

Theoretical Modeling and Experimental Investigation of Propanol and Phenol in Mainstream Cigarette Smoking

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There is substantial evidence that inhaled toxicants such as cigarette smoke can cause irreparable damage to the genetic material, cell injury, and general respiratory landscape. Accordingly, this paper will describe the quantum mechanical and thermodynamic characteristics of selected tobacco toxins, propanol and phenol, which are known to cause adverse medical effects to cigarette smokers. To simulate actual cigarette smoking conditions, theoretical calculations were conducted for temperatures between 100 °C and 950 °C at 1 atmosphere pressure using Density Functional theory (DFT) analytical gradient with 6-31++G(d,p) basis set. *Gaussian 03* computational set of programs was used to perform thermo-chemical calculations as well as electronic properties of propanol and phenol. To complement theoretical studies, Gas-Chromatography and Mass-Spectrometry (GC-MS) results showing the yield distribution of propanol and phenol from the combustion of SME01 cigarette in the temperature range 200-700 °C are presented. The experimental result indicates that the yield of propanol and phenol reached a maximum at about 400 °C before decreasing exponentially to about 9.0×10^7 and 1.2×10^6 GC area counts at 700 °C, respectively. Detailed discussions on their clinical effects as well as their thermo-chemical properties are presented in this paper.

1. Introduction

Several scientific and epidemiological evidences have explicitly established that cigarette smoking is a risk factor for various degenerative diseases like cancer of the lungs and other organs and cardiovascular disease [1]. Pyrolysis experiments offer the possibility of unraveling mechanistic information about the complex processes involved in the thermal decomposition of Tobacco biomass [2]. The most abundant phenolic compound identified in cigarette smoke is phenol [3]. However, studies on the formation of propanol from the pyrolysis of tobacco are scanty in literature. Consequently, this paper presents the first detailed investigation of propanol and its corresponding propanoxy radical from a quantum chemical perspective. Considering the intricate nature of tobacco smoke, with more than 7,000 identified constituents, and its biological variety typified by the presence of carcinogens, toxicants, irritants, tumor promoters, co-carcinogens, and inflammatory agents, any effort to identify individual compounds which cause lung cancer in smokers is arduous [4,5]. Inhalation studies of cigarette smoke have many difficulties which have

been previously summarized, all relating to the fact that laboratory animals do not voluntarily inhale cigarette smