

Novel application of quantum chemical investigation in terms of substituent parameters: Statistical comparison of dual and single substituent parameter treatments

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Abstract

The correlation analysis of Mulliken charge (Q_M) calculated by using density functional theory (B3LYP/STO-3G) calculations of 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione, were done by using mono substituent parameter (Hammett's model), and dual substituent parameter (Taft's, Reynolds', and Swain's models). The dual substituent parameter correlations of the Q_M data gave no significant improvement over single parameter correlations, the best correlation observed with the Taft's Model as compared with the Swain's and Reynolds' Models, respectively. The correlation analysis of Mulliken charge can be used successfully to demonstrate the existence or absence of the interaction between the oxygen of the carbonyl group and selenium atom.

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1. Introduction

Weak nonbonded interactions are useful chemical tools for controlling stability, conformation, and assembly of molecules [1]. It is, therefore, of great interest to determine the strengths and directional propensities of such interactions at an atomic resolution. However, detection as well as characterization of nonbonded interactions in situ is still challenging research in fundamental chemistry [2].

The high reactivity of organoselenium reagents allows the insertion of various functional groups to organic compounds under mild conditions with high stereoselectivity [3]. For this reason, organoselenium chemistry has been widely applied in the synthesis of various organic compounds [4]. In view of the molecular design of useful selenium reagents, it is of valuable importance to investigate

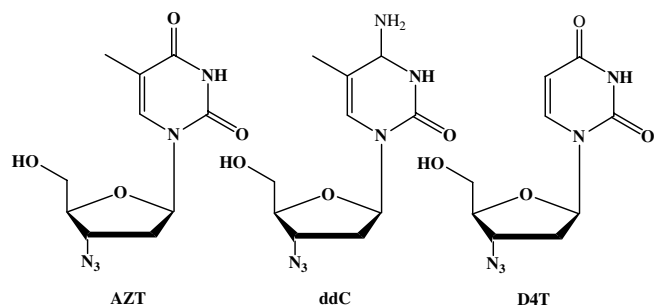
weak nonbonded interactions involving a divalent selenium (Se) atom because the interactions should play a role in the molecular recognition to a substrate as well as in the molecular conformation. Nonbonded interactions involving a divalent Se have also attracted much attention not only because of their chemical reactivities, but also because the biological activities of Se...O interaction [5,6].

The studied molecules (1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione) analogs 3'-azido-3' deoxythymidine (AZT) [7] ddC and D4T [8] (Scheme 1) which are potent inhibitors of HIV reverse transcriptase (RT) marked a decisive advance in the search for anti-AIDS drugs.

Because of the biological activities of the studied molecules, I have extensively studied the presence or absence of nonbonded interactions between a divalent selenium (Se) and an oxygen (O) atom depending on the Mulliken charge (Q_M) for the first time, by using mono substituent parameter (Hammett's model), and dual substituent parameter (Taft's, Reynolds', and Swain's models).

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Scheme 1.

2. Method of calculation

Density functional theory (DFT) and Semi-empirical methods are done on HYPERCHEM program version 7.5 [9] running on a windows XP workstation with a Pentium IV PC. The Q_M for O^* and Se atoms of 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione, were done by performing density functional theory (DFT) [10], and semi-empirical methods. DFT considering B3LYP exchange-correlation functional, [11,12], STO-3G basis set [13] has been chosen in the DFT calculations. Semi-empirical self-consistent-field molecular orbital (SCF-MO) method at PM3 level [14] within the restricted Hartree-Fock (RHF) [15] formalism has been considered. Geometry optimization is carried out by using a conjugate gradient method (Polak-Ribiere algorithm) [16]. The SCF convergence is set to 0.001 kcal mol⁻¹ and the RMS gradient is set to 0.001 kcal/(Å mol) in the calculations.

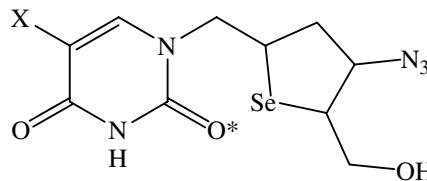
Regression analysis calculations were performed by using MINITAB data analysis software release 11.11 standard version [17].

3. Results and discussion

The Mulliken charges (Q_M) of the O^* and Se atoms, as well as Se- O^* distance values for 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione are given in Table 1. Examined of the Mulliken charges of O^* demonstrate that the substituted compound with electron withdrawing groups (EWGs) have lower Q_M values than those with electron donating groups (EDGs).

