

Density Functional Theory Studies on Electronic Properties of Thiophene S-oxides as Aromatic Dienophiles for Reactivity Prediction in Diels-Alder Reactions

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Abstract. The reactivity of thiophene S-oxides was discussed with special emphasis on the use of thiophene S-oxides as dienophiles in Diels-Alder type reactions. The ω values obtained for thiophene S-oxide (TO) with electron-donating group (-CH₃) increased the nucleophilicity power whereas substitution with electron-withdrawing groups (such as -NO₂ and -CO₂CH₂CH₃) increased the electrophilicity power, indicating an increase of reactivity towards a nucleophiles. The higher the value of $\Delta\omega$ the more favourable the D-A process, therefore apart from (4+2) addition reactions of these TO as diene with the typical dienophiles like 1,2-dicyanoethene and 1,2-dicyanoethne, it could be possible for TO with strong electron withdrawing substituents to serve as dienophile, e.g. heterocycles 1e and 1f. Also, from the value of $\Delta\omega$ heterocycle 1d could involve in (4+2) addition reactions with heterocycles 1e and 1f.

Keywords: thiophene S-oxide, reactivity, global properties, density functional theory

Introduction

Thiophene S-oxide have remained an elusive species until fairly recent times; although thiophene S, S-dioxides are well-known compounds. They are viewed as building blocks with the *proviso* that they could be synthesized from thiophenes directly and would prove suitable cyclic dienes for cycloaddition reactions that would lead to multi-functionalized arenas (Thiemann *et al.*, 2009). Furthermore, thiophene S-oxides have been found to exhibit a wealth of interesting reactivity (Fujii *et al.*, 2002; Furukawa *et al.*, 1998; 1997; Pouzet, 1997; 1995), as good dienes in Diels-Alder type reactions and add stereoselectively to a row of dienophiles (Thiemann *et al.*, 2003; 2000a; Ho *et al.*, 1998), however, this depends on the substituents on the frame of the thiophene-S-oxide and also on the nature of the dienophile present in these reactions (Fujii *et al.*, 2002).

In solution and upon exposure to light, *e.g.* daylight, thiophene-S-oxides enjoy a much shorter lifetime and appreciable amount of thiophenes can be isolated from the ensuing mixtures (Ohira *et al.*, 2005). Thiophene-S-oxides have been found to be active against a number of cancer cell strains. Whether this activity is attri-

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butable to a slight but continued deoxygenation of the compounds is still under study (Fujii *et al.*, 2002). The use of aromatic compounds as dienes has been widely studied in D-A reactions (Thiemann *et al.*, 2003; 2000a; 2000b; Lautens and Fillion, 1996; Paquette *et al.*, 1982), however, their use as dienophiles is a new and interesting branch that allows to state large and versatile synthetic sequences.

Moreover, nowadays, computational chemistry methods offer a unique ability for organic chemists to generate optimal geometry structures, the structural and electronic properties of reactants and products make decisions as to which of the chemical transformations will occur in reactions. From the theoretical point, the differences in the stability of heterocycles are explained in terms of aromaticity and delocalization of electron densities on π molecular orbitals. For the stable compounds, a high π molecular orbital delocalization established between two aromatic rings, which may not be presented in the less stable isomers. It is evident that the aromaticity correlates with the thermodynamic stability of a system, and also is relationship between hardness and stability. Bird (1997), Chamizo *et al.* (1993) Zhou and Navangul (1990) and Parr and Pearson (1983) had reported the principle of maximum

hardness (absolute hardness) η . For an N-electron system with total energy E and η are defined as:

$$\eta = \left(\frac{\delta^2 E}{\delta N^2} \right)_{v(r)} \approx (I - A) \approx (E_{\text{LUMO}} - E_{\text{HOMO}}) \quad (1)$$

In the formula I is the vertical ionization energy and A stands for the vertical electron affinity. According to the Koopmans theorem (1934), the hardness corresponds to the gap between the HOMO and LUMO orbitals. Hence, the principle of maximum hardness confirms the results that show that stability of aromatic hydrocarbons depends on HOMO-LUMO energy gap. The larger the HOMO-LUMO energy gap, the harder is the molecule. The higher HOMO energy corresponds to the more reactive molecule in the reactions with electrophiles.

