Cumhuriyet Science Journal

Cumhuriyet Sci. J., 46(2) (2025) 319-328
DOI: https://doi.org/10.17776/csj.1646890

| csj.cumhuriyet.edu.tr | Founded: 2002 ISSN: 2587-2680 e-ISSN: 2587-246X Publisher: Sivas Cumhuriyet University

Potential Application of Al Doped Carbon Nanotubes for Tretinoin: a Theoretical Study

Fatma Genç [1,a,*], **Serap Senturk Dalgic** [2,b], **Fatma Kandemirli** [3,c]

[1] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Istanbul YeniYuzyil University, Istanbul, Türkiye*
[2] *Department of Physics, Atomic and Molecular Physics, Faculty of Science, Trakya University, Edirne-Türkiye*
[3] *Departmento f Biomedical Engineering, Faculty of Engineering & Architecture, Kastamonu University, Kastamonu, Türkiye*
**Corresponding author*

Research Article

History
Received: 28/02/2025
Accepted: 17/04/2025

ABSTRACT

In this research, a Density Functional Theory (DFT) calculation was performed to study the interaction of Tretinoin drug (TRE) known as a valuable medication in treating mild, moderate, and severe acne that can be used topically or systemically into Al-doped carbon nanotube (Al-CNT) with the use of M062X/6-31G(d) level of theory in the gas, n-octanol and water environment. The Quantum Theory of Atoms in Molecules (QTAIM) study was performed for complexes in gas, n-octanol and water environments. The contributions of atomic orbitals to the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) for TRE and its complex with Al-CNT in gas, n-octanol and water environment were found using the multifunctional wavefunction analyzer program (Multiwfn). Surface analysis, global minimum and global maximum of TRE and its complexity in different environments were performed. The adsorption, interaction, and deformation energies of TRE drug on Al-CNT have been calculated, along with the changes in the enthalpy and Gibss-free energy in different environments. Calculations indicate that Al-CNT is a promising device for drug carriers for TRE drugs due to the more negative adsorption energies. The Gibbs free energy for adsorption of TRE on Al-CNTs is also more favorable in water.

Keywords: Quantum theory of atoms in molecules (QTAIM), Quantum theory, Density functional theory (DFT), Al doped carbon nanotube, Integral equation formalism PCM (IEFPCM).

a *ftmgenc@yahoo.com* *https://orcid.org/0000-0002-5304-5347*
b *serapd@trakya.edu.tr* *https://orcid.org/0000-0003-2541-9214*
c *fatma_kandemirli@yahoo.com* *https://orcid.org/0000-0001-6097-2184*

Introduction

Acne, also known as Acne Vulgaris, is a chronic and persistent skin inflammation of hairy sebaceous follicles that affects people worldwide. Acne is estimated to affect 9.4 % of the global population and ranks eighth among skin diseases [1]. TRE is a generic name for a medication derivative of vitamin A (retinol), also commonly known as all-trans retinoic acid (ATRA). TRE can be given systemically or topically for various indications [2]. Historically used as a comedolytic agent to treat mild to moderate acne, TRE can stimulate the growth of new cells, unclog pores, and support the normal flow of sebum when used both as a standalone treatment and in combination with antibacterials [3].

Nano emulations and colloidal nano-sized particles increase the therapeutic efficacy of TRE and minimize side effects. The number of acne lesions and the size and intensity of porphyrin production were significantly reduced after topical application of TRE-loaded Nano emulations in a pilot clinical study of nanoparticles developed in the form of a stable oil-in-water emulsion with a particle size of approximately 150 nm and containing circular and separated particles [4].

TRE is an important component of topical treatments because it causes the loss of comedones and eliminates the lesions they form. TRE also stimulates collagen formation, aggregation of sebaceous glands and control of cell proliferation and differentiation, although it has typical side effects such as skin irritation, burning and erythema [5]. Recently, new drug delivery systems such as solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) have been designed to increase the therapeutic efficacy of TRE [6-8].

They studied the interaction of a nanotube with an anticancer agent named TRE in methanol, ethanol, and water using quantum mechanics and semi-empirical methods and revealed that these composites are more stable in water than in the other solvents [9]. The main objective of developing Nanocarrier drug delivery systems using cylindrical molecules made of carbon atoms such as CNTs is to increase the therapeutic effect or reduce the toxicity of therapeutically active materials [10].

Features such as efficient and augmented tumour targeting, thanks to the improved permeability and retention effect of CNTs, are among the advantages of using a CNT-supported drug delivery system [11].

Al doping increases the surface reactivity of CNTs, allowing stronger interactions and better adsorption of drug molecules. The presence of Al atoms increases loading efficiency by creating active sites that enable covalent and non-covalent binding of a wide range of drug molecules. To our knowledge, no computational studies have included an analysis of TRE and its complexes with Al-CNT or the solvent effects for the TRE and Al-CNT/TRE complex.

Materials and Methods

Computational methods

The molecular geometries of TRE and its complex with Al-CNT ($AlC_{35}H_{12}$, composed of one aluminum, 35 carbon, and 12 hydrogen atoms) were optimized in a vacuum, n-octanol, and water environment at the M062X/6-31G(d) level of theory [12]. The M062X/6-31G(d) method was selected as the main level of theory because recent works [13-16] indicate that the M062X level in DFT calculations successfully describes intermolecular interactions by comparison with other traditional functionals. The M062X model is due to the long-range corrected energy, which can successfully investigate drug adsorption [13-16]. The M062X function/6-31G(d) method has been provide more relieable results for recent drug delivery applications by describing non-covalent and weak interactions [17]. The obtained geometries of isolated molecules were subsequently optimized in the presence of gas, n-octanol and water environment, using the same level and Integral Equation Formalism Polarisable Continuum Models (IEFPCM) solvation model [18].

Results and Discussion

Molecular Geometry, Molecular Electrostatic Potentials (ESP), HOMO-LUMO and Surface Analysis

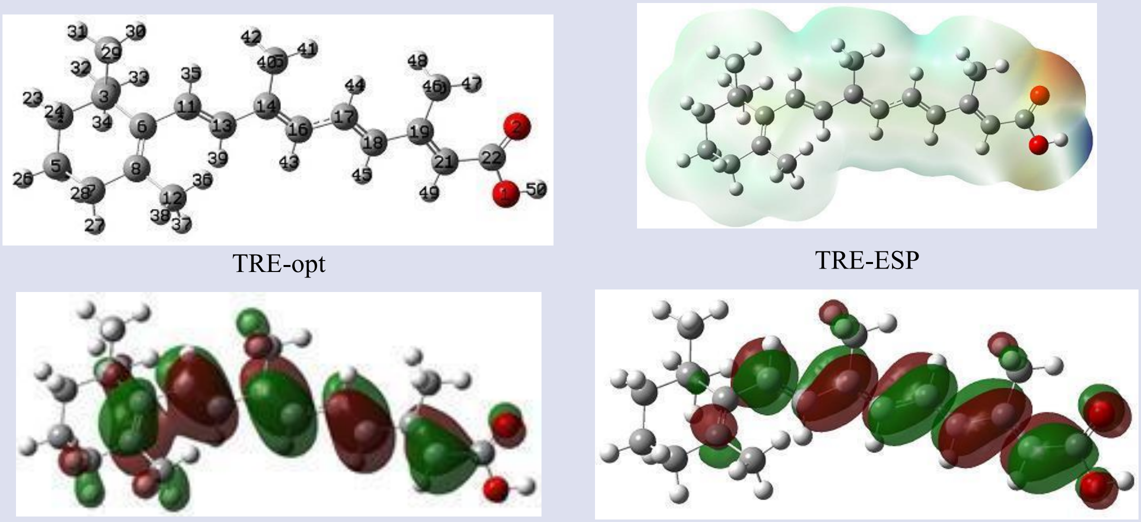
The optimized form with atomic number of TRE and Al-CNT and HOMO, LUMO and electrostatic potential (ESP) shape of TRE calculated at M062X level with 6-31G(d) basis set with the generated via Gauss view 5.0 [19] for gas environment are represented in Fig.1. Besides the percentage composition of atoms to HOMO and LUMO for TRE are given in Table 1 in gas, water and n-octanol environment.

Table 1. Contribution of atoms orbitals to HOMO andLUMO for TRE in gas, water and n-octanol environment

Atoms	Gas	Water	n-octanol	Atoms	Gas	Water	n-octanol
	HOMO (eV)				LUMO (eV)		
C6	4.76	5.59	5.47	O2	4.74	4.99	5.02
C8	9.04	10.14	9.96	C8	2.44	2.42	2.45
C11	14.18	13.91	13.97	C11	10.07	9.62	9.57
C13	7.40	8.12	8.02	C13	2.82	2.45	2.41
C14	11.31	10.40	10.53	C14	12.74	12.58	12.55
C16	14.61	15.00	14.96	C16	5.86	5.06	4.96
C17	5.46	4.58	4.69	C17	13.96	14.46	14.50
C18	13.90	13.68	13.72	C18	11.47	10.49	10.34
C21	9.96	9.17	9.27	C19	11.44	12.67	12.82
				C21	13.46	13.18	13.12
				C22	6.09	6.99	7.11

HOMO of the TRE consist of mainly C6, C8, C11, C13, C14, C16, C17, C18, C21 atoms of TRE for gas, water and n-octanol form. The contributios of these atoms as a percentage are 4.76, 9.04, 14.18, 7.40, 11.31, 14.61, 5.46, 13.90, 9.96 in gas environment. The contributios of these atoms change due to the media used. As seen in Table 1. LUMO of the TRE consist of mainly O2, C8, C11, C13, C14, C16, C17, C18, C19, C21 and C22 atoms of TRE for gas, water and n-octanol form. The contributios of these atoms as a percentage are 4.74, 2.44, 10.07, 2.82, 12.74, 5.86, 13.96, 11.47, 11.44, 13.46, 6.09. The contributios of these atoms changes due to the media used as seen in Table 1.

The theoretical basis of the molecular electrostatic potential (ESP), which has been widely used for predicting nucleophilic and electrophilic sites and for the mode of molecular recognition, is that molecules always approach each other in a complementary manner. ESP on TRE van der Waals (vdW) surface for the gas environment is given in Fig.1. The molecular structure of TRE and surface extrema, which pink and green spheres correspond to minima and maxima, respectively, are given in Figure 2.



TRE-opt TRE-ESP

TRE-HOMO TRE-LUMO

Figure 1. HOMO, LUMO and ESP shape of TRE and optimized form of TRE

The number of surface maxima and minima for TRE in a gas environment is 24 and 20. A minimum of 20 (-34.02 kcal/mol) of TRE is the global minimum on the surface for the gas environment (Figure 2). This large negative value is due to the lone pair of oxygen in the carbonyl group for gas, n-octanol and water environments. Maximum energy for gas, n-octanol and water environment 47.79, 50.66 and 51.13 kcal/mol, respectively (Table 2). The global maximum arises from a hydroxyl group's positively charged H atom.

