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Original Article

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Investigation of Chemical Properties in Fullerene Derivatives of Fluoxetine Drug : A DFT Study

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Abstract

In this research at the first fluoxetine drug and its fullerene derivative were optimized. NBO calculations and NMR for the complexes were carried out at the B3LYP/6-31G*quantum chemistry level. Different parameters such as energy levels, the amount of Chemical Shift in different atoms, the amount of HOMO/LUMO, chemical potential (μ), chemical hardness (η), Thermodynamic Properties was determined and the coefficients of hybrid bonds (π, σ) and the orbital portion of the bonds p (π, σ) was performed. In another part, the core and the valence electrons of atoms were compared. This drug as a major therapeutic category is antidepressant drug. In this study of fullerenes, we used nano drug carriers. The data in tables and graphs and shapes were compared and discussed.

Keywords: Fluoxetine, Fullerenes, Chemical potential, Nano drug carriers.

1. Introduction

Nanostructures can be categorized into following forms according to their structures: diamonds with sp^3 hybridization, Graphite with sp^2 hybridization, Hexagonal diamonds with sp^3 hybridization, fullerenes with SP^2 hybridization, Nanoparticles, Graphene, single-layer and multi-layer nanotubes, Crystal Nanostructures. All these forms of nanostructures produce unique Pharmaceutical and

electronic properties. Graphenes have a two-dimensional structure of a single layer of carbon chicken wire [1-5]. A fullerene is any molecule composed of carbon in the form of a hollow sphere, ellipsoid, tube, and many other shapes. Spherical fullerenes are also called Bucky balls, and they resemble the balls used in football (soccer). Cylindrical ones are called carbon nanotubes or Bucky tubes. Fullerenes are similar in structure to graphite, which is composed of stacked Graphene sheets of linked hexagonal rings; but they may also contain pentagonal (or sometimes heptagonal) rings. The first fullerene molecule to be discovered, and the family's namesake, buckminsterfullerene (C_{60}), was prepared in 1985 by Richard Smalley, Robert Curl, James Heath, Sean O'Brien, and Harold Kroto at Rice University. The discovery of fullerenes greatly expanded the number of known carbon allotropes, which until recently were limited to graphite, diamond, and amorphous carbon such as soot and charcoal. Buckyballs and buckytubes have been the subject of intense research, both for their unique chemistry and for their technological applications, especially in materials science, electronics, and nanotechnology. Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Fluoxetine was first documented in 1974 by scientists from Eli Lilly and Company [6]. It was approved by the U.S. Food and Drug Administration for the treatment of major depressive disorder in December 1987 [7]. Fluoxetine is used for the treatment of major depressive disorder (including pediatric depression), obsessive-compulsive disorder (in both adults and children), bulimia nervosa, panic disorder and premenstrual dysphoric disorder [9]. In addition, fluoxetine is used to treat trichotillomania if cognitive behavior therapy has been un successful [10]. Fluoxetine's mechanism of action is predominantly that of a serotonin reuptake inhibitor [11-12]. Fluoxetine delays the reuptake of serotonin, resulting in serotonin persisting longer when it is released. Fluoxetine may also produce some of its effects via its weak 5-HT2C receptor antagonist effects [13]. In addition, fluoxetine has been found to act as an agonist of the σ1-receptor, with a potency greater than that of citalopram but less than that of fluvoxamine. However, the significance of this property is not fully clear [14-15]. Fluoxetine also functions as a channel blocker of anoctamin 1, a calcium-activated chloride channel.

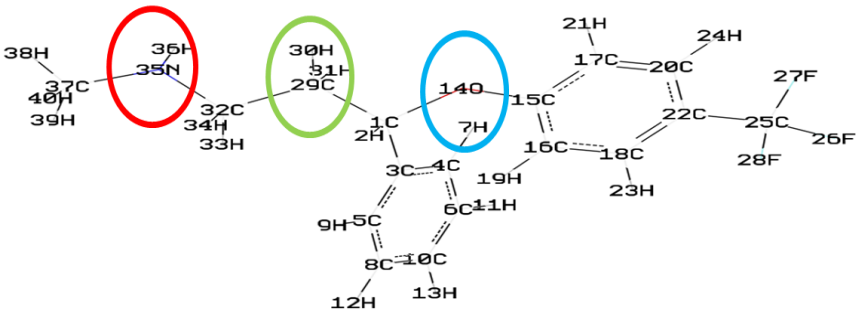

Fig 1. View of Fluoxetine alone and location of connectable (C37, C32, C29) to Fullerene and shown briefly FS.