The electron affinity can also be used in combination with ionization energy to give electronic chemical potential μ defined by Parr and Pearson (1983), as the characteristic of electronegativity of molecules:

$$\mu = \left(\frac{\delta E}{\delta N} \right)_{v(r)} \approx -\frac{1}{2}(I - A) \approx \frac{1}{2}(E_{\text{HOMO}} + E_{\text{LUMO}}) \quad (2)$$

The global electrophilicity index ω was introduced by Parr *et al.* (1999) and calculated by using the electronic chemical potential μ and chemical hardness η .

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

According to the definition, this index measures the propensity of a species to accept electrons. As Domingo *et al.* (2002) proposes the high nucleophilicity and electrophilicity of heterocycles corresponds to opposite extremes of the scale of global reactivity indexes. A good, more reactive, nucleophile is characterized by a lower value of μ , ω and in opposite a good electrophile is characterized by a high value of μ , ω .

In this work, as a contribution to the understanding of the reactivity of heteroaromatic dienophiles in D-A reactions with normal electron demand, the electronic properties of some selected dienophiles and some dienes were studied from a theoretical point of view. The dienes investigated are benzo[b]thiophene S-oxide, dibenzon-thiophene S-oxide, 2-methylbuta-1,3-diene, Danishefky's diene and disubstituted thiophene S-oxides with electron donating groups, while the dienophiles were 1,2-dicyanoethene, 1,2-dicyanoethyne and disubstituted thiophene S-oxide with electron withdrawing groups

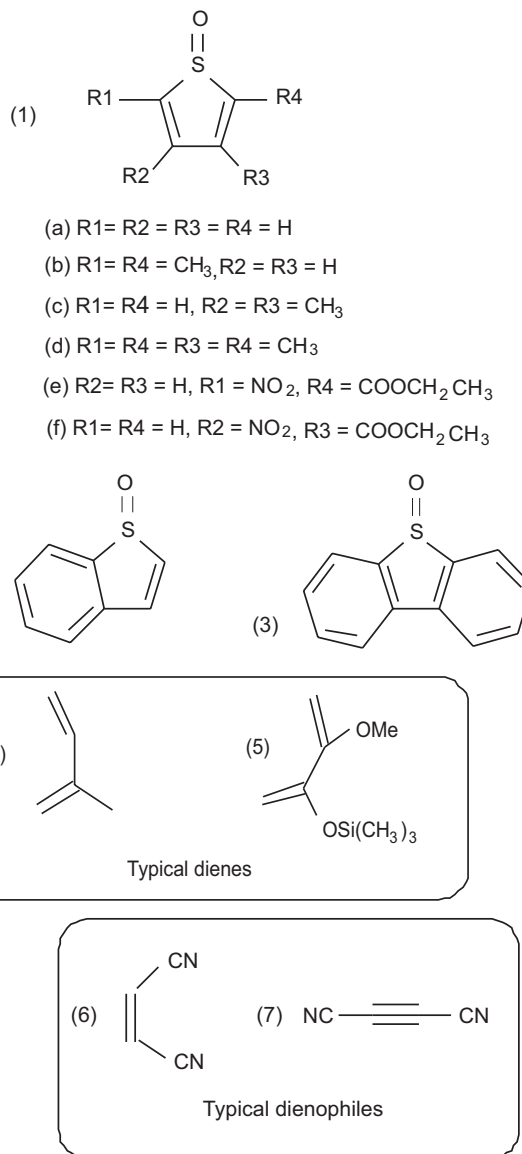


Fig. 1. The studied molecules.

(Fig. 1). In addition, the effect of dienophilic substitution on the reactivity was also examined in order to select suitably the substituents leading to the most favourable reaction conditions.

Computational details. The geometries 1-7 were fully optimized at the DFT B3LYP level of theory with a 6-31G* basis set. The basis set 6-31G* was used for all atoms in ab initio methods, this has been used by several researchers in studying heterocycles (Armelin *et al.*, 2009; Brasca *et al.*, 2007; Amazonas *et al.*, 2006; Bouzzine *et al.*, 2005). The harmonic vibrational frequencies are positive. All calculations were performed using Spartan (2006).

