

The investigation of interaction between Cyclophosphamide and single walled Carbon Nanotubes with DFT and NBO

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ABSTRACT

The molecular structure of Cyclophosphamide ('N, N-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide' is the anti cancer drug and used to treat cancer and immune diseases) and SWCNTs were calculated by the B3LYP density functional model with 6-311G* basis set with Gaussian 09 program. The nanotube used in this study, includes 120 C atoms (5, 5) type. The NBO analysis showed there is a hyperconjugative interaction between Oxygen lone – pair electrons of Cyclophosphamide and σ^* or π^* orbitals of carbon atom of nanotube. Also chemical shift isotropy(σ), chemical shift anisotropy($\Delta\sigma$), asymmetry parameter(η) of this compounds have been reported.

Keywords: Cyclophosphamide; NBO; Chemical shift; DFT

INTRODUCTION

Cyclophosphamide (Fig. 1) known as cytophosphane. An alkylating agent adds an alkyl group (C_nH_{2n+1}) to DNA. It attaches the alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the imidazole ring. This interferes with DNA replication by forming intrastrand and interstrand DNA crosslinks. Cyclophosphamide uses with other chemotherapy agents in the treatment of lymphomas, some forms of brain cancer, leukemia[1] and some solid tumors [2] It is a chemotherapy drug that works by inducing the death of certain T cells. Cyclophosphamide has severe and life-threatening adverse effects, including acute myeloid leukemia, bladder cancer, hemorrhagic cystitis, and permanent infertility, especially at higher doses. For

autoimmune diseases, doctors often substitute less-toxic methotrexate or azathioprine after an acute crisis [3].

Our study, Based on the Density Functional Theory (DFT) methods and Natural Bond Orbital (NBO) analysis, electron transport mechanism of carbon nanotube with Cyclophosphamide have investigated.

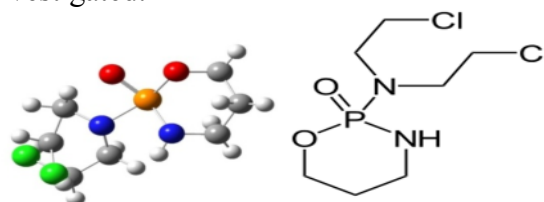


Fig 1. Cyclophosphamide structures.

COMPUTATIONAL METHODS

In this paper we used Density functional

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theory (DFT). DFT has become very popular in recent years. At first we have modeled the structure of Cyclophosphamide with Gauss view package and Single Walled Carbon Nanotube (SWCNTs) with Nanotube Modeler then optimized those structures. All the calculations were performed with the Gaussian 09 program package by DFT method at the B3LYP/6-311G* level. After fully optimization structures of Cyclophosphamide - SWCNTs, we have calculated of Energy value, NMR

parameters and NBO at the levels of B3LYP/6-311 G*.

RESULTS AND DISCUSSION

In this work at first we employed DFT method with different basis set for investigating the structures optimization and energy minimization of Cyclophosphamide, Single Walled Carbon Nanotube (5, 5) and then Cyclophosphamide – SWCNTs (Fig .2) their data have been summarized in Table 1.

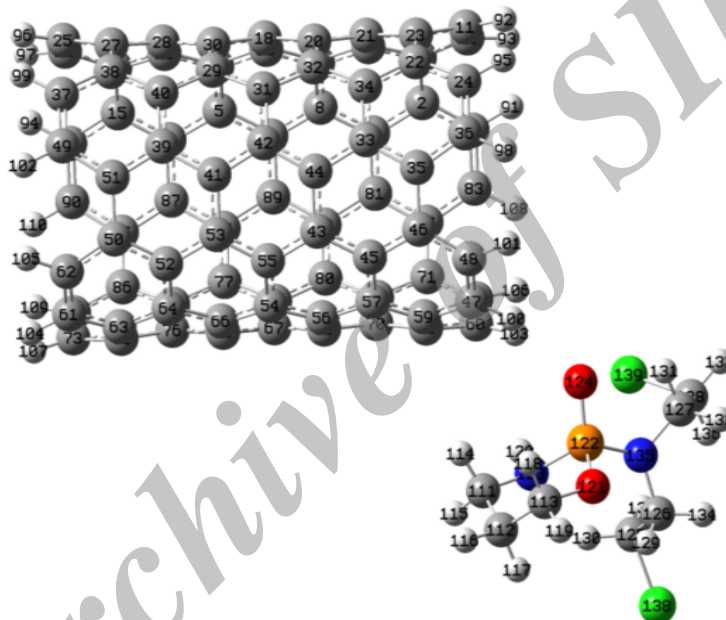


Fig. 2. Optimization of Cyclophosphamide-SWCNTs.