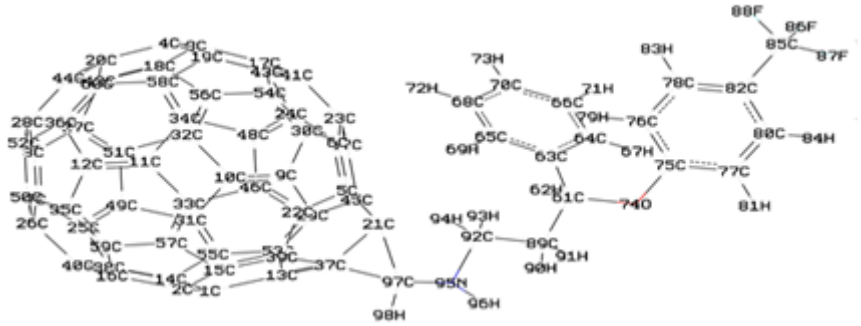

Fig 2. View of Nano-drug Fluoxetine has been obtained from carbon connection of Fluoxetine C37 to Fullerene and shown briefly FFS (1).

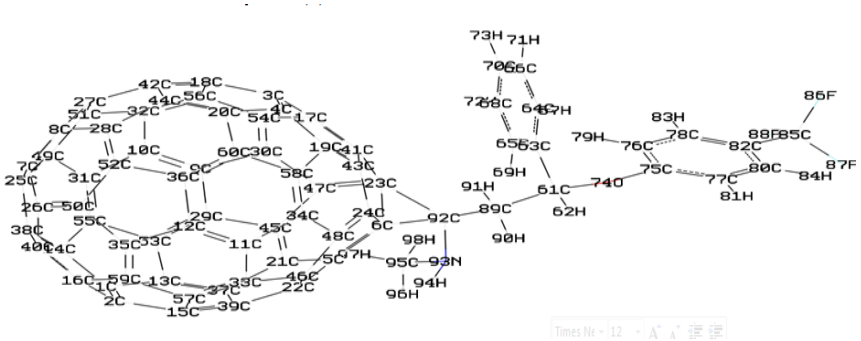

Fig 3. View of Nano-drug Fluoxetine has been obtained from carbon connection of Fluoxetine C32 to Fullerene and shown briefly FFS (2).

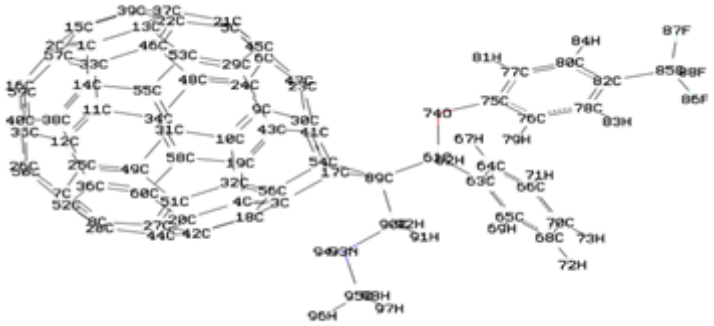

Fig 4. View of Nano-drug Fluoxetine has been obtained from carbon connection of Fluoxetine C29 to Fullerene and shown briefly FFS (3).

2. Computational details

All Computations are performed by means of GAUSSIAN 03 packing [9]. Geometries for all compounds are computed by means of the density functional theory (DFT) with Becke's three-parameter functional (B3) plus Lee, Yang, and Parr (LYP) correlation functional. For all atoms, the standard 6-31G basis set is utilized. The structures of Fluoxetine on Fullerene were designed primarily using of Gauss View 5.0.8 and nanotube modeler 1.3.0.3 soft wares. The interaction effects of Fluoxetine on Fullerene were investigated

through attachment to three different base positions. All these calculations are done under the assumption of standard state of gas phase, pressure of 1 atmosphere, and temperature of 25 degrees centigrade. The calculations are performed, using a Pentium 4 PC with a Windows 7 OS and a Core i5 processor.

