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Electronic Structure and Properties of Anticancer Active Molecule *Ansa*-titanocene Dichloride

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Abstract

A DFT study of the electronic properties of *ansa*-titanocene dichloride is reported. Molecular orbital analysis, polarizability, hyperpolarizability, thermodynamic analysis and natural bond orbital (NBO) theory are the main aim of the present research. The computed structural parameters show a good agreement with the similar experimental results. The calculated HOMO and LUMO energies show that charge transfer occurs within molecule. The NBO charges, the values of electric dipole moment (μ) of the molecule are computed using DFT calculations.

Key words: *Ansa-titanocene dichloride, DFT calculation, Molecular orbital analysis, NBO analysis, Density of state, Thermodynamic parameters.*

Introduction

Anticancer activity of titanocene dichloride(namely bis(cyclopentadienly) titanocene dichloride, (Cp_2TiCl_2) has been discovered in the 1980s, and since then it has attracted continuous attention in the experimental literature [1-3]. The mechanism of action of the Cp_2TiCl_2 is not well known, initial studies suggested that it might be correlated with the purine bases of DNA [4-6]. The hydrolysis chemistry of anticancer drug titanocene dichloride has been studied theoretically[7]. Later, more synthetic attempts have been employed to enhance the cytotoxicity of titanocene dichloride derivatives[8-10]. A novel process starting from titanium dichloride and fulvenes [11, 12] allowed direct access to highly substituted *ansa*-titanocenes[13-15].

The present work is aimed at studying structure and properties of ansa-titanocenes. The structural parameters, molecular orbital,

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density of state, natural bond orbital have been analyzed. Also, theromdynamic parameters have been calculated in different temperatures.

Computational method

All calculations were carried out with the Gaussian 2003 suite of program [16] using the standard 6-311G (d,p) basis set [17-20] for C, H and Cl atoms. For Ti element standard LANL2DZ basis set [21-23] are used and Ti described by effective core potential (ECP) of Wadt and Hay pseudopotential [24] with a doublet-ξ valance using the LANL2DZ. Geometry optimization was performed utilizing one parameter hybrid functional with modified Perdew-Wang exchange and correlation (mpw1pw91) [25]. A vibrational analysis was performed at each stationary point found, that confirm its identity as an energy minimum.

Geometries were optimized at this level of theory without any symmetry constraints followed by the calculations of the first order hyperpolarizabilities. The total static first hyperpolarizability β was obtained from the relation:

$$\beta_{tot}=\sqrt{(\beta_x^{\,2}+\beta_y^{\,2}+\beta_z^{\,2})}$$

upon calculating the individual static components

$$\beta_i = \beta_{iii} + \frac{1}{3}\sum_{i\neq j}(\beta_{ijj} + \beta_{jij} + \beta_{jji})$$

Due to the Kleinman symmetry [26]:

$$\beta_{xyy} = \beta_{yxy} = \beta_{yyx}\ ;\ \beta_{yyz} = \beta_{yzy} = \beta_{zyy}, \ldots$$

one finally obtains the equation that has been employed:

$$\beta_{tot} = \sqrt{(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz}\, zxx + \beta_{zyy})^2}$$

The population analysis has also been performed by the natural bond orbital method [27] using the natural bond orbital (NBO) program [28] under Gaussian 2003 program package.

Natural bond orbital analysis stresses the role of intermolecular orbital interaction in the complex, particularly charge transfer. This is carried out by considering all possible interactions between filled donor and empty acceptor NBOs and estimating their energetic importance by second-order perturbation theory. For each donor NBO (i) and acceptor NBO (j), the stabilization energy E(2) associated with electron delocalization between donor and acceptor is estimated as:

$$E^{(2)} = -q_i \frac{(F_{i,j})^2}{\varepsilon_j - \varepsilon_i}$$

Where q_i is the orbital occupancy, ε_i, ε_j are diagonal elements and $F_{i,j}$ is the off-diagonal NBO Fock matrix element.

GaussSum 2.2.6.1 was used to prepare total density of state (TDOS) or density of state [29].

Results and Discussion

Molecular geometry

The ansa-titanocene dichloride studied in this work with atom labelling is depicted in Figure

1. The global minimum energy, zero-point vibrational energies, rotational constants, entropies and dipole moments obtained for this optimized geometry are presented in Table 1.

