutic properties of the active molecules increase considerably [4]; indeed, the coordination of the bio-ligands profoundly modifies both the physiological properties of the metals and those of the ligands with an overall improvement in the activity of the ligand taken alone in the pure state or that of the salt of the complexing metal [5-8]. In addition, the chlorine atom, a preferred substituent in pharmacy, improves the effectiveness of these drugs by increasing their activities and also by reducing their side effects [9-11]. A probable advantage of the presence of the chlorine atom in a bioactive molecule such as N-chlorine derivatives of biguanides is the presence of the three electron lone pairs on its last layer; indeed, the + M mesomeric donor effect due to these lone pairs would allow to modify the nucleophilic character of the nitrogen atoms. So the chlorine atom could constitute a potential coordination site. That situation would contribute to increase the number of coordination sites in those N-chlorosubstituted derivatives.

In addition, recent experiments with Zinc complexes on animals suffering from diabetes have been very successful [12-14]. Zinc complexes with biguanides and their N-chlorosubstituted derivatives should improve the treatment of this disease reducing substantially the side effects.

In this work, the Theoretical Study of the Coordination of N-chlorosubstituted Derivatives of the N-deprotonated tautomer of the Biguanide has been realized. Complexes of these ligands have been modeled.

The general objective is to determine among the five nitrogen and chlorine atoms, that which constitutes the most favorable coordination site in the N-chlorosubstituted derivatives of the N-deprotonated biguanide.

2. MATERIALS AND METHODS

The investigations were made in the "Laboratoire de Chimie Théorique et de Spectroscopie Moléculaire (LaCTheSMo)" of Abomey-Calavi University (Benin) with the precious help of the intensive computing server of Loraine University (France).

The materials used in this investigation consists mainly of 09 and 03 versions of the Gaussian software [15] and the DCENT-QSAR [16] program for calculations; for the drawings, Gauss View 5.08 and Chemdraw [17] were used. The calculations were performed by the DFT / B3LYP method in the 6-31G (d, p) orbital basis set. Five coordination indicators have been taken into account: interatomic bond lengths, atomic charges, molecular electrostatic potentials, frontier orbital structures and electrophilic superdelocalizability indices. After the study about the coordinating possibility of each ligand, the formation of its complex with zinc (II) has been calculated. We attempted to elucidate the geometric layout of the obtained complexes.

3. RESULTS AND DISCUSSION

Biguanide exists in four main conformers (Fig. 1). It has been agreed to designate them, in this study, according to the abbreviations below:

- Cis-1: The biguanide conformer in which both π bonds are in the cis position relative to each other and with respect to the hydrogen atom carried by the nitrogen atom N^7.
- Cis-2: The biguanide conformer in which both π bonds are in cis position relative to each other both trans with respect to the hydrogen atom carried by the nitrogen atom N^7.

- trans: The biguanide conformer in which the two π bonds are in trans position with respect to each other.
- N-dep: N-deprotonated
- Bgde: biguanide

The N-monochlorosubstituted derivatives of the N-deprotonated conformer are the ligands studied in the present research works; the study focused on determining the most favorable site of this molecule for a coordination link.

The molecules involved in this research are the N-monochlorosubstituted derivatives of the tautomeric form of the biguanide. This conformer is indeed the most stable of the four that the biguanide possesses [18].
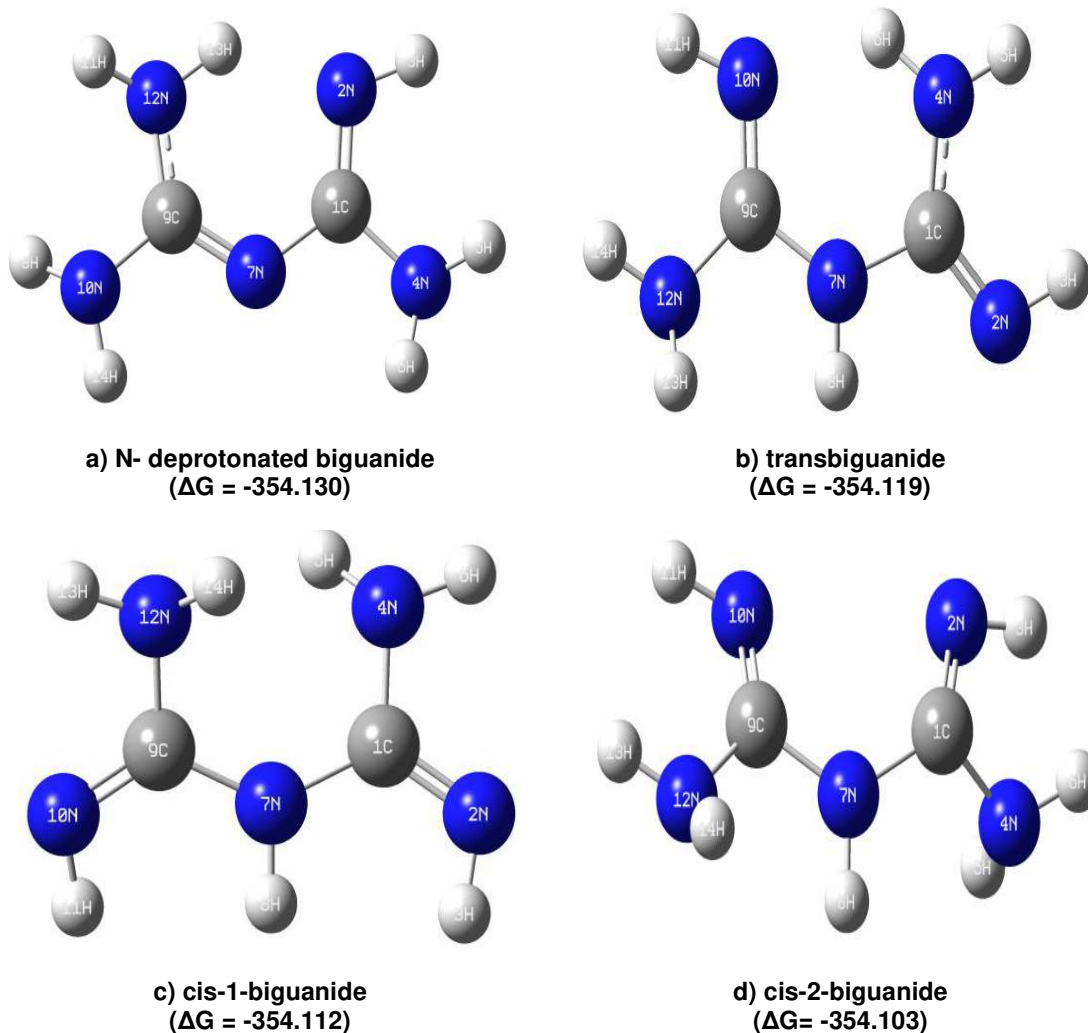

a) N- deprotonated biguanide
(ΔG = -354.130)

b) transbiguanide
(ΔG = -354.119)

c) cis-1-biguanide
(ΔG = -354.112)

d) cis-2-biguanide
(ΔG= -354.103)

Fig.1. The different main forms of the biguanide with their energies in hartrees

3.1 Study of Ligands

The N-deprotonated form results from a tautomerization reaction (Fig. 2). The N-monochlorosubstituted derivatives of this form of biguanide are represented in Fig. 3.