3. Results

In this study, fluoxetine drug and its 3 fullerene derivatives investigated. The related structures are named in the following way:

NO	Symbol	Mater
1	FS	Fluoxetine
2	FFS (1)	Nano-drug from binding of Fluoxetine C37 to Fullerene
3	FFS (2)	Nano-drug from binding of Fluoxetine C32 to Fullerene
4	FFS (3)	Nano-drug from binding of Fluoxetine C29 to Fullerene

The results showed that the calculated energy gap is typically much higher of the Fluoxetine than Fluoxetine attached to Fullerene in each three connection is different and the other hand the amount of that in each three Fluoxetine binds to Fullerene to connection forms is different and mostly the same compared with the accuracy of thousands FS> FFS (2)> FFS (1)> FFS (3) (Fig5).

Table 1. Values of energies of the frontier molecular orbitals (ε_{HOMO} and ε_{LUMO}, eV), Electronic chemical potential, μ (eV), Chemical hardness, η (eV), calculated at the B3LYP/6-31G (d) level of theory.

Compound	LUMO (a.u)	HOMO (a.u)	Energy Gap LUMO – HOMO	Dipole moment	Chemical hardness	Chemical potential
FS	0.11693	-0.33913	0.45606	5.8517	0.22803	-0.111085
FFS(1)	-0.01511	-0.28742	0.27231	1.9267	0.136155	-0.15125
FFS(2)	-0.01481	-0.28721	0.2724	2.3388	0.1362	-0.151
FFS(3)	-0.01398	-0.28545	0.27147	5.5197	0.135735	0.14975

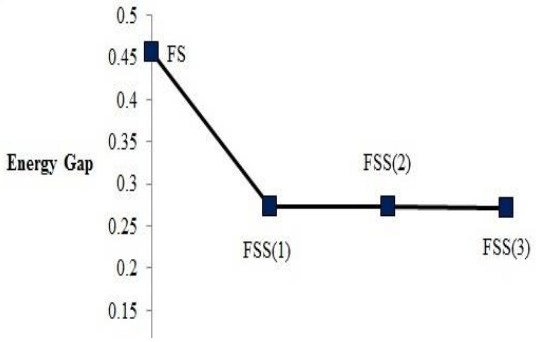

Fig 5. Results of the survey molecular orbital energy levels of the drug and three Fullerene derivative in B3LYP/6-31 level

Since most of the weight is composed of water and water is a polar solvent, so the amount and the process of the change in dipole moment in Nano-drugs and Fluoxetine in free mode is also important .the results showed that the minimum value of dipole moment in order first is related to FFS (1) next FFS (2) and next is Nano-drug and difference amount of dipole moment between Fluoxetine and Nano-drug (3) is little. In total

the dipole moment Fluoxetine alone is higher than the other combinations. So we expect that when Fluoxetine arrived our body than other three combinations easily in water that is a polar solvent dissolved and has more solubility so after Fluoxetine FFS (3) has a dipole moment higher and higher solubility (Fig 6).

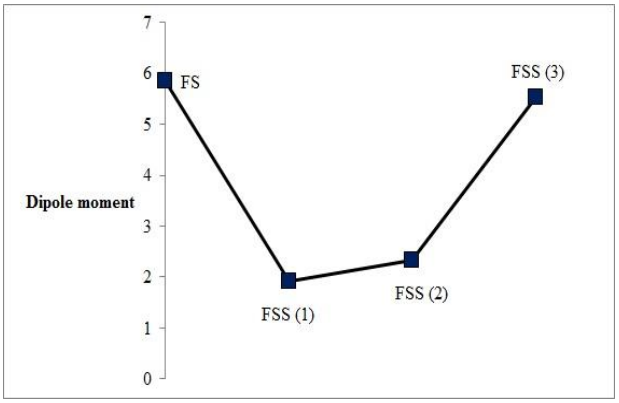

Fig 6. The amount of dipole moment in FS, FFS (1), FFS (2), FFS (3) is calculated in B3LYP/6-31 level.

