



# Quantum Chemical Studies on Molecular Structure and Reactivity Descriptors of A Series of Trimethyltetrathiafulvalene Functionalized by Conjugated Substituent

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## ABSTRACT

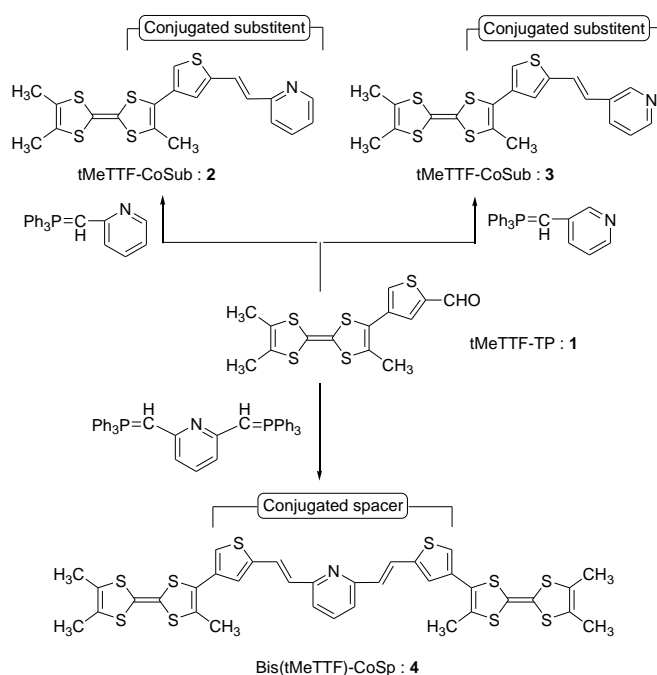
The principal objective of this work was to study the molecular structure and chemical reactivity (electronic affinity,  $A$ ; ionization potential,  $I$ ; electronegativity,  $\chi$ ; hardness,  $\eta$ ; electrophilicity,  $\omega$ ; Fukui functions) of some trimethyltetrathiafulvalene functionalized by conjugated substituent employing the density functional theory (DFT) method. The electronic properties, such as excitation energies, HOMO and LUMO energies were performed which confirms the charge transfer of the molecules. Molecular electrostatic potential has also been computed. The chemometric methods PCA and HCA were employed to find the subset of variables that could correctly classify the compounds according to their reactivity. The theoretical results are valuable for providing a reliable insight into the molecular properties.

## 1. Introduction

In density functional theory (DFT), electron density is the key quantity determining the properties of a molecular system. Electron density is always positive and its value constitutes a fundamental descriptor. However, chemical reactivity of a molecule cannot be described by its electron density alone, because the course of a reaction is rather determined by its response toward different perturbations caused by an approaching reagent. Sensitivities of an electron density toward structural modifications and its responses to changes in external potential and conditions are actually more important in reflecting the reactivity of the corresponding system, than its absolute values. The reactivity descriptors derived from conceptual density functional theory (DFT) have recently been the foci of organic chemistry researchers as a tool to describe global and/or local reactivity in molecules [1-3]. The descriptors are defined in terms of general chemical parameters like ionization potential ( $I$ ), electron affinity ( $A$ ), electronegativity ( $\chi$ ), hardness ( $\eta$ ), chemical potential ( $\mu$ ), electrophilicity index ( $\omega$ ) and local reactivity descriptors such as Fukui function and local hardness [4-7]. Recently the bond strength of metal and ligand has been evaluated with the help of reactivity descriptors [8, 9]. The global parameters help understanding the behavior of a system and lead to applicable and useful principles [10]. In order to have the convenient evaluations and synthetic usefulness for a number of compounds with range of properties for variable applications and vast exploitation, there is need to evaluate his structural, spectral and his reactivity. Using quantum chemical calculations these aspects have been evaluated. The molecular electrostatic potential (MEP) and electronic descriptors are used for the chemical reactivity descriptions of molecule. Evaluation of chemical reactivity finds their suitability to react and give new class of compounds suiting pharmacological activities and material applications. In this work, the objective is to perform a detailed calculation of the molecular structure and chemical reactivity of some functionalized trimethyltetrathiafulvalene.

## 2. Experimental Methods

All computational calculations have been performed on personal computer using the Gaussian 09W program packages developed by Frisch and coworkers. The Becke's three parameter hybrid functional using the LYP correlation functional (B3LYP), one of the most robust functional of the hybrid family, was herein used for all the calculations, with 6.31G (d, p) basis set. Gaussian output files were visualized by means of GAUSSIAN VIEW 05 software. Principal component analysis (PCA) and Hierarchical cluster analysis (HCA) are two chemometric methods were performed using software XLSTAT.



**Scheme 1** Synthetic route for tMeTTF substituted molecules (1-4)

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### 3. Result and Discussion

In our previous work [11], we have described the synthesis of new series of trimethyltetrafulvalene functionalized by conjugated substituent **1-4** indicated in Scheme 1. The synthesis of these electron donors was carried out using a Wittig type condensation [12, 13] involving the tMeTTF-thiophenecarboxaldehyde **1** and an appropriate phosphonium ylide (Scheme 1). The later was generated in situ in refluxing acetonitrile in presence of an excess of triethylamine and of the corresponding phosphonium salt, respectively: the triphenyl(2-pyridylmethyl) phosphonium chloride (one equivalent for **2**), the triphenyl(3-pyridylmethyl)phosphonium chloride (1 equiv. for **3**) and the triphenyl(2,6-pyridylmethyl)phosphonium dichloride (0.5 equiv. for **4**).

#### 3.1 Molecular Geometry

The geometric parameters of title compounds **1-4** were optimized with B3LYP method at 6-31G(d,p) level. No solvent corrections were made with these calculations. The computations were converged upon a true energy minimum, which were supported by the absence of imaginary frequencies. The chemical structure of compounds **1-4** are shown in Scheme 1 and the final optimized molecular structures of compounds in accordance with the atom numbering scheme were shown in Fig. 1. The optimized energy for compounds varies between -76681.5 eV and -67677.5 eV, which indicate that this compounds were stable. Based on these, some structural parameters such as bond distances, bond angles and dihedral angles have been calculated. From the optimized geometries, various molecular properties such as energy of highest occupied molecular orbital ( $E_{\text{HOMO}}$ ) and the lowest unoccupied molecular orbital ( $E_{\text{LUMO}}$ ), energy gap  $\Delta E_{\text{gap}}$ , ionization potential (I), electron affinity (A) and global reactivity parameters were also calculated to analyze the reactivity of title molecules. The optimized geometrical parameters, namely Bond length, Bond Angles and dihedral angles calculated with 6-31G(d,p) basis set were listed in Tables 1-4.

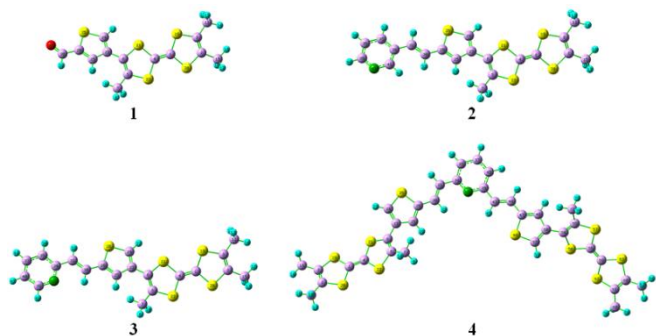


Fig. 1 Optimized molecular structure of tMeTTF substituted molecules (**1-4**)

Table 1 Optimized geometric parameters of compound (**1**)

Compound 1				
Bond Length(Å)	Bond Angles (°)		Dihedral Angles (°)	
R(5,6)	1.35	A(2,3,11)	127.97	D(6,5,7,9) 07.30
R(1,4)	1.35	A(1,4,21)	123.68	D(3,2,20,1) 07.89
R(2,3)	1.34	A(5,6,21)	116.98	D(4,1,20,2) 168.11
R(7,8)	1.10	A(7,5,22)	115.64	D(1,4,21,6) 164.56
R(3,11)	1.50	A(19,1,20)	113.02	D(22,5,7,8) 67.04
R(6,21)	1.79	A(11,3,19)	115.02	D(5,6,23,25) 44.69
R(4,21)	1.78	A(15,2,20)	115.01	D(11,3,19,1) 173.21
R(26,28)	1.75	A(21,6,23)	115.69	D(2,3,11,12) 115.78
R(24,26)	1.72	A(3,11,12)	111.19	D(20,2,15,18) 65.22
R(28,30)	1.46	A(23,24,26)	113.35	D(19,3,11,14) 174.00
R(23,24)	1.38	A(24,23,25)	110.88	D(21,6,23,24) 44.41
R(25,28)	1.38	A(16,15,17)	107.80	D(25,28,30,31) 179.61
R(30,31)	1.22	A(13,11,14)	107.78	D(27,24,26,28) 179.53
R(11,12)	1.10	A(12,11,13)	107.36	D(24,26,28,30) 179.17
R(15,16)	1.09	A(17,15,18)	107.35	D(29,25,28,26) 177.55

Table 2 Optimized geometric parameters of compound (**2**)

Compound 2				
Bond Length(Å)	Bond Angles (°)		Dihedral Angles (°)	
R(5,6)	1.35	A(6,5,7)	127.63	D(6,5,7,9) 06.33
R(1,4)	1.35	A(8,7,10)	107.27	D(3,2,20,1) 08.07
R(2,3)	1.34	A(1,19,3)	95.58	D(22,5,7,8) 66.33
R(7,8)	1.10	A(2,3,11)	127.94	D(6,5,7,10) 126.36
R(4,21)	1.78	A(4,1,20)	123.61	D(5,6,21,4) 09.46
R(3,11)	1.50	A(1,4,22)	123.60	D(1,4,21,6) 165.40

R(11,12)	1.10	A(4,1,19)	123.42	D(7,5,22,4)	169.22
R(37,41)	1.09	A(5,6,21)	116.91	D(4,1,20,2)	167.81
R(15,16)	1.09	A(7,5,22)	115.58	D(2,3,11,12)	115.62
R(40,43)	1.09	A(9,7,10)	108.16	D(21,4,22,5)	16.05
R(24,27)	1.08	A(6,23,25)	124.94	D(20,1,19,3)	13.12
R(26,28)	1.76	A(3,11,14)	111.42	D(3,2,15,17)	124.57
R(35,37)	1.39	A(16,15,18)	108.01	D(5,6,23,25)	44.26
R(23,24)	1.38	A(13,11,14)	107.78	D(20,2,15,18)	65.16
R(30,31)	1.35	A(12,11,13)	107.34	D(19,3,11,14)	173.78