From the analysis of the Gibbs free energy values presented in Table 1, it appears that the N-deprotonated N^2-chlorobiguanide is the most stable molecule of the N-monochloro substituted derivatives of the N-deprotonated biguanide.
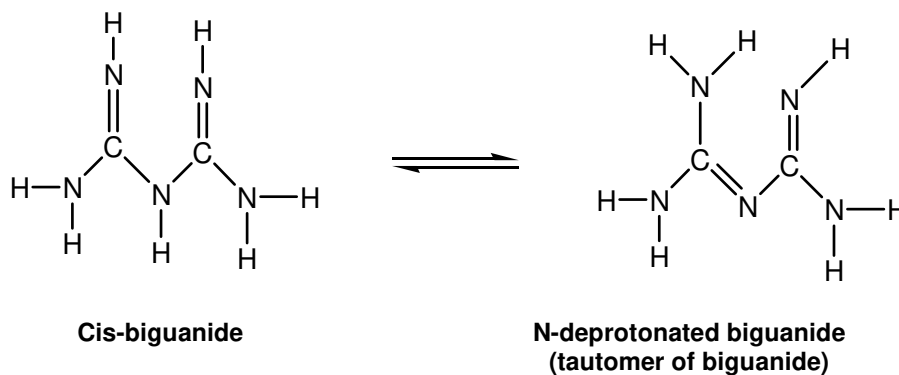

Cis-biguanide

N-deprotonated biguanide (tautomer of biguanide)

Fig. 2. Tautomerisation of the biguanide

a)N^2-chlorobgnde N-dep

b)N^4-chlorobgnde N-dep

c)N^{12}-chlorobgnde N-dep

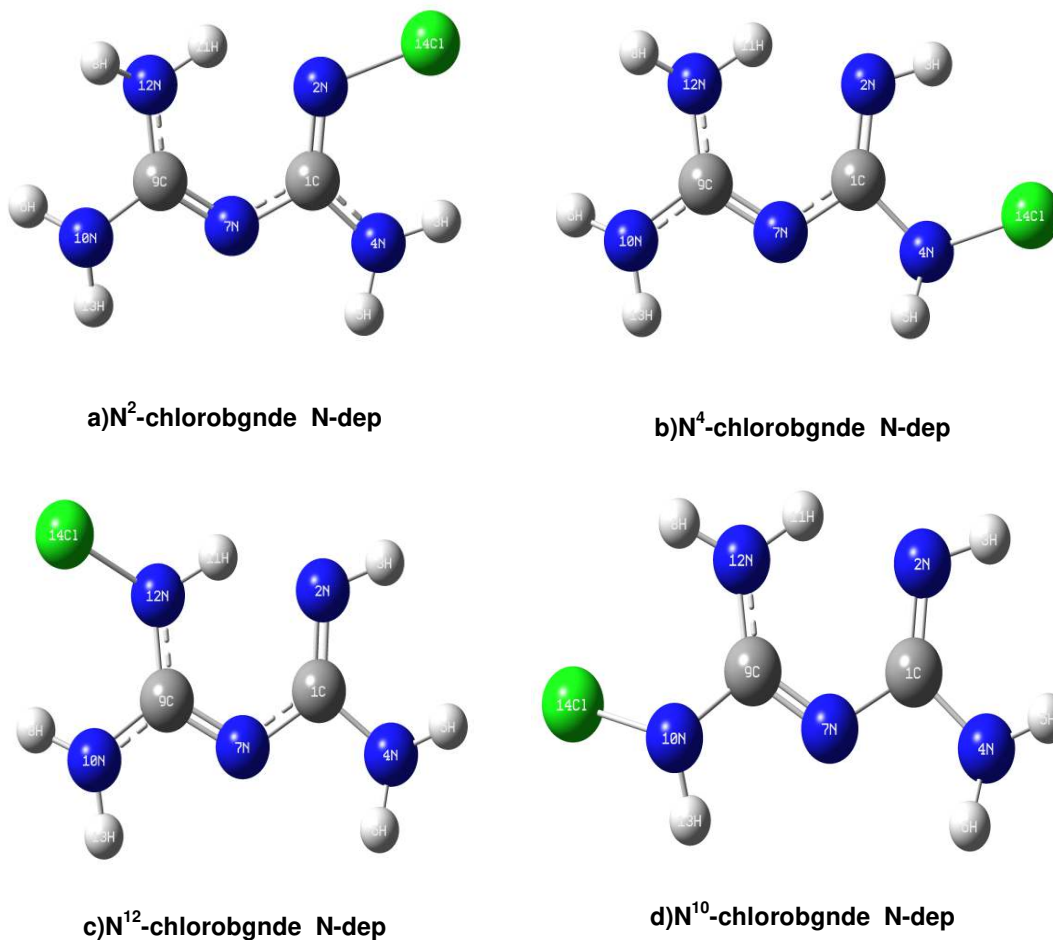**d)N^{10}-chlorobgnde N-dep**

Fig. 3. N-chlorosubstituted derivatives of the N-deprotonated biguanide

Table 1. Enthalpies and Gibbs free energy of the N-chlorosubstituted derivatives of the N-deprotonated biguanide

Energies (hartrees)	N^2- chlorobgde N-dep	N^4-chlorobgde N-dep	N^{10}- chlorobgde N-dep	N^{12}- chlorobgde N-dep
Enthalpy	-813.6654	-813.6502	-813.6482	-813.6499
Free enthalpy	-813.7089	-813.6932	-813.6916	-813.6930

The Table 1 reveals that the N-deprotonated N^2-chlorobiguanide is the most stable among the studied N-chlorosubstituted derivatives. The least stable is the N-deprotonated N^{10}-chlorobiguanide; it is followed by N-deprotonated N^{12}- chlorobiguanide.