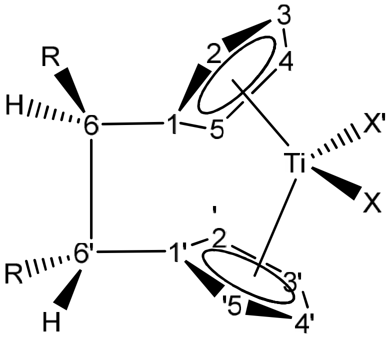


Figure 1. Structure of *ansa*-titanocene dichloride (R=H; X=Cl).

Table 1. Absolute energy, Zero point vibration energy, energy, Molar capacity at constant volume, Entropy, Dipole moment of *ansa*-titanocene dichloride.

Parameters			
Absolute energy (Hartree)	-1443.2333845		
Zero point vibration energy (Joules/Mol)	550939.3		
Rotational constants(GHZ)	0.62592	0.53025	0.45952
Rotational temperature (K)	0.03004	0.02545	0.02205
Energy (KCal/Mol)			
Translational	0.889		
Rotational	0.889		
Vibrational	138.384		
Total	140.162		
Molar capacity at constant volume (Cal/Mol-Kelvin)			
Translational	2.981		
Rotational	2.981		
Vibrational	48.065		
Total	54.026		
Entropy (Cal/Mol-Kelvin)			
Translational	42.722		
Rotational	32.022		
Vibrational	40.170		
Total	114.915		
Dipole moment (Debye)	6.5986		

Polarizability

Polarizabilities describe the response of a system in an applied electric field [30]. They determine not only the strength of molecular interactions (such as the long range intermolecular induction, dispersion forces, etc.) as well as the cross sections of different scattering and collision processes, but also the nonlinear optical properties of the system[31]. The isotropic polarizability <α> is calculated as the mean value as given in the following equation [32]:

$$\langle \alpha \rangle = \frac{(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})}{3}$$

And anisotropic polarizability with:

$$\Delta\alpha = \left[\frac{(\alpha_{XX} - \alpha_{YY})^2 + (\alpha_{YY} - \alpha_{ZZ})^2 + (\alpha_{ZZ} - \alpha_{XX})^2}{2}\right]^{\frac{1}{2}}$$

The calculated isotropic and anisotropic polarizability values are tabulated in Table 2.

Table 2. Anisotropic and isotropic polarizability values and β components and β_{tot} values (10–30 esu) for *ansa*-titanocene dichloride.

Parameters	
xx	184.253
yy	171.762
zz	162.758
iso	172.9243
aniso	18.69669
β_{XXX}	-90.6496492
β_{XXY}	86.9332946
β_{XYY}	-7.5876723
β_{YYY}	-146.3810742
β_{XXZ}	169.1974149
β_{XYZ}	-48.047915
β_{YYZ}	-52.4245103
β_{XZZ}	75.077964
β_{YZZ}	221.5120721
β_{ZZZ}	206.5140556
β_{tot}	3.13E-30
β_{tot} **10^{-30}**	3.13

Hyperpolarizability

Theoretical investigation plays an important role in understanding the structure-property relationship, which is able to assist in designing novel NLO chromophores. The electrostatic first hyperpolarizability (β) and dipole moment (μ) of the *ansa*-titanocene dichloride have been calculated. From Table 2, it is found that the ansa-titanocene dichloride shows small β_{total} value.

Structural parameters

The optimized structural parameters of *ansa*-titanocene dichloride are listed in Table 3. In the literature, we have found experimental data for ansa-titanocene dithiocyanato[15] and compared these values with our calculations. Most of the optimized bond lengths are similar with the experimental values. Although theoretical results are not exactly close to the experimental values for the title molecule, this may due to the fact that the theoretical calculations were aimed at the isolated molecule in gaseous phase and the experimental results were aimed at the molecule in the solid state, the calculated geometric parameters also represents good approximation and they can be used as foundation to calculate the other parameters for the compound.

Table 3. Structural parameters of *ansa*-titanocene dichloride.