Table 1. Calculation Energy with B3LYP method by 3-21g*, 6-31g* and 6-311g* for Cyclophosphamide, SWCNTs and Cyclophosphamide-SWCNTs

Molecule	Method/Basis set	Energy(kcal/mol))
Cyclophosphamide	B3LYP/3-21g*	-4692069.1231
Cyclophosphamide	B3LYP /6-31g*	-4714853.7208
Cyclophosphamide	B3LYP /6-311g*	-4699672.7367
CNTs	B3LYP /3-21g*	-8977573.0324
CNTs	B3LYP /6-31g*	-9027550.2068
CNTs	B3LYP /6-311g*	-9082370.2296
Cyclophosphamid-CNTs	B3LYP /3-21g*	-13669703.2823
Cyclophosphamid-CNTs	B3LYP /6-31g*	-13742430.565
Cyclophosphamid-CNTs	B3LYP /6-311g*	-13744637.6751

All the relative NMR shielding parameters were calculated supposing Gauge Included Atomic Orbital (GIAO) method. The GIAO calculations of NMR chemical shielding tensors were performed using DFT method. The chemical shielding tensor were calculated with the GAUSSIAN 09 program [5-7].

The chemical shift of a nucleus, i , in a molecule arises from the nuclear shielding effect of an applied magnetic field, caused by an induced magnetic field resulting from circulation of surrounding electrons [7-15]. The magnitude of such an induced magnetic field is proportional to the strength of the applied external magnetic field B_0 , so that the effective field B_{eff} at the nucleus is given as

$$B_{eff} = B_0(1 - \sigma_i) \quad (1)$$

where σ_i is the second-rank nuclear shielding tensor and 1 is the unit matrix. In normal NMR experiments B_0 is a uniform field along the z-axis; therefore, $\sigma_i = \sigma_{izz}$. For chemical shielding tensor, we often use x, y and z diagonalizes matrix to give the three principal components (δ_{XX} , δ_{YY} , δ_{ZZ} or in the "Mehring notation", the principal components, δ_{11} , δ_{22} and δ_{33}). The isotropic average of the tensor is given by

$$\delta_{iso} = 1/3(\delta_{11} + \delta_{22} + \delta_{33}) \quad (2)$$

The three principal components is related to δ_{iso} by [15]

$$|\delta_{33} - \delta_{iso}| \geq |\delta_{11} - \delta_{iso}| \geq |\delta_{22} - \delta_{iso}| \quad (3)$$

where δ_{33} is the principal component farthest from the isotropic value, and δ_{33} is the component closest to δ_{iso} : the ordering of the components can be either $\delta_{33} \geq \delta_{22} \geq \delta_{11}$ depending on the chemical structure in question. Therefore, the "reduced anisotropy" is defined as

$$\Delta\delta = \delta_{33} - 1/2(\delta_{XX} + \delta_{YY}) \text{ or } \delta = \delta_{ZZ} - \delta_{iso} \quad (4)$$

The shielding asymmetry η is defined as

$$\eta = (\delta_{22} - \delta_{11}) / \delta \approx 3(\delta_{22} - \delta_{11}) / 2\Delta\delta \quad \text{Or} \\ \eta = |\sigma_{22} - \sigma_{11}| / |\sigma_{33} - \sigma_{iso}| \quad (5)$$

These anisotropy/asymmetry conventions can be replaced by span (Ω) and skew (κ) parameter with the following definitions [8, 16]:

$$\Omega = \delta_{11} - \delta_{33} \quad (6)$$

$$\kappa = 3(\delta_{22} - \delta_{iso}) / \Omega \quad (7)$$

The chemical shielding (σ_{iso}), anisotropy shielding ($\Delta\sigma$), asymmetry parameter (η), span (Ω) and skew (κ) for atoms of Cyclophosphamide-SWCNTs in (Figure 2) have been summarized in Table 3.