Table 3 Optimized geometric parameters of compound (**3**)

Compound 3					
Bond Length(Å)	Bond Angles (°)		Dihedral Angles (°)		
R(7,8)	1.10	A(5,7,9)	110.89	D(6,5,7,9)	6.17
R(7,9)	1.09	A(3,2,15)	127.96	D(7,5,6,23)	03.16
R(2,15)	1.50	A(5,6,23)	127.47	D(3,2,20,1)	08.02
R(6,23)	1.47	A(1,19,3)	95.59	D(5,6,21,4)	09.58
R(6,21)	1.79	A(9,7,10)	108.14	D(4,1,20,2)	167.87
R(1,19)	1.78	A(5,6,21)	116.92	D(1,4,21,6)	165.14
R(26,28)	1.76	A(7,5,22)	115.59	D(6,5,7,10)	126.18
R(24,26)	1.73	A(19,1,20)	112.98	D(7,5,22,4)	169.05
R(31,34)	1.46	A(2,15,16)	111.41	D(22,5,7,8)	66.16
R(28,30)	1.45	A(28,25,29)	122.31	D(20,1,19,3)	13.04
R(23,25)	1.43	A(36,38,40)	120.66	D(21,4,22,5)	16.27
R(34,35)	1.41	A(34,35,36)	119.87	D(11,3,19,1)	173.07
R(35,36)	1.39	A(13,11,14)	107.78	D(5,6,23,25)	44.39
R(23,24)	1.38	A(35,36,38)	118.51	D(20,1,4,21)	178.79
R(24,27)	1.08	A(24,26,28)	91.75	D(2,3,11,12)	115.62

Table 4 Optimized geometric parameters of compound (**4**)

Compound 4					
Bond Length(Å)	Bond Angles (°)		Dihedral Angles (°)		
R(1,4)	1.35	A(5,7,8)	111.43	D(6,5,7,9)	7.43
R(2,3)	1.34	A(1,20,2)	95.55	D(22,5,7,8)	67.33
R(7,8)	1.10	A(19,1,20)	112.96	D(7,5,22,4)	168.88
R(5,6)	1.35	A(6,23,25)	125.05	D(4,1,20,2)	167.42
R(3,11)	1.50	A(30,31,34)	123.89	D(1,4,21,6)	164.68
R(6,21)	1.79	A(35,34,36)	121.86	D(6,5,7,10)	127.42
R(4,21)	1.78	A(43,44,46)	119.85	D(21,4,22,5)	16.65
R(23,24)	1.38	A(34,35,37)	118.77	D(3,2,15,16)	04.86
R(47,49)	1.76	A(31,30,32)	117.43	D(11,3,19,1)	172.79
R(28,30)	1.44	A(33,31,34)	115.84	D(3,2,15,17)	124.94
R(34,35)	1.41	A(36,39,43)	114.62	D(20,2,15,18)	65.49
R(37,40)	1.39	A(39,43,44)	126.89	D(21,6,23,24)	42.68
R(25,28)	1.38	A(24,26,28)	91.76	D(6,23,25,28)	178.90
R(40,42)	1.08	A(25,28,26)	109.96	D(62,61,68,71)	53.54
R(52,53)	1.08	A(16,15,17)	107.80	D(63,59,62,61)	13.63

#### 3.2 Molecular Electrostatic Potential

Molecular electrostatic potential has been found to be a very useful tool in the investigation of the correlation between molecular structures with its physicochemical property relationship [14]. The total electron density mapped with molecular electrostatic potential (MEP) surface has been plotted for all compounds **1-4** at the B3LYP/6-31G(d,p) basis set as shown in Fig. 2. The MEP is a useful property to study reactivity given that an approaching electrophile will be attracted to negative regions (where the electron distribution effect is dominant). The different electrostatic potential values of the surface are represented by different colors, the maximum negative region, which preferred site for electrophilic reactive as a show red and yellow region. The importance of MEP lies in the fact that it simultaneously displays molecular size, shape as well as positive, negative and neutral electrostatic potential regions in terms of color grading. The resulting surface simultaneously displays molecular size and shape and electrostatic potential value. Potential increases in the order red < orange < yellow < green < blue, where blue colored area indicates the strongest attraction and red colored area indicates the strongest repulsion. As can be seen from the MEP map of the title molecule, the maximum positive region, which preferred site for nucleophilic reactivity as a show blue region and green represent by zero potentials. In the present work, the calculated result shows that the negative potentials are mainly over the electron negative Oxygen and Nitrogen atoms and positive potential are over the nucleophilic reactive hydrogen atoms. From these results, we can say that the N (Nitrogen) atoms indicate the strongest attraction and O (Oxygen) atoms indicate the strongest repulsion. This result also gives information for the region from where the compound can have intermolecular interaction.

