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Spectroscopic Analyses of Modified Fulleropyrrolidine Derivatives

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Abstract: Fullerene (C_{60}) is enhanced with pyrrolidine group to produce fulleropyrrolidine which is considered as one of the most important derivatives of fullerene. Fulleropyrrolidine is further modified in order to enhance its solubility which in turn could enhance its biological applications. Accordingly this work is dedicated to modify fulleropyrrolidine carbodithioic acid as NO_2 group introduced at meta position.

Quantitative structure–activity relationship models (QSAR) was utilized to evaluate the biological activates of the investigated compounds through some descriptors. Later on chalcogenide could be subtitled in order to form three derivative groups. The QSAR descriptors were compared with the QSAR of the parent compound. Results indicate that, NO_2 group enhances the biological activity.

Keywords: Fullerene (C_{60}), fulleropyrrolidine, molecular modeling, PM3, QSAR.

1. INTRODUCTION

Fullerenes are the famous member of the so called allotropes of carbon beside diamond, graphite, amorphous carbon. The carbon allotropes formed at the nano scale are the fullerenes. The fullerenes family involves a wide variety of mass number from 60 up to 290, for example: C_{60}, C_{70}, C_{76}, C_{80}, C_{84}, C_{94}, C_{120}, C_{130}, C_{140}, C_{180}, C_{228}, C_{240} and C_{540} [1,2]. There are different shapes of fullerene family. These are spherical fullerene (buckyball), ellipsoidal fullerenes, elongated cylindrical carbon nano tubes, and planar graphene [2]. The highest symmetry and stability member in fullerenes isC_{60} [3].The fullerene-based system is considered as the most abundant representative member of the fullerene family. In 1970, the existence of $C_{60}$was proposed as nanospheres formed by 60 carbon atoms [4]. While in 1985, the method to synthesize a fullerene C_{60} in arc-discharged carbon-soot in laboratory was discovered by Kroto and his teamwork researchers [5]. These researchers won the Nobel Prize in Chemistry in 1996 [6]. Later C_{60} was found in various natural environments, like in rocks and in space [7, 8]. C_{60} is an aromatic structure with a soccer-ball-like shape and also known as buckyball or buckminsterfullerene [3]. It has fused rings of 12 pentagonal rings with 20 hexagonal ones [5] with 7.065 Å diameter [9]. As a result of the distinctive and effective characteristics of C_{60} several technological applications of fullerene-based (C_{60}) derivatives are predicted and discovered in physics and biology. Fullerene-based derivatives could be divided into three groups: endohedral compounds, exohedral compounds and hetero fullerenes [10]. Superconductors, sensors, catalysts, optical and electronic devices, polymer composites, and high-energy fuels are considered as the physical applications of fullerene based system C_{60} [11]. The electronic and physical properties of fullerene-based derivatives are studied to understand the behavior and application of its derivatives [12-16]. Due to the fact that C_{60} is an aromatic structure with a soccer-ball-like shape, it is insoluble in water or biological systems. So it requires optimization for its physicochemical properties to increase the potentialities of its biological activities [17, 18]. These fullerene-based derivatives are aimed to increase its solubility and bioactivity *via* maximizing low toxicity and advantageous adsorption, distribution, metabolism and elimination properties. The water-soluble fullerene-based derivatives are particularly important for many biological applications [19-27].

The molecular modeling and Computer aided-drug design plays an essential role in the field of drug design and discovery of best compounds which have good inhibition or treatment properties [28, 29]. The computer aided-drug design consists of quantitative structure activity relationship (QSAR) and docking techniques [30, 31]. This technique saves time, money and allows the study of the properties of a large set of compounds in order to choose the best.

The functionality of fulleropyrrolidine is considered as the most important and famous water-soluble fullerene-based derivative which has been used for numerous biological applications [32-35]. In the present study the molecular modeling techniques were used to calculate the QSAR properties for modified fulleropyrrolidine derivatives. This

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calculation was performed at PM3 semi-empirical level of theory.

2. COMPUTATIONAL DETAILS

The SCIGRESS molecular modeling software was used to build the investigated compounds [36]. The geometries of the suggested compounds were defined by performing geometry optimization calculations using MO-G at PM3 level of theory. Then depending on the optimized compounds, the electronic and QSAR properties are calculated. These calculations were performed by SCIGRESS molecular modeling software.

3. RESULTS AND DISCUSSION

"In a previous study, the QSAR calculations were performed at PM3 for some fullerene derivatives with substituent function groups (NH_2, NHMe, OH, OMe, F, Cl, CO_2Me, COMe, CN and NO_2) at ortho, meta, or para positions relative to the methylene group at position no. 1 as seen in Fig. (**1**)" [12]. Depending on these calculated QSAR properties, the fullerene derivative with NO_2 group at meta position is biologically more active than the rest of the derivatives, as it had the highest dipole moment value (5.853 Debye) and the lowest log p value (10.15) [12]. In this study some modifications have been introduced to the fullerene derivative with NO_2 group at meta position. These

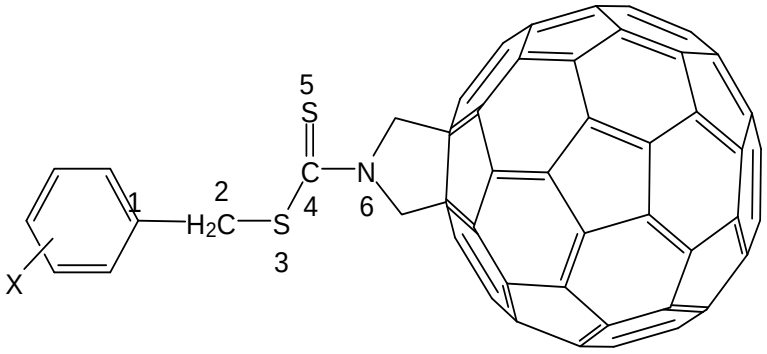

Fig. (1). Structure of [C_{60}] fulleropyrrolidine-1-carbodithioic acid 2; 3 and 4-substituted-benzyl esters molecules [12].

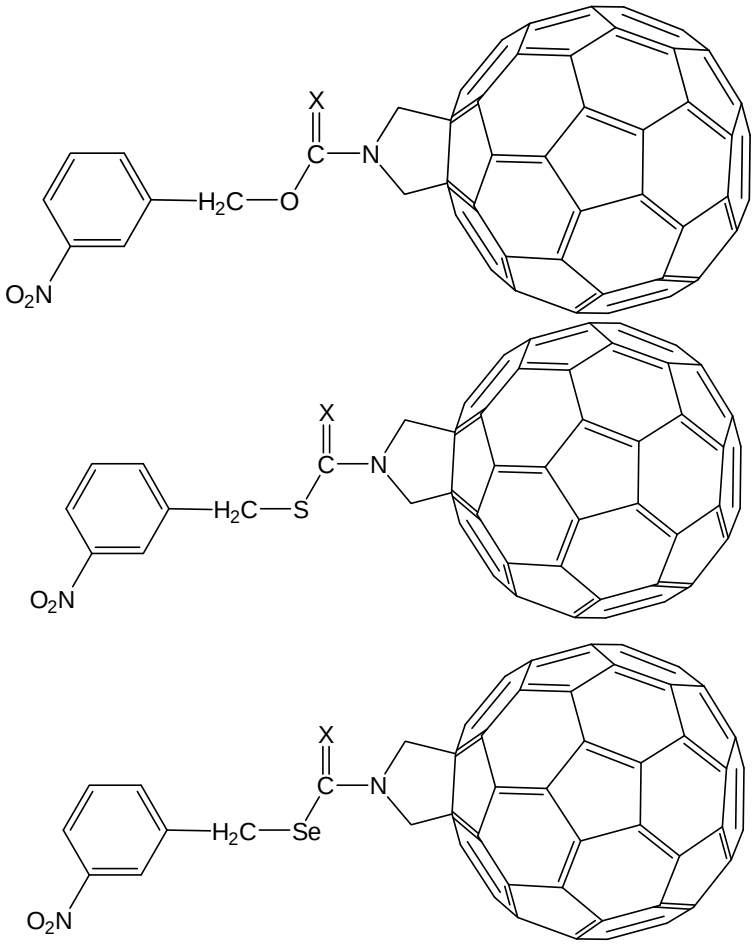

Fig. (2). The general structure of studied compounds with NO_2 group at meta position, X atom is O, S or Se.

