

## Research Article

# A Thermochemical Parameters and Theoretical Study of the Chlorinated Compounds of Thiophene

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This contribution sets out to compute thermochemical and geometrical parameters of the complete series of chlorinated isomers of thiophene based on the accurate chemistry model of CBS-QB3. Herein, we compute standard entropies, standard enthalpies of formation, standard Gibbs free energies of formation, and heat capacities. Our calculated enthalpy values agree with available limited experimental values. The DFT-based reactivity descriptors were used to elucidate the site selectivity for the chlorination sequence of thiophene. The relative preference for chlorination was found to be in accord with the thermodynamic stability trends inferred based on the H scale. Calculated Fukui indices predict a chlorination sequence to ensue as follows: 2-chloro  $\rightarrow$  2,5-dichloro  $\rightarrow$  2,3,5-trichloro  $\rightarrow$  2,3,4,5-tetrachlorothiophene.

## 1. Introduction

Thiophene (C<sub>4</sub>H<sub>4</sub>S) is a heterocyclic organic compound with a five-membered ring similar to cyclopentadiene with replacement of a -CH<sub>2</sub>- group by sulfur atom [1]. Thiophene and its derivatives can be found in some natural resources such as petroleum and coal and in several pharmacologically active compounds [2]. Thiophene has high potential for bioactivation which in some cases has been linked to toxicity [3]. Medicinal chemistry approaches to minimize the bioactivation potential of thiophenes often include substitution at the  $\alpha$ -carbon position to provide a potential site for metabolism. Such thiophene derivative that is often used in medicinal chemistry is the  $\alpha$ -chlorothiophene, and there are several examples of marketed drugs containing this moiety such as tioconazole, lornoxicam, and rivaroxaban [4].

Halothiophenes and their secondary products are intermediate compounds in the synthesis of drugs and plant

protection agents [5]. Chlorothiophene isomers may be used in the synthesis of many important organic compounds [6–8]. Experimentally, nine isomers of chlorothiophene could be produced by chlorination of thiophene in several methods [9] and all isomers were isolable. Monochlorothiophene was formed in high percent during substitution reaction of chlorine with thiophene. Similarly [10], chlorination of 2-chlorothiophene yielded a dichlorothiophene fraction composed of high percent of 2,5-dichlorothiophene and 2,3-dichlorothiophene, 2,3-, 2,4-, and 3,4-dichlorothiophenes were formed largely by dehydrohalogenation of 2,3,4,5-tetrachlorothiophene and not by substitution. 2,5-Dichlorothiophene was formed by substitution. On the other hand 2,3,4-trichlorothiophene was prepared by low temperature chlorination and was formed largely after the chlorination by the action of alkali on 2,2,3,4,5-pentachlorothiophene. 2,3,5-Trichlorothiophene was prepared by high temperature chlorination and was formed both

by the substitution of 2,5-dichlorothiophene and by the pyrolysis of pentachlorothiophene. Tetrachlorothiophene was formed both by substitution of 2,3,5-trichlorothiophene and by pyrolytic or alkaline dehydrohalogenation of 2,2,3,4,5,5-hexachlorothiophene [11, 12]. 2,5-dichlorothiophene was used in the preparation of chalcones compounds which have been evaluated for antimicrobial activity [13]. The effects of the number and the position of the chlorine atoms on the properties of the thiophene ring for the chlorothiophenes have been studied theoretically by the CBS-QB3 composite method [14]. It is well-established that this method performs very well in predicting thermochemistry in general applications pertinent to halogenated systems. In previous studies, we have demonstrated the accuracy of the CBS-QB3 methodology against analogous experimental values and calculated parameters by CBS-QB3 in these studies span kinetics reaction rate constants [15],  $pK_a$  values [16], and bond dissociation enthalpies [17]. The focus in this study is on acquiring standard entropies, heat capacities, enthalpy, and the free energy barrier for the addition of Cl to the ring-carbon sites at selected temperature for the optimized structures of chlorinated thiophene compounds which are calculated.

