

The relation between haptotropic rearrangements and RBA in estradiol complexed

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ABSTRACT

In this work, we examine the dependence of relative binding affinity (RBA) and atomic properties studied in detail by density functional theory (DFT) and time-dependent DFT (TD-DFT) methods, of estradiol derivatives compounds.

Geometric descriptors show hapticity η^2 with aromatic ring and quantum descriptors identify the compounds studied as very weak electrophilic. The absorption spectrum is spread between 100 and 150 nm and corresponds to the electromagnetic transitions between the UV and X-rays. The complexation of estradiol decreases the intensity of the absorptions. The transitions of HOMO/LUMO; is MLTC nature for all chrome complexes and ICT type for those of manganese; this is related to their metal orbital compositions.

The relative binding affinity (RBA) is not dependent of intrinsic proprieties of compounds.

KEY WORDS: Haptotropic Rearrangements, RBA, TD-DFT, Estradiol Complexes.

1. INTRODUCTION

Haptotropic rearrangement is a migration of a transition metal fragment from one coordination site to the other on a π -conjugated polyene or polyaromatic ligands (Anh N T, 1978). Haptotropic shifts play an important role in reactions with electronically saturated complexes and associative substitution reactions.

The complexation of the aromatic ring of estradiol with the entity $\text{Cr}(\text{CO})_3$; generated two isomers. The β isomer, the one in which the $\text{Cr}(\text{CO})_3$ group is on the same side as the $17\beta\text{-OH}$ and $13\beta\text{-CH}_3$ groups (**Fig.1**), show only weak recognition for the estrogen receptor (relative binding affinity (RBA) = 1.8) while recognition of the α complex is much better (RBA = 28) (Jaouen G, Vessieres A, 1989; Vessieres A, 1988) by against the isomer $\text{E}(\alpha\text{SiCr})$ (**Table.1**) when $\text{Cr}(\text{CO})_3$ complexes with the aromatic ring in the α position, shows a weak recognition for the estrogen receptor, this disagreement that leads us to discuss theoretically these organometallic compounds and other by the density functional theory (DFT) approach and the time dependent density functional theory (TDDFT) method calculations, were employed to determine which the parameter that affects relative binding affinity.

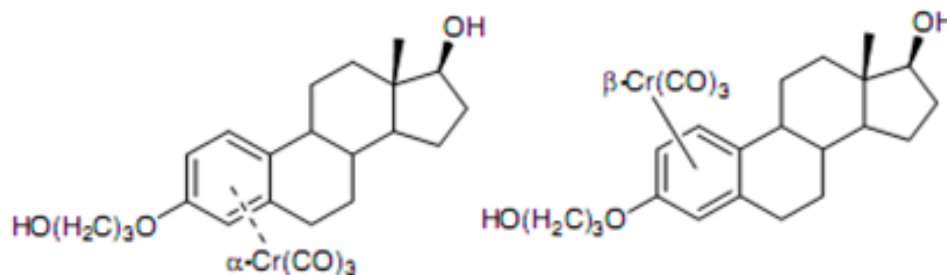


Fig.1: Estradiol isomer complexes with $\text{Cr}(\text{CO})_3$

Table.1.Substituted estradiol derivatives and their receptor binding affinity

Code	R1	R2	R3	L1	L2	RBA
E(αMn)	CH3	CH3	CH3	-	$\alpha\text{Mn}(\text{CO})_3$	1.741
E(βMn)	CH3	CH3	CH3	$\beta\text{Mn}(\text{CO})_3$	-	1.812
E(αCr)	$(\text{CH}_2)_3\text{OH}$	H	H	-	$\alpha\text{Cr}(\text{CO})_3$	28
E(βCr)	$(\text{CH}_2)_3\text{-OH}$	H	H	$\beta\text{Cr}(\text{CO})_3$	-	1.800
E(αSiCr)	$\text{Si}(\text{CH}_3)_2\text{tBu}$	H	H	-	$\alpha\text{Cr}(\text{CO})_3$	1.100
E(βSiCr)	$\text{Si}(\text{CH}_3)_2\text{tBu}$	H	H	$\beta\text{Cr}(\text{CO})_3$	-	0.400
E	$(\text{CH}_2)_3\text{-OH}$	H	H	-	-	37
E(Si)	$\text{Si}(\text{CH}_3)_2\text{tBu}$	H	H	-	-	11