Table 1

Calculated Mulliken charges, as well as the Se- O^* distance for 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione



Compound No.	Sub. X	Mulliken charge (Q_M) ^a		Se-O distance ^b
		O^* atom	Se atom	
1	OCH ₃	-0.214	0.162	1.942
2	CH ₃	-0.211	0.165	1.943
3	H	-0.207	0.191	1.951
4	F	-0.209	0.158	1.948
5	COCH ₃	-0.205	0.167	1.945

^a DFT calculations.

^b Semi-empirical PM3 method.

3.1. MSP models

The correlation analysis of Mulliken charge (Q_M) for O^* atom by using Hammett's model [18], is summarized in Eq. (1). Generally, the empirical Hammett σ^+ constants (Table 2) exhibited good correlation with the Mulliken charge values of this series.

$$Q_{M(O^*)} = -0.208 + 0.00732\sigma^+ \quad (1)$$

$$n = 5, \quad r = 0.979, \quad s = 0.001, \quad F = 69.53$$

Where n is the number of compounds, r is the correlation coefficient, s is the standard deviation, and F is the Fisher ratio. This correlation is illustrated in Fig. 1. There were no outliers in the set.

While the Se atom do not give any correlation with all σ Hammett's constant, this can be attributed to longer distance between the substituent and Se atom, as well as the absence of conjugated systems.

3.2. DSP models

Table 2 shows the Taft's σ_1 , σ_R^+ , Swain's F , R and Reynolds' σ_1 , σ_R^0 constants. DSP analysis of the Mulliken charge (Q_M) for O^* and Se atoms, by using Taft's [19], Reynolds' [20,21], and Swain's [22] models are shown in Table 3. The correlation analysis for the Se atom are sim-

Table 2
Hammett, Taft, Swain, Reynolds substituent constants

Sub. X	Hammett σ^+	Taft		Swain		Reynolds	
		σ_1	σ_R^+	F	R	σ_1	σ_R^0
OCH ₃	-0.78	0.27	-0.45	0.54	-1.68	0.242	-0.417
CH ₃	-0.31	-0.04	-0.11	-0.01	-0.41	0.025	-0.137
H	0.00	0.00	0.00	0.00	0.00	0.000	0.000
F	-0.07	0.50	-0.34	0.74	-0.60	0.454	-0.297
COCH ₃	0.50	0.28	0.16	0.50	0.90	0.229	0.161

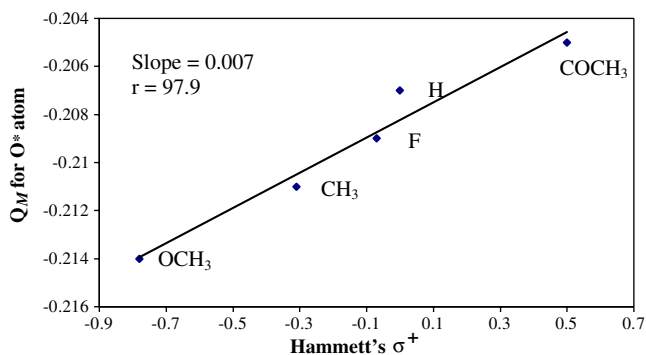


Fig. 1. Correlation between Hammett substituent constants σ^+ against Q_M for O^* atom. r is the correlation coefficient.

ilar to those noted in MSP analysis, do not give any correlation with all DSP models. In contrast, O^* atom give good correlation with all DSP Models especially with the Taft's Model. For example, the correlation coefficient (R) is 0.983 in Taft's Model, while 0.964, 0.956 in Swain's and Reynolds' Models, respectively. Because of the higher accuracy of the Taft's Model, I will use its results to interpret the substituent effects through O^* atom.

Normal substituent effects are also seen for O^* atom, as shown by positive ρ values (Table 2). Interestingly, studies on the analogs O^* atom site undergo reverse substituent effects and negative ρ values. Our major interest in the

studied molecules is the blending constant (λ), which is more than one (1.145, 2.571 and 2.208 in Taft's, Swain's and Reynolds' Models, respectively), this means that the large substituent resonance effect affects the O^* atom in the studied compound. The normal substituent effects and positive ρ values can be attributed to a type of interaction that indeed occurs between the Se and O^* atoms. DFT computations suggest that the $Se \cdots O$ contact observed in the studied molecules is stabilized by an electrostatic interaction between a positively charged selenium atom and a negatively charged oxygen atom. The distances between the Se atom and O of the $C=O$ group are around 2.305 Å, which is relatively consistent with previous calculations of similar systems [17]. Scheme 2 shows the distance between Se and O^* atoms for the most stable studied compounds.