Bond	R(Å)^{theo}	R(Å)^{exp,a}
C6-C6'	1.532	1.463
C6-C1	1.499	1.506
C1-C2	1.412	1.441
C2-C3	1.420	1.400
C3-C4	1.397	1.403
C4-C5	1.417	1.403
C5-C1	1.415	1.408
Ti-C1	2.375	2.353
Ti-C2	2.338	2.352
Ti-C3	2.385	2.379
Ti-C4	2.398	2.377
Ti-C5	2.346	2.332
Ti-C6	3.362	-
Ti-X	2.346	2.048
Ti-X'	2.328	2.018
C1'-C2'	1.406	1.409
C2'-C3'	1.417	1.399
C3'-C4'	1.402	1.387
C4'-C5'	1.410	1.393
C5'-C1'	1.425	1.400
C6'-C1'	1.497	-
Ti-C1'	2.350	2.366
Ti-C2'	2.361	2.324
Ti-C3'	2.380	2.378
Ti-C4'	2.389	2.362
Ti-C5'	2.324	2.345
Ti-C6'	3.324	-

[a] R=C_6Me_5, X=NCS[15]

Analysis of molecular orbitals

Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important parameters for quantum chemistry. The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor[33]. The MOs are defined as eigen functions of the Fock operator, which exhibits the full symmetry of the nuclear point group, they necessarily form a basis for irreducible representations of full point-group symmetry. The energies of HOMO, LUMO, and their orbital energy gaps, have been gathered in Table 4.

The pictorial illustration of the frontier molecular orbitals and their respective positive and negative regions are shown in Figure 2. Molecular orbitals, when viewed in a qualitative graphical representation, can provide insight into the nature of reactivity, and some of the structural and physical properties of molecules. The positive and negative phase is represented in red and green colour, respectively. The region of HOMO-3, and LUMO+1 levels spread over the entire molecule. In other molecular orbitals, the levels spread over the Ti, cp and Cl ligands. The calculated energy gap of HOMO–LUMO's explains the ultimate charge transfer interface within the molecule[34].

Global reactivity descriptors

Global reactivity descriptors [35-38] electronegativity (χ) chemical potential (μ), global hardness (η), global softness (S), and electrophilicity index (ω), determined on the basis of Koopman's theorem[39] are listed in Table 4.

$$\mu = \frac{E(HOMO)+E(LUMO)}{2}$$

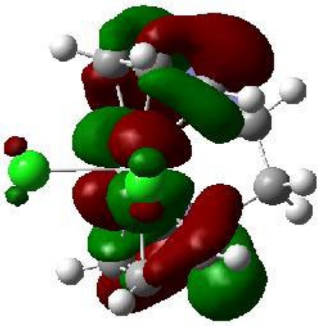
$$\chi = -\frac{E(HOMO)+E(LUMO)}{2}$$

$$\eta = \frac{E(LUMO)+E(HOMO)}{2}$$

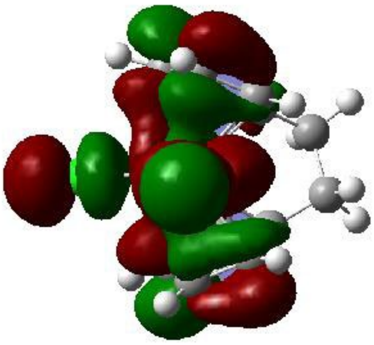
where I and A which are called ionization potential and electron affinity, respectively and is I = -E(HOMO) and A = - E(LUMO). The chemical hardness and softness of a molecule is a good indicator of the chemical stability of a molecule. From the HOMO–LUMO energy gap, one can find whether the molecule is hard or soft. The molecules having large energy gap are known as hard and molecules having a small energy gap are known as soft molecules. The soft molecules are more polarizable than the hard ones because they need small energy to excitation.

Table 4. The frontier orbitals energies (Hartree), HOMO-LUMO gap (eV), Hardness (eV), softness (eV^{-1}), chemical potential and electrophilicity of *ansa*-titanocene dichloride.