## 2. Computational Details

The Gaussian 09 [18] suite of programs carries out all structural optimization and energy estimations for the complete series of chlorinated congeners of thiophene at the composite chemistry model of CBS-QB3 [19]. CBS-QB3 performs structural optimization and frequency calculations at the B3LYP/6-311+G(d,p) theoretical level. This is followed by several subsequent single point energies at higher theoretical levels including MP2 and CCSD(T) methodologies. We have shown in our previous studies that the CBS-QB3 method performs very well in estimating thermo-kinetics parameters for general applications of halogenated hydrocarbons [17, 20, 21]. The DMol<sup>3</sup> software [22] was deployed to acquire Fukui ( $f^1$ ) [23] indices of electrophilic attack. The values are then used to underpin the preferred chlorination sequence of thiophene.

We compute standard  $\Delta_f G_{298}^{\circ}(g)$  via utilizing our calculated standard entropies (Table 3) and the standard entropies of elements (C, H, N, and Cl) in their standard state according to

$$\Delta_f G_{298}^{\circ}(g) = \Delta_f H_{298}^{\circ}(g) - TS_{298}^{\circ} - T \sum S_{298}^{\circ}(\text{elements}) \quad (1)$$

Calculating Gibbs free energies of formation in the aqueous phase,  $\Delta_f G_{298}^{\circ}(aq)$ , requires estimation of the energy of solvation,  $\Delta G_{solv}^{\circ}$ :

$$\Delta_f G_{298}^{\circ}(aq) = \Delta_f G_{298}^{\circ}(g) + \Delta G_{solv}^{\circ} \quad (2)$$

Standard entropies and heat capacities are computed based on vibrational frequencies and moments of inertia via the ChemRate code [24].

## 3. Result and Discussion

**3.1. The Optimized Geometries.** Optimized structures for all chlorinated isomers are presented in Figure 1. Change in the position and the extent of chlorination exerts rather minimal changes in the structural parameters when contrasted with analogous values in the unsubstituted thiophene molecule. For instance, all C-C distances in the chlorinated isomers of thiophene are within 0.007 Å. Likewise, all C-C-C and C-S-C angles in the chlorinated isomers of thiophene reside with 0.02° of the corresponding angles of the thiophene molecule.

**3.2. Sequence of Chlorination.** Chlorination of thiophene occurs via electrophilic aromatic substitution (Scheme 1). These substitutions ensue by an initial electrophile addition, followed by a hydrogen atom loss from the intermediate forming the aromatic ring.

We have previously utilized Fukui  $f^1$  indices for electrophilic substitution to reproduce the experimentally observed halogenation patterns for chlorinated several aromatic compounds [25]. Herein, we adapt the same approach to calculate the chlorination pattern of chlorinated compounds of thiophene.

Calculated  $f^1$  values in Figure 2 predict the chlorination sequence as follows: 2-chloro  $\rightarrow$  2,5-dichloro  $\rightarrow$  2,3,5-trichloro  $\rightarrow$  2,3,4,5-tetrachlorothiophene. This sequence of chlorination allows less repulsion between the chlorine atoms. Experimentally, chlorination of thiophene is preferred at the C-2 ( $\alpha$ -position) of the ring. An explanation for the  $\alpha$ -selectivity of this substitution reaction is apparent from the mechanism in Scheme 1. The intermediate that is formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack.

**3.3. Standard Enthalpies of Formation.** The standard entropies, heat capacities, enthalpy, and the free energy barrier for the addition of Cl to the ring-carbon sites at selected temperature for these reactions were calculated. The results are given in Tables 1, 2, and 3. We calculated standard enthalpies of formation ( $\Delta_f H_{298}^{\circ}$ ) based on two isodesmic reactions shown in Scheme 2.

Based on the  $\Delta_f H_{298}^{\circ}$  of chlorobenzene ( $13.01 \pm 0.50$  kcal/mol) [26], benzene ( $19.8 \pm 0.2$  kcal/mol) [27], thiophene (52.20 kcal/mol) [28], and the  $\Delta_f H_{298}^{\circ}$  for the selected chlorothiophene compounds were estimated using CBS-QB3 along with the selected isodesmic reaction Scheme 2 (Table 2).