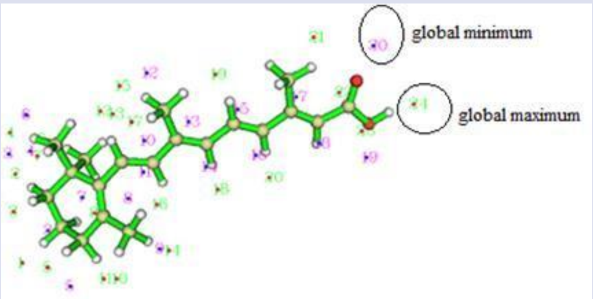


Figure 2. Molecular structure and surface extrema for TRE in gas environment (pink and green spheres correspond to maxima and minima)

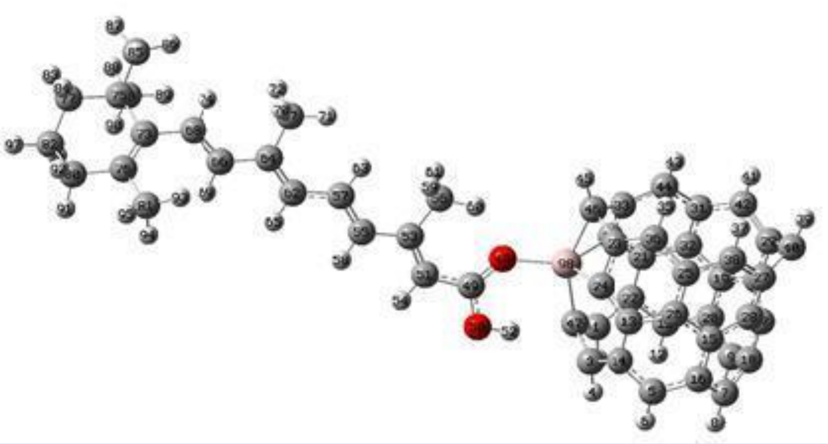
Summary of surface analysis of TRE global minimum (Gmin) and global maximum (Gmax) energy values are given in Table 2 with the surface maxima and minima for gas, n-octanol and water environment. Surface analysis was evaluated according to Volume (V) in Bohr^3 unit, Overall surface area (OSA), Positive surface area (PSA), Negative surface area (NSA) in Bohr^2 unit, Overall average value (OAV), Positive average value (PAV) Negative average value (NAV) in kcal/mol unit, Overall variance (OV), Positive variance (PV), Negative variance (NV) in (kcal/mol)^2 unit, Balance of charges (BC) in miu unit, Product of and Miu (PSM) in (kcal/mol)^2 unit, Internal charge separation (ICS) in kcal/mol unit.

Table 2. Summary of surface analysis of TRE

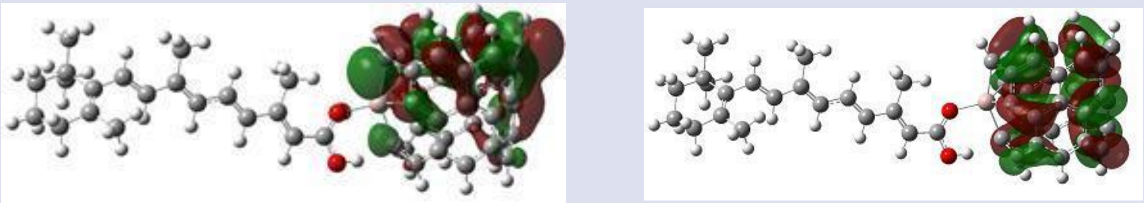
Properties	Gas	n-octanol	Water
V	2852.57	2848.67	2848.00
OSA	1366.40	1364.96	1364.65
PSA	881.93	881.45	880.95
NSA	484.47	483.51	483.71
OAV	1.23	1.28	1.28
PAV	6.66	7.50	7.65
NAV	-8.64	-10.05	-10.32
OV	100.52	125.08	129.28
PV	34.93	39.26	40.18
NV	65.59	85.82	89.10
BC	0.23	0.22	0.21
PSM	22.79	26.94	27.69
ICS	7.08	8.09	8.28
Gmin	-34.02	-38.90	-39.67
Gmax	47.79	50.66	51.13

As seen from Table 2, the summarized values change with the change in the environment. The results show that the presence of a solvent lowers the Global minimum value of TRE and increases the Global maximum value of TRE. The order of Gmin according to medium for TRE is gas>n-octanol>water. However, the order of Gmax according to medium for TRE is gas<n-octanol<water.

