Original research article

DFT Study of Coordination of N-Monochlorosubstituation Derivatives of Biguanide

ABSTRACT

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. It is known that some transition metal complexes with given organic compoundsdeeplyincrease both therapeutic actions of the metal and the organic compound. The chlorine atom, a preferred substitute in pharmacy, improves the effectiveness of drugs and reduces their side effects. The mesomeric +M effect of the chlorine atom would make it possible to enhance the nucleophilic character of any N-chlorosubstituted nitrogen.

In this work a theoretical study of coordination of N-chlorine derivatives of biguanide is carried out mainly at the DFT/B3LYP/6-31G (d, p) level. The Gaussian 09 & 03, HyperChemsoftwares and the DCENT-QSAR program are used.

The results of the calculations revealed the imine nitrogen atoms as the most favorable coordination sites. Bioactive complexes of these ligands with Zn (II) are modelled. They can be considered as drug-candidates.

Keywords*: Coordination; N-chlorosubstituted biguanides; Diabetes; DFT; Drug Candidats*

1. INTRODUCTION

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] 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 common skeleton of the biguanides are potential coordination sites. 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.[5,6,7,8]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.[9,10,11] A probable advantage of the presence of the chlorine atom in a bioactive molecule such as biguanides is the presence of the three free electron pairs on its last layer; indeed, the mesomeric donor effect +M due to these 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.

Recent experiments with zinc complexes on animals suffering from diabetes have been very successful[12,13,14]. Zinc (II) complexes with biguanides and their N-chlorosubstituted derivatives should improve the treatment of this disease while substantially reducing their side effects.

In this work, we carried out aDFT study of the coordination of N-monochlorosubstituted derivatives of biguanide. Complexes of these ligandswith zinc (II) have been modeled, and their bioavailability were tested by Lipinski rules of 5. The general aim is to determine among the five nitrogen and chlorine atoms, that which is the most favorable coordination site in the N-monochlorosubstituted biguanide derivatives.

2. MATERIAL AND METHODS

The hardware used in this investigation consists mainly of versions 09 and 03 of the Gaussian software[15] and the DCENT-QSAR[16] program for calculations; for the drawings, GaussView 5.08 and Chemdraw[17] were used. Molecules of monochlorosubstituted biguanide derivatives were used as organic material. Interatomic bond lengths, atomic charges, molecular electrostatic potentials, frontier orbital structures and electrophilic superdelocalizability indexes were the coordination indicators (CI) taken into account. After the study about the coordinating possibility of each ligand, the formation of its complex with zinc (II) has been calculated. After that, the bioavailability of obtained complexes was considered, so calculation of their hydrogen donor number, hydrogen acceptor number, molecular mass and partition coefficients has been carried out.The calculations were performed mainly by the DFT/B3LYP method in the 6-31G (d, p)[1] orbital basis set on a computer hp inthe Abomey-Calavi university Laboratory of Physical Chemistry, Material and Molecular Modeling (LCP3M)/Unity of Theoretical Chemistry and Molecular Modeling (UCT2M).

3. RESULTS AND DISCUSSION

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

- Cis-1-biguanide: The biguanide conformer in which the two π bonds 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-biguanide: The biguanide conformer in which the two π bonds are in cis position relative to each other but both trans with respect to the hydrogen atom carried by the nitrogen atom number 7.
- transbiguanide: The biguanide conformer in which the both π bonds are in trans position with respect to each other.
- N-dep: N-deprotonated
- bgde = biguanide.