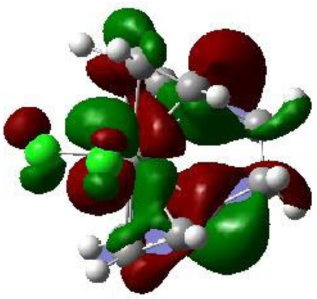
E(HOMO)	**E(LUMO)**	**E**			
-0.24801	-0.09760	4.092897	2.046448	-4.7023	2.70122



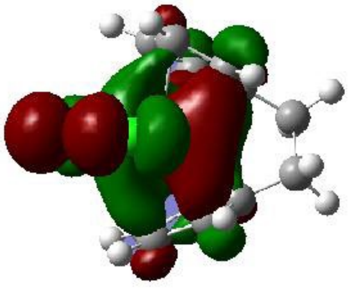
LUMO+3



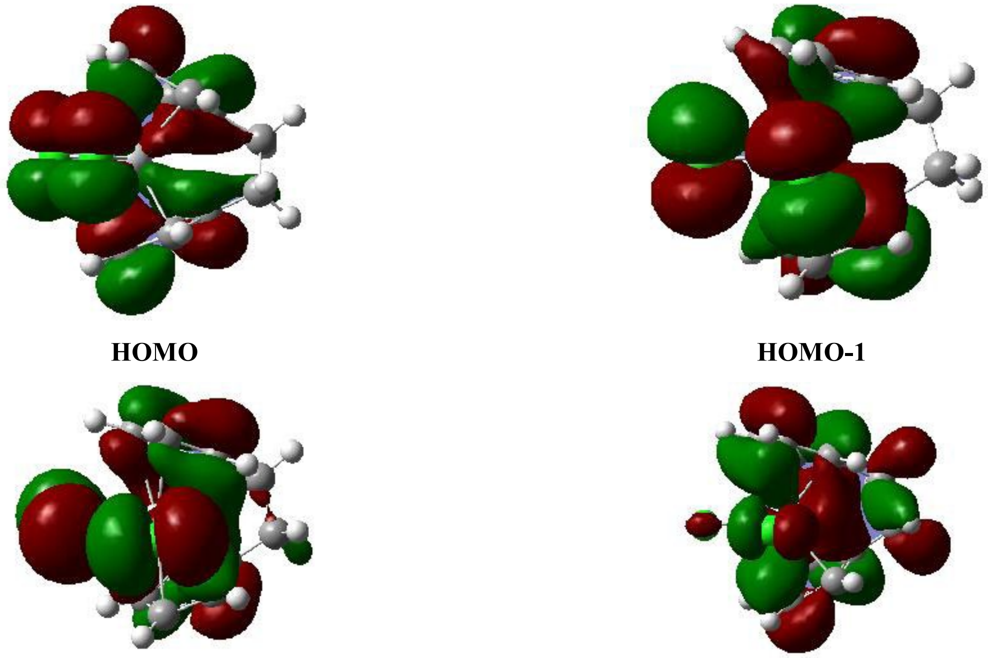
LUMO+2



LUMO+1



LUMO



HOMO

HOMO-1

HOMO-2

HOMO-3

Figure 2. The plot of molecular orbitals for ansa-titanocene dichloride.

Total and partial density of states

The partial density of states (PDOS), total density of states (TDOS) [40-42] of ansa-titanocene dichloride were calculated and generated by convoluting the molecular orbital information with Gaussian curves using the Gauss Sum 2.2 program [29] to show quasi degenerate energy levels. The calculated TDOS diagram of the ansa-titanocene dichloride was given in Figure 3. The PDOS mainly presents the composition of the fragment orbitals contributing to the molecular orbitals which was seen from Figure. 4. Figures 3 and 4 provide a pictorial representation of molecule orbital (MO) compositions and their contributions to chemical bonding.