Similarly, the  $\Delta_f H_{298}^{\circ}$  for the 2-chlorothiophene calculated at 46.507 kcal/mol is less than 3-chlorothiophene isomer (47.330 kcal/mol). This indicates that the 2-chlorothiophene isomer is more stable than the 3-chlorothiophene isomer. Along the same line of discussion, the  $\Delta_f H_{298}^{\circ}$  of 2,5-dichlorothiophene (44.403 kcal/mol) is less than the other dichloro isomers. This infers that the 2,5-dichloro isomer is more stable than the other dichloro isomers. Such finding is attributed the S-atom that separates between the two chlorine atoms in thiophene. These positions are denoted as  $\alpha$ -positions with respect to sulfur atom. Obviously, higher thermodynamic stability for this isomer stems from a smaller

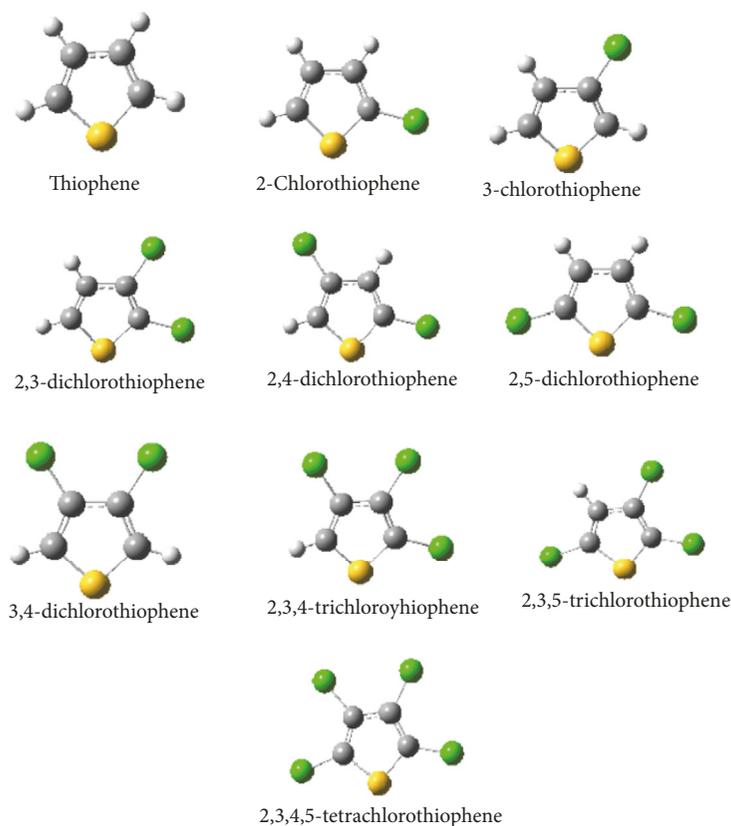
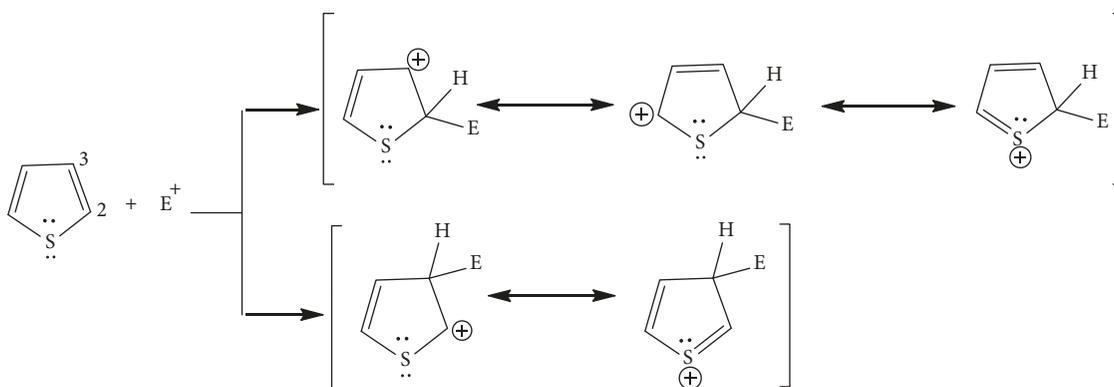


FIGURE 1: Optimized structures at the B3LYP/6-311+G(d,p) level of theory for chlorinated isomers of thiophene.