2. COMPUTATIONAL METHODS

All calculations were obtained with the Amsterdam Density function (ADF) software (Baerends E J, Ellis D E, Ros P, 1973) and the geometry optimization of molecules were carried out by the density functional theory DFT using the Perdew, Burke, and Ernzerhof's exchange functional along with generalized gradient approximations, exchange and correlation functional GGA (PBE) (John Perdew P, 1997; Langreth D C, Vosko S H, 1990) employing the TZP (Triple Zeta Polarized) basis set. Frequency calculations have been performed in all cases to ensure that the calculated geometries correspond to true minima. The electronic chemical potential μ , the chemical hardness η and the global electrophilicity ω , of substrates were approximated in terms of energy of the frontier molecular orbitals (FMO) E_{HOMO} and E_{LUMO} , respectively (Becke A D, 1993; Harned H S, Hamer W J, 1933; Parr R G, Pearson R G, 1983; Parr R G, Yang W, 1989; Pearson R G, 1997).

First singlet excited state was optimized using the Time-Dependent Density Functional Theory calculations (TDDFT) (Bauernschmitt R, Ahlrichs, 1996; Casida M E, 1995; Gross E U K, Dobson J F, 1996; Gross E K U, Kohn W, 1990) with same functional and basis Set.

3. RESULTS AND DISCUSSION

3.1 Structural analysis: The compounds used in this work are given in **Table.1** and **Fig.2** taken from literature (Jaouen G, Vessieres A, 1989; Vessieres A, 1988). Optimized distances and angles of molecules are given in **Table.2** and they are described by the DFT method. Calculated structural parameters reveal a good agreement with the literature (Jaouen G, Vessieres A, 1989; Vessieres A, 1988). The atoms in molecules approach 2AIM) (Bader R.F. W, 2007) was applied to analyses the electron densities and their properties, details obtained from this approach are shown in **Table.3**, we notice from the AIM properties, that there are a very weak interaction between the transition metals (Mn and Cr) and the carbon of the aromatic ring, all ligand compounds display a hapticity η^2 .

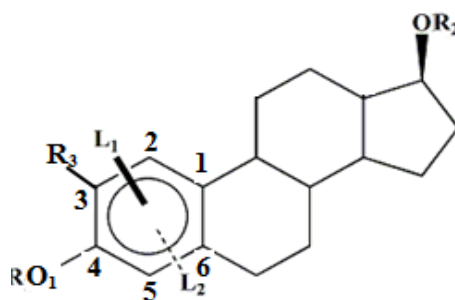


Fig.2: Substituted estradiol derivative structures

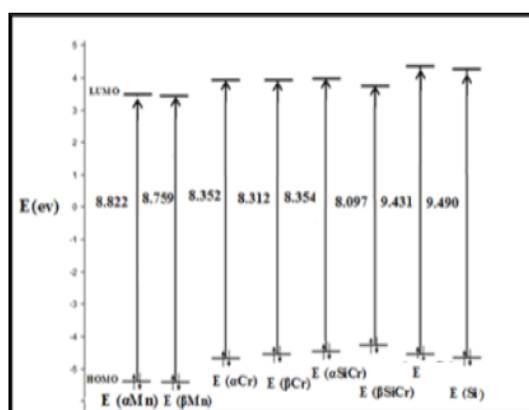
Table.2. Selected bond lengths (Å) and angles (°) of [E(α Mn), E(β Mn), E(α Cr), E(β Cr), E(α SiCr), E(β SiCr), E and E(Si)]

	Distance and angles				
	M-C	M-C(CO)	C-O1	C- \hat{M} -C	C- \hat{O}_1 -C
E(α Mn)	2,31	1,81	1,37	92	117
E(β Mn)	2,33	1,81	1,37	92	117
E(α Cr)	2,26	1,85	1,36	89	118
E(β Cr)	2,28	1,85	1,36	88	118
E(α SiCr)	2,27	1,85	1,35	89	129
E(β SiCr)	2,28	1,85	1,35	88	129
E	*	*	1,36	*	119
E(Si)	*	*	1,37	*	129