modifications were made by adding the O, S or Se atom at position no. 3 in Fig. (**1**). to form three derivative groups. Each group has O, S or Se atom at position no. 5 in Fig. (**1**).to form three compounds in each derivative group. These suggested compounds are represented in Fig. (**2**). The QSAR properties of the investigated compounds are calculated at PM3 method then compared with the QSAR properties of the suggested parent compounds at PM3 level. These parent compounds are the suggested compound without NO_2 group as shown in Fig. (**3**).

The calculated QSAR parameters are: total energy, heat of formation, dipole moment, ΔE (LUMO–HOMO energy difference), ionization potential, log p, surface area and volume. Table **1** shows some calculated QSAR properties of suggested three derivatives groups with NO_2 group at meta position. As shown in Table **1**, the oxygen compounds in each group have the lowest total energy (-9919.69 eV, -9811.86 eV and -9821.98 eV for O, S and Se derivatives groups respectively). The most stable compound is oxygen compound in O derivatives group (-9919.69 eV). The calculated heat of formation is listed in Table **1**. In natural and stable states of compound, the heat of formation is known as the needed change in enthalpy to form one mole of a compound from its elements under standard conditions of one atmosphere at a given temperature. The oxygen compounds in all group derivatives have low heat of formation. These values are 719.35 Kcal/mol, 770.92 Kcal/mol and 740.32 Kcal/mol for O, S and Se group derivatives respectively.

The parameter which indicates the reactivity of compounds with the surrounding system is the dipole moment. From Table **1**, the dipole moment of selenium compounds in all three derivatives groups is high. These compounds are more reactive with surrounding systems and the selenium compound in Se derivatives group has the most reactivity (the highest dipole moment value 6.52 Debye). The sulfur compounds in O and Se derivative groups have the lowest reactivity because they have the lowest dipole moment values (3.86 Debye and 2.89 Debye for O and Se derivatives group respectively). ΔE is the Frontier molecular orbital energy gap and equal to the LUMO–HOMO energy difference. The smaller the frontier molecular orbital energy gap (ΔE) of the molecule, the more the reactivity of the compound. The selenium compounds in all three derivatives groups have low ΔE value. These ΔE values are 5.73 eV, 5.68 eV and 5.82 eV for O, S and Se derivatives groups respectively. The ionization potential is the electron detachment energy from the molecule to a practically infinite distance. The oxygen compounds in each group can remove easily the electron and interact with the other system. This is because these compounds have lower ionization potential values (nearly equal to -9.3 eV). Log p is considered as