Table 1. Calculated HOMO, LUMO and global properties of studied molecules (eV)

Studied molecule	HOMO	LUMO	Global properties		
			η	μ	ω
1a Thiophene S-oxide	-6.27	-1.91	4.36	-4.09	1.92
1b 2,5-Dimethylthiophene S-oxide	-6.03	-1.50	4.53	-3.77	1.60
1c 3,4-Dimethylthiophene S-oxide	-5.99	-1.58	4.41	-3.79	1.63
1d 2,3,4,5-Tetramethylthiophene S-oxide	-5.82	-1.21	4.61	-3.52	1.34
1e 2-Nitro-5-ethoxycarbonylthiophene S-oxide	-7.15	-3.75	3.40	-5.45	4.37
1f 3-Nitro-4-ethoxycarbonylthiophene S-oxide	-7.21	-3.29	3.92	-5.25	3.52
2 Benzo[b]thiophene S-oxide	-6.12	-1.74	4.38	-3.93	1.76
3 Dibenzothiophene S-oxide	-6.07	-1.55	4.52	-3.81	1.61
4 2-Methylbuta-1,3-diene	-6.19	-0.41	5.78	-3.30	0.94
5 Danishefky's diene	-5.33	-0.17	5.16	-2.75	0.73
6 1,2-Dicyanoethene	-8.90	-2.99	2.67	-5.66	3.00
7 1,2-Dicyanoethyne	-8.32	-3.20	5.70	-6.05	3.21

Results and Discussion

Dienes and dienophiles classified in decreasing order of electrophilicity power (ω) are shown in Table 1. Some global properties are also included, such as the values of chemical potential (μ) and chemical hardness (η). It is assumed that high nucleophilicity and high electrophilicity are in opposite ends of this scale and, therefore, a molecule that shows a low electrophilicity power can be considered as a nucleophile (Parr *et al.*, 1999). Therefore, the larger the difference between ω index of both diene and dienophile, a higher reactivity is expected. It can be appreciated that the structural and electronic characteristics induced by chemical substitution are reflected as different responses of the global electrophilicity power.

The ω values obtained for thiophene S-oxide (TO) with electron-donating group ($-\text{CH}_3$) increases the nucleophilicity power (*i.e.* decreasing in electrophilicity power) of thiophene S-oxide increases in the number of substitutions with electron-donating groups further increases the nucleophilic character of TO (*i.e.* 1a, 1b, 1c and 1d in Table 2), although the position of the substitution affect reactivity of TO. For instance, substitution of TO at positions 2 and 5 with $-\text{CH}_3$ increases the nucleophilicity power as compared to substitution at positions 3 and 4 (1b and 1c). The heterocycle 2 with fused benzene is better electrophile than 3 with two fused benzene rings.

Likewise, upon substitution of two hydrogen atoms of TO by two different electron-withdrawing groups

Table 2. Difference in electrophilicity index of dienophiles and dienes

*Cpd	ω	$\Delta\omega^1$	$\Delta\omega^2$	$\Delta\omega^3$	$\Delta\omega^4$	$\Delta\omega^5$
1e	4.37	3.64	3.43	3.03	2.77	2.76
1f	3.52	2.79	2.58	2.18	1.92	1.91
7	3.21	2.48	2.27	1.87	1.61	1.60
6	3.01	2.27	2.07	1.67	1.41	1.40
1a	1.92	1.19	-	-	-	-
2	1.76	1.03	-	-	-	-
1c	1.63	-	-	-	-	-
3	1.61	-	-	-	-	-
1b	1.60	-	-	-	-	-
1d	1.34	-	-	-	-	-
4	0.94	-	-	-	-	-
5	0.73	-	-	-	-	-

The molecules are arranged in order of ω values calculated at B3LYP/6-31G

$$\Delta\omega = (\omega_{\text{Dienophile}} - \omega_{\text{Diene}}) \quad (4)$$

$$\Delta\omega^1 = (\omega_{\text{Dienophile}} - \omega_5), \quad \Delta\omega^2 = (\omega_{\text{Dienophile}} - \omega_4),$$

$$\Delta\omega^3 = (\omega_{\text{Dienophile}} - \omega_{1d}), \quad \Delta\omega^4 = (\omega_{\text{Dienophile}} - \omega_{1b}),$$