According to the result of NMR parameters (Table 3) σ_{iso} , $\Delta\sigma$, η in all atoms are positive value expect $\Delta\sigma$ in H_{114} , N_{123} , C_{125} , H_{126} , H_{129} that these are the negative value. Chemical shifts (σ) and ($\Delta\sigma$) for each of the atom are shown in Figure 2. In this diagram biggest signals belong of atoms C_{112} , P_{122} , N_{135} , Cl_{138} . And in the diagram of $\Delta\sigma$ biggest signals belong of atoms C_{111} , O_{121} , N_{135} , C_{1138} and smallest signal belong of atoms H_{91} , H_{114} , N_{123} , C_{128} , N_{136} .

Natural bond orbital (NBO) has an important role in interaction in complex, specially charge transfer. This analysis is done according 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:

$$E^{(2)} = q_i (F_{ij})^2 / \epsilon_j - \epsilon_i \quad (8)$$

where q_i is the orbital occupancy, " ϵ_i ", " ϵ_j " are diagonal elements and F_{ij} is the off

diagonal NBO Fock matrix element [17-20]. If $E^{(2)}$ amount is very large, interaction between electron donor (NBO_i) and electron acceptor (NBO_j) will be more intensive. The result of second order perturbation theory analysis at B3LYP/6-311G* level of theory are collected in Table 4. Also the NBOs result shown in Table 4 we used natural population analysis (NPA). For each donor NBO and acceptor NBO the stabilization energy $E^{(2)}$ is presented as the second-order perturbation interaction energy $E^{(2)}$.

The stability of compound confirmed by $E^{(2)}$. According to result of the calculation natural hybrids, occupancies and second-orbital perturbation energy $E^{(2)}$ hyperconjugation can occur between electrons lone pair of oxygen (Lews-type NBOs) with some σ^* or π^* (Non-Lews NBOs). The most important transfer in compound (Cyclophosphamide -SWCNTs) is $LP(1)O124 \rightarrow \sigma^* C47 - H100$ that is highest energy a stable structure.

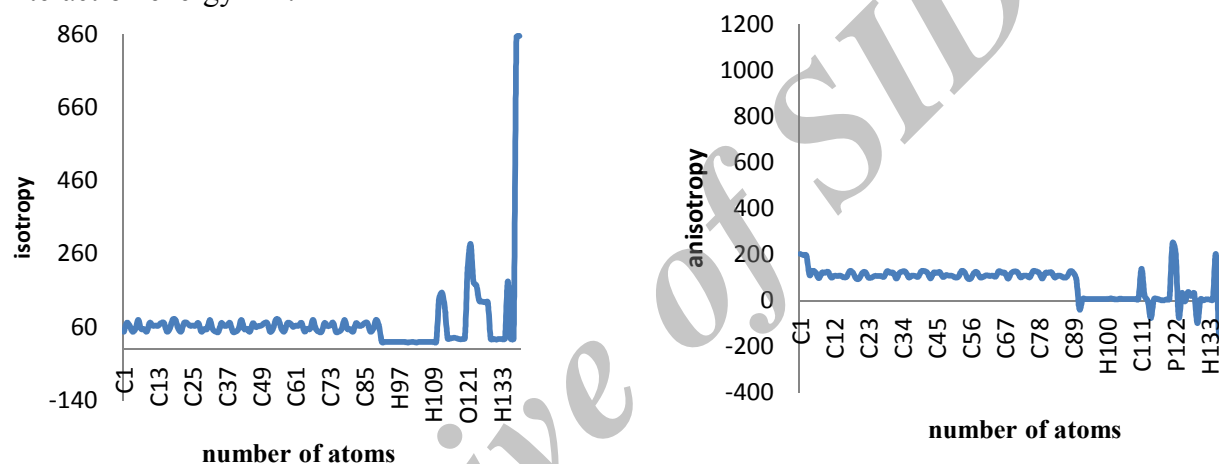


Fig. 2. Diagrams which show chemical shifts for each of the atom at the Cyclophosphamide-SWCNTs.