SCHEME 1: Resonance stabilization of 2-substitution intermediate is greater than that of the 3-substitution intermediate.

enthalpic penalty associated with the repulsion between the chlorine atoms.

It is noticed that the heat of formation  $\Delta_f H_{298}^{\circ}$  of the chlorothiophene compounds decreases with the addition of the number of chlorine atoms. To the contrary and as expected, entropies ( $S^{\circ}$ ) and the heat capacities at constant pressure ( $C_p^{\circ}$ ) for chlorothiophene compounds increase with the addition of chlorine atoms. Table 1 lists calculated standard entropies and heat capacities at selected temperatures.

#### 3.4. Gaseous and Aqueous Gibbs Free Energies of Formation.

The polarizable continuum model (PCM) [29] is used to estimate values of  $\Delta G_{solv}^{\circ}$ . This approach utilizes a continuum surface charge formalism that incorporates a robust and a smooth perturbing reaction field. Values of  $\Delta G_{solv}^{\circ}$  are modestly negative indicating an exothermic nature for dissolving of pyridine and its chlorinated compounds in water. Values of  $\Delta G_{solv}^{\circ}$  randomly vary among isomers but reside in the narrow range of -1.5 and  $\sim 2.25$  kcal/mol. Nevertheless, no

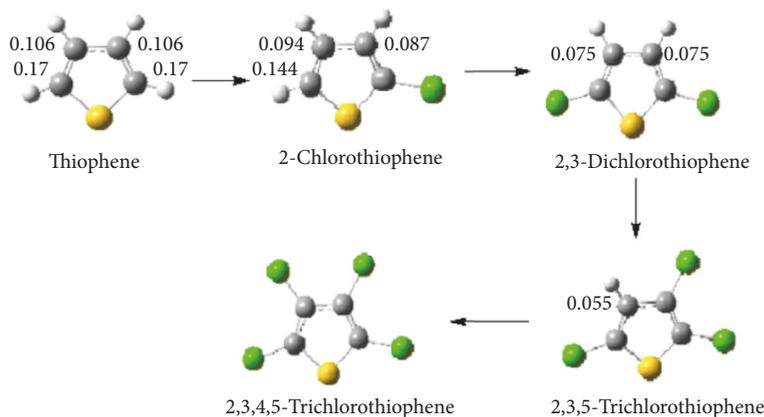


FIGURE 2: Chlorination sequence of thiophene predicted based on Fukui indices of electrophilic attack,  $f^{-1}(r)$ .

TABLE 1: Values of standard entropy ( $S^\circ$ ) and heat capacity at constant pressure ( $C_p^\circ$ ) at selected temperatures for chlorinated thiophene isomers.  $S^\circ_{298}$  in cal/(mol K) and  $C_p^\circ(T)$  in cal/(mol K).

	$S^\circ_{298}$	$C_p^\circ$					
		298.15K	300K	500K	800K	1000K	1500K
Thiophene	70.566	17.895	18.006	27.771	35.679	38.827	43.453
2-Chlorothiophene	77.534	21.624	21.730	26.875	37.967	40.709	44.612
3-Chlorothiophene	78.109	21.685	21.792	30.929	38.022	40.738	44.614
2,3-Dichlorothiophene	85.559	25.327	25.429	33.915	40.280	42.608	45.776
2,4-Dichlorothiophene	85.716	25.431	25.533	33.995	40.320	42.630	45.781
2,5-Dichlorothiophene	85.860	25.354	25.455	33.881	40.257	42.595	45.775
3,4-Dichlorothiophene	85.377	25.379	25.483	34.024	40.344	42.645	45.784
2,3,4-Trichlorothiophene	92.799	29.059	29.158	37.041	42.625	44.532	46.956
2,3,5-Trichlorothiophene	93.197	29.067	29.163	36.968	42.573	44.497	46.942
2,3,4,5-Tetrachlorothiophene	100.252	32.697	32.789	40..005	44.875	46.395	48.114

TABLE 2:  $\Delta_f H^\circ_{298}$  (kcal/mol) for chlorinated thiophene isomers.