3.1.1 Geometric parameters

The geometric parameters of the N-chloro-substituted derivatives of the N-deprotonated tautomer of biguanide are recorded (Table 2). This table shows that, in the different N-chlorosubstituted isomers of the N-deprotonated biguanide, the bond lengths C^1N^4, C^1N^7, N^7C^9 and C^9N^{12} are included between 1.35 and 1.40 Å, intermediate lengths between that of a C-N (1.47 Å) and a C = N (1.27 Å) bonds. This supposes a free circulation of clouds of free electron pairs of nitrogen atoms from N^4 to N^{12} via C^1, N^7 and C^9.

This delocalization makes the relevant doublets unavailable for coordination of the studied molecules via N^4, N^{10} or N^{12}. The C^1N^2 and N^7C^9 bonds lengths in these molecules are of the order of 1.28 to 1.30 Å, values very close to those of the double bonds (about 1.27 Å); so it can be assumed that the free electron pairs of N^2 and N^7 are the most available for coordination in addition to the free pairs of the chlorine atom.

3.1.2 Analysis of atomic charges

The nitrogen atoms N^2, N^4, N^{10}, N^{12} and N^7 have the highest electron densities. It should, however, be noted that the hydrogen atoms bonded to N^4, N^{10} and N^{12} are positively charged, which is likely to disadvantage the accessibility of these atoms to a positive complexing ion due to the interaction of repulsion that would be established between these nitrogen atoms and the complexing ion. N^2 and N^7 (both nitrogen atoms of the C=N groups) would be the most favorable coordination sites if we consider the NBO atomic charges.

It is found that the presence of a chlorine atom in place of the hydrogen atom on a N atom causes a considerable drop in the negative charge of the nitrogen atom (it went from -0.86 ua in the N-deprotonated biguanide to -0.60 ua in the N-deprotonated N^2-chlorobiguanide, for example), which corresponds to a depletion of the chlorosubstituted nitrogen electron density. At the same time, the C atom directly linked to this N atom has become enriched (its charge varied from 0.611ua in the biguanide N-deprotonated to 0.59ua in the N^4-chlorobiguanide N-deprotonated for example) during which the atom of chlorine is positive, sign of the impoverishment of its electronic density. These observations

Table 2. Geometric parameters of the N-deprotonated biguanide and its N-chlorosubstituted derivatives

Distances (Å)	N-dep bgde	N-chlorosubstituted ligands of N-depronated biguanide				DFT* stand values	Exp ** stand values
		N^2- hloro bgde N-dep	N^4- chloro bgde N-dep	N^{10}- chloro bgde N-dep	N^{12}- chloro-bgde N-dep		
$C^1=N^2$	1.30	1.31	1.29	1.30	1.30	1.27	1.27 [19]
C^1-N^4	1.39	1.36	1.42	1.38	1.38	1.46	1.47
C^1-N^7	1.38	1.38	1.37	1.39	1.38	1.46	1,47
$N^7=C^9$	1.31	1.31	1.31	1.30	1.32	1.27	1.27
C^9-$N^{10)}$	1.38	1.38	1.38	1.41	1.36	1.46	1.47
C^9-N^{12}	1.36	1.36	1.35	1.34	1.37	1.46	1.47
N^2-Cl^{14}	-	1.78	-	-	-	1.79	1.75 [20]
N^4-Cl^{14}	-	-	1.75	-	-	1.79	1.75
$N^{10-}Cl^{14}$	-	-	-	1.77	-	1.79	1.75
N^{12}-Cl^{14}	-	-	-	-	1.74	1.79	1.75

*DFT standard; **Experimental standard*

Table 3. Atomic NBO charges of the N-deprotonated biguanide and its N-chlorosubstituted derivatives

Atoms	N-dep bgde	N-chlorosubstituted derivatives of the N-deprotonated biguanide			
		N^2- chloro-bgde N-dep	N^4- chloro-bgde N-dep	N^{10}- chloro-bgde N-dep	N^{12}- chloro-bgde N-dep
C^1	0.61	0.60	0.59	0.61	0.62
N^2	-0.86	-0.60	-0.82	-0.85	-0.86
N^4	-0.87	-0.85	-0.64	-0.87	-0.86
N^7	-0.67	-0.65	-0.67	-0.65	-0.66
C^9	0.66	0.66	0.66	0.64	0.65
N^{10}	-0.86	-0.86	-0.86	-0.64	-0.85
N^{12}	-0.87	-0.86	-0.86	-0.85	-0.66
H^5	0.36	0.42	0.38	0.37	0.37
H^6	0.41	0.42	0.43	0.40	0.40
H^{10}	0.40	0.41	0.41	0.42	0.42
H^{12}	0.40	0.41	0.41	0.43	0.42
H^{13}	0.41	0.46	0.46	0.47	0.48
H^{14}	0.46	0.42	0.43	0.44	0.43
Cl^{14}	-	0.02	0.08	0.07	0.09

suggest that the fixing of the N atom has caused a repulsion of the electronic doublet cloud of the NC bond towards C by the very dense initial electronic cloud of the chlorine atom (it indeed carries three free electronic doublets); this justifies the decrease of the positive charge at C^1 level. The electronic deficit thus created at the level of the chlorosubstituted N atom would be partially filled by the impoverishment of the electronic cloud of chlorine.

3.1.3 Analysis of electrostatic potentials (PES)

The content of the Table 4 reveals that the most negative electrostatic potential is at the level of the chlorine atom in all the chlorosubstituted derivatives studied in the present work (about -64.35 ua). It is followed from far away by the N^2 and N^7 atoms (about -18.4 ua); in the N^4-chlorosubstituted derivative, the PES at N^2 is equal to -18.39 ua. It is noted that the

replacement of a hydrogen atom of the nitrogen atom with a chlorine atom hardly influences the electrostatic potentials of the atoms since these values do not change much when we pass from N-deprotonated biguanide to its N-chloro substituted derivatives; but we must not lose sight of the fact that in the N-chlorosubstituted ligands, the PES of the chlorine atom is almost three times higher than that of the nitrogen atoms. It is therefore conceivable that chlorine is the most favorable coordination site of the studied ligands.

3.1.4 Analysis of the frontier orbitals

In the Table 5, only the atomic coefficients at least equal to 0.40 have been considered.

The analysis of the boundary orbitals reveals that in the N-chlorosubstituted derivatives, the HOMO and HOMO-1 are essentially made up of atomic orbitals of N^4, N^{10}, N^7 and N^2 and of the chlorine atom.

Table 4. Electrostatic potentials of the N-deprotonated biguanide and its N-chlorosubstituted derivatives

Atoms	N-dep bgde	N-Chloro-substituted molecules of the N- deprotonated biguanide			
		N^2-chlorobgde N-dep	N^4-chlorobgde N-dep	N^{10}-chlorobgde N-dep	N^{12}-chlorobgde N-dep
N^2	-18.386	-18.359	-18.398	-18.402	-18.399
N^4	-18.359	-18.333	-18.299	-18.340	-18.339
N^7	-18.377	-18.382	-18.385	-18.383	-18.388
N^{10}	-18.364	-18.321	-18.321	-18.284	-18.319
N^{12}	-18.332	-18.327	-18.330	-18.328	-18.301
Cl^{14}	-	-64.389	-64.359	-64.349	-64.352
C^1	-14.660	-14.639	-14.644	-14.645	-14.644
C^9	-14.636	-14.617	-14.618	-14.618	-14.618

Table 5. Frontier orbitals of the N-deprotonated biguanide and its N-chlorosubstituted derivatives

Orbitals	N-dep bgde		N^2-chlorobgde N-dep		$ZnCl_2$	
	Dominant atomic orbitals	Coefficients	Dominant atomic orbitals	Coefficients	Dominant atomic orbitals	Coefficients
HOMO -1	N^4(pz) ;N^7(pz) N^{12}(pz)	0,80 ;0,52 0,42	N^4(pz); N^7(pz); N^{12}(pz) ;	0,75 ; 0,61 ; 0,44	-	-
HOMO	N^2(pz); N^7(pz)	0,77 ;0,58	N^2(pz);N^7(pz) Cl (pz)	0,42 ;0,46 ; 0,72	-	-
LUMO					Zn(s)	2,01
LUMO+1					Zn(py)	1,43
Favorable sites	N^2 ; N^4 N^7 ; N^{10}		N^2 ; N^4 ; N^7 ; Cl			

Orbitals	N^4-chlorobgde N-dep		N^{10}-chlorobgde N-dep		$ZnCl_2$	
	Atomic orbitals dominant	Coefficients	Atomic orbitals dominant	Coefficients	-	-
HOMO -1	N^4(pz) ; Cl (pz)	0,80 ; 0,55	N^4(pz); N^7(pz); N^{12}(pz)	0,79 ;0,50 ; 0,40	-	-
HOMO	N^2(pz); N^7(pz)	0,68 ; 0,69;	N^2(pz); N^7(pz);	0,76 ; 0,55 ;	-	-
LUMO	-	-	-	-	Zn(s)	2.01
LUMO+1	-	-	-	-	Zn(py)	1,43
Favorable sites	N^2 ; N^4 ; N^7 ; Cl		N^2 ; N^4; N^7; N^{10}		-	-

Orbitals	N^{12}-chlorobgde N-dep		$ZnCl_2$	
	Atomic orbitals dominant	Coefficients	Atomic orbitals dominant	Coefficients
HOMO -1	N^2(pz); N^4(pz); N^{12}(pz) ;	0,42; 0,73; 0,54 ;	-	-
HOMO	N^2(pz) ; N^7(pz)	0,70 ; 0,67 ;	-	-
LUMO	-	-	Zn(s)	2,01
LUMO+1	-	-	Zn(py)	1,43
Favorable sites	N^2 ; N^4; N^7; N^{12}			

3.1.5 Analysis of atomic indices of Electrophilic Superdelocalizability (ESDI)

In Table 6 are found the electrophilic superdelocalizabilities indices of the ligand atoms.

The electrophilic atomic superdelocalizability indices of the N-chlorosubstituted derivatives of the N-deprotonated biguanide is more negative at the level of the chlorine atom. It is followed by that of the N^2 and N^7 atoms, which suggests that the Cl, N^2 and N^7 atoms are the most favorable sites for coordination.

It can be concluded from this analysis that the N-chlorosubstituted nitrogen atom seems least favorable to lend its free electron pair during a coordination reaction; this confirms the conclusions drawn above from the analyzes of CN interatomic bond lengths and NBO charges; thus, the electrophilic superdelocalisability indices indicate that the sp^2 nitrogen atoms, N^7 and chlorine atom are the most favorable coordination sites in the N-chlorosubstituted derivatives of the N-deprotonated biguanide.

3.1.6 Summary analysis

Table 7 reveals that the sites most favorable to the coordination of the N-chlorosubstituted derivatives of the N-deprotonated biguanide would be the chlorine atom and the imine nitrogen atoms (N^2 and N^7); indeed, the coordination indicators in the present study are favorable for N^2 (80%), Cl (80%) and N^7 100%) in the N-deprotonated N^2-chloro-biguanide and are favorable for N^2 (100%).), N^7 100%) and Cl (80 or 60%) in the other N-chlorosubstituted derivatives.

3.1.7 The energies of the HOMO and LUMO

The HOMO-LUMO gaps are 0.212 hartree, 0.199 hartree, 0.174 hartree and 0.187 hartree respectively for N-deprotonated N^2-chloro-biguanide, N-deprotonated N^4-chlorobiguanide, N- deprotonated N^{10}-chlorobiguanide and N-deprotonated N^{12}-chlorobiguanide (Table 8). These gaps are all smaller than that of the N-deprotonated biguanide (0.231 hartree). Thus, all N-chloro-substituted derivatives of the N-deprotonated biguanide should be more electron-donor than it. The values of these gaps show that N-deprotonated N^{10}-chlorobiguanide has the

smallest gap. It follows, therefore, that among all N-chlorosubstituted derivatives studied in this work, the N-deprotonated N^{10}-chlorobiguanide must be more electron-donor [21-25]. As a result, the N-deprotonated N^{10}-chlorobiguanide would more easily complex than the N-deprotonated biguanide and the other studied N-chlorosubstituted molecules.

The study of the ligands thus carried out, it is necessary to simulate corresponding complexes in order to verify the results of the partial conclusions resulting from this study. This constitutes 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 provided by Zinc (II) chloride. The coordination of ligands with zinc (II) has been envisaged through each potential coordination site identified in the first part of this research. To reach this goal, the Zn (II) was placed at about 3 Å from the identified atom. The obtained systems were then optimized and complexes were formed according to the structures shown on Tables 9 to 12.