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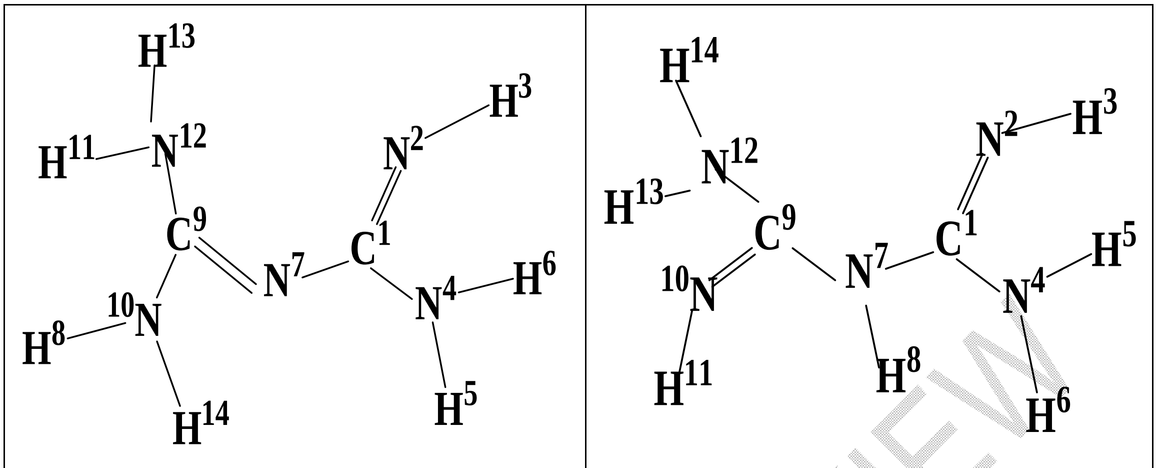
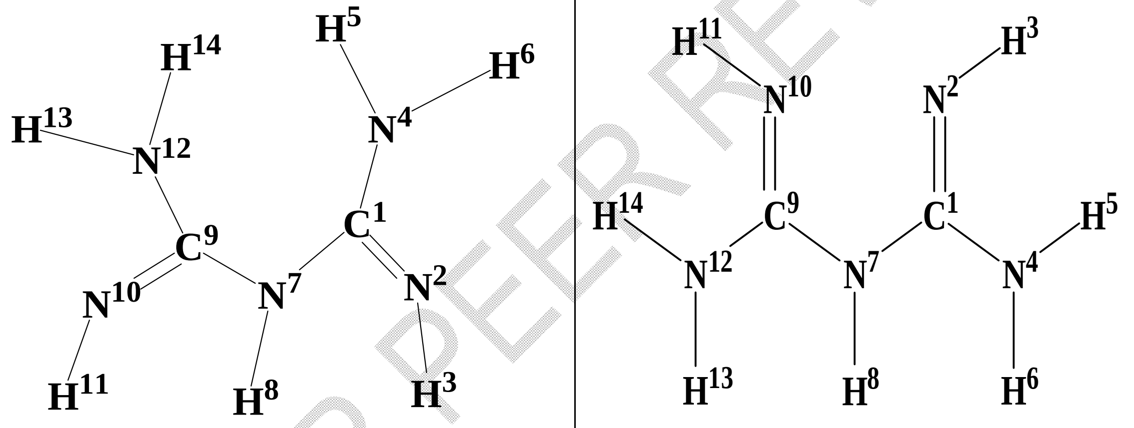
[1] Unless otherwise specified, data are at the B3LYP/6-31G(d,p) level.



a) BgdeN-dep
(∆G = -354,130; ΔH=-354,091)

b)π-trans-bgde
(∆G = -354,120 ; ΔH=-354,073)



c)π-Cis1- bgde
(∆G=-54 ,112;ΔH=-354,072)

d)π-Cis-2-bgde
(∆G=-354,104; ΔH=-354,060)

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

The cis-2-biguanide form is the least stable conformer of the four that are studied in this work but, at the same time, its complexes are the most encountered in the products of synthesis.[18,19,20,21,22] This conformer, widely used in the literature, is simply designated "biguanide". The present research work is focused on the N-monochlorosubstituted derivatives of this form. The investigations consisted of looking for the site of these molecules that is best able to coordinate with a complexing metal.

3.1. Study of the ligands

The N-monochlorosubstituted derivatives of the biguanide molecule are shown on the figure2. From the analysis of the free enthalpy values presented in table 1, it appears that N^2-chlorobiguanide is the most stable molecule of the N-chlorosubstituted derivatives of the biguanide.

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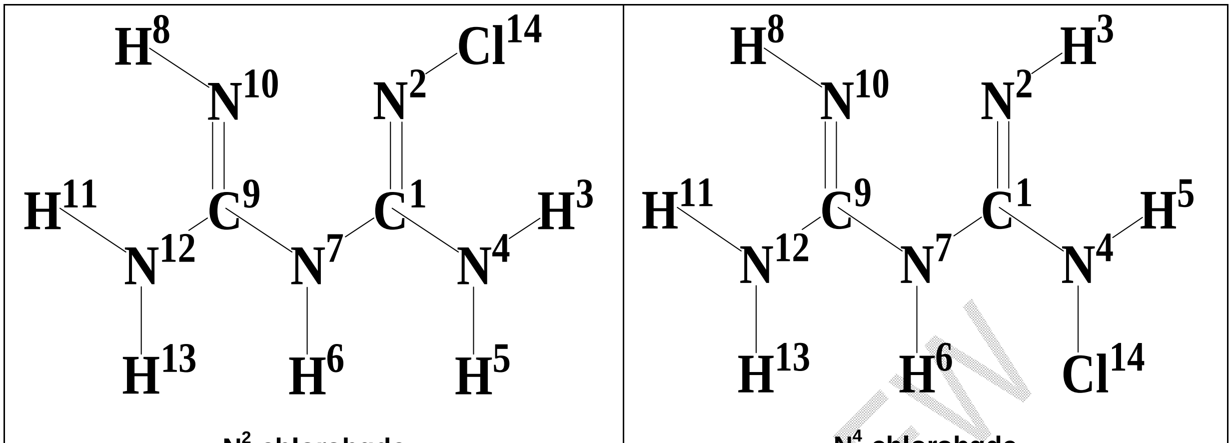
Table1. Free enthalpies (ΔG) and enthalpies (ΔH) of N-chlorosubstituted derivatives of the biguanide