Chemical hardness indicate the measurement of the stability of the material as much as chemical hardness is more electron transfer from HOMO to LUMO is harder and consequently system reactivity decrease .In comparison whit chemical hardness among Fluoxetine and three combination of Nano-drug . We resulted like energy gap that chemical hardness is more than three other combination in the other hand Nano-drug has indicate chemical hardness can be finer species and changes in the density of the electron can occur more easily the more difficult chemical hardness is less reactive species is better and chemical hardness FFS (3) is the minimum (Fig 7).

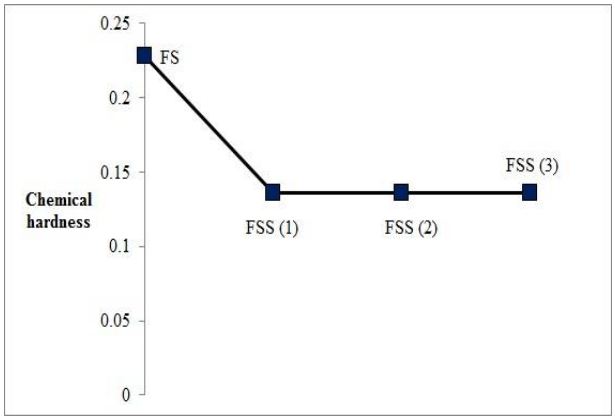

Fig 7. Result obtained from chemical hardness in FFS (3), FFS (2), FFS (1), FS is calculated in B3LYP/6-31 level.

Negative chemical potential is a symbol of system stability. The calculated results showed that the chemical potential Nano-drug 1,2 and that is the same and the lowest and then is a chemical potential, the calculated

highest value of the chemical potential allocate to Nano-drug 3 the more chemical potential the more reaction molecular or in the other words that type is more reactive (Fig 8).

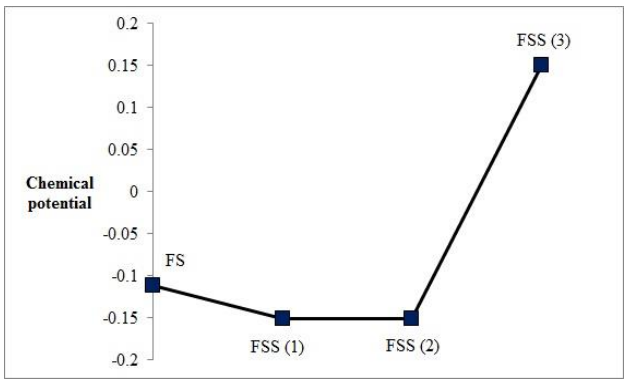

Fig 8. The result of survey of the chemical potential of Fluoxetine and its Fullerene derivatives.

The results of the study of natural charge of oxygen atoms in order from Fluoxetine to Nano-drugs has decreasing trend and the Lowest value is related to FFS (3). The valence electron set on the similar oxygen atoms in order from Fluoxetine to derivatives Fullerene that has decreasing trend and the minimum amount of isotropic is FFS (2) and the maximum occupancy is related to FFS (3) so oxygen FFS (3) Lewis is stronger (Fig 9).

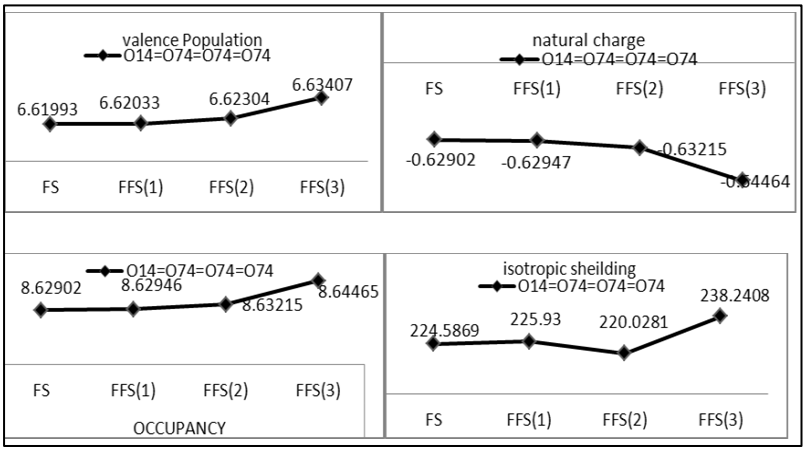

Fig 9. The comparison chart of natural charge , the number of valence electrons, covering factor and occupancy of similar oxygen atoms in the Fluoxetine, the combination of 1, 2, 3 Nano- drug in level B3LYP/6-31 level.