Further support of this interaction occurs, the DSP analysis of carbonyl substituted chemical shift (SCS) which reveals that the reverse polar component of SCS effects at $C\alpha$ in para substituted acetophenones ($\rho_1 = -2.6$ in Eq. (2)) changes to normal effect ($\rho_1 = +5.3$) when the carbonyl π -bond is removed by protonation, as shown in Eq. (3)

$$\delta_X - \delta_X = -2.6\sigma_1 + 0.80\sigma_R^+ \quad (2)$$

$$\delta_X - \delta_X = +5.3\sigma_1 + 10.9\sigma_R^+ \quad (3)$$

Fig. 2 demonstrates that the unsubstituted compound (compound 3) when substituted with electron withdrawing groups (EWGs) or electron donating groups (EDGs), the

Table 3

Correlation analysis of Mulliken charge for O^* and Se atoms in series of 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione derivatives by using Taft's, Reynolds' and Swain's Models

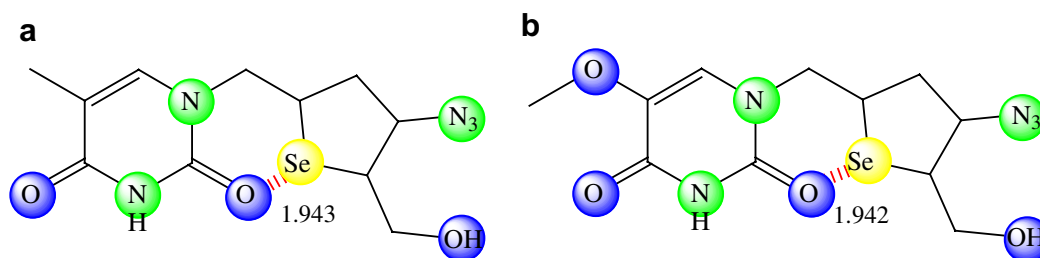
Model	Atoms	Conc.	ρ_1	ρ_R	λ^a	R^b	SD ^c	F^d
Taft	O^*	-0.208	0.0069	0.0079 ^c	1.145	0.983	0.001	29.11
	Se	0.178	-0.0291	0.0097	-	0.714	0.013	1.05
Swain	O^*	-0.208	0.0014	0.0036	2.571	0.964	0.001	11.69
	Se	0.178	-0.0245	0.0031	-	0.725	0.0127	1.10
Reynolds	O^*	-0.208	0.0072	0.0159	2.208	0.956	0.0014	10.60
	Se	0.179	-0.042	0.0147	-	0.753	0.0121	1.31

^a $\lambda = \rho_R/\rho_1$.

^b R is the correlation coefficient.

^c SD is the standard deviation.

^d F is the Fisher ratio e: with the σ_R^+ .



Scheme 2. Structural of 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-Substituted-1H-pyrimidine-2,4-dione: (a) $X = CH_3$, total energy = -2040440.63 (kcal/mol); (b) OCH_3 , total energy = -2086952.32 (kcal/mol), with bond lengths shown in angstroms (Å) (Semi-empirical PM3 methods).

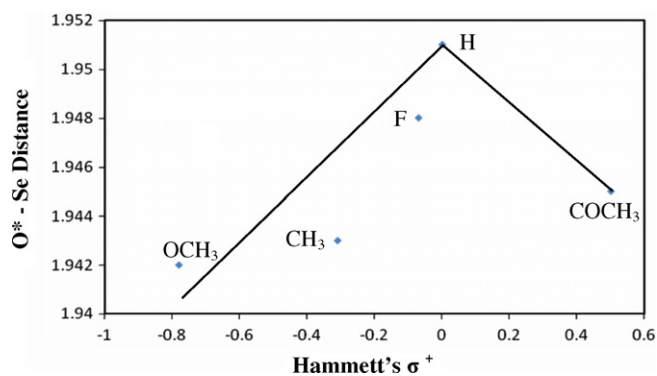


Fig. 2. Plot of Hammett's σ^+ vs. O*-Se Distance in 1-(4-azido-5-hydroxymethyl-tetrahydro-selenophen-2-ylmethyl)-5-substituted-1H-pyrimidine-2,4-dione.

interaction between O* of carbonyl group and Se atom is increases.

4. Conclusions

The preliminary correlation have been obtain from Mulliken charges (Q_M) data demonstrate several important points. First, the dual substituent parameter correlations of the Q_M data gave no significant improvement over single parameter correlations. Second, a comparison of the DSP equations shows, as expected, that the superiority of Taft's Model over both Swain's and Reynolds' Models, respectively. Finally, we can used the correlation analysis of the Mulliken charges, which is measured by quantum chemical parameters, to prove the existence or absence of the interaction between the oxygen of the carbonyl group and other atoms (Se or Te) found in the organometallic compounds.

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