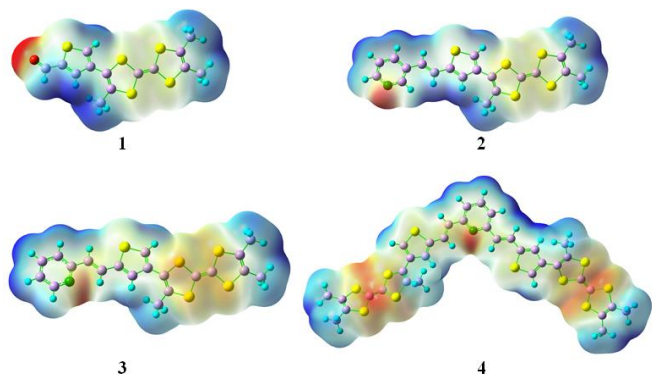


Fig. 2 Molecular electrostatic potential surface of compounds (1-4)

### 3.3 Frontier Molecular Orbitals

Molecular orbitals (MO's) both the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) and their energy gap ( $E_{\text{gap}}$ ) are very useful parameters for quantum chemistry. We can determine the way the molecule interacts with other species; hence, they are called the Frontier molecular orbitals (FMO's). HOMO, which can be thought the outermost orbital containing electrons, tends to act as electron donor. On the other hand, LUMO can be thought the innermost orbital containing free places to accept electrons. To explain several types of reactions and for predicting the most reactive position in conjugated systems, molecular orbital and their properties are used. A molecule having a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity and low kinetic stability [15]. This is also used by the frontier electron density for predicting the most reactive position in  $\pi$ -electron systems and also explains several types of reaction in conjugated system [16]. The conjugated molecules are characterized by a small energy gap, which result a significant degree of intra-molecular charge transfer (ICT) from the end-gapping electron-donor groups to the efficient electron acceptor group through  $\pi$ -conjugated path [17]. Surfaces for the frontier orbitals are drawn to understand the bonding scheme of present compound. The energy is a critical parameter in determining molecular electrical transport properties because it is a measure of electron conductivity, calculated 2.536eV, 2.632eV, 2.618eV and 2.569eV for title molecules. The plot of MO's (HOMO and LUMO) for compounds (4) is shown in Fig. 3 and the energy values are given in Table 5.

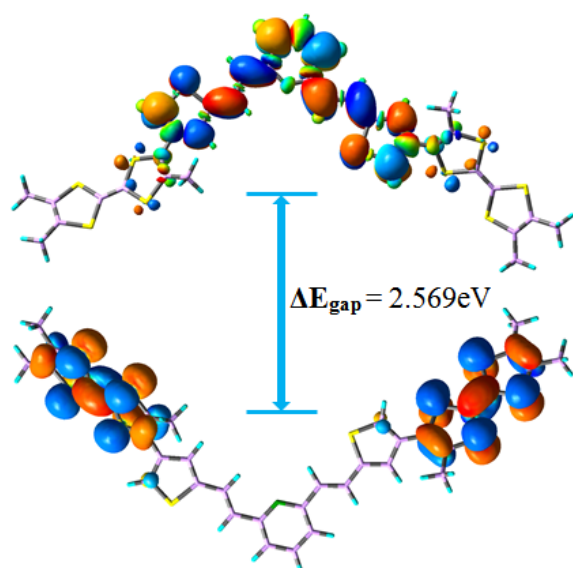


Fig. 3 Highest occupied molecular orbitals and lowest unoccupied molecular orbitals of compounds 4

### 3.4 Global Reactivity Descriptors

As well known, the frontier molecular orbitals (HOMO and LUMO) help to characterize the electron donating and accepting ability. The energy gap between HOMO and LUMO can be used to characterize the molecular chemical stability. In general, a small energy gap means a low excitation energy and it is associated with a high chemical reactivity.

According to the Koopman's theorem, the energies of HOMO and LUMO are directly related to the ionization potential (I) and the electron affinity (A) [18], respectively, which can be expressed as  $I = -E_{\text{HOMO}}$  and  $A = -E_{\text{LUMO}}$ . The chemical potential ( $\mu$ ) and global hardness ( $\eta$ ) [19] can also be expressed by the energy of HOMO and LUMO as  $\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2$  and  $\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2$ . And the global electrophilic index ( $\omega$ ), introduced by Parr et al. [20], was expressed by  $\mu$  and  $\eta$  as  $\omega = \mu^2 / 2\eta$ . These chemical reactivity descriptors were calculated and summarized in Table 5 and 6. The chemical potential ( $\mu$ ) describes the escaping tendency of electrons from a stable system, and the molecule with a negative  $\mu$  is quite stable. The chemical hardness ( $\eta$ ) was correlated with the resistance towards the deformation of electron cloud of chemical systems under small perturbation occurred. A small global hardness means that the compound has a high polarizability.