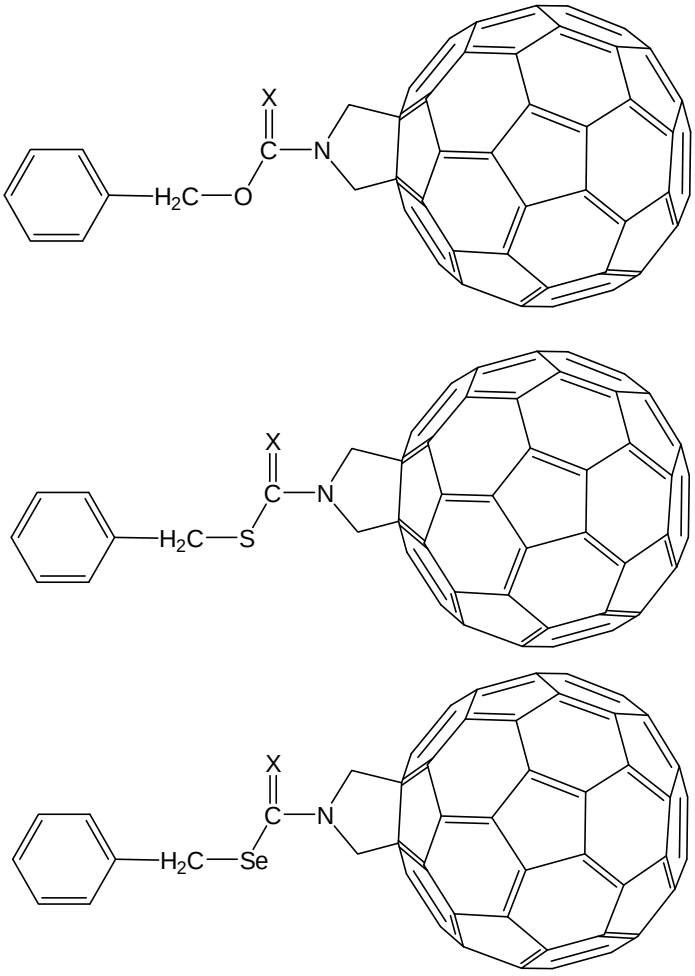

Fig. (3). The general structure of studied parent compounds, X atom is O, S or Se.

indicator to the solubility of compounds. The negative value of log p indicates that the compound is hydrophilic and the positive value indicates that the compound is hydrophobic. The fullerene C_{60} is hydrophobic while the suggested compounds make modification in the hydrophobicity of fullerene C_{60}. The oxygen compounds in each group are low hydrophobic (10.65, 10.99 and 10.52 for O, S and Se derivatives groups respectively) and may be favored in biological and medical applications. The final QSAR parameters in this study are surface area and volume which are listed in Table **1**. In periodic table, the atomic number of elements in the same group increases as move from top to bottom. Accordingly the volume and size of selenium is larger than sulfur and oxygen. From Table **1**, in the same derivatives group, the surface area and volume of selenium compound is larger than sulfur compound then comes oxygen compound. In addition to the surface area and volume of the compounds selenium derivatives group are larger than that in sulfur derivatives group and oxygen derivatives group.

Table 1. Some of the calculated QSAR properties of the suggested compounds with NO_2 group at meta position according to PM3 method.

	Total energy [eV]	Heat of formation [kcal/mol]	Dipole moment [Debye]	ΔE [eV]	Ionization potential [eV]	Log P	Surface Area [A^2]	Volume [A^3]
O derivatives group								
O	-9919.69	719.35	4.04	6.37	-9.31	10.65	560.85	645.56
S	-9810.77	795.97	3.86	6.26	-9.31	12.30	569.06	663.65
Se	-9820.46	775.37	4.52	5.73	-8.81	11.92	569.35	668.19
S derivatives group								
O	-9811.86	770.92	4.16	6.37	-9.32	10.99	572.04	661.87
S	-9703.36	838.02	5.03	6.22	-9.28	12.64	577.01	677.30
Se	-9713.02	818.14	6.15	5.68	-8.78	12.26	577.47	683.85
Se derivatives group								
O	-9821.98	740.32	4.48	6.37	-9.26	10.52	577.01	665.69
S	-9713.49	807.15	2.89	6.10	-9.12	12.18	580.90	684.38
Se	-9722.77	796.04	6.52	5.82	-8.94	11.79	579.85	692.24

Table 2. Some of the calculated QSAR properties of the suggested parent compounds according to PM3 method.

	Total energy [eV]	Heat of formation [kcal/mol]	Dipole moment [Debye]	ΔE [eV]	Ionization potential [eV]	Log P	Surface Area [A^2]	Volume [A^3]
O derivatives group								
O	-9188.28	727.99	1.91	6.36	-9.24	10.69	542.97	631.90
S	-9079.37	804.69	3.28	6.05	-9.02	12.35	551.45	650.24
Se	-9089.04	784.45	3.71	5.50	-8.50	11.96	551.60	654.25
S derivatives group								
O	-9080.47	779.19	1.89	6.36	-9.23	11.04	553.6	648.52
S	-8971.95	846.74	2.47	6.03	-9.01	12.69	558.86	664.05
Se	-8981.59	827.32	3.21	5.46	-8.47	12.31	558.86	670.16
Se derivatives group								
O	-9090.62	748.08	2.33	6.36	-9.23	10.57	551.26	653.51
S	-8982.11	815.28	2.60	5.83	-8.81	12.22	562.25	670.36
Se	-8991.34	805.33	3.16	5.61	-8.65	11.84	561.47	678.06