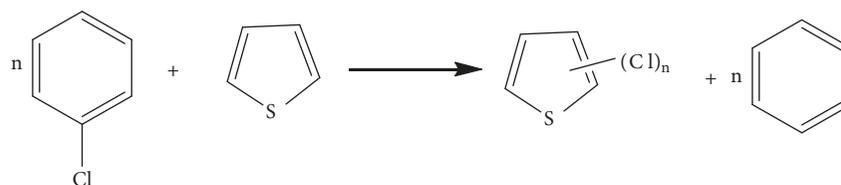
	$\Delta_f H^\circ_{298}$
Thiophene	+ 52.200
2-Chlorothiophene	+ 46.507
3-Chlorothiophene	+ 47.330
2,3-Dichlorothiophene	+ 45.846
2,4-Dichlorothiophene	+ 45.077
2,5-Dichlorothiophene	+ 44.403
3,4-Dichlorothiophene	+ 45.395
2,3,4-Trichlorothiophene	+ 41.334
2,3,5-Trichlorothiophene	+ 43.119
2,3,4,5-Tetrachlorothiophene	+ 40.366

TABLE 3: The calculated properties of chlorinated thiophene at 298 K: the Gibbs free energies in the gas phase  $G_f(g)$ , the Gibbs free energies for solvation ( $G_{Solv}$ ), and the standard and relative Gibbs free energies in aqueous phase  $G_f(aq)$ . All are in kcal/mol.

	$\Delta_f G(g)$	$\Delta G_{Solv}$	$\Delta_f G(aq)$
Thiophene	-40.656	-2.028	-42.683
2-Chlorothiophene	-48.723	-1.949	-50.670
3-Chlorothiophene	-51.070	-2.272	-53.342
2,3-Dichlorothiophene	-56.867	-2.144	-59.011
2,4-Dichlorothiophene	-57.083	-1.936	-59.019
2,5-Dichlorothiophene	-54.600	-1.636	-56.236
3,4-Dichlorothiophene	-60.464	-2.506	-62.970
2,3,4-Trichlorothiophene	-68.030	-2.128	-70.158
2,3,5-Trichlorothiophene	-66.363	-1.551	-67.914
2,3,4,5-Tetrachlorothiophene	-74.512	-1.511	-76.023

conclusive observation can be drawn regarding the effect of degree and pattern of chlorination on computed values of  $\Delta G_{Solv}^\circ$ . Values of  $\Delta_f G_{298}^\circ(g)$  and  $\Delta_f G_{298}^\circ(aq)$  highlight a highly spontaneous nature for the formation of chlorinated compounds of thiophene in the gas phase as well as in the aqueous medium. Water is a polar solvent so the solvation effect depends on the dipole moments of chlorinated

thiophenes: 3,4-dichlorothiophene should have the greatest dipole moment and, thus, the greatest interaction with polar solvent. This explains why this isomer acquires lower  $\Delta_f G(aq)$  among other dechlorinated congeners. Calculating polarizability effects on the selected chlorinated thiophene



SCHEME 2: Hypothetical reaction between thiophene and chlorobenzene.

using various other solvents will be investigated in a due course.

#### 4. Conclusion

The thermochemical and the optimized geometrical parameters are presented for the selected chlorothiophene isomers. Isodesmic reactions were used to estimate standard enthalpies of formation. The standard enthalpies of formation decrease as the degree of chlorination increases in both the gaseous and aqueous media. No trend can be deduced with respect to the effect of degree and pattern of chlorination on the computed solvation energies. Similarly, geometries of chlorinated isomers of thiophene exhibit to a large extent the analogous structural parameters in the thiophene molecule. The degree and pattern of chlorination indices a minor in.

#### Data Availability

The data used to support the findings of this study are included within the article.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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