Table 5 Energetic parameters of tMeTTF substituted molecules (1-4)

Compounds	$E_{\text{HOMO}}$ (eV)	$E_{\text{LUMO}}$ (eV)	$\Delta E_{\text{gap}}$ (eV)	I (eV)	A (eV)
1	-4.635	-2.100	2.536	4.635	2.100
2	-4.436	-1.804	2.632	4.436	1.804
3	-4.493	-1.875	2.618	4.493	1.875
4	-4.445	-1.876	2.569	4.445	1.876

Table 6 Quantum chemical descriptors of tMeTTF substituted molecules (1-4)

Compounds	$\mu$ (eV)	$\chi$ (eV)	$\eta$ (eV)	S(eV)	$\omega$ (eV)
1	-3.367	3.367	1.268	0.394	4.472
2	-3.120	3.120	1.316	0.380	3.699
3	-3.184	3.184	1.309	0.382	3.873
4	-3.161	3.161	1.285	0.389	3.889

The chemical potential  $\mu$  measures the escaping tendency of an electron and it can be associated with the molecular electronegativity then, as  $\mu$  becomes more negative, it is more difficult to lose an electron but easier to gain one. As shown in Table 6, compound 2 is the least stable and the most reactive among all the compounds.

Electronegativity ( $\chi$ ), representing the ability of molecules to attract electrons, The ( $\chi$ ) values displayed in Table 6 shows that compound 1 has higher electronegativity value compared to all the molecules.

Hardness ( $\eta$ ) and softness (S) are a useful concept for understanding the behaviour of chemical systems. A hard molecule has a large energy gap and a soft molecule has a small energy gap. Therefore, soft molecules will be more polarizable than hard molecules. From theoretical calculations established, it was found that the molecule 2 has the highest hardness value ( $\eta = 1.316$  eV), which indicates that is the hardest molecule. The molecules 1 has the highest softness ( $S = 0,394$  eV), so it is the softest molecule.

Electrophilicity ( $\omega$ ), that gives an idea of the stabilization energy when the system gets saturated by electrons which come from the external environment. These reactivity information shows if a molecule is capable of donating charge. A good, more reactive, nucleophile is characterized by a lower value of ( $\omega$ ), while higher values indicate the presence of a good electrophile. Our results indicate that, molecule 2 has lower values of ( $\omega$ ), so that compound is good nucleophile. However molecule 1 is a good electrophile.

### 3.5 Local Reactivity Descriptors

The condensed Fukui functions indices allow us to distinguish each part of the molecule on the basis of its distinct chemical behavior due to the different substituent functional groups. It is known that the Fukui indices were widely used as descriptors of site selectivity for the soft-soft reactions [21]. Parr and Yang proposed that larger value of Fukui function indicate more reactivity [22, 23]. Hence greater the value of condensed Fukui function, the more reactive is the particular atomic centre in the molecule. The  $f_k^+$  measures the changes of density when the molecules gains electrons and it corresponds to reactivity with respect to nucleophilic attack. On the other hand,  $f_k^-$  corresponds to reactivity with respect to electrophilic attack or when the molecule loss electrons. The calculated Fukui functions for the tMeTTF substituted molecules (1-4) are presented in Tables 7 and 8. The Fukui functions can be defined in terms of the ionization potential (I) and the electron affinity (A) which lead to:

$$f^+(r) = \rho_{N+1}(r) - \rho_N(r) \quad \text{For nucleophilic attack}$$

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r) \quad \text{For electrophilic attack}$$

$$f^0(r) = \frac{1}{2}[\rho_{N+1}(r) - \rho_{N-1}(r)] \quad \text{For radical attack}$$

**Table 7** Values of the Fukui function of compounds 1 and 2

Compound 1				Compound 2			
Atom	f <sup>+</sup>	f <sup>-</sup>	f <sup>0</sup>	Atom	f <sup>+</sup>	f <sup>-</sup>	f <sup>0</sup>
1 C	-0.016	0.008	-0.004	1 C	-0.014	0.004	-0.005
2 C	0.002	0.007	0.004	2 C	0.002	0.007	0.004
3 C	0.002	0.007	0.004	3 C	0.002	0.007	0.004
4 C	0.025	0.002	0.013	4 C	0.019	0.006	0.013
5 C	-0.019	0.006	-0.006	5 C	-0.015	0.006	-0.004
6 C	0.009	0.007	0.008	6 C	0.007	0.006	0.007
7 C	-0.048	-0.083	-0.066	7 C	-0.030	-0.082	-0.056
11 C	-0.039	-0.087	-0.063	11 C	-0.028	-0.082	-0.055
15 C	-0.041	-0.087	-0.064	15 C	-0.030	-0.083	-0.056
19 S	-0.042	-0.160	-0.101	19 S	-0.027	-0.152	-0.089
20 S	-0.053	-0.160	-0.107	20 S	-0.037	-0.151	-0.094
21 S	-0.050	-0.160	-0.105	21 S	-0.027	-0.153	-0.090
22 S	-0.083	-0.160	-0.122	22 S	-0.055	-0.158	-0.106
23 C	0.006	0.018	0.012	23 C	0.006	0.013	0.009
24 C	-0.122	-0.009	-0.066	24 C	-0.095	-0.009	-0.052
25 C	-0.090	-0.021	-0.056	25 C	-0.072	-0.012	-0.042
26 S	-0.179	-0.068	-0.123	26 S	-0.122	-0.062	-0.092
28 C	0.021	0.006	0.013	28 C	0.008	-0.003	0.003
30 C	-0.160	-0.033	-0.097	30 C	-0.089	-0.004	-0.047
31 O	-0.122	-0.031	-0.076	31 C	-0.085	-0.023	-0.054
				34 C	-0.014	0.002	-0.006
				35 C	-0.055	-0.015	-0.035
				36 N	-0.029	0.000	-0.014
				37 C	-0.068	-0.019	-0.044
				39 C	-0.059	-0.016	-0.037
				40 C	-0.093	-0.025	-0.059