With N-deprotonated N^2-chlorobiganide, it obtained coordinations N^4-Zn-N^4 and N^2-Zn-N^{10}; with N-deprotonated N^4-chlorobiganide, it obtained coordinations N^2-Zn-N^2, N^4-Zn-N^7, N^7-Zn-N^7 and N^2-Zn-N^{12}; the coordinations N^2-Zn-N^2, N^4-Zn-N^4, N^7-Zn-N^7 and N^2-Zn-N^4 are obtained with N-deprotonated N^{10}-chlorobiganide; with N-deprotonated N^{10}-chlorobiganide, the coordinations N^2-Zn-N^2 and N^7-Zn-N^7 take place.

As can be seen, no coordination via chlorine atom has been obtained.

In total twelve coordination compounds of N-chlorosubstituted derivatives of N-deprotonated biguanide with Zinc (II) were obtained. The table 13 gathers the calculated interatomic distances Zn-N of the complexes.

The coordinations took place especially via the imine nitrogen atoms N^2 and N^7. The coordinations involving other N atoms are weaker, as shown by the corresponding longer Zn-N lengths (2.11 to 2,29Å).

Table 6. Atomic electrophilic superdelocalizabilitiy indices of the N-deprotonated biguanide and its N-chlorosubstituted derivatives

Atoms	N-dep bgde	N-Chloro-substituted ligands of biguanide N- deprotonated			
		N^2- chlorobgde N-dep	N^4-chlorobgde N-dep	N^{10}-chloro-bgnde N-dep	N^{12}- chlorobgde N-dep
N^2	-16,492	-14,925	-15,323	-15,671	-15.619
N^4	-13,372	-12,644	-12,403	-12,872	-12.862
N^7	-15,622	-14,638	-14,763	-14,615	-14.941
N^{10}	-12,671	-12,209	-12,187	-11,841	-12.144
N^{12}	-12,949	-12,274	-12,371	-12,248	-12.392
Cl^{14}	-	-19,870	-18,237	-17,762	-17.965
C^1	-7,420	-6,973	-7,188	-7,148	-7.082
C^9	-6,940	-6,654	-6,644	-6,658	-6.622

Table 7. Summary analysis

Coordination indicator (C I)		N-dep bgde	N-chlorosubstituted derivatives of N- deprotonated biguanide			
			N^2-chloro-bgde N-dep	N^4- chloro-bgde N-dep	N^{10}- chloro-bgde N-dep	N^{12}- chloro-bgde N-dep
Bond lengths		N^2 ; N^7	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl
Atomic charge		N^2 ; N^7	N^7	N^2 ; N^7	N^2 ; N^7	N^2 ; N^7
ESP		N^2, N^7	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl
ESDI		N^2, N^7	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl	N^2 ; N^7 ; Cl
HOMO and HOMO-1		N^2, N^4, N^7, N^{10}	N^2 ; N^4 ; N^7 ; Cl	N^2 ; N^4 ; N^7 ;Cl	N^2 ; N^4; N^7; N^{10}	N^2 ; N^4; N^7; N^{12};
% of favorabl e C I	N^2	100	80	100	100	100
	N^4	20	20	20	20	20
	N^7	100	100	100	100	100
	N^{10}	20	-	-	20	-
	N^{12}	-	-	-	-	20
	Cl	-	80	80	60	60

Table 8. Energies (in hartree) of the frontier molecular orbitals of the N-chlorosubstituted derivatives of the N-deprotonated biguanide

Frontier orbitals	N-dep bgde	N-chlorosubstituted derivatives of N- deprotonated biguanide				$ZnCl_2$
		N^2- chloro-bgde N-dep	N^4- chloro-bgde N-dep	N^{10}- chlorobgde N-dep	N^{12}- chlorobgde N-dep	
HOMO	-0.211	-0.215	-0.229	-0.226	-0.222	-0.321
HOMO-1	-0.234	-0.248	-0.242	-0.245	-0.240	-0.321
LUMO	0.020	-0.002	-0.030	-0.052	-0.035	-0.069
LUMO+1	0.077	0.004	0.011	0.018	0.016	-0.021
Gap $_{HOMO-LUMO}$	0.231	0.212	0.199	0.174	0.187	-0.252

These results confirm the observations previously made during the study of ligands; indeed, during this investigation it appeared that:

- The percentages of the coordination indicators selected in the present work which are favorable for the coordination via the imine nitrogen atoms are much higher than those favorable to the other atoms.
- The positive charge of the chlorine atoms repels the Zn^{2+} ion, which justifies the absence of coordination of the Cl-Zn-Cl or Cl-Zn-N nature.