According to the survey Carried out calculation the natural charge of N in FS in order is higher than FFS (1), FFS (3), FFS (2) the process about valence electrons, which acts as reverse the natural charge is evident, so valence electrons of FFS (2) is higher. Occupation number follow such process and the nature of nitrogen can be discussed (Fig 10).

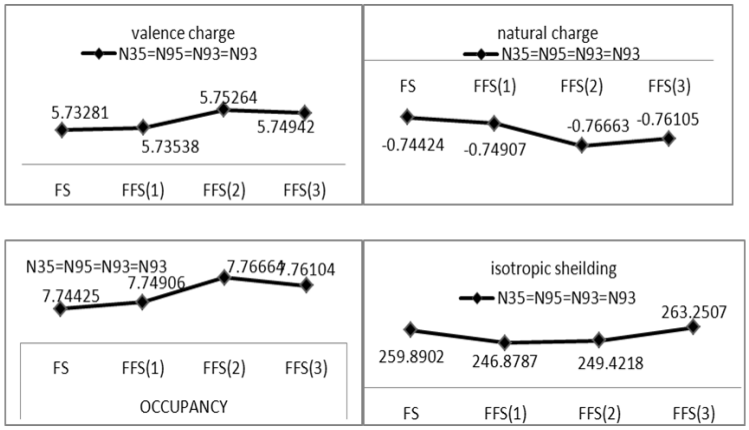

Fig 10. The comparison chart of natural charge ,the covering factor and occupancy of similar nitrogen atoms in Fluoxetine , the combination of 1,2,3 Nano- drug in level B3LYP/6-31 level.

Current ring creates a magnetic field perpendicular to the ring and the effect of H ring outside circle of caused more chemical shift for H, consequently reduce the amount of covering factor. Survey results of the calculations show that among of derivatives Fullerene Fluoxetine the most negative value of NICS is related to FFS (3) so the Hydrogen of ring 1 in FFS (3) has more chemical shift then this Hydrogen are better than others that participate in electrophilic substitution reaction (Table 2).

Table 2. Amount of NICS (ppm)

Parameters	NICS					
	0.0	0.5	1.0	1.5	2.0	Distance
FS	bq41	bq42	bq43	bq44	bq45	Ring1
	-8.4497	-11.267	-12.069	-8.7903	-5.4811	
	bq46	bq47	bq48	bq49	bq50	Ring2
	-9.6516	-11.796	-12.002	-8.6211	-5.3703	
FFS(1)	bq99	bq100	bq101	bq102	bq103	Ring1
	-8.3443	-11.167	-11.982	-8.7146	-5.4144	
	bq104	bq105	bq106	bq107	bq108	Ring2
	-9.6208	-11.762	-11.958	-8.569	-5.3146	
FFS(2)	bq99	bq100	bq101	bq102	bq103	Ring1
	-8.4082	-11.202	-11.945	-8.6737	-5.4227	
	bq104	bq105	bq106	bq107	bq108	Ring2
	-9.5546	-11.716	-11.935	-8.5752	-5.3492	
FFS(3)	bq99	bq100	bq101	bq102	bq103	Ring1
	-8.3148	-11.295	-12.191	-8.9783	-5.727	
	bq104	bq105	bq106	bq107	bq108	Ring2
	-9.8344	-12.092	-12.365	-8.9695	-5.6926	

4. Survey of the Thermodynamics

The value obtained of Thermodynamics indicate that preparation of Nano - drug reaction is a reaction heat retention and Do not be spontaneously and we need to changing conditions and precise control (Table 3).

Table 3. Thermodynamics properties

Compound	ΔG	ΔE	ΔH	ΔS	K
FFS(1)	1.194022	1.171297	1.170341	-49.721	0.999518183
FFS(2)	1.20973	1.187335	1.186379	-49.027	0.999511846
FFS(3)	1.217618	1.193244	1.192288	-53.192	0.999508664

The relate of bond length and orbital p participation show that Whenever orbital p participation increase bond length is increased.

Table 4. Bond length and orbital p participation

Bond	compound	B3LYP/6-31g*	Occupancy	Orbital p participation
N35=H36	FS	σ=0.8357(sp^2.85)N35 +0.5492(s)H36	1.98723	1.1908725
N95=H96	FFS(1)	σ=0.8420(sp^2.69)N95 +0.5395(s)H96	1.98721	1.13249
N93=H94	FFS(2)	σ=0.8431(sp^2.62)N93 +0.5377(s)H94	1.98680	1.104461
N93=H94	FFS(3)	σ=0.8380(sp^2.90)N93 +0.5457(s)H94	1.98650	1.2151
N35=C37	FS	σ=0.7776(sp^2.13)N35 +0.6288(sp^3.06)C37	1.99307	1.790208
N95=C97	FFS(1)	σ=0.7657(sp^2.01)N95 +0.6432(sp^2.99)C97	1.98576	1.7311125
N93=C95	FFS(2)	σ=0.7849(sp^1.91)N93 +0.6197(sp^3.17)C95	1.99277	1.731804
N93=C95	FFS(3)	σ=0.7809(sp^2.17)N93 +0.6246(sp^3.14)C95	1.99199	1.8278985
C32=N35	FS	σ=0.6328(sp^3.18)C32 +0.7743(sp^2.09)N35	1.98979	1.8152955
C92=N95	FFS(1)	σ=0.6235(sp^3.28)C92 +0.7818(sp^1.98)N95	1.98882	1.796522
C92=N93	FFS(2)	σ=0.6414(sp^3.16)C92 +0.7672(sp^1.80)N93	1.98475	1.703892
C90=N93	FFS(3)	σ=0.6328(sp^3.28)C90 +0.7743(sp^2.15)N93	1.98965	1.8701645
O14=C15	FS	σ=0.8226(sp^1.92)O14 +0.5686(sp^3.02)C15	1.99159	1.648282
O74=C75	FFS(1)	σ=0.8230(sp^1.92)O74 +0.5680(sp^3.04)C75	1.99157	1.62344
O74=C75	FFS(2)	σ=0.8232(sp^1.90)O74 +0.5678(sp^3.04)C75	1.99144	1.645096
O74=C75	FFS(3)	σ=0.8231(sp^2.00)O74 +0.5679(sp^3.06)C75	1.9899	1.691987
C1=O14	FS	σ=0.5480(sp^4.54)c1 +0.8365(sp^2.12)o14	1.98871	2.13065
C61=O74	FFS(1)	σ=0.8357(sp^4.49)c61 +(-0.5492)(sp^2.13)O74	0.02762	1.2912485
C61=O74	FFS(2)	σ=0.8364(sp^4.63)c61 +(-0.5481)(sp^2.16)O74	0.02802	1.344318
C61=O74	FFS(3)	σ=0.5520(sp^4.45)c61 +0.8338(sp^2.24)O74	1.98289	2.162056

Table 5. Bond length (Angstrom)

Bond	FS	FFS (1)	FFS (2)	FFS (3)
N-H36	0.99757	0.99577	0.99343	0.9989
C1-O	1.44648	1.44497	1.45009	1.43977
O-C15	1.36671	1.36815	1.3678	1.37759
C37-N	1.45125	1.43563	1.44942	1.45741
N-C32	1.45308	1.45489	1.44356	1.45594

5. Conclusion:

Computational Quantum Mechanics at the theory level of B3LYP/6-31G on the structure of Fullerene and Fullerene Derivatives of Fluoxetine drug was done separately and only when the structure of Fluoxetine was attached to Fullerene and the results of this computation can be classified as follows:

- The investigation of all the parameters show that the attachment of Fluoxetine structure to Fullerene structure will influence the energy levels and dipole moment changes and these changes are able to be investigated in the electrical and chemical parameters of Fullerene Derivatives structure.
- The results showed that energy gap of FS is the highest and FFS (3) is the lowest. It should be noted that conductivity of FFS (3) is the highest and FS is the lowest.
- Chemical potential of FFS (3) is more than FS and after of them is FFS (1) and (2).
- Chemical hardness of FS is the highest and the lowest value is related to FFS (3).
- Dipole moment of FS is first and FFS (3) is the second.
- Bond length in FFS (3) in each bond is the most but bond of C1 and O in FFS (2) is the most.

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