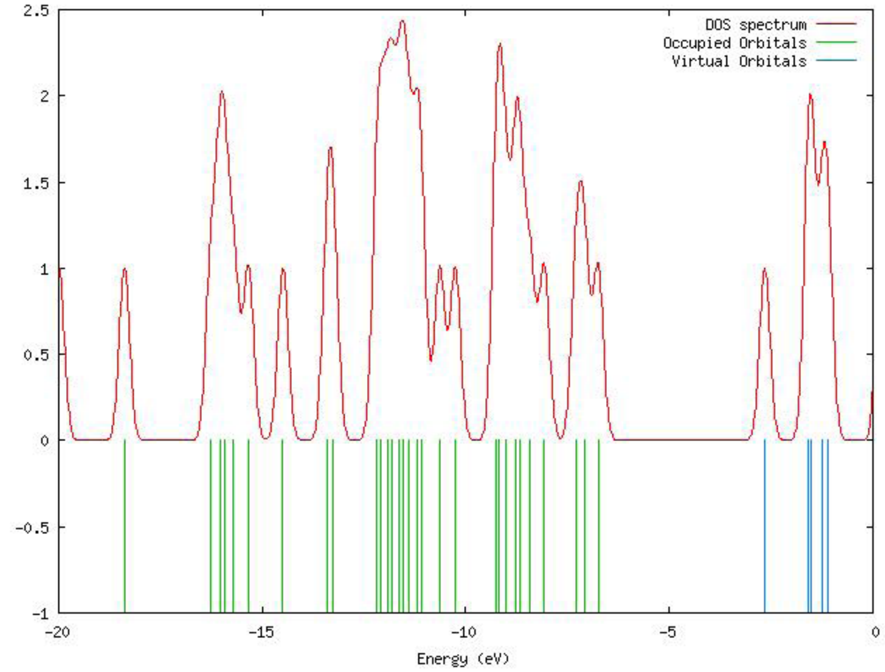


Figure 3. The calculated total electronic density of states diagrams for the ansa-titanocene dichloride.

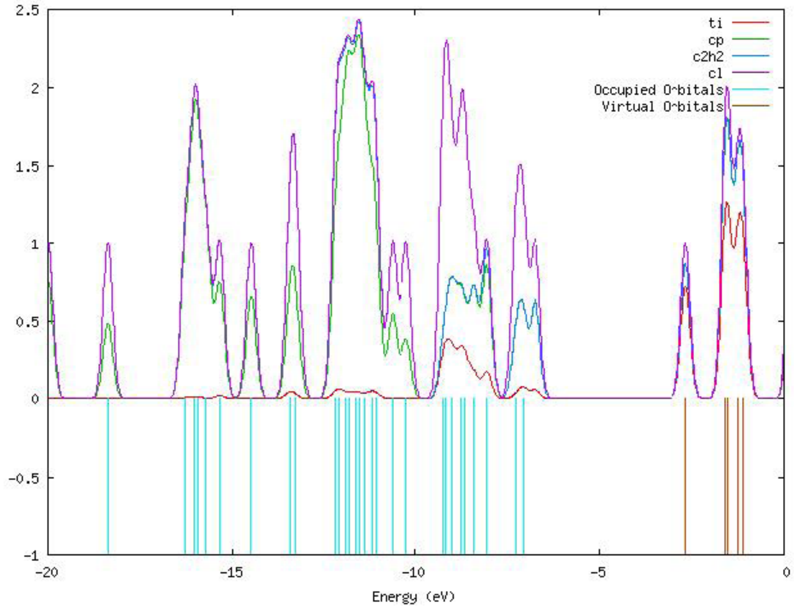


Figure 4. The calculated partial electronic density of states diagrams for ansa-titanocene dichloride.

Temperature dependence of thermodynamic properties

The themodynamic parameters have been tabulated in Tables 1 and 5. Also, the temperature dependence of the thermodynamic properties heat capacity at constant pressure (Cp), entropy (S) and enthalpy change for *ansa*-titanocene dichloride were also determined and listed in Table 5. Figure 5 depicts the correlation of heat capacity at constant pressure (Cp), entropy (S) and enthalpy change with temperature along with the correlation equations. From Table 5, one can find that the entropies, heat capacities, and enthalpy changes are increasing with temperature ranging from 100 to 1000 K due to the fact that the molecular vibrational intensities increase with temperature. These observed relations of the thermodynamic functions vs. temperatures were fitted by quadratic formulas, and the corresponding fitting regression factors (R^2) are all not less than 0.9. The corresponding fitting equations for ansa-titanocene dichloride are:

$G = -1.15 \times 10^{-7} T^2 - 1.01 \times 10^{-4} T - 1365.62;$ $R^2 = -0.99242$

$Cv = 8.25 \times 10^{-5} T^2 + 1.82 \times 10^{-1} T + 1.457;$ $R^2 = .9745111019$

$H = 7.22 \times 10^{-8} T^2 + 3.94 \times 10^{-5} T - 1365.62;$ $R^2 = 0.9880745830$