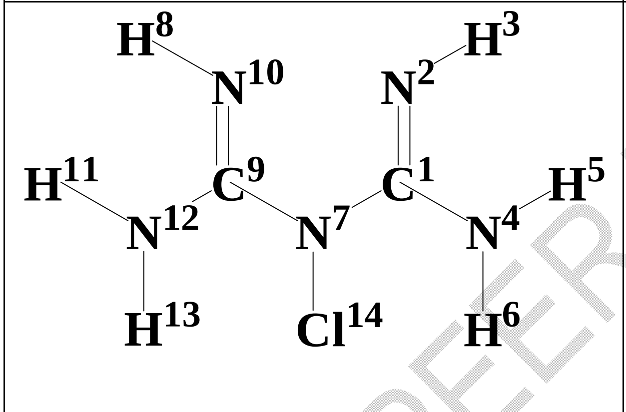
E[a]	**Methods**	**Bgde**	**N-chlorosubstituted derivatives of biguanide**		
			N^2-chloro-bgde	**N^4- chloro-bgde**	**N'- chloro-bgde**
-ΔH	B3LYP/6-31G (dp)	354.06	813.65	813.64	813.61
	B3LYP/cc-pvdz	354.07	813.66	813.65	813.64
	B3PW91/6-31G (dp)	353.93	813.44	813.43	813.43
	B3PW91/cc-pvdz	353.94	813.48	813.47	813.46
-ΔG	B3LYP/6-31G (dp)	354.10	813.70	813.68	813.65
	B3LYP/cc-pvdz	354.11	813.71	813.70	813.69
	B3PW91/6-31G (dp)	353.97	813.49	813.47	813.47
	B3PW91/cc-pvdz	353.98	813.53	813.51	813.51

[a] energies (hartees)



N^2-chlorobgde

N^4-chlorobgde



N^7-chlorobgde

Figure2: N-chlorosubstituted derivatives of the biguanide

3.1.1.Bond lengths

Some bond lengths of the N-chlorosubstituted derivatives of the biguanide are recorded (Table 2).

This table shows that, in the different N-chlorosubstituted isomers of the biguanide, the lengths of the bonds C^1N^4, C^1N^7, N^7C^9 and C^9N^{12} are about 1.40 ´, lengths intermediate between that of a C-N bond (1.47 ´) and a C=N bond (1.27 ´). This supposes a free circulation of the free electron pairs clouds of the nitrogen atoms, from N^4 to N^{12} via C^1, N^7 and C^9.This delocalization makes the concerned pairs unavailable for a coordination of the studied molecules via N^4, N^7 or N^{12}. Since the C^1N^2 and C^9N^{10} bonds are really double (their lengths being about 1.27 ´), it can be assumed that the free electron pairs of N^2 and N^{10} are the most available for coordination in addition to the free electron pairs of the chlorine atom.However, one note that when the chlorine atom is attached to the N^2 or N^{10} atoms, the π pair of the CN bond concerned is also delocalized since the length of this bond is then about 1.30 ´ intermediate between that of a single bond and a double bond; in doing so, the interaction between this π doublet and the N^7 free doublet is enhanced, as shown by the slight shortening of C^1N^7 from 1.40 ´ (in biguanide) to 1.39 ´ (in N^2-chlorobiguanide).

Table 2. Some bond lengths of the biguanide and its N-chlorosubstituted derivatives

Bond lengths (Å)	Bgde	N-chlorosubstituted derivatives of the biguanide				
		N^2-chlorobgde	N^4-chlorobgde	N^7-chlorobgde	DFT[a]	Exp[b]23, 24
C^1=N^2	1.275	1.295	1.276	1.278	1.27	1.270
C^1-N^4	1.390	1.385	1.395	1.381	1.46	1.470
C^1-N^7	1.431	1.398	1.411	1.416	1.46	1.470
N^7-C^9	1.438	1.405	1.383	1.416	1.46	1.470
C^9=N^{10}	1.280	1.272	1.288	1.278	1.27	1.270
C^9-N^{12}	1.372	1.410	1.391	1.381	1.46	1.470
N^2-C^{l14}	-	1.786	-	-	1.79	1.750
N^4-Cl^{14}	-	-	1.739	-	1.79	1.750
N^7-Cl^{14}	-	-	-	1.748	1.79	1.750

[a]DFT standard [b]Experimental standard

3.1.2.Atomic charge NBO

The nitrogen atoms N^2, N^4, N^7, N^{10} and N^{12} have the highest electron densities. It should nevertheless be noted that the N^4 and N^{12} atoms each carry two positively charged hydrogen atoms, which is likely to disadvantage the accessibility of these atoms to a positive complexing ion due to the repulsive interaction which would settle between these nitrogen atoms and the complexing ion. N^2 and N^{10} (the both N imine atoms) would then be the most favorable coordination sites according to NBO atomic charge values.

Table 3. Atomic charge NBO

Atom	Biguanide	N-chlorosubstituted derivatives of biguanide		
		N^{2-}chlorobgde	N^{2-}chlorobgde	N^{2-}chlorobgde
C^1	0.594	0.605	0.591	0.601
N^2	-0.754	-0.560	-0.766	-0.719
N^4	-0.884	-0.865	-0.670	-0.878
N^7	-0.771	-0.661	-0.664	-0.514
C^9	0.584	0.622	0.626	0.604
N^{10}	-0.745	-0.820	-0.827	-0.719
N^{12}	-0.853	-0.884	-0.877	-0.878
$H^{5,}$	0.352	0.455	0.378	0.357
$H^{6,}$	0.408	0.429	0.465	0.422
$H^{8,}$	0.405	0.444	0.442	0.413
H^{11}	0.426	0.376	0.379	0.357
H^{13}	0.352	0.414	0.415	0.413
H^{14}	0.405	0.412	0.410	0.422
Cl^{14}	-	0.032	0.097	0.114

It is found that the presence of a chlorine atom in place of a hydrogen atom on an N atom causes a considerable drop in the negative charge of the nitrogen atom compared to his peers contained in the biguanide (it went from -0.754 u.a. in the biguanide to -0.559 u.a. in N^2-chlorobiguanide), which corresponds to a decrease of the electron density at the level of the N-chlorosubstituted derivative. At the same time the C atom directly bound to this N atom has also become impoverished in electron (itscharge varied from 0.594 ua in biguanide to 0.605 ua in N^2-chlorobiguanide) while the chlorine atom is positive, sign of the impoverishment of its electronic density. These observations suggest that the Cl fixation on an N atom caused a repulsion of the electron doublet cloud of the NC bond, beyond C linked to the chlorosubstituted nitrogen atom to the other nitrogen atoms of the molecule (N^{10} passing from -0.745 u.a. in the biguanide to -0.820 ua in N^2-chlorobiguanide) by the very dense initial electronic cloud of the chlorine atom (it indeed carries three free electronic doublets). The electronic deficit thus created at the level of the chlorosubstituted nitrogen atom would be partially filled by the impoverishment of the electronic cloud of chlorine.

3.1.3. Electrostatic potentials (ESP) of some atoms

The content of Table 4 reveals that the most negative electrostatic potential is at the level of the chlorine atom in all chlorosubstituted derivatives studied in this work (about -64.35 ua). It is followed from far away by the N^2 and N^7 atoms (approximately -18.4 ua); in the N^2-chlorosubstituted derivative, the PES at N^2 is equal to -18.40 ua. It is noted that the replacement of an hydrogen atom of the nitrogen atom with a chlorine atom does not virtually influence the electrostatic potentials of the atoms with respect to the biguanide since these values do not change much when we pass from biguanide to its N-chlorosubstituted 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.

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

Atom	Bgnde	N-chlorosubstituted derivatives of biguanide		
		N^2- chlorobgnde	N^4- chlorobgnde	N^7- chlorobgnde
N^2	-18.404	-18.350	-18.412	-18.398
N^4	-18.337	-18.316	-18.268	-18.325
N^7	-18.323	-18.298	-18.302	-18.281
N^{10}	-18.33	-18.398	-18.418	-18.397
N^{12}	-18.404	-18.321	-18.326	-18.325
Cl^{14}	-	-64.385	-64.336	-64.351
C^1	-14.642	-14.618	-14.629	-14.627
C^9	-14.642	-14.626	-14.634	-14.627

3.1.4. Border orbitals

In the table 5, the atomic coefficients are recorded.

The analysis of the HOMO and HOMO-1 orbitals of the N-chlorosubstituted derivatives of biguanide reveals that the nitrogen atoms N^2 and N^{10} are dominant; nevertheless, in N^7-chlorobiguanide, a not negligible participation of N^7 and N^{12} is observed alongside these.

Table 5: Border orbitals in the biguanide and its N-chlorosubstituted derivatives

Border orbitals	**Bgde**		**N^2-chlorobgde**	
	Dominant atomic orbitals	**Coefficients**	**Dominant atomic orbitals**	**Coefficients**
HOMO -1	N^{10}(px; pz) ; N^{12}(px; pz)	(0,50; 0,48); (0,39 ;0,58)	N^{10}(py)	0,45 ;
HOMO	N^2(pz); N^4(pz) ; N^7(pz) ;	0,65 ; 0,48 ; 0,50 ;	N^2(pz); N^7(pz) ; Cl (pz)	0,64 ; 0,47 ; 0,51
Favorable sites	N^2 ; N^{10} ; N^{12}		N^2 ; N^{10}	
Border orbitals	**N^4-chlorobgnde**		**N^7chlorobgnde**	
	Atomic orbitals dominant	**Coefficients**	**Atomic orbitals dominant**	**Coefficients**
HOMO -1	N^4(px) ; N^{10}(pz);	0,50; 0,73 ;	N^2(pz) ; N^4(py); N^{10}(pz) ; N^{12}(pz)	0,47 ; 0,51 ; 0,46 ; 0,49
HOMO	N^2(px); N^{10}(s, px) ;	0,48 ; (0,40 ; 0,40)	N^2(py ;pz); N^7(pz) ; Cl (pz)	(0,36 0,37); 0,69 ; 0,41
Favorable sites	**N^2 ; N^{10}**		**N^2 ; N^7; N^{12}**	