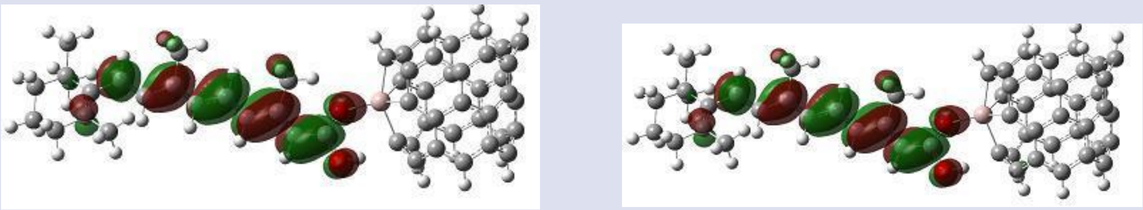
HOMO, LUMO and ESP shape and the optimized form with an atomic number of complex calculated at M062X level with 6-31G(d) basis set with the generated via Gauss view 5.0 for the gas environment are represented in Fig.3. Besides the percentage composition of atoms to HOMO and LUMO for the complex are given in Table 3 in gas, water and n-octanol environment. HOMO and LUMO are given as α-HOMO, β-HOMO, α-LUMO, and β-LUMO due to the spin multiplicity of the complex is 2. As seen from the Table 3, the contribution of atoms to α-HOMO, β-HOMO are different. α-HOMO consist of C17, C24, C27, C29, C34, C36, C38, C40, C42, C44 and C46 atoms belonging to Al-CNT, β-HOMO consist of C1, C3, C7, C9, C13, C15, C19, C21, C28, C30, C36, C38, C42, C44 atoms belonging to Al-CNT, but the contribution to β-HOMO is made by atoms other than those contributing to the α-HOMO.



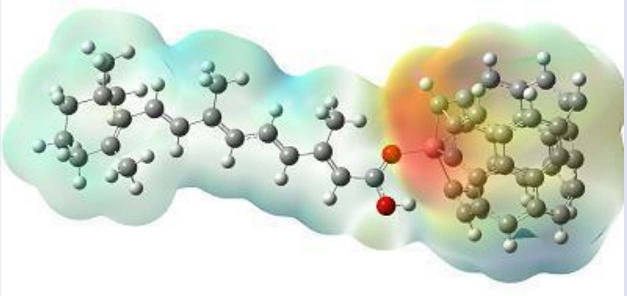
Al-CNT/TRE-opt



α-HOMO β-HOMO



α-LUMO β-LUMO



Al-CNT/TRE-ESP

Figure 3. α-HOMO, β-HOMO, α-LUMO, and β-LUMO and ESP shape of complex and optimized form of complex

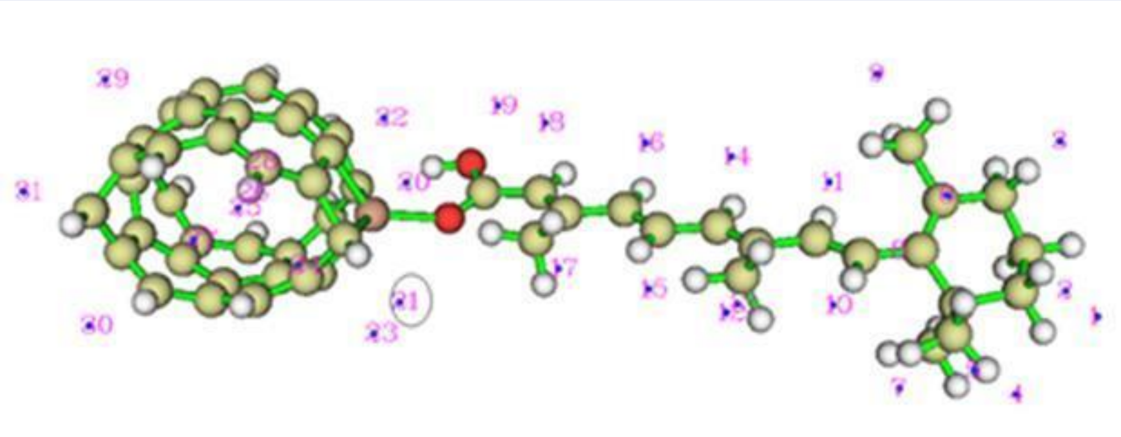
Table 3.Percentage contribution of atoms orbitals to HOMO and LUMO for Al-CNT/TRE complex in gas, water and n-octanol form

Atoms	Gas	Wat	n-oct		Gas	Wat	n-oct		Gas	Wat	n-oct	Gas	Wat	n-oct
	α-HOMO				β-HOMO				α-LUMO			β-LUMO		
C17	3.1	3.4	3.3	C1	3.7	3.7	3.6	C1		4.1	4.9		9.2	10.4
C24	4.6	4.7	4.7	C3	3.1	3.5	3.4	C3		4.1	4.9		8.9	10.1
C27	4.5	4.6	4.6	C7	6.4	6.3	6.3	C5		3.8	4.6		8.4	9.5
C29	3.0	3.3	3.2	C9	5.9	6.1	6.1	C7		3.0	3.6		6.9	7.8
C34	4.5	4.9	4.8	C13	7.0	6.6	6.7	C9		3.2	3.9		7.4	8.2
C36	6.5	7.4	7.2	C15	4.8	4.8	4.8	C11		3.9	4.7		8.8	9.8
C38	25.3	27.6	27.1	C19	5.1	4.9	4.9							
C40	6.5	7.1	7.0	C21	7.4	6.7	6.9	O48	4,7	3.6	3.4	4.7	2.1	
C42	4.5	4.6	4.6	C28	4.7	5.0	4.9	C49	12,3	11.1	10.2	12.3	6.7	5.6
C44	12.8	8.4	9.4	C30	4.7	5.0	5.0	O50	3,3	2.8	2.5	3.3		
C46	4.4	3.4	3.6	C36	7.7	7.2	7.3	C51	10.0	6.6	6.2	9.9	3.8	3.3
Al98	4.39	3.37	3.58	C38	5.4	5.6	5.5	C53	16,8	14.1	13.1	16.7	8.5	7.1
				C42	5.5	5.6	5.6	C55	7,0	4.2	4.0	7.0	2.4	
				C44	7.5	7.1	7.2	C57	15,4	11.9	11.1	15.4	7.1	6.0
								C64	11,5	8.4	7.9	11.4	5.0	
								C68	7,7	5.5	5.1	7.7	3.2	

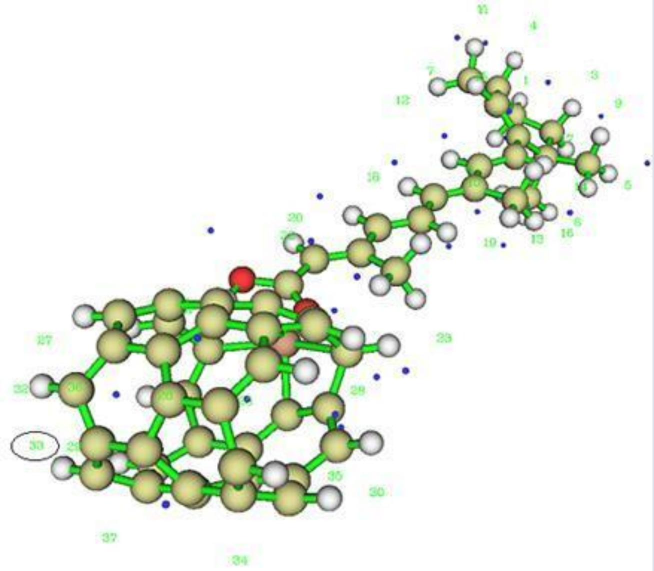
A summary of surface analysis of Al-CNT/TRE complex global minimum (Gmin) and global maximum (Gmax) energy value is given in Table 4 with the surface maxima and minima number for gas, n-octanol and water environment. The number of surface minima and maxima for complexes in gas environments is 21 and 33. The complex's minimum 21 (-36.37, -49.59, and -53.34 kcal/mol) is the global minimum on the surface for gas, n-octanol and water environment (Figure 4 and Table 4).

This large negative value is due to the lone pair of oxygen in the carbonyl group for gas, n-octanol and water environments. Maximum energy for gas, n-octanol and water environment 28.88, 41.76 and 45.45 kcal/mol, respectively. The global maximum arises from the positively charged H atom belonging to Al-CNT.

The results show that the presence of a solvent lowers the Global minimum value of the complex and increases the global maximum value. The order of Gmin, according to the complex, is gas>n-octanol >water. However, The order of Gmax according to medium is gas<n-octanol <water in Table 4.



a-minima



b-maxima

Figure 4. Molecular structure and surface extrema (pink and green spheres correspond to maxima and minima) for complex

Table 4. Summary of surface analysis of Al-CNT/TRE complex

Properties	Gas	n-octanol	Water
V	6038.97	6030.80	6028.96
OSA	2400.99	2401.49	2400.81
PSA	1432.51	1420.81	1413.62
NSA	968.48	980.69	987.19
OAV	0.42	-0.06	-0.23
PAV	9.79	11.96	12.48
NAV	-13.44	-17.49	-18.45
OV	130.73	261.31	305.62
PV	43.01	87.64	104.55
NV	87.72	173.68	201.08
BC	0.22	0.22289574	0.22505901
PS	28.86	58.24	68.78
ICS	11.18	14.23	14.98
Gmin	-36.37	-49.59	-53.34
Gmax	28.88	41.76	45.45

Stability and Energetics

Adsorption energy resulting from the interaction of TRE and Al-CNT in the gas, n-octanol, and water environments is -40.70, -40.36, and -40.65 kcal/mol, and negative adsorption energy indicates that TRE / Al-CNT systems are stable in these environments (Table 5). In addition to the bond lengths and angles, the electronic properties of TRE changed in all three environments with the interaction of the TRE molecule with the Al-CNT.

The Fermi energy, known as the midpoint of the HOMO−LUMO energy gap at a temperature equal to 0 K, is calculated, and The fermi energy of Al-CNT in gas, n-octanol and water environment found as -4.79, -4.87, -4.91 eV. E_{HOMO} of the drug in gas, n-octanol and water environment are -6.570, -6.569, and -6.573 eV. It is likely that electrons are transferred from the TRE drug to the Al-CNT because the Fermi level of the Al-CNT is higher (less negative) than the HOMO energy of the TRE drug. The energy difference between the Fermi level of Al-CNT and the HOMO of the drug acts as the driving force for charge transfer. The driving force increases with the increase of the dielectric constant of the media. TRE is a hydrophobic drug. Since hydrophobic drug molecules try to escape from the aqueous environment in water, they adsorb more easily on CNTs and in n-octanol, hydrophobic interactions with the solvent reduce adsorption on CNTs, so the adsorption energy calculated in the n-octanol environment is lower than the adsorption energy calculated in the water environment. As seen from Table 5, Gibbs free energy in adsorption is negative, indicating a spontaneous process in gas, n-octanol and water environment. The Gibbs free energy for adsorption of TRE on Al-CNTs is more favourable in water than in n-octanol due to the hydrophobic nature of the drug.

Table 5. Adsorption, interaction and deformation energies in terms of Sum of electronic and zero-point Energies, Sum of electronic and thermal Enthalpies, Sum of electronic and thermal Free Energies in Kcal/mol unit for the formation of Al-CNT / TRE complex in gas, water and n-octanol environment, charged values and recovery time (τ) in sec.