3.2.2 Energy study of complexes of N-chlorosubstituted derivatives of N-deprotonated biguanide

It is easy to notice that all ΔGcoord and ΔHcoord values are negative: The coordination processes studied in this work are Spontaneous and exothermic.
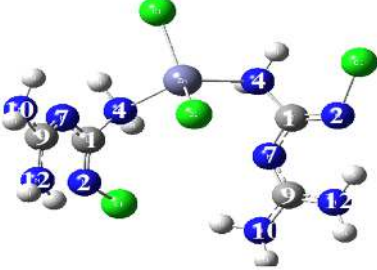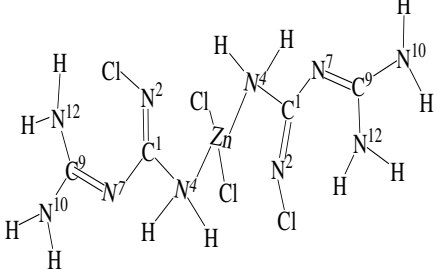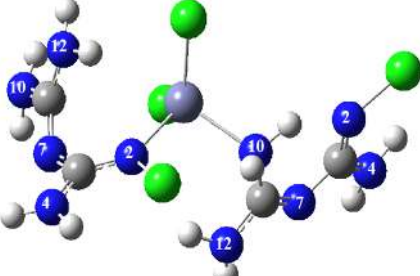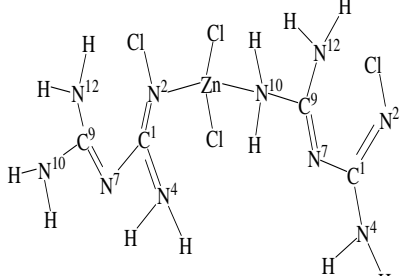
Table 9. Complexes of N-deprotonated N^2-chlorobiganide
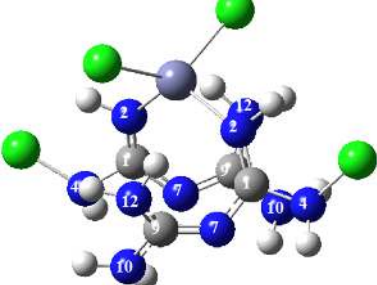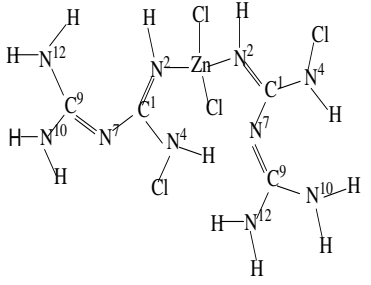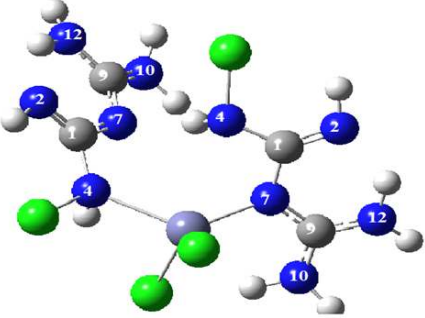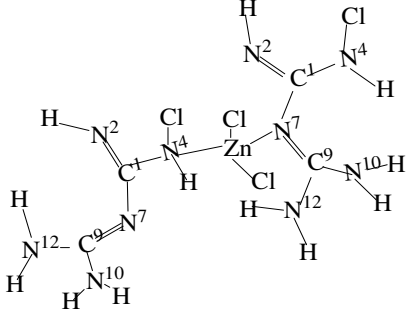
No.	Complexes	
	Gaussview representation	**Chemdraw representation**
1	ZnCl$_2$(N-dep N^2-chlorobgde)$_2$	ZnCl$_2$(N-dep N^2-chlorobgde)$_2$
2	ZnCl$_2$(N-dep N^2-chlorobgde)$_2$	ZnCl$_2$(N-dep N^2-chlorobgde)$_2$

Table 10. Complexes of N-deprotonated N^4-chlorobiganide

No	Complexes	
	Gaussview representation	**Chemdraw representation**
3	ZnCl$_2$(N-dep N^4-chlorobgde)$_2$	ZnCl$_2$(N-dep N^4-chlorobgde)$_2$
4	ZnCl$_2$(N-dep N^4-chlorobgde)$_2$	ZnCl$_2$(N-dep N^4-chlorobgde)$_2$
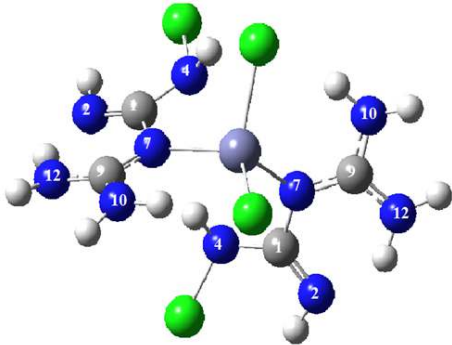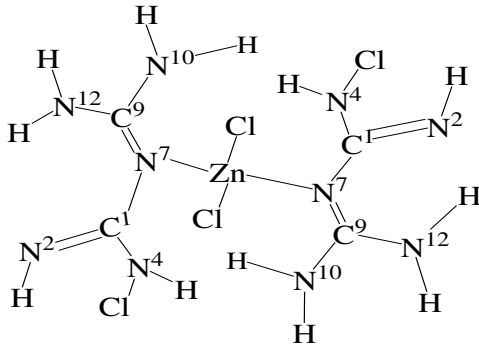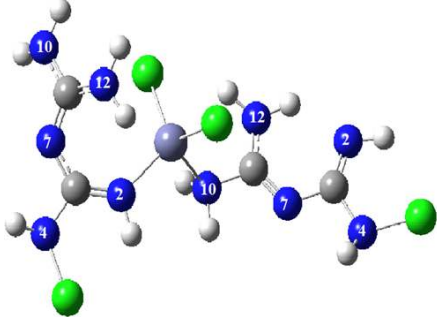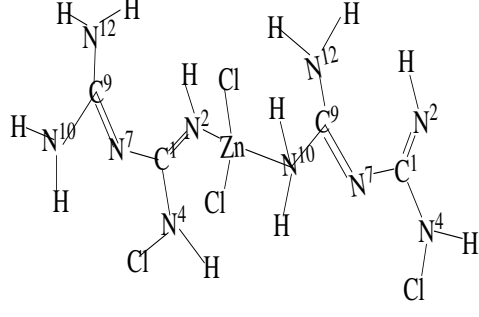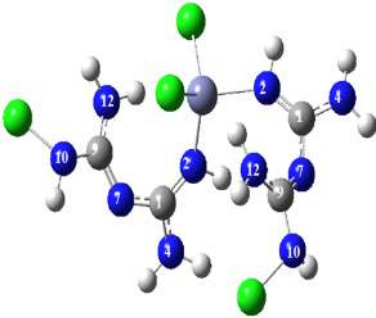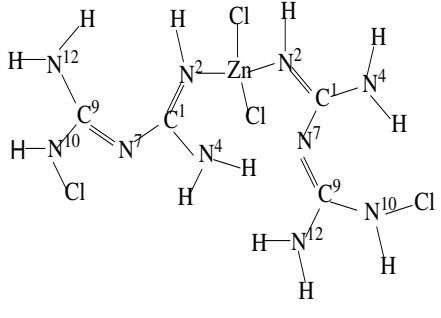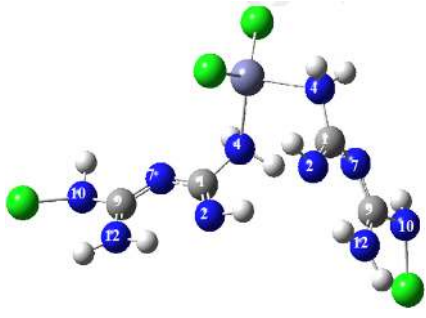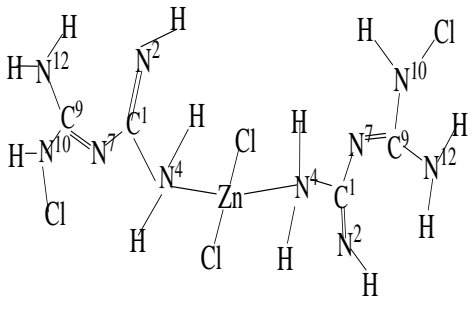
5		
	ZnCl$_2$(N-dep N^4-chlorobgde)$_2$	ZnCl$_2$(N-dep N^4-chlorobgde)$_2$
6		
	ZnCl$_2$ (N-dep N^4-chlorobgde)$_2$	ZnCl$_2$ (N-dep N^4-chlorobgde)$_2$