Table.3.Results of atom in molecule approach (AIM) for compounds E(α Mn), E(β Mn), E(α Cr), E(β Cr), E(α SiCr) and E(β SiCr)

		ρ	Δ	V /G	H
E(α Mn)	M-C2	0.07	0.22	1.22	-0.02
	M-C4	0.06	0.17	1.27	-0.02
E(β Mn)	M-C2	0.07	0.22	1.23	-0.02
	M-C4	0.06	0.17	1.27	-0.02
E(α Cr)	M-C1	0.06	0.20	1.20	-0.01
	M-C5	0.06	0.19	1.19	-0.01
E(β Cr)	M-C1	0.06	0.19	1.21	-0.01
	M-C5	0.06	0.17	1.19	-0.01
E(α SiCr)	M-C1	0.06	0.20	1.21	-0.01
	M-C5	0.06	0.19	1.20	-0.01
E(β SiCr)	M-C1	0.06	0.19	1.21	-0.01
	M-C5	0.06	0.18	1.19	-0.01

3.2 Orbital Analysis:The molecular orbital diagram obtained by DFT method, optimized for different compounds [E(α Mn), E(β Mn), E(α Cr), E(β Cr), E(α SiCr), E(β SiCr), E and E(Si)] are shown in **Fig.3**. We notice a large energy gap between the vacant and occupied orbitals occurred near 8.352ev. The composition of the frontier orbital of [E(α Mn), E(β Mn), E(α Cr), E(β Cr), E(α SiCr) and E(β SiCr)] are shown in **Table.4**. The HOMO orbital derived principally of d metal orbital, while the LUMO is nonmetallic character except for E(α Mn) and E(β Mn) (39 and 41%) respectively. From **Table.5** ($\omega = 0.06, 0.07, 0.02, 0.02, 0.02, 0.0, 0.00$ and 0.00), we conclude that all compounds are weak electrophilic.

**Fig.3:Energy diagram of: E(α Mn), E(β Mn), E(α Cr), E(β Cr), E(α SiCr), E(β SiCr), E and E(Si)****Table.4.Frontier molecular orbital composition (%) of E(α Mn), E(β Mn), E(α Cr), E (β Cr), E(α SiCr) and E(β SiCr)**

			Contribution (%)		
	Orbital	E(ev)	M	C and others	
E(α Mn)	HOMO	-5.161	Mn	41d	59
	LUMO	3.661	Mn	39d	61
E(β Mn)	HOMO	-5.181	Mn	38d	62
	LUMO	3.598	Mn	41d	59
E(α Cr)	HOMO	-4.547	Cr	53d	47
	LUMO	3.805	Cr	4d	96
E(β Cr)	HOMO	-4.510	Cr	56d	44
	LUMO	3.802	Cr	3 d	57
E(α SiCr)	HOMO	-4.531	Cr	57d	43
	LUMO	3.823	Cr	2d	95
E(β SiCr)	HOMO	-4.320	Cr	56d	44
	LUMO	3.777	Cr	00	100

Table.5.Frontier molecular orbital energy, electronic chemical potential, chemical hardness and global electrophilicity index of compounds

	E_{HOMO}	E_{LUMO}	gap	η	μ	ω
$E(\alpha\text{Mn})$	-5.16	3.66	8.82	4.41	-0.75	0.06
$E(\beta\text{Mn})$	-5.16	3.60	8.76	4.38	-0.78	0.07
$E(\alpha\text{Cr})$	-4.55	3.80	8.35	4.17	-0.37	0.02
$E(\beta\text{Cr})$	-4.51	3.80	8.31	4.16	-0.35	0.02
$E(\alpha\text{SiCr})$	-4.53	3.82	8.35	4.18	-0.35	0.02
$E(\beta\text{SiCr})$	-4.32	3.78	8.10	4.05	-0.27	0.01
E	-4.77	4.66	9.43	4.71	-0.05	0.00
$E(\text{Si})$	-4.89	4.59	9.49	4.74	-0.15	0.00