Environment		ΔE	ΔH	ΔG	Charge transfer TRE → Al-CNT	$\tau(sec)$
Gas	Eads	-40.70	-40.55	-27.77	0.205888	2.13x1013
	Eads*	-27.31*	-32.61*	-21.20*	0.2113*	1.75x104
	Eint	-37.96	-36.99	-26.16		
	Edef	-2.74	-3.57	-1.61		
n-octanol	Eads	-40.36	-40.25	-27.06	0.23192	1.203x1013
	Eint	-37.31	-36.37	-25.80		
	Edef	-3.05	-3.87	-1.26		
Water	Eads	-40.65	-40.47	-27.65	0.237163	1.961x1013
	Eint	-37.61	-36.62	-26.38		
	Edef	-3.03	-3.84	-1.27		

*Those values calculated for BMSF-BENZ drug adsorption O_{35}/Al-CNT as given in Ref [16].

The adsorption process for TRE drug/Al-CNT complex is in chemisorption nature with higher adsorption energy value in the gas phase of -40.70 kcal/mol (-1.76492 eV) than 1 eV as given in Table 5. Thus, it indicates that the strong interactions between O atom (in TRE) and Al (in CNT) with considerable negative adsorption energy is considered to occur and compared with those obtained from BMSF-BENZ drug/Al-CNT for O_{35}/Al-CNT as -1.184 eV [16].

The more negative the adsorption energy, representing a higher stable system. For drug delivery sensor devices, the adsorption process is expected to negatively value adsorption energy, thus the adsorbent must have a strong interaction with the drug. We have found that O/Al-CNT configuration have more negative adsorption energy than others for both drug. Thus Al-CNT can be used as a drug carrier device [16] because of the high recovery time values which was obtained in vacuum UV light conditions with frequency 3×10^{16} s^{-1} at room temperature in the gas phase have given in Table 5 by

$$\tau = \nu^{-1}\exp(\frac{-E_{ads}}{kT}) \tag{1}$$

Where temperature and the attempt frequency are defined by T in K and $\boldsymbol{\nu}$, respectively. K is Boltzman constant. The desorption time values for TRE(O)/Al-CNT in gas, n-octanol and water are $2.13\text{x}10^{13}$, $1.203\text{x}10^{13}$ and $1.961\text{x}10^{13}$ sec, respectively. Thus, it can be extended as drug delivery system with reasonable recovery times.

Mulliken Charge Analysis

Geometric parameters such as bond length are critical in interpreting drug interactions with nanotubes in drug delivery systems. Table 6 gives some bond lengths and Mulliken charges of free TRE and its complex with Al-CNT for the gas, n-octanol, and water environments. According to the results, some bond lengths of the TRE drug change after interaction with Al-CNT. The bond lengths of C18-C19, C19-C20, C19-C21, C21-H49, C21-C22, C22-O1, O1-H50, and C22-O2 in the molecule TRE are 1.46099 Å, 1.50451 Å, 1.35188 Å, 1.08582 Å, 1.47317 Å, 1.35368 Å, 0.97242 Å, and 1.21193 Å in gas environment and after the interaction Al-CNT with TRE drug change to 1.45620 Å, 1.50510 Å, 1.36067 Å, 1.08500 Å, 1.44729 Å, 1.31498 Å, 0.98973 Å, 1.24848 Å, 1.90598 Å respectively (Table 6).

Table 6. Some Bond lengths and Mulliken charges for TRE and its complex with Al-CNT

	TRE				**Al-CNT / TRE complex**		
	Gas	n-octanol	Water		Gas	n-octanol	Water
Atoms		Bond-Length (Å)		Atoms		Bond-Length (Å)	
C18-C19	1.46099	1.46062	1.46057	C55-C53	1.45620	1.45396	1.45350
C19-C20	1.50451	1.50432	1.50433	C53-C56	1.50510	1.50395	1.50385
C19-C21	1.35188	1.35366	1.35397	C53-C51	1.36067	1.36359	1.36400
C21-H49	1.08582	1.08579	1.08579	C51-H54	1.08500	1.08482	1.08481
C21-C22	1.47317	1.47130	1.47106	C51-C49	1.44729	1.44326	1.44265
C22-O1	1.35368	1.35068	1.35021	C49-O50	1.31498	1.31511	1.31465
O1-H50	0.97242	0.97356	0.97374	O50-H52	0.98973	0.98838	0.98800
C22-O2	1.21193	1.21540	1.21592	C49-O48	1.24848	1.25352	1.25494
				O48-Al98	1.90598	1.89636	1.89584
	Mulliken charges (e)				**Mulliken charges (e)**		
O1	-0.61632	-0.62433	-0.62535	O50	-0.60539	-0.60742	-0.606314
O2	-0.50047	-0.52982	-0.53432	O48	-0.55411	-0.57264	-0.576618
C18	-0.19216	-0.2086	-0.21167	C55	-0.19901	-0.21427	-0.216746
C19	0.174503	0.169024	0.167682	C53	0.180032	0.182693	0.181782
C20	-0.57373	-0.57551	-0.57581	C57	-0.13363	-0.1416	-0.14343
C21	-0.29252	-0.30424	-0.30625	C51	-0.29161	-0.30532	-0.30647
C22	0.589938	0.595185	0.596024	C49	0.671515	0.683415	0.684315
H49	0.176347	0.18552	0.187164	H54	0.1891	0.203317	0.20644
H50	0.430826	0.448969	0.451763	H52	0.472336	0.478688	0.481551
				Al	0.478181	0.468809	0.457716

The bond length of C18-C19, C19-C20, C21-H49, C21-C22, C22-O1 and C22-O2 of molecule TRE in gas environment decreased in n-octanol and water environment, whereas C19-C21, O1-H50 bond length increased. The Mulliken charge of O1, O2, C18, C20, C21, C22 of TRE in gas environment increased in n-octanol and water environment as a negative and H49 and H50 atoms of the TRE increased as a positive. Mulliken charges of these atoms have also changed in the interaction with Al-CNT.