$S = 5.03 \times 10^{-5} T^2 + 1.98 \times 10^{-1} T + 55.14;$ $R^2 = 0.9961407154$

Table 4. The temperature dependence of thermodynamic parameters of *ansa*-titanocene dichloride

T	G	H	S Cal/Mol-K	Cv Cal/Mol-Kelvin
100	-1365.630406	-1365.618576	74.238	19.288
200	-1365.643817	-1365.614019	93.493	33.646
300	-1365.660100	-1365.607182	110.688	48.236
400	-1365.679053	-1365.598071	127.042	61.771
500	-1365.700543	-1365.587000	142.499	72.756
600	-1365.724415	-1365.574378	156.916	81.318
700	-1365.750499	-1365.560545	170.283	88.052
800	-1365.778635	-1365.545749	182.673	93.484
900	-1365.808674	-1365.530167	194.185	97.974
1000	-1365.840484	-1365.513927	204.918	101.753

NBO analysis

The Natural Bond Orbital (NBO) analysis of ansa-titanocene dichloride has provided the detailed insight into the nature of electronic conjugation between the bonds in this molecule. Figure 6 indicates bar diagram representing the charge distribution in ansa-titanocene dichloride. The largest negative charges (-0.39 e) are located on two carbon atoms, C6 and C6’.