3.1.5 Atomic electrophilic superdelocalisability indices (AESI) of ligands

The values of the electrophilic superdelocalisability indices of the ligands atoms are shown in table 6.

Table 6: Electrophilic superdelocalisability indices of nitrogen atoms of biguanide and its N-chlorosubstituted derivatives

Atoms	**Bgde**	**N-chlorosubstituted ligands of biguanide**		
		N^2- chlorobgde	**N^4- chlorode**	**N^7- chlorobgde**
N^2	-15.422	-14.799	-15.334	-15.13
N^4	-12.714	-12.486	-12.457	-12.412
N^7	-12.370	-11.412	-11.510	-12.225
N^{10}	-14.928	-14.397	-14.448	-15.134
N^{12}	-12.408	-11.863	-11.831	-12.412
C^1	-7.332	-6.786	-7.082	-7.071
C^9	-7.316	-6.559	-6.498	-7.071
Cl^{14}	-	-19.608	-18.176	-17.944

The electrophilic superdelocalisability indices of atoms in the N-chlorosubstituted biguanide derivatives is more negative at the level of the chlorine atom. It is followed by that of the N^{2} and N^{10} atoms. This suggests that the C^{l}, N^{2} and N^{10} atoms are the most favorable sites for coordination in consideration of this indices.

3.1.6. Summary analysis

Table 7: Summary analysis

Coordi-nation indicators (CI)	**Ligands**			
	Bgde	**N^{2}-chloro-bgde**	**N^{4}- chloro-bgde**	**N^{7}- chloro-bgde**
Bond length	N^{2}, N^{10}	N^{2}, N^{10},	N^{2}, N^{10},	N^{2}, N^{10}
Atomic Charge (NBO)	N^{2}, N^{10}	N^{4} , N^{10}	N^{2}, N^{10}	N^{2},N^{10}
EP	N^{2}, N^{10}	N^{2}, N^{10}, Cl	N^{2}, N^{10}, Cl	N^{2}, ^{10}, Cl
Superdelocali-sabilityindice	N^{2}, N^{10}	N^{2}, N^{10}, Cl	N^{2}, N^{10}, Cl	N^{2}, ^{10}, Cl
HOMO and HOMO-1	N^{2} , N^{10}	N^{2}, N^{10}	N^{2}, N^{10}, N^{4}	N^{2}, N^{10} , N^{7}
N^{2} [a]	100	80	100	100
N^{4} [a]	-	20	20	-
N^{7} [a]	-	-	-	20
N^{10} [a]	100	100	100	100
N^{12} [a]	-	-	-	-
Cl[a]	-	40	40	40
More favorable site of coodi-nation	N^{2}, N^{10}	N^{2}, N^{10}	N^{2}, N^{10}	N^{2}, N^{10}

[a] % of favorable coordination indicators

The table 7 reveals that the sites most favorable to the coordination of the N-chlorosubstitutedderivatives of biguanide would be the imine nitrogen atoms; indeed, the coordination indicators in the present study are favorable for N^{2} (100%) and N^{10}(100%); they are followed by chloride atom favored by 40% only off the retained CI.

3.1.6. HOMO and LUMO energies

Table 8 : Energies (in hartree) of the boundary molecular orbitals of the biguanide and its N-chlorosubstituted derivatives

Border orbitals	Methods	Bgde	N-Chlorosubstituted ligands of Biguanide			$ZnCl_2$
			N^2- chloro-bgde	N^4- chloro-bgde	N^7- chloro-bgde	
-HOMO	B3LYP/631G(dp)	0.218	0.216	0.227	0.225	0.318
-LUMO		0.030	0.002	0.027	0.047	0.105
$Gap_{(HOMO-LUMO)}$		0.248	0.214	0.200	0.178	0.284
-HOMO	B3LYP/ccpvdz	0.219	0.232	0.235	0.235	0.322
-LUMO		0.030	0.013	0.056	0.053	0.077
$-Gap_{(HOMO-LUMO)}$		0.189	0.219	0.179	0.182	0.245
-HOMO	B3PW91/631G(dp)	0.220	0.233	0.236	0.240	0.324
-LUMO		0.068	0.007	0.051	0.050	0.062
$-Gap_{(HOMO-LUMO)}$		0.152	0.226	0.185	0.190	0.262
-HOMO	B3PW91/ccpvdz	0.221	0.233	0.237	0.235	0.326
-LUMO		0.029	0.007	0.051	0.049	0.070
$-Gap_{(HOMO-LUMO)}$		0.192	0.226	0.186	0.186	0.256