Table 3. Values of parameters (ppm) of Cyclophosphamide such as isotropic (σ_{iso}), anisotropic (σ_{anis}) shielding and asymmetry parameter (η)

Atom	σ_{iso}	$\Delta\sigma$	η	Atom	σ_{iso}	$\Delta\sigma$	η
C1	47.8765	203.9768	0.157448	C71	71.7156	124.6747	0.913799
C2	72.2063	198.9373	0.900884	C72	63.8823	102.1202	0.593075
C3	64.838	196.6742	0.719754	C73	65.0237	109.4999	0.62382
C4	48.1186	112.514	0.141386	C74	72.72	109.1171	0.902388
C5	55.4715	130.3965	0.142483	C75	47.7207	102.4447	0.144419
C6	80.1051	123.0052	0.96149	C76	48.152	128.2925	0.144493
C7	55.927	98.5006	0.132385	C77	55.2583	128.764	0.148466
C8	55.4352	122.6787	0.126292	C78	80.07	121.0518	0.996738
C9	48.673	122.0933	0.15672	C79	55.3891	97.0418	0.127538
C10	72.5262	125.9018	0.899344	C80	54.9371	121.3023	0.117986
C11	64.6577	101.2322	0.614916	C81	48.4234	121.6121	0.170437
C12	64.6928	108.9067	0.612068	C82	71.4667	124.0827	0.899234
C13	64.4639	108.3885	0.626712	C83	64.4335	101.7884	0.601296
C14	71.981	109.2097	0.885896	C84	64.8642	109.1821	0.623048
C15	71.8588	102.4407	0.879206	C85	71.674	107.8561	0.896864
C16	48.3822	105.0099	0.147315	C86	71.8253	101.0824	0.903457
C17	55.7404	129.8238	0.139529	C87	48.5335	105.023	0.140805
C18	80.8491	121.8527	0.995431	C88	55.2245	128.7086	0.141534
C19	80.5551	97.5743	0.973103	C89	80.5135	122.6518	0.972061
C20	55.5747	96.8488	0.128922	C90	64.847	92.9892	0.62739
C21	48.74	121.3558	0.162509	H91	20.1097	-35.9228	0.329389
C22	72.0964	124.1371	0.916546	H92	20.0246	8.0452	0.247487