Table 11. Complexes of N-deprotonated N^{10}-chlorobiganide

No	Complex	
	Gaussview representation	**Chemdraw representation**
7		
	ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$	ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$
8		
	ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$	ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$

9	 ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$	 ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$
10	 ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$	 ZnCl$_2$(N-dep N^{10}-chlorobgde)$_2$
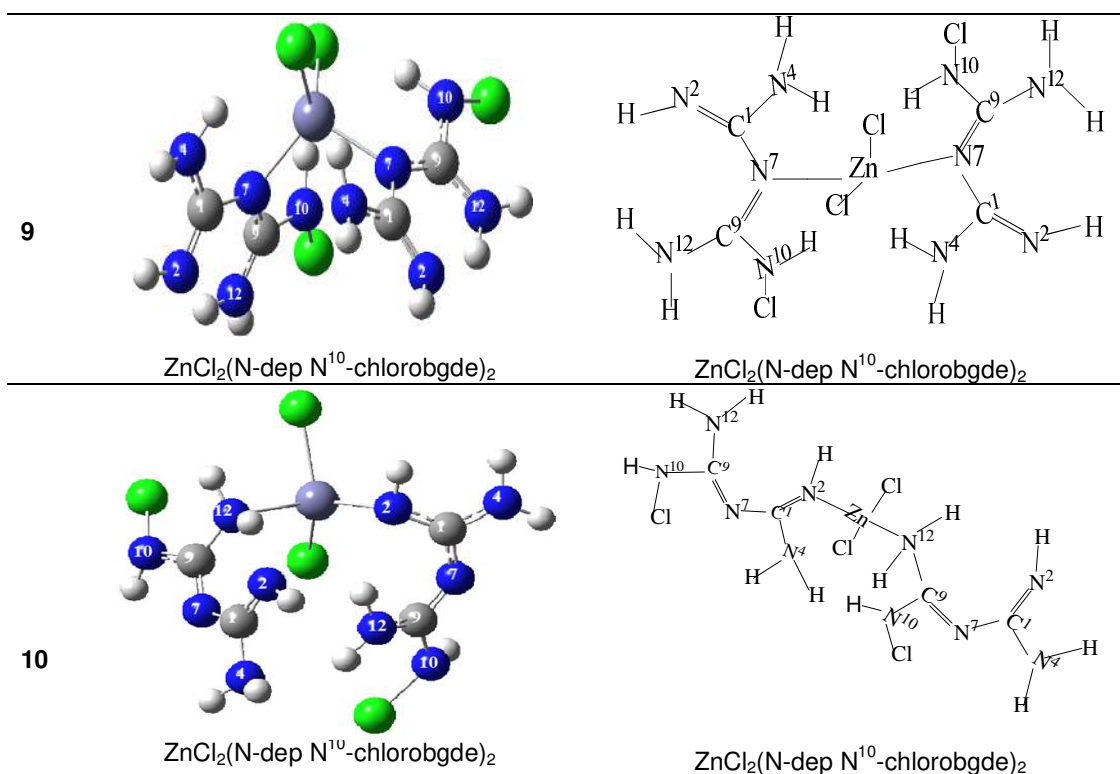
Table 12. Complexes of N-deprotonated N^{12}-chlorobiganide

NO	Complex	
	Gaussview representation	**Chemdraw representation**
11	 ZnCl$_2$(N-depN^{12}-chlorobgde)$_2$	 ZnCl$_2$(N-depN^{12}-chlorobgde)$_2$
12	 ZnCl$_2$ (N-dep N^{12}-chlorobgnde)$_2$	 ZnCl$_2$ (N-dep N^{12}-chlorobgnde)$_2$

Table 13. Zn-N interatomic distances of the complexes obtained

Complexes	Ligand 1					Ligand 2				
	ZnN^2	ZnN^4	ZnN^7	ZnN^{10}	ZnN^{12}	ZnN^2	ZnN^4	ZnN^7	ZnN^{10}	ZnN^{12}
$ZnCl_2$ (N-depbgnde)$_2$	2.00	4.31	3.55	4.38	3.20	2.01	4.31	3.55	4.39	3.19
$ZnCl_2$(N^2-chlorobgde N-dep)$_2$ (n°1)	3.97	2.17	3.19	4.79	5.01	3.94	2.12	3.35	5.13	5.25
$ZnCl_2$(N^2-chlorobgde N-dep)$_2$(n°2)	2.09	4.41	3.47	4.29	3.18	4.16	5.61	3.94	2.11	3.41
$ZnCl_2$(N^4-chlorobgde N-dep)$_2$(n°3)	2.04	4.36	3.64	4.48	3.42	2.04	4.36	3.64	4.48	3.42
$ZnCl_2$(N^4-chlorobgde N-dep)$_2$(n°4)	4.07	2.80	2.05	3.24	4.19	4.46	2.30	3.51	5.38	5.80
$ZnCl_2$ (N^4-chlorobgde N-dep)$_2$(n°5)	4.14	3.14	2.06	3.15	4.18	4.27	2.93	2.10	3.19	4.32
$ZnCl_2$ (N^4-chlorobgde N-dep)$_2$(n°6)	5.47	5.98	3.92	2.13	3.40	2.00	4.31	3.49	4.33	3.08
$ZnCl_2$ (N^{10}-chlorobgde N-dep)$_2$(n°7)	2.00	4.32	3.64	4.55	3.21	2.02	4.34	3.68	5.06	3.53
$ZnCl_2$ (N^{10}-chlorobgde N-dep)$_2$(n°8)	3.72	2.09	3.73	5.75	5.46	3.59	2.16	3.69	5.80	5.49
$ZnCl_2$ (N^{10}-chlorobgde N-dep)$_2$(n°9)	4.13	2.93	2.06	3.24	4.26	4.23	3.18	2.05	2.98	4.20
$ZnCl_2$ (N^{10}-chlorobgde N-dep)$_2$(n°10)	2.00	4.10	3.50	4.68	3.60	3.92	5.28	3.90	3.8	2.24
$ZnCl_2$(N^{12}-chlorobgde N-dep)$_2$(n°11)	1.99	4.24	3.33	5.04	4.09	1.99	4.26	3.51	4.51	3.35
$ZnCl_2$(N^{12}-chlorobgde N-dep)$_2$(n°12)	4.18	3.00	2.05	3.31	4.22	4.28	3.23	2.06	3.03	4.09