The HOMO-LUMO gaps are 0.214, 0.200 and 0.178 hartree [B3LYP/6-31G(d,p)],0.219, 0.179 and 0.182hartree (B3LYP/cc-pvdz), 0.226, 0.185 and 0.190hartree (B3PW91/631G(dp)), 0,226, 0.186 and 0.186hartree (B3PW91/cc-pvdz)respectively for N^2-chlorobiguanide, N^4-chlorobiguanide, and N^7-chlorobiguanide (Table 8). These gaps show thatN^4-chlorobiguanide and N^7-chlorobiguanide have the smallest gaps. It follows, therefore, that N^4-chlorobiguanide and N^7-chlorobiguanide must be more electron-donor[25,26,27,28,29] than N^2- chlorobiguanide. As a result, N^4-chlorobiguanide and N^7-chlorobiguanide would more easily complex than N^2-chlorobiguanide.

After carrying out thus the study of the ligands, it is necessary to simulate corresponding complexes in order to verify the results from this study.This constitutes the second part of the present investigative work.

3.2. Coordination modeling of N-chlorosubstituted derivatives of biguanide

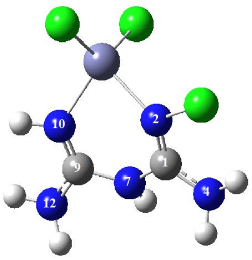
3.2.1. Modeling

The modeling of the complex of each ligand with zinc (II) has been considered. This element was provided by the 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 do this, the Zn (II) was arranged at a reasonable distance (about 3 Å) of the atom, potential coordination site considered. The whole was then optimized and complexes were formed according to the structures shown (figure 3).

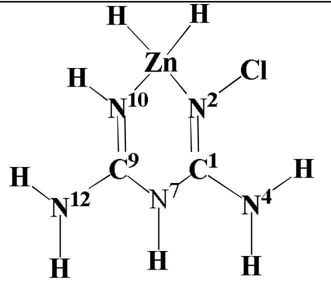
Schems from GaussView	**Schems from Chemdraw**

Figure3: Complexes of biguanide and its N-chlorosubstituted derivatives

As can be seen, no coordination via the chlorine atom (Cl-Zn-Cl or Cl-Zn-N) has been obtained. Three complexes of the N-monochlorosubstituted derivatives of biguanide with zinc (II) were modeled; they are some chelates. The coordinations took place via the imine nitrogen
atoms, especially N^2 and N^{10}(table 9); the ZnN^{10} and ZnN^2interatomic distances are around
2 ´.This corresponds to chemical bonds. The coordinations involving other N atoms are weaker, since the corresponding Zn-N lengths are longer (about 2.15 ´). The corresponding complexes are not exposed here.



[ZnCl$_2$(N^2- chlorobgde)]
N^{2}chlorobiguanidedichloro zinc(II)



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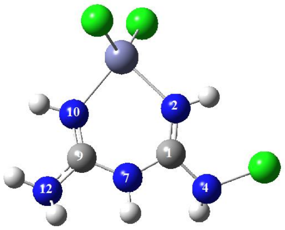

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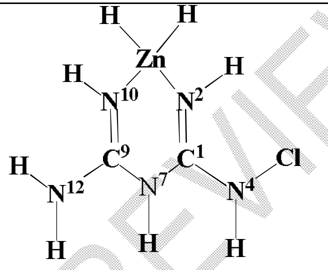
N^{4}chlorobiguanidedichloro zinc(II)



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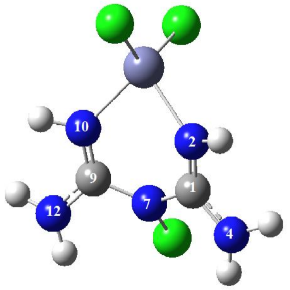
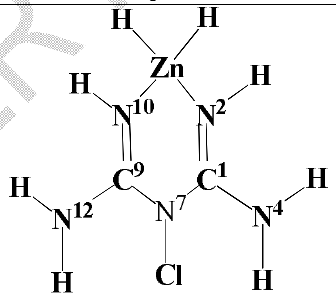
N^4- chlorobiguanidedichloro zinc(II)



[ZnCl$_2$(N^7- chlorobgnde)]
N^{7}chlorobiguanidedichloro zinc(II)



[ZnCl$_2$(N^7- chlorobgnde)]
N^7- chlorobiguanidedichloro zinc(II)

These results confirm the observations previously made during the study of ligands. Indeed, during this study:

- 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.

Table 9: ZnN interatomic distances of the complexes obtained.