3.3 Population analysis: Our calculations were performed by employing the Hirshfeld charges (Hirshfeld F L,1977), the results in **Table.6** show that the Cr atoms of [$E(\alpha\text{Cr})$, $E(\beta\text{Cr})$, $E(\alpha\text{SiCr})$ and $E(\beta\text{SiCr})$] are more positively charged (0.285,0.288, 0.287 and 0.289 respectively) than the compound with manganese, and the carbon atoms connected to metals more negatively charged (**Table.6**). We conclude that the interactions are electrostatic, and they are stronger in $E(\text{Cr})$ than in $E(\text{Mn})$.

Table.6.Hirshfeld charge analysis of [$E(\alpha\text{Mn})$, $E(\beta\text{Mn})$, $E(\alpha\text{Cr})$, $E(\beta\text{Cr})$, $E(\alpha\text{SiCr})$, $E(\beta\text{SiCr})$, E and $E(\text{Si})$]

	M	C (benz)	C(CO)	O(CO)	O1
$E(\alpha\text{Mn})$	0.012	-0.069	0.209	-0.410	-0.923
$E(\beta\text{Mn})$	0.013	-0.069	0.215	-0.405	-0.092
$E(\alpha\text{Cr})$	0.285	-0.147	0.009	-0.476	-0.092
$E(\beta\text{Cr})$	0.288	-0.151	0.006	-0.473	-0.091
$E(\alpha\text{SiCr})$	0.287	-0.144	0.009	-0.476	-0.165
$E(\beta\text{SiCr})$	0.289	-0.142	0.009	-0.470	-0.164
E	*	-0.140	*	*	-0.114
$E(\text{Si})$	*	-0.126	*	*	-0.187

3.4 TD-DFT absorption spectra: The time-dependent density functional theory (TD-DFT) calculations were performed on Complexes, with the aim to identify the nature of the electronic transitions and the influence of substituent and metal on the optical properties. The most representative calculated optical transitions in all compounds are shown in **Table.7**.The calculated absorption spectra of all complexes are shown in **Fig.4**. These complexes absorb in the same domain of wavelengths, in the region 110-140 nm.

The spectra of uncomplexed compounds [E and $E(\text{Si})$] intensively absorbs in the region ($\lambda=115-125\text{nm}$) appear on the Fig.3 with ligand to ligand transfer charge (LLTC).The complexes [$E(\alpha\text{Mn})$, $E(\beta\text{Mn})$, $E(\alpha\text{Cr})$, $E(\beta\text{Cr})$, $E(\alpha\text{SiCr})$ and $E(\beta\text{SiCr})$], with metals present lower intensity absorption bands with mainly metal to ligand transfer charge (MLTC).The absorption bands correspond to the HOMO \rightarrow LUMO transitions of [$E(\alpha\text{Mn})$, $E(\beta\text{Mn})$, $E(\alpha\text{Cr})$, $E(\beta\text{Cr})$, $E(\alpha\text{SiCr})$, $E(\beta\text{SiCr})$, E and $E(\text{Si})$] are [(ICT), (ICT), (MLTC), (MLTC), (MLTC), (MLTC), (ICT) and (ICT)] respectively (see **Fig.4**). Consistent with energy HOMO / LUMO, the low values of the gap lead to a bathochromic shift of the corresponding spectrum.

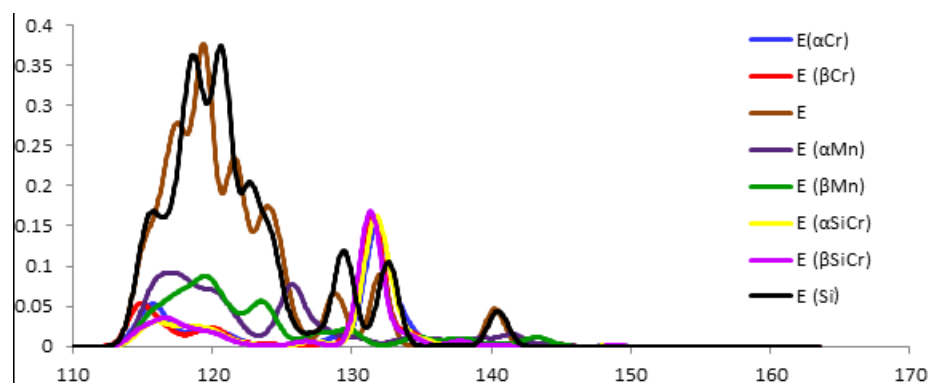
**Fig.4.TD-DFT absorption spectra of: $E(\alpha\text{Mn})$, $E(\beta\text{Mn})$, $E(\alpha\text{Cr})$, $E(\beta\text{Cr})$, $E(\alpha\text{SiCr})$, $E(\beta\text{SiCr})$, E and $E(\text{Si})$**