Table 14. Energy study of complexes obtained

Molecule	Type of coordination	ΔG, eV	ΔGcoord, eV	ΔH, eV	ΔHcoord, eV	Type of process
N-dep bgnde	-	-9636.13	-	-9635.07	-	-
N-dep N^2-chlorobgde	-	-22141.59	-	-22140.41	-	-
N-dep N^4-chlorobgde	-	-22141.16	-	-22140.00	-	-
N-dep N^{10}-chlorobgde	-	-22141.12	-	-22139.94	-	
N-dep N^{12}-chlorobgde	-	-22141.16	-	-22141.34	-	-
$ZnCl_2$	-	-73459.09	-	-73458.28	-	-
$ZnCl_2$ (N-dep bgde)$_2$		-92733.13	-1.78	-92731.04	-2.62	Spo, exo
$ZnCl_2$ (N-dep N^2-chlorobgde)$_2$,(n°1)	N^4-Zn-N^4	-117742.86	-0.60	-117740.51	-1.41	Spo, exo
$ZnCl_2$ (N-dep N^2-chlorobgde)$_2$,(n°2)	N^2-Zn-N^{10}	-117743.10	-0.82	-117740.80	-1.70	Spo, exo
$ZnCl_2$ (N-depN^4-chlorobgde)$_2$,(n°3)	N^2-Zn-N^2	-117742.76	-1.35	-117740.50	-2.23	Spo, exo
$ZnCl_2$ (N-dep N^4-chlorobgde)$_2$(n°4)	N^4-Zn-N^7	-117742.35	-0.93	-117740.12	-1.85	Spo, exo
$ZnCl_2$ (N-dep N^4-chlorobgde)$_2$(n°5)	N^7-Zn-N^7	-117742.92	-1.50	-117740.73	-2.46	Spo, exo
$ZnCl_2$ (N-dep N^4-chlorobgde)$_2$(n°6)	N^2-Zn-N^{10}	-117742.58	-1.17	-117740.30	-2.03	Spo, exo
$ZnCl_2$ (N-dep N^{10}-chlorobgde)$_2$(n°7)	N^2-Zn-N^2	-117742.80	-1.48	-117740.47	-2.31	Spo, exo
$ZnCl_2$ (N-dep N^{10}-chlorobgde)$_2$(n°8)	N^4-Zn-N^4	-117742.19	-0.86	-117739.90	-1.74	Spo, exo
$ZnCl_2$ (N-dep N^{10}-chlorobgde)$_2$(n°9)	N^7-Zn-N^7	-117742.86	-1.54	-117740.70	-2.54	Spo, exo
$ZnCl_2$ (N-dep N^{10}-chlorobgde)$_2$(n°10)	N^2-Zn-N^{12}	-117742.57	-1.24	-117740.26	-2.10	Spo, exo
$ZnCl_2$ (N-dep N^{12}-chlorobgde)$_2$(n°11)	N^2-Zn-N^2	-117743.73	-2.32	-117741.46	-0.50	Spo, exo
$ZnCl_2$ (N-dep N^{12}-chlorobgde)$_2$(n°12)	N^7-Zn-N^7	-117743.48	-2.08	-117741.30	-0.33	Spo, exo

ΔG = Gibbs free energy of species; ΔG$_{coord}$ =Gibbs free energy of coordination; ΔG$_{coord}$ = ΔG$_{complex}$ − (2.ΔG$_{ligand}$ + ΔG$_{ZnCl2}$); ΔH$_{coord}$ = ΔH$_{complex}$ − (2.ΔH$_{ligand}$ + ΔH$_{ZnCl2}$); Spo= Spontaneous; Exo= exothermic

A comparison of the complexes of a given chlorosubstituted ligand shows, in each case, that the complexes involving the imide nitrogen atoms (N^2 and N^7) have the lowest Gibbs free enenergies ΔG and the Gibbs free coordination energies ΔGcoord, which suggests that these complexes are the most stable and that the coordinations involving the imide nitrogen atoms are the most solid, therefore the most probable; this means that these nitrogen atoms are the most likely coordination sites. This observation further confirms the results of the ligand study carried out above.

The Gibbs free energies of coordination of $ZnCl_2$.(N-dep N^{12}-chlorobgnde) $_2$ (-2,32 eV and -2,08 eV respectively) are lower than that of $ZnCl_2$(N-dep bgnde)$_2$ (-1,78 eV), suggesting that these N-chlorosubstituted derivatives coordinate more easily than the deprotonated biguanide.

4. CONCLUSION

All coordination processes involved in the present studies have been spontaneous and exothermic.

The present research work aims to identify, in monochlorosubstituted derivatives of the N deprotonated tautomer from of biguanide, the most likely coordination site. This was done by analyzing five coordination indicators, namely interatomic distances, atomic charges, electrostatic potentials at the atomic level, frontier orbitals and atomic electrophilic superdelocalizabilities indices. It has been found that the sites most favorable for the coordination of these ligands are the imide atoms. As showed by the coordination indicators, coordination via N^2 is disadvantageous when this atom is linked to a chlorine atom; that is evidenced by the almost absence of complexes of this type.

The modelling of complexes of these ligands with Zinc(II) has been carried out. Coordination with chlorine, contrary to all expectations, has proved unfavorable. All situations with Cl-Zn-Cl and N-Zn-Cl coordinations bonds have been envisaged have evolved towards N^2-Zn-N^2, N^2-Zn-N^7 or N^7-Zn-N^7 coordination, thus promoting N^2 nitrogen atoms and N^7.

This work showed that:

- The coordination of N-chlorosubstituted derivatives of N-deprotonated biguanides with Zinc (II) is possible;

- The N-depronated N^{12}-chlorobiguanide coordinates (via N^2 and N^7) easier than the N-depronated biguanide;
- Among the obtained complexes of N-chlorosubstituted derivatives, the more stable are those obtained with N-depronated N^{12}-chlorobiguanide and N-depronated N^{10}-chlorobiguanide via N^2 and N^7;
- The most favorable coordination sites are the N atoms involved in the C = N bond (N^2 and N^7).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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