C23	72.1384	101.0653	0.921516	H93	20.056	8.082	0.231683
C24	64.8601	101.2803	0.616223	H94	20.044	8.1991	0.277595
C25	64.6919	108.4304	0.6229	H95	20.0452	8.3906	0.278433
C26	64.6193	108.2327	0.627274	H96	20.0713	8.0914	0.250114
C27	71.6762	107.8048	0.903422	H97	20.1045	8.2022	0.263268
C28	48.4399	104.5566	0.147334	H98	19.9455	7.8179	0.193182
C29	55.3186	129.0375	0.145341	H99	20.0374	8.157	0.257208
C30	55.3994	122.1093	0.141786	H100	18.6034	7.6781	0.494056
C31	79.9607	121.8808	0.982238	H101	19.9498	10.6222	0.367537
C32	55.029	97.0092	0.125758	H102	20.0854	8.2888	0.266086
C33	48.1423	120.9954	0.164114	H103	18.6275	6.1252	0.555614
C34	47.7764	127.8821	0.164251	H104	20.0818	9.6999	0.27092
C35	71.7549	125.6728	0.885762	H105	20.0781	8.1536	0.26119
C36	64.1729	101.7225	0.614465	H106	19.8565	8.2767	0.418917
C37	64.8967	109.5001	0.626032	H107	20.072	8.385	0.265682
C38	72.125	108.278	0.903674	H108	20.0023	7.9706	0.198302
C39	48.2252	104.6286	0.141213	H109	20.0709	8.1593	0.252731
C40	48.1807	128.0087	0.137845	H110	20.0427	8.185	0.270909
C41	55.8659	129.6546	0.145982	C111	138.3986	139.5114	0.723552
C42	80.1029	121.9524	0.965908	C112	154.8139	21.8319	0.786785
C43	55.1243	97.8297	0.116337	C113	112.48	1.2967	0.612907
C44	55.7007	122.6431	0.119012	H114	29.4558	-75.3781	0.638934
C45	48.3758	121.3891	0.169059	H115	30.0956	7.4979	0.441099
C46	71.2652	124.9954	0.897433	H116	31.4945	8.565	0.536638
C47	60.8839	103.956	0.470145	H117	30.4066	4.688	0.311674
C48	63.7176	111.7118	0.631477	H118	27.7559	1.9926	0.638059
C49	64.9107	109.8541	0.627488	H119	28.1171	6.3742	0.841577
C50	71.5398	108.2669	0.887162	H120	30.9065	8.3516	0.922956
C51	72.0356	101.6764	0.890255	O121	227.6944	250.3925	0.438837
C52	48.2472	105.1227	0.141127	P122	287.4171	208.9132	0.258384
C53	55.4467	129.8843	0.144676	N123	183.7518	-69.7683	0.531348
C54	80.8335	123.2684	0.978959	O124	174.7259	33.0422	0.919305
C55	80.2929	97.4015	0.965332	C125	132.6888	-2.1884	0.545744
C56	55.5597	97.7032	0.131368	C126	130.4501	38.5558	0.710618
C57	48.7097	121.321	0.18992	C127	128.4196	21.6926	0.883417
C58	71.1407	124.3228	0.936791	C128	128.6614	33.1739	0.951896
C59	71.3448	101.8918	0.941621	H129	28.4465	-96.1655	0.499398
C60	61.546	104.4667	0.476693	H130	28.3783	6.6627	0.947556
C61	64.7797	111.4278	0.627273	H131	26.6866	2.9208	0.426819
C62	64.4465	108.1857	0.627244	H132	28.5452	7.3965	0.892751
C63	72.395	109.4909	0.896573	H133	27.7242	5.5679	0.812597
C64	48.7866	105.5509	0.13686	H134	29.4393	5.833	0.707255
C65	55.9616	128.8744	0.152071	N135	185.5757	201.1494	0.177698
C66	55.8878	122.3979	0.145833	H136	28.2188	-153.043	0.65364
C67	80.6468	121.4016	0.995891	H137	28.8214	7.6628	0.989235
C68	55.4174	96.7154	0.123495	Cl138	852.5086	1061.921	0.37115
C69	48.0117	120.0187	0.163457	Cl139	855.4762	227.1863	0.506277
C70	48.168	127.9293	0.179657				

Table 4. Calculated natural hybrids, occupancies and the second-order perturbation energy E2 at B3LYP 6-311G*

Type	Lews-type NBOs		Non Lews NBOs		
	Hybride	Occupancy	Type	Occupancy	E ⁽²⁾ (kcal/mol ⁻¹)
LP(1)O ₁₂₄	sp ^{0.54}	1.97497	σ*C47-H100	0.01747	1.02
			σ*C60-H103	0.01931	0.55
LP(2)O ₁₂₄	sp ^{1.00}	1.82074	σ*C47-H100	0.01747	0.56
			σ*C60-H103	0.01931	0.92
LP*(1)P ₁₂₂	sp ^{2.23}	0.60662	σ*C47-H100	0.01747	0.17
			σ*C60-H103	0.01931	0.11
LP*(2)P ₁₂₂	sp ^{66.30}	0.53200	σ*C47-H100	0.01747	0.25
			π*C60-H72	0.24660	0.12
LP(1)N ₁₂₃	sp ^{7.05}	1.89296	π*C60-C72	0.24660	0.06

CONCLUSION

In our study we investigate on stability of Cyclophosphamide with Single Walled Carbon Nanotube according to our results the following conclusions are derived for this compound:

1-The compound of Cyclophosphamide-SWCNTs is more stable than the single structure. This result confirmed by energy and second-order perturbation interaction $E^{(2)}$.

2-When the p orbital share of the lone pair electrons of oxygen increasing, the occupancy decreased.

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