The negative charge on the O1, C20, and C21 atoms in Al-CNT TRE is smaller than that of the bond length, which was 1.21193 in free TRE and increased to 1.24848 in the Al-CNT / TRE complex. This increase is due to the interaction between TRE and the Al-CNT / TRE complex. Free TRE, however, on the O2, C18 atoms in Al-CNT/TRE is larger than that of free TRE. Since aluminium is an electropositive element with lower electronegativity than carbon and oxygen, in Al-CNT, the Al atom offers electron deficient sites that can interact with the oxygen atom of the C=O group and due to the interaction, charge transfer from the carbonyl oxygen to the Al-CNT decreases the electron density around the oxygen, and this means at the same time carbon becomes more electron-deficient. Therefore, the bond between the attached carbonyl carbon groups can gain more electron density, leading to the shortening and strengthening of the C22-O1 and C22-C21 bonds. The bond lengths of C22-O1 and C22-C21 bonds in free TRE are 1.35368 and 1.47317, while they are 1.31498 and 1.44729 in Al-CNT.

Topology Analysis: Quantum Theory of Atoms in Molecules (QTAIM)

The nature of interactions and bonding characteristics between TRE and Al-CNT have been investigated using the QTAIM [20] method, which was employed with the MULTIWFN program [21]. They are obtained in terms of electron densities at bond critical points (BCPs) between two neighbouring atoms [15]. Thus, the topology parameters of QTAIM theory, which are the Lagrangian kinetic energy (GBCP), electron density (ρ_{BCP}), energy density (HBCP), potential energy density (VBCP), Laplacian ($\nabla^2\rho_{BCP}$), $|V_{BCP}|/G_{BCP}$ values of complex in gas, n-octanol, and water environments, are given in Table 7 (they are given in Hartrees).

Table 7. Potential Energy Density, Total Energy Density, Lagrangian Kinetic Energy, Electron Density, Laplacian of $\nabla^2\rho_{BCP}$ of Al-CNT / TRE complex (in a.u units)

Structure	Gas	n-octanol	Water
ρ_{BCP} (a.u)	0.05426	0.05554	0.05572
GBCP (a.u.)	0.08954	0.09286	0.09317
VBCP	-0.08091	-0.08380	-0.08415
HBCP	0.00863	0.00906	0.00902
$\nabla^2\rho_{BCP}$	0.39267	0.40769	0.40874
$|V_{BCP}|/G_{BCP}$	0.90362	0.90243	0.90319

In QTAIM analysis for the studied complex, the electron density of the bond formed by the interaction of TRE and Al-CNT was analyzed to understand this interaction. In this interaction, the electron density in BCP was found to be 0.05426, which means that a moderate electron density can be **s**uitable for controlled release and moderate stability of the drug in the system.

The Lagrangian kinetic energy of the drug complex plays an important role in drug delivery as it affects the system's stability, transport and release dynamics. Table 7 shows the (GBCP)Lagrangian kinetic energy of the Al-CNT/TRE complex at BCP is 0.08954 a.u. (56.19 kcal/mol) in the gas environment and those in the n-octanol and water environment are 0.09286 and 0.09317, indicating that the Lagrangian kinetic energy increases with the increase of the dielectric constant of the solvent.

The energy density values at the BCP, including Potential Energy Density V(r) and Total Energy Density H(r), provide insight into the nature and strength of interactions. A negative VBCP value indicates that the interaction is stabilizing and attractive. VBCP −0.08091 means moderate binding strength, likely due to π-π stacking (Table 7).

HBCP>0 and a negative VBCP value show weak interactions, meaning the drug will be easily released from the carrier. This means that it is beneficial for rapid drug delivery, where you need the drug to be released quickly upon reaching the targetρ_{BCP}, GBCP, VBCP, and HBCP values increase with the increase of the dielectric coefficient of the solvent.

In QTAIM, BCPs also separate attractive (negative $\nabla^2\rho$) and repulsive (positive $\nabla^2\rho$) interactions that are critical for drug binding. The Laplacian reveals regions of electron density accumulation and depletion and helps classify hydrogen bonding, van der Waals interactions, and charge transfer interactions. Positive ($\nabla^2\rho > 0$) → Electron density is locally depleted, e.g., closed-shell interactions like hydrogen bonds, van der Waals forces, ionic interaction $\nabla^2\rho_{BCP}$ values of the complex in gas, n-octanol, and water media are 0.39267, 0.40769, 0.40874 means that suggests a closed-shell interaction (Table 7).

Conclusion

The interaction of TRE with Al-doped carbon nanotubes (Al-CNT) has been thoroughly analyzed at the level of M062X theory and 6-31G(d) basis set in gasi n-octanol and water environments. In this paper, our investigations show that the polarity of solvent has effect in the percentage composition of atoms to HOMO and LUMO, charge transfer interaction energy for TRE and its complex. The adsorption energy found in the n-octanol environment is lower than the adsorption energy in the water environment. The complex can be suitable for controlled release and moderate stability of the drug in the system. Gibbs free energy values indicate that the process is a spontaneous process in gas, n-octanol and water environment. The Gibbs free energy for adsorption of TRE on Al-CNTs is more favorable in water. The results indicate that Al-CNT serves as an effective carrier for TRE, with stable interactions confirmed by adsorption energy calculations and charge transfer analysis. The study provides valuable insights into the molecular-level interactions between the drug and nanotubes, demonstrating how environmental factors, such as solvent type, influence the stability and electronic properties of the complex.