Table **2** represents the QSAR parameters of suggested parent compounds. These parent compounds are without NO_2 function group. The first parameter in Table **2** is the total energy. The oxygen compounds in all derivatives groups have lower total energy and are more stable. The total energy of oxygen compounds in O, S and Se derivatives groups are equal to -9188.28 eV, -9080.47 eV and -9090.62 eV respectively. The heat of formation of oxygen compounds of all derivatives groups is lower than that of rest compounds. The heat of formation of oxygen compounds are 727.99 Kcal/mol, 779.19 Kcal/mol and 748.08 Kcal/mol for O, S and Se derivatives groups respectively. The Se compounds in three derivatives groups are highly reactive with the surrounding systems because they have high value of dipole moment and low value of frontier molecular orbital energy gap (ΔE). From Table **2**, the values of dipole moment of selenium compounds are 3.71 Debye, 3.21 Debye and 3.16 Debye for O, S and Se derivatives groups respectively. The ΔE value of selenium compounds are 5.50 eV, 5.46 eV and 5.61 eV for O, S and Se derivatives group respectively. As the ionization potential is low, the molecule can easily remove an electron. The ionization potential of parent compounds is listed in Table **2**. The compounds which have low values of ionization potential are oxygen compounds in all derivatives groups (-9.24 eV for O derivatives group and -9.23 eV for S and Se derivatives groups). From log p values in Table **2**, also the oxygen compounds in all derivatives groups are low hydrophobic (10.69, 11.04 and 10.57 for O, S and Se derivatives groups respectively). The surface area and volume of parent compounds behave in the same manner of the surface area and volume of compounds with NO_2 group at the meta position. In the same derivatives groups, the surface area and volume of selenium compound is larger than sulfur compound then comes the oxygen compound. Also the surface area and volume of the compounds of selenium derivatives group are larger than in sulfur derivative group then oxygen derivatives group. While the surface area and volume of compounds with NO_2 group at meta position are larger than that of parent compounds due to the addition and presence of NO_2 group.

CONCLUSION AND GENERAL REMARKS

The two compound families (parent compounds and compounds with NO_2 group at meta position) have the similar behavior in many of electronic and QSAR properties as follow:

As a general conclusion some points could be mentioned as in the following, (a) The oxygen compounds in all derivatives groups of parent compounds as well as compounds with NO_2 group at meta position are more stable (low total energy and heat of formation), easily remove electron (low ionization potential) and low of hydrophobic properties (low log p). (b) The selenium compounds in all derivatives groups of parent compounds and compounds with NO_2 group at meta position are more reactive (high dipole moment and low ΔE).

Spatially, (a) the oxygen compounds in O derivatives group of parent compounds and compounds with NO_2 group at meta position are the most stable (lowest total energy and heat of formation). (b) The oxygen compounds in Se derivatives group of parent compounds and compounds with NO_2 group at meta position are the lowest hydrophobic (lowest log p).(c) The selenium compound in Se derivatives group of compounds with NO_2 group at meta position is the most reactive (highest dipole moment), while the selenium compound in O derivatives group of parent compounds is the most reactive (highest dipole moment). (d) The oxygen compound in S derivatives group of compounds with NO_2 group at meta position is the most easily to remove electron (lowest ionization potential), while the oxygen compound in O derivatives group of parent compounds is the most easily to remove electron (lowest ionization potential). Finally, the addition of NO_2 group to the suggested compounds causes the enhancement of the biological activity (i.e. the compounds with NO_2 group at meta position have lower total energy, heat of formation, ΔE, ionization potential and log p and higher dipole moment than those of parent compounds).Computational work offers valuable spectral, physical and structural data for many systems and molecules. These findings are in good agreement with previous findings [37-39].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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