Complexes	Fonction-nals/basis	Zn-N distances ( )				
		ZnN^2	ZnN^4	ZnN^7	ZnN^{10}	ZnN^{12}
N^2-chloro-bgde.ZnCl$_2$		**2.12**	4.34	3.29	**2.06**	4.28

N^4-chloro-bgde.ZnCl$_2$	B3LYP/6-31G(d,p)	**2.08**	4.37	3.36	**2.07**	4.31
N^7-chloro-bgde.ZnCl$_2$		**2.06**	4.307	3.27	**2.06**	4.30
N^2-chloro-bgde.ZnCl$_2$	B3LYP/ccpdz	**2.20**	4.41	3.36	**2.12**	4.34
N^4-chloro-bgde.ZnCl$_2$		**2.15**	4.40	3.40	**2.13**	4.41
N^7-chloro-bgde.ZnCl$_2$		**2.13**	4.36	3.33	**2.13**	4.36
N^2-chloro-bgde.ZnCl$_2$	B3PW91/6-31G(d,p)	**2.10**	4.29	3.23	**2.04**	4.23
N^4-chloro-bgde.ZnCl$_2$		**2.07**	4.29	3.31	**2.05**	4.31
N^7-chloro-bgde.ZnCl$_2$		**2.05**	4.27	3.23	**2.05**	4.27
N^2-chloro-bgde.ZnCl$_2$	B3PW91/ccpvdz	**2.18**	4.36	3.30	**2.11**	4.30
N^4-chloro-bgde.ZnCl$_2$		**2.14**	4.36	3.38	**2.11**	4.38
N^7-chloro-bgde.ZnC$_{l2}$		**2.05**	4.27	3.23	**2.05**	4.27

3.2.2 Energy study of the complexes

The energy study of the coordination process was performed. Its results are recorded in the table 10.

Table 10: Energy study of the complexes

Molecules	Fonction-nals/basis	$-\Delta G$, eV	$-\Delta G_{coord}$, eV	$-\Delta H$, eV	$-\Delta H_{coord}$, eV	Process
N^2-chloro-cis-2-bgde	B3LYP/6-31G(d,p)	22141.231	-	22140.049	-	-
	B3LYP/cc-pvdz	22141.591		22140.367		
	B3PW91/6-31G(d,p)	22135.55		22134.553		
	B3PW91/cc-pvdz	22136.612		22135.415		
N^4- chloro-cis-2-bgde	B3LYP/6-31G(d,p)	22140.805	-	22139.614	-	-
	B3LYP/cc-pvdz	22141.238		22140.035		
	B3PW91/6-31G(d,p)	22135.221		22134.000		
	B3PW91/cc-pvdz	22136.277		22135.061		
N^7- chloro-cis-2-bgde		22140.115	-	22138.932	-	

	B3LYP/6-31G(d,p)					-
	B3LYP/cc-pvdz	22141.047		22139.839		
	B3PW91/6-31G(d,p)	22135.134		22133.918		
	B3PW91/cc-pvdz	22136.094		22134.870		
$ZnCl_2$	B3LYP/6-31G(d,p)	73459.090	-	73458.280	-	-
	B3LYP/cc-pvdz	73470.495		73469.643		
	B3PW91/6-31G(d,p)	73455.121		73454.251		
	B3PW91/cc-pvdz	73466.550		73465.701		
$ZnCl_2$ (N^2- chloro-cis-2-bgde)	B3LYP/6-31G(d,p)	95601.246	0.925	95599.641	1.311	Spo., exo
	B3LYP/cc-pvdz	95613.170	1.084	95611.543	1.530	Spo., exo
	B3PW91/6-31G(d,p)	95592.296	**1.625**	95590.699	**1.895**	Spo., exo
	B3PW91/cc-pvdz	95604.277	1.115	95602.672	1.556	Spo., exo
$ZnCl_2$ (N^4- chloro-cis-2-bgde)	B3LYP/6-31G(d,p)	95601.015	1.120	95599.389	1.494	Spo., exo
	B3LYP/cc-pvdz	95613.012	1.279	95611,379	1.801	Spo., exo
	B3PW91/6-31G(d,p)	95592.114	**1.772**	95590.482	2.231	Spo., exo
	B3PW91/cc-pvdz	95604.114	1.287	95602.481	1.719	Spo., exo
$ZnCl_2$ (N^7- chloro-cis-2-bgde)	B3LYP/6-31G(d,p)	95600.799	1.594	95599.216	2.004	Spo., exo
	B3LYP/cc-pvdz	95612.756	1.214	95611.107	1.626	Spo., exo
	B3PW91/6-31G(d,p)	95591.896	**1.641**	95590.264	**2.095**	Spo., exo
	B3PW91/cc-pvdz	95603.869	1.225	95602.231	1.660	Spo., exo