$$\text{and } \Delta\omega^5 = (\omega_{\text{Dienophile}} - \omega_3),$$

($-\text{NO}_2$ and $-\text{CO}_2\text{CH}_2\text{CH}_3$) the electrophilicity power further increases, thus indicating an increase of reactivity towards a nucleophile (1e and 1f). Similarly, electron-withdrawing groups at positions 2 and 5 of TO increase the electrophilic character as compared to substations

at 3 and 4 (Tables 1 and 2). The observed behaviour in these pairs of isomers (1b and 1c, 1e and 1f) was supported by the values of dipole moments and stability. Isomer 1b with higher nucleophilic character had lower HOMO energy, higher LUMO energy, lower dipole moment and higher stability, whereas isomer 1c with lower nucleophilic character had higher HOMO, lower LUMO, higher dipole moment and less stability. However, in isomers 1e and 1f the observed properties were in opposite in the sense that 1e with higher electrophilic character had the properties corresponded to that of 1c.

The reactivity of the D-A process depends on the energy separation between frontier molecular orbitals (FMO) of reagents, HOMO of the diene, and LUMO of dienophile. A small energy difference between interacting FMO will contribute to a higher stabilization of the transition state, therefore, all factors that decrease HOMO-LUMO distance will increase reaction rate. Then, from the energy point of view, the most favourable HOMO-LUMO interaction will be that of less ΔE and high value of difference in ω of dienophile and ω of diene ($\Delta\omega$) as shown in Table 2. The higher the value of $\Delta\omega$ the more favourable the D-A process, therefore, apart from (4+2) addition reactions of these TO as diene with the typical dienophiles like 1,2-dicyanoethene and 1,2-dicyanoethyne, it could be possible for TO with strong electron withdrawing substituents to serve as dienophile e.g. heterocycles 1e and 1f. Also, from the value of $\Delta\omega$ heterocycle 1d could involve in (4+2) addition reactions with heterocycles 1e and 1f.

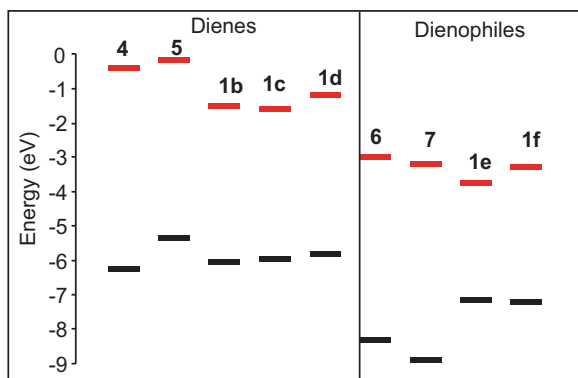


Fig. 2. The frontal molecular orbital (FMO) energies showing the effect of substitution on thiophene S-oxide (TO).

Figure 2 shows FMO energies for 2, 5-dimethylthiophene S-oxide (1b), 3,4-dimethylthiophene S-oxide (1c), 2,3,4,5-tetramethylthiophene S-oxide (1d), 2-methylbuta-1,3-diene (4) and Danishefky's diene (5) as dienes and 2-nitro-5-ethoxycarbonylthiophene S-oxide (1e), 3-nitro-4-ethoxycarbonylthiophene S-oxide (1f), 1,2-dicyanoethene (6) and 1,2-dicyanoethyne (7) as dienophiles. This figure reveals the effect on substitution on the TO, it can be clearly seen that electron-withdrawing substituents decrease LUMO energy, which would result in an acceleration of the reaction rate. These results are in agreement with those obtained by analysing the global electrophilicity index (Table 1).

Conclusion

Global electrophilic index is a useful tool for explaining the effect of substituents in the diene/dienophile interacting pair. Upon substitution of TO with electron-withdrawing groups, there is an increase in ω index, thus reflecting a higher electrophilic character. On the other hand, substitution of TO with electron-donating groups there is a decrease in ω index, thus reflecting a higher global nucleophilic nature.

Based on such theoretical calculations the influence of the combination and positional relationship of the substituents of each dienophile can be analysed in order to develop most suitable reactions for the design of possible precursor to be integrated in synthetic sequences. It could be possible for TO with strong electron withdrawing substituents to serve as dienophile and from the value of $\Delta\omega$ heterocycle 1d could involve in (4+2) addition reactions with heterocycles 1e and 1f.

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