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(cyclopentadienyl) titanocene dichloride, ( Cp2TiCl2) 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 Cp2TiCl2 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,
density of state, natural bond orbital have been analyzed. Also, thermodynamic 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

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

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:

$$\beta_{tot} = \sqrt{(\beta_{xxx} + \beta_{xxy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxy})^2 + (\beta_{zzz} zzx + \beta_{zzy})^2}$$

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:

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

Where $q_i$ is the orbital occupancy, $\varepsilon_j, \varepsilon_i$ are diagonal elements and $F_{ij}$ 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.

![Structure of ansa-titanocene dichloride (R=H; X=Cl).](image)

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute energy (Hartree)</td>
<td>-1443.2333845</td>
</tr>
<tr>
<td>Zero point vibration energy (Joules/Mol)</td>
<td>550939.3</td>
</tr>
<tr>
<td>Rotational constants (GHZ)</td>
<td>0.62592 0.53025 0.45952</td>
</tr>
<tr>
<td>Rotational temperature (K)</td>
<td>0.03004 0.02545 0.02205</td>
</tr>
<tr>
<td>Energy (KCal/Mol)</td>
<td>0.889 0.889 138.384</td>
</tr>
<tr>
<td>Molar capacity at constant volume (Cal/Mol-Kelvin)</td>
<td>2.981 2.981 48.065</td>
</tr>
<tr>
<td>Entropy (Cal/Mol-Kelvin)</td>
<td>42.722 32.022 40.170</td>
</tr>
<tr>
<td>Dipole moment (Debye)</td>
<td>6.5986</td>
</tr>
</tbody>
</table>

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

**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 $\langle \alpha \rangle$ 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:

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

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

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

| Parameters | \(\alpha_{XX}\) | \(\alpha_{YY}\) | \(\alpha_{ZZ}\) | \(\alpha_{iso}\) | \(\beta\text{\textsubscript{XXX}}\) | \(\beta\text{\textsubscript{XXY}}\) | \(\beta\text{\textsubscript{XYY}}\) | \(\beta\text{\textsubscript{YYY}}\) | \(\beta\text{\textsubscript{XXZ}}\) | \(\beta\text{\textsubscript{XYZ}}\) | \(\beta\text{\textsubscript{YYZ}}\) | \(\beta\text{\textsubscript{XZZ}}\) | \(\beta\text{\textsubscript{YZZ}}\) | \(\beta\text{\textsubscript{ZZZ}}\) | \(\beta\text{\textsubscript{tot}}\) | \(\beta\text{\textsubscript{tot}}\times10^{-30}\) |
|------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|

**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 (\(\beta\)) and dipole moment (\(\mu\)) of the ansa-titanocene dichloride have been calculated. From Table 2, it is found that the ansa-titanocene dichloride shows small \(\beta\text{\textsubscript{\text{total}}}\) 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.
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

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

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

\*\(R=C_6\text{Me}_5, X=\text{NCS}[15]\)
interface within the molecule[34].

**Global reactivity descriptors**

Global reactivity descriptors [35-38] electronegativity ($\chi$), chemical potential ($\mu$), global hardness ($\eta$), global softness ($S$), and electrophilicity index ($\omega$), determined on the basis of Koopman’s theorem[39] are listed in Table 4.

\[
\begin{align*}
\mu &= \frac{E(\text{HOMO}) + E(\text{LUMO})}{2} \\
\chi &= -\frac{E(\text{HOMO}) + E(\text{LUMO})}{2} \\
\eta &= \frac{E(\text{LUMO}) + E(\text{HOMO})}{2}
\end{align*}
\]

where $I$ and $A$ which are called ionization potential and electron affinity, respectively and is $I = -E(\text{HOMO})$ and $A = -E(\text{LUMO})$. 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.

<table>
<thead>
<tr>
<th>$E(\text{HOMO})$</th>
<th>$E(\text{LUMO})$</th>
<th>$\Delta E$</th>
<th>$\eta$</th>
<th>$\mu$</th>
<th>$\omega$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.24801</td>
<td>-0.09760</td>
<td>4.092897</td>
<td>2.046448</td>
<td>-4.7023</td>
<td>2.70122</td>
</tr>
</tbody>
</table>
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 2. The plot of molecular orbitals for ansa-titanocene dichloride.
Temperature dependence of thermodynamic properties

The thermodynamic 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 (R²) are all not less than 0.9. The corresponding fitting equations for ansa-titanocene dichloride are:

\[
G = -1.15 \times 10^{-7} T^2 - 1.01 \times 10^{-4} T - 1365.62; \quad R^2 = -0.99242 \\
C_v = 8.25 \times 10^{-5} T^2 + 1.82 \times 10^{-1} T + 1.457; \quad R^2 = 0.9745111019 \\
H = 7.22 \times 10^{-8} T^2 + 3.94 \times 10^{-5} T - 1365.62; \quad R^2 = 0.9880745830 \\
S = 5.03 \times 10^{-5} T^2 + 1.98 \times 10^{-1} T + 55.14; \quad R^2 = 0.9961407154
\]

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

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

**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:

\[
\text{[core]} 4S(0.22) 3d(3.35) 4p(0.58) 4d(0.10)
\]

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

\[
(1.98485) \text{BD (1) Ti-Cl} : (26.97\%) 0.5193*\text{Ti} 6\ s(12.02\%)p\ 0.99(11.86\%)d\ 6.33(76.12\%)
\]
\[+ (73.03\%) 0.8546*\text{Cl} 20\ s(36.32\%)p\ 1.75(63.56\%)d\ 0.00(0.11\%)
\]

\[
(1.98448) \text{BD (1) Ti-Cl'} : (26.80\%) 0.5176*\text{Ti} 6\ s(12.23\%)p\ 0.97(11.87\%)d\ 6.20(75.90\%)
\]
\[+ (73.20\%) 0.8556*\text{Cl} 21\ s(37.51\%)p\ 1.66(62.38\%)d\ 0.00(0.12\%)
\]

These values show that the \(\sigma(\text{Ti-Cl})\) bonds are formed from a \(\text{sp}^n\text{d}^a\) 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 \(\sigma(\text{Ti-Cl})\) bonds are formed from a \(\text{sp}^n\text{d}^a\) hybrid on Ti atom.

**References**

18.