ΔG=Free enthalpy of species; ΔG_{coord} *= Free enthalpie of coordination;*
$\Delta G_{coord} = \Delta G_{complexe} - (\Delta G_{ligand} + \Delta G_{ZnCl2})$; $\Delta H_{coord} = \Delta H_{complexe} - (\Delta H_{ligand} + \Delta H_{ZnCl2})$.
Spo.= spontaneous; exo = exothermic

It is easy to notice that all ΔG_{coord} and ΔH_{coord} values are negative. Therefore, the complexation process is spontaneous and exothermic as a whole. Thissuggests that it is possible to synthesize complexes of N-chlorosubstituted biguanide derivatives. Complexes [$ZnCl_2$(N^4-chlorobgde)] and[$ZnCl_2$(N^7-chlorobgde)] seem more stable than [$ZnCl_2$(N^2-chlorobgde)] since their $\Delta G_{coord}$are the lowest and the Zn-N^2bonds are longer in [$ZnCl_2$(N^2-chlorobgde)]: $\Delta G_{coord}$are respectively 0.925, 1.120 and 1.594 eV (B3LYP/6-31G(d,p)),1.084, 1.279 and 1.214 eV (B3LYP/ccpvdz), 1.625, 1.772 and 1.641 eV (B3PW91/6-31G(d,p)), 1.115, 1.287 and 1.225 eV (B3PW91/ccpvdz) while the Zn-N^2 lengths equal respectively 2.12, 2.08 and 2.06 Å (B3LYP/6-31G(d,p)), 2.20, 2.15 and 2.13Å (B3LYP/ccpvdz), 2.10, 2.07 and 2.05Å (B3PW91/6-31G(d,p)), 2.18, 2.14 and 2.05Å(B3PW91/ccpvdz) for [$ZnCl_2$(N^2-chlorobgde)], [$ZnCl_2$(N^4-chlorobgde)] and [$ZnCl_2$(N^7-chlorobgde)] (tables 9 and 10); this confirms the HOMO-LUMO gap study (table 8).

3.2.3- Bioavailability of obtained complexes

The bioavailability of the complexes was tested according to the Lipinski rules of 5. In table 11
we have gathered the Lipinski[30] properties concerning these complexes.
Lipinski's rules are as follows:
1-) nDH $\leq$ 5;
2-) nAH $\leq$ 10;
3-) M $\leq$ 500 amu;
4-) $-2 \leq \log P \leq 5$;
a molecule is bioavailable if it has a violation number less than or equal to 2.
Table 11 shows that all the complexes obtained are bioavailable since their number of violations is equal to 1 (1< 2).

Table 11: Lipinski properties of ligands and complexes

Molecules	logP[b]	M[c]	nDH[d]	nAH[e]	Violation Nomber	Observation
Biguanide	0.42	101.11	7	5	1	+[a]
$_{N}{}^{2}$chlorobgde	0.54	135.56	6	5	1	+[a]
N^{4-}chlorobgde	0.70	135.56	6	5	1	+[a]
N^{7-}chlorobgde	0.48	135.56	6	5	1	+[a]
$ZnCl_2$.cis2-Bgde	0.86	237.39	7	5	1	+[a]
$ZnCl_2$ (N^2-chlorobgde)	1.54	271.83	6	5	1	+[a]
$ZnCl_2$ (N^4-chlorobgde)	1.70	271.83	6	5	1	+[a]
$ZnCl_2$ (N^7-chlorobgde)	1.35	271.83	6	5	1	+[a]

[a] bioavailable, [b] partition coefficient, [c] molecular mass, [d] hydrogenbond donor number, [e] hydrogenbond acceptor number

It is interesting to note that the partition coefficient increases when switching from ligands to complexes, which means that the complexes are more available in the organic phase than the ligands. Also the chlorosubstitution of biguanide makes it more lipophilic. Then the obtained complexes can more concentrated in cells than ligands could before complexation. They can thus be considered as drug candidates.

4. CONCLUSION

As a whole, the complexation process is spontaneous and exothermic.
Coordination via the imine nitrogen atoms is more likely; it confirms the result from the coordination indicator analysis. The coordination with chlorine, contrary to all expectations, proved unfavorable certainly because of the positive charge it bears.
This work has shown that:
-the most favorable coordination sites in the N-chlorosubstituted derivatives of biguanide are the N imine atoms;
- the coordination of N-chlorosubstituted derivatives of biguanide with zinc (II) is possible;
- the modelled complexes are chelates formed via both imine nitogen atoms;

-the coordination bonds are solider in the [$ZnCl_2$(N^4-chlorobiguanide)] and [$ZnCl_2$(N^7-chlorobiguanide)] complexes;
- the N-chlorosubstituted derivatives of biguanide are more bioavailable than the biguanide;
- The complexes of N-chlorosubstituted derivatives of biguanide are more available than N-chlorosubstituted derivatives: the obtained complexes can more concentrated in cells than ligands could before complexation, so these complexes can be considered as drug candidates.

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