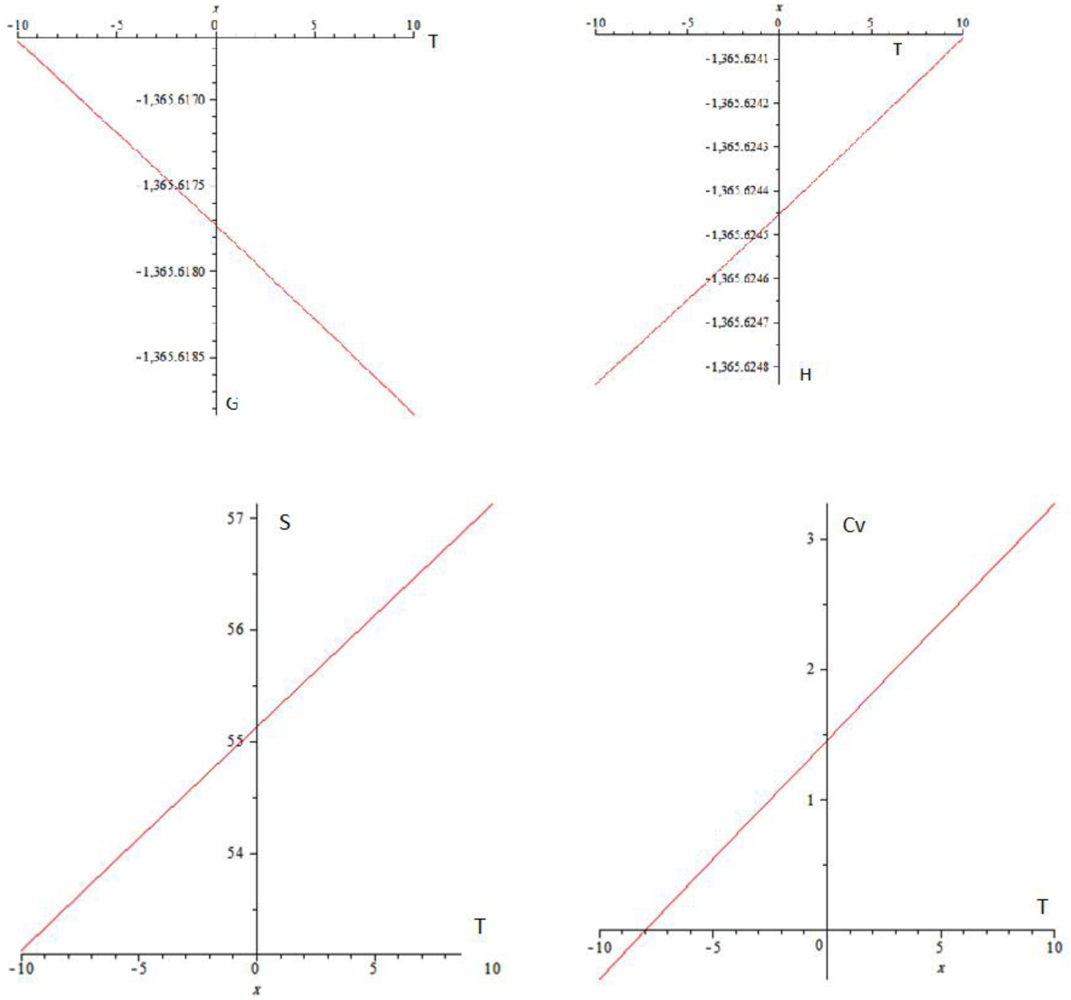


Figure 5. The correlation of heat capacity at constant pressure (Cp), entropy (S) and enthalpy change with temperature.

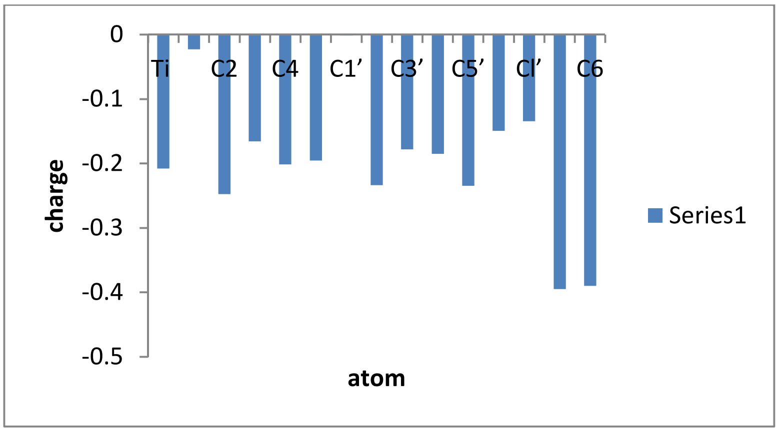


Figure 6. Bar diagram representing the charge distribution in *ansa*-titanocene dichloride.

According to the NBO results, the electron configuration of Ti is:

[core]4S(0.22)3d(3.35)4p(0.58)4d(0.10)

Thus, 18 core electrons, 3.57 valence electrons (on 3d and 4s atomic orbitals) and 0.68 Rydberg electrons (mainly on 4d and 4p orbitals) give the total of 22.25 electrons. This is consistent with the calculated natural charge on Ti atom in ansa-titanocene dichloride -0.25 e, which corresponds to the difference between 22.25 e and the total number of electrons in the isolated Ti atom (22e).

According to calculations, the titanium atom forms single bonds (sigma bond) with atoms Cl and Cl' atoms. Occupancy of natural orbitals (NBOs) and hybrids of the σ(Ti-Cl) bonds are:

```
(1.98485) BD ( 1)Ti -Cl : ( 26.97%)  0.5193*Ti   6 s( 12.02%)p 0.99( 11.86%)d 6.33( 76.12%)
                        +  ( 73.03%)  0.8546*Cl  20 s( 36.32%)p 1.75( 63.56%)d 0.00(  0.11%)
(1.98448) BD ( 1)Ti-Cl':  ( 26.80%)  0.5176*Ti   6 s( 12.23%)p 0.97( 11.87%)d 6.20( 75.90%)
                        + ( 73.20%)  0.8556*Cl  21 s( 37.51%)p 1.66( 62.38%)d 0.00(  0.12%)
```

These values show that the σ(Ti-Cl) bonds are formed from a sp^md^n hybrid on titanium.

Conclusion

Efforts have been made in the present study for exploration of structure, molecular orbitals, thermodynamic parameters, and NBO analysis of ansa-titanocene dichloride. The calculated structural parameters indicated good better fit to experimental result in similar molecule. Molecular orbital analysis shows that region of HOMO-3, and LUMO+1 levels spreads over entire molecule Also, thermodynamic parameters calculation, these calculated in various temperatures. Then relations of the thermodynamic functions vs. temperatures were fitted by quadratic formulas. The Natural Bond Orbital (NBO) analysis provided the detailed insight into the type of hybridization and the nature of bonding in ansa-titanocene dichloride. The σ(Ti-Cl) bonds are formed from a sp^md^n hybrid on Ti atom.

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