Table.7.The most representative calculated optical transitions

λ (nm)	f	E (ev)	Composition	character
E(αMn)				
138	0.008	08.95	HOMO \rightarrow LUMO	ICT
123	0.125	10.11	HOMO-5 \rightarrow LUMO+1	MLTC
115	0.016	10.79	HOMO-4 \rightarrow LUMO+7	MLTC
E(βMn)				
139	0.007	08.94	HOMO \rightarrow LUMO	ICT
121	0.040	10.26	HOMO \rightarrow LUMO+5	MLTC
117	0.066	10.54	HOMO-1 \rightarrow LUMO+8	MLTC
E(αCr)				
148	0.002	08.37	HOMO \rightarrow LUMO	MLTC
132	0.191	09.42	HOMO \rightarrow LUMO+4	MLTC
116	0.045	10.68	HOMO-5 \rightarrow LUMO+1	MLTC
E(βCr)				
149	0.002	08.34	HOMO \rightarrow LUMO	MLTC
131	0.289	09.42	HOMO-2 \rightarrow LUMO+1	MLTC
115	0.075	10.82	HOMO-6 \rightarrow LUMO+1	LMTC
E(αCr Si)				
148	0.002	08.38	HOMO \rightarrow LUMO	MLTC
131	0.282	09.42	HOMO-2 \rightarrow LUMO	MLTC
117	0.023	10.63	HOMO-5 \rightarrow LUMO+1	LMTC
E(βCr Si)				
149	0.002	08.33	HOMO \rightarrow LUMO	MLTC
132	0.325	09.40	HOMO-2 \rightarrow LUMO	MLTC
117	0.033	10.76	HOMO-5 \rightarrow LUMO+1	LLTC
E				
127	0.073	09.43	HOMO \rightarrow LUMO	ICT
112	0.017	11.03	HOMO-2 \rightarrow LUMO+2	LLTC
110	0.155	11.24	HOMO-1 \rightarrow LUMO+5	LLTC
108	0.030	11.50	HOMO-5 \rightarrow LUMO+2	LLTC
E(Si)				
125	0.066	09.94	HOMO \rightarrow LUMO	ICT
118	0.160	10.50	HOMO \rightarrow LUMO+4	LLTC
115	0.178	10.75	HOMO \rightarrow LUMO+4	LLTC
108	0.165	11.48	HOMO-3 \rightarrow LUMO+2	ICT
106	0.106	11.70	HOMO \rightarrow LUMO+15	LLTC

4. CONCLUSION

Our theoretical approach presented in this work highlight the electronic structure of the various organometallic complexes with DFT calculations. The results show that the metallic character of the HOMO is very strong in compounds [E (α Mn), E (β Mn), E (α Cr), E (β Cr), E (α SiCr) and E (β SiCr)].

A good agreement between the calculated distances and angles with literature, the atom in molecule (AIM) analyses show that, all compounds complexed their ligand displays a hapticity η^2 , and also existence of very weak interactions among metal and carbons of the benzene cycle. Quantum descriptors demonstrate the low electrophilicity of the investigated compounds. The absorption spectrum is spread between 100 and 150 nm and corresponds to the electromagnetic transitions between the UV and X-rays. Metal contributes largely in transitions, except for manganese; because of its low contribution in the frontier orbitals. The relative binding affinity (RBA) is not dependent of intrinsic properties of the molecule.

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