Conflicts of interest

The authors declare that there is no conflict of interest

References

[1] Hazarika N., Acne Vulgaris: New Evidence in Pathogenesis and Future Modalities of Treatment, *Journal of dermatological treatment*, 32(3) (2021) 277-285.

[2] Yoham A.L., Casadesus D., Tretinoin, *In StatPearls [Internet], StatPearls Publishing*: Tampa, FL, USA, (2023).

[3] Schmidt N., Eugene H. G., Tretinoin: a Review of Its Anti-inflammatory Properties in the Treatment of Acne, *The Journal of Clinical and Aesthetic Dermatology*, 4(11) (2011) 22-29.

[4] Sabouri M., Samadi A., Nasrollahi S.A., Farboud E.S., Mirrahimi B., Hassanzadeh H., Kashani M.N., Dinarvand R., Firooz A., Tretinoin Loaded Nanoemulsion for Acne Vulgaris: Fabrication, Physicochemical and Clinical Efficacy Assessments, *Skin Pharmacology and Physiology*, 31 (6) (2018) 316-323.

[5] Thielitz A., Abdel-Naser M. B., Fluhr J. W., Zouboulis C. C., Gollnick H., Topical Retinoids in Acne–an Evidence-based Overview, *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, 6(12) (2008) 1023-1031.

[6] Amidouche D., Montassier P., Poelman M. C., Duchêne, D., Evaluation by Laser Doppler Velocimetry of The Attenuation of Tretinoin Induced Skin Irritation by β-cyclodextrin Complexation, *International Journal of Pharmaceutics*, 111(2) (1994) 111-116.

[7] Naseri N., Valizadeh H., Zakeri-Milani P., Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application, *Advanced Pharmaceutical Bulletin*, 5(3) (2015) 305.

[8] Falcocchio S., Ruiz C., Pastor F. J., Saso L., Diaz P., Propionibacterium Acnes GehA Lipase, an Enzyme Involved in Acne Development, can be Successfully Inhibited by Defined Natural Substances, *Journal of Molecular Catalysis B: Enzymatic*, 40 (3-4) (2006) 132-137.

[9] Ghadamgahi M., Ajloo D., Molecular Dynamic Insight into the Ethanol Effect on Tretinoin Drug Delivery Through Carbon Nanotubes, *Journal of Nanostructure in Chemistry*, 4 (2014) 1-11.

[10] Chen Q., Wang Q., Liu Y. C., Wu T., Kang Y., Moore J. D., Gubbins K. E., Energetics Investigation on Encapsulation of Protein/Peptide Drugs in Carbon Nanotubes, *The Journal of Chemical Physics*, 131 (1) (2009).

[11] Bianco A., Kostarelos K., Prato M., Applications of Carbon Nanotubes in Drug Delivery, *Current Opinion in Chemical Biology*, 9 (6) (2005) 674-679.

[12] Hariharan P. C., Pople J. A., The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies, *Theoretica Chimica Ccta*, 28(3) (1973) 213-222.

[13] Sayiner H. S., Kandemirli F., Dalgic S. S., Monajjemi M., Mollaamin F., Carbazochrome Carbon Nanotube as Drug Delivery Nanocarrier for Anti-bleeding Drug: Quantum Chemical Study, *Journal of Molecular Modeling*, 28 (1) (2022) 11.

[14] Al-Sawaff Z. H., Dalgic S. S., Kandemirli F., Monajjemi M., Mollaamin F., DFT Study Adsorption of Hydroxychloroquine for Treatment COVID-19 by SiC Nanotube and Al, Si Doping on Carbon Nanotube Surface: A Drug Delivery Simulation, *Russian Journal of Physical Chemistry A,* 96 (13) (2022) 2953-2966.

[15] Dalgic S. S., Al-Sawaff Z. H., Dalgic S., Kandemirli, F., A Comparative DFT Study on Al-and Si-doped Single-Wall Carbon Nanotubes (SWCNTs) for Ribavirin Drug Sensing and Detection, *Materials Science in Semiconductor Processing*, 158 (2023) 107360.

[16] Al-Sawaff Z. H., Dalgic S. S., Kandemirli F., Theoretical study of the adsorption of BMSF-BENZ drug for osteoporosis disease treatment on Al-doped carbon nanotubes (Al-CNT) as a drug vehicle, *European Journal of Chemistry* , 12 (3) (2021) 314-322.

[17] Dalgic Senturk S, Burucu DK, Dalgic S, Kandemirli F., A comparative DFT study on the interaction of Aldara drug molecule with SiC and Si-carbon nanotubes, *Journal of Applied Physics*, 137 (3) (2025) 135104.

[18] Tomasi J., Mennucci B., Cammi R., Quantum Mechanical Continuum Solvation Models, *Chemical Reviews*, 105 (8) (2005) 2999-3094.

[19] Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E. Et al., Gaussian 09, Gaussian Inc., Wallingford, (2013).

[20] [20] Bader R.F.W., Atoms in molecules, *Accounts of Chemical Research*., 18 (1985) 9–15.

[21] [21] Lu T., Chen F., Multiwfn: a multifunctional wave function analyser, *Journal of Computational Chemistry*, 33 (2012) 580–592.