**Table 8** Values of the Fukui function of compounds 3 and 4

Compound 3				Compound 4			
Atom	f <sup>+</sup>	f <sup>-</sup>	f <sup>0</sup>	Atom	f <sup>+</sup>	f <sup>-</sup>	f <sup>0</sup>
1 C	-0.015	0.005	-0.005	1 C	-0.011	0.008	-0.001
2 C	0.002	0.007	0.004	2 C	0.001	0.004	0.003
3 C	0.002	0.007	0.004	3 C	0.001	0.004	0.003
4 C	0.019	0.005	0.012	4 C	0.013	0.005	0.009
5 C	-0.015	0.006	-0.005	5 C	-0.009	0.002	-0.004
6 C	0.007	0.006	0.007	6 C	0.004	0.006	0.005
7 C	-0.031	-0.082	-0.056	7 C	-0.011	-0.040	-0.026
11 C	-0.028	-0.083	-0.056	11 C	-0.018	-0.046	-0.032
15 C	-0.031	-0.083	-0.057	15 C	-0.019	-0.046	-0.033
19 S	-0.027	-0.153	-0.090	19 S	-0.015	-0.085	-0.050
20 S	-0.037	-0.152	-0.095	20 S	-0.021	-0.084	-0.053
21 S	-0.027	-0.154	-0.090	21 S	-0.011	-0.086	-0.049
22 S	-0.056	-0.158	-0.107	22 S	-0.028	-0.085	-0.057
23 C	0.005	0.013	0.009	23 C	0.004	0.012	0.008
24 C	-0.097	-0.009	-0.053	24 C	-0.059	-0.008	-0.034
25 C	-0.073	-0.012	-0.043	25 C	-0.042	-0.006	-0.024
26 S	-0.123	-0.061	-0.092	26 S	-0.066	-0.033	-0.049
28 C	0.007	-0.003	0.002	28 C	0.006	-0.001	0.003
30 C	-0.086	-0.005	-0.046	30 C	-0.046	-0.001	-0.023
31 C	-0.098	-0.022	-0.060	31 C	-0.039	-0.013	-0.026
34 C	0.014	0.007	0.011	34 C	-0.015	0.001	-0.007
35 C	-0.068	-0.016	-0.042	35 C	-0.074	-0.014	-0.044
36 C	-0.053	-0.018	-0.035	36 N	-0.001	0.000	-0.001
38 C	-0.104	-0.027	-0.066	37 C	-0.045	-0.013	-0.029
41 C	-0.067	-0.012	-0.039	39 C	-0.010	-0.001	-0.006
43 N	-0.020	-0.007	-0.014	40 C	-0.069	-0.010	-0.039
				43 C	-0.048	-0.006	-0.027
				44 C	-0.060	-0.007	-0.034
				47 C	0.007	0.000	0.003
				48 C	-0.051	-0.011	-0.031
				49 S	-0.067	-0.023	-0.045
				50 C	0.003	0.010	0.007
				52 C	-0.064	-0.006	-0.035
				54 C	0.005	0.006	0.005
				55 C	-0.010	0.002	-0.004
				56 C	0.014	0.005	0.010
				57 S	-0.034	-0.084	-0.059
				58 S	-0.011	-0.080	-0.046
				59 C	-0.011	0.008	-0.002
				60 C	0.001	0.004	0.003
				61 C	0.001	0.004	0.003
				62 S	-0.015	-0.080	-0.048
				63 S	-0.024	-0.083	-0.053
				64 C	-0.021	-0.045	-0.033
				68 C	-0.018	-0.043	-0.031
				72 C	-0.017	-0.041	-0.029

Where,  $\rho_{N-1}$ ,  $\rho_N$  and  $\rho_{N+1}$  are the electron density of cationic, neutral and anionic species, respectively. They are calculated under the frozen core approximation [2] which means a single calculation is done for the neutral species without any changes in the calculation method for the charged species, especially anions, under the natural population analysis approach. The condensation of this Fukui function, to an individual atomic site  $k$  in a molecule gives rise to the following expressions in terms of electron population  $q_k$ . [24]

$$f_k^+ = [q_k(N+1) - q_k(N)]$$

$$f_k^- = [q_k(N) - q_k(N-1)]$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)]/2$$

Where,  $q_k(N+1)$ ,  $q_k(N)$ , and  $q_k(N-1)$  stand for the gross NPA charges on atom  $k$  in a molecule with  $N+1$ ,  $N$ , and  $N-1$  electrons, respectively.

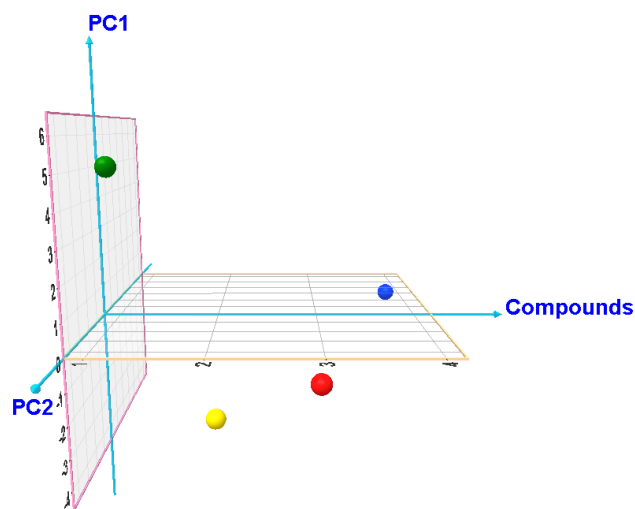
$$f^2(r) = \Delta f(r) \approx \rho_{N+1}(r) - \rho_{N-1}(r) - 2\rho(r) = f^+(r) - f^-(r)$$

The reactivity descriptor  $\Delta f(r)$  provides useful information on both stabilizing and destabilizing interactions between a nucleophile and an electrophile and helps in identifying the electrophilic/nucleophilic behavior of a specific site within a molecule. Since the dual descriptor has been very versatile for describing the regional stereo selectivity of a chemical reaction, it seems interesting to be used for assessing of the nucleophilicity of the nitrogen and oxygen atoms in a biological system.

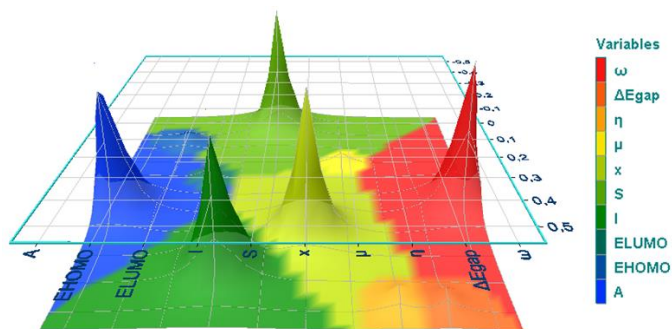
### 3.6 Principal Component Analysis (PCA)

In this work, we auto scaled all calculated variables in order to compare them in the same scale. Afterwards, PCA (principal component analysis) was used to reduce the number of variables and select the most relevant ones, i.e. those responsible for the tetrathiafulvalenes derivatives reactivity. After performing many tests, a good separation is obtained between more active and less active tetrathiafulvalenes compounds using ten variables:  $I, A, \chi, \eta, s, \mu, \omega, E_{HOMO}, E_{LUMO}, \Delta E_{gap}$  (Tables 5 and 6).

We can observe from PCA results that the first three principal components (PC1, PC2 and PC3) describe 99.99% of the overall variance as follows: PC1 = 92.30%, PC2 = 7.67% and PC3 = 0.02%. The score plot of the variances is a reliable representation of the spatial distribution of the points for the data set studied after explaining almost all of the variances by the first two PCs. The most informative score plot is presented in Figure 4 (PC1 versus PC2) and we can see that PC1 alone is responsible for the separation between more active (**1** and **4**) and less active compounds (**2** and **3**) where PC1 > 0 for the more active compounds and PC1 < 0 for the less active ones. The same results follow in the case of global reactivity trend based on  $\omega$ .

**Fig. 4** Score plot for tMeTTF substituted molecules (1-4) in gas phase

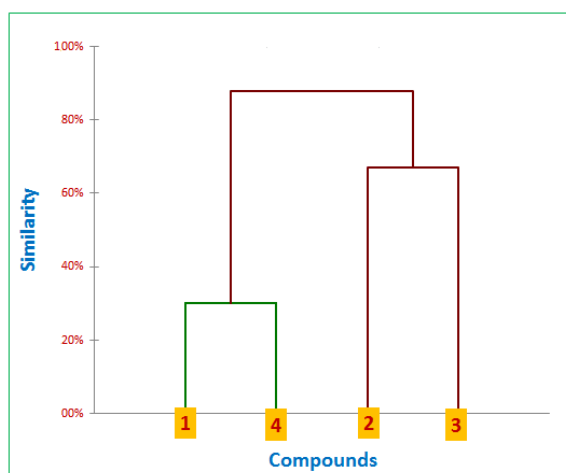
The loading vectors for the first two principal components (PC1 and PC2) are displayed in figure 5. We can see that more active compounds (PC1 > 0) can be obtained when we have higher  $A, I, S, \chi, \omega$ , values. In this way, some important features on the more active compounds can be observed.



**Fig. 5** Loading plot for the variables responsible for the classification of the tMeTTF substituted molecules studied

### 3.7 Hierarchical Cluster Analysis (HCA)

Fig. 6 shows HCA analysis of the current study. The horizontal lines represent the compounds and the vertical lines the similarity values between pairs of compounds, a compound and a group of compounds and among groups of compounds. We can note that HCA results are very similar to those obtained with the PCA analysis, i.e. the compounds studied were grouped into two categories: more active (compounds **1** and **4**) and less active (compounds **2** and **3**).



**Fig. 6** Dendrogram obtained for tMeTTF substituted molecules studied

## 4. Conclusion

From the whole of the results presented in this contribution it has been clearly demonstrated that the sites of interaction of the title compounds (**1-4**) can be predicted by using DFT-based reactivity descriptors such as the hardness, softness, and electrophilicity, as well as Fukui-function calculations. These descriptors were used in the characterization and successful description of the preferred reactive sites and provide a firm explanation for the reactivity of the functionalized trimethyltetrathiafulvalene.

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## References

- [1] T. Mineva, N. Russo, Atomic Fukui indices and orbital hardnesses of adenine, thymine, uracil, guanine and cytosine from density functional computations, *J. Mol. Struct. Theochem.* 943(1-3) (2010) 71-76.
- [2] J. Melin, F. Aparicio, V. Subramanian, M. Galvan, P.K. Chattaraj, Is the Fukui function a right descriptor of hard-hard interactions?, *J. Phys. Chem. A.* 108 (13) (2004) 2487-2491.
- [3] L.R. Domingo, P. Pérez, Global and local reactivity indices for electrophilic/nucleophilic free radicals, *Org. Biomol. Chem.* 11(26) (2013) 4350-4358.
- [4] R.G. Parr, R.A. Donnelly, M. Levy, W.E. Palke, Electronegativity: The density functional viewpoint, *J. Chem. Phys.* 68 (8) (1978) 3801-8807.
- [5] J.P. Perdew, R.G. Parr, M. Levy, J.L. Balduz, Density-functional theory for fractional particle number: derivative discontinuities of the energy, *Phys. Rev. Lett.* 49 (23) (1982) 1691-1694.
- [6] S. Pal, R.R.K. Chandra, Change of hardness and chemical potential in chemical binding: a quantitative model, *J. Phys. Chem.* 98 (9) (1994) 2314-2317.
- [7] S.K. Ghosh, M. Berkowitz, A classical fluid-like approach to the density-functional formalism of many-electron systems, *J. Chem. Phys.* 83 (6) (1985) 2976-2983.
- [8] W. Yang, R.G. Parr, Hardness, softness, and the Fukui function in the electronic theory of metals and catalysis, *Proc. Natl. Acad. Sci. USA* 82 (3) (1985) 6723-6726.
- [9] D. Singh, S. Ahmad, P.P. Singh, DFT based calculation of interaction energy between metal halides and organic bases, *J. Mol. Struct. Theochem.* 905 (1-3) (2009) 13-23.
- [10] R.G. Pearson, The principle of maximum hardness, *Acc. Chem. Res.* 215 (5) (1993) 250-255.
- [11] T. Abbaz, A.K. Gouasmia, H. Fujiwara, T. Hiraoka, T. Sugimoto, M. Taillefer, J.M. Fabre, New TTF and bis-TTF containing thiophene units: electrical properties of the resulting salts, *Synth. Met.* 157 (13-15) (2007) 508-516.
- [12] A. Bitoh, Y. Kohchi, T. Otsubo, F. Ogura, K. Ikeda, Syntheses and properties of 2,5-bis[2-(tetrathiafulvalen-2-yl)ethenyl]thiophene and related compounds as novel dumbbell-type electron donors, *Synth. Met.* 70 (1-3) (1995) 1123-1124.
- [13] S. Gonzalez, N. Martin, J.L. Segura, C. Seoane, Convenient regioselective syntheses of isomeric bis(tetrathiafulvalenylethenyl)naphthalene  $\pi$ -donors, *Tetrahedron Lett.* 39 (19) (1998) 3051-3054.
- [14] E. Scrocco, J. Tomasi, The electrostatic molecular potential as a tool for the interpretation of molecular properties, *Curr. Chem.* 42 (1973) 95-170.
- [15] D.F. V. Lewis, C. Loannides, D.V. Parke, Interaction of a series of nitriles with the alcohol-inducible isoform of P450: Computer analysis of structure-activity relationships, *Xenobiotica.* 24 (5) (1994) 401-408.
- [16] K. Fukui, T. Yonezawa, H. Shingu, A molecular orbital theory of reactivity in aromatic hydrocarbons, *J. Chem. Phys.* 20 (4) (1952) 722-725.
- [17] L.H. Cho, M. Kerterz, Conformational information from vibrational spectra of styrene, trans-stilbene, and cis-stilbene, *J. Phys. Chem. A* 101 (20) (1997) 3823-3831.
- [18] T. Koopmans, Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den einzelnen Elektronen eines Atoms, *Physica* 1 (1-6) (1933) 104-113.
- [19] R.G. Parr, R.G. Pearson, Absolute hardness: companion parameter to absolute electronegativity, *J. Am. Chem. Soc.* 105 (26) (1983) 7512-7516.
- [20] R.G. Parr, L.V. Szentpály, S. Liu, Electrophilicity index, *J. Am. Chem. Soc.* 121 (9) (1999) 1922-1924.
- [21] P.W. Ayers, M. Levy, Perspective on density functional approach to the frontier-electron theory of chemical reactivity, *Theor. Chem. Acc.* 103 (2000) 353-360.
- [22] R.G. Parr, W. Yang, Density functional approach to the frontier-electron theory of chemical reactivity, *J. Am. Chem. Soc.* 106 (14) (1984) 4049-4050.
- [23] R.G. Parr, W. Yang, Density functional theory of atoms and molecules, Oxford University Press, Oxford, United Kingdom, 1989.
- [24] W. Yang, W.J. Mortier, The use of global and local molecular parameters for the analysis of the gas-phase basicity of amines, *J. Am. Chem. Soc.* 108(19) (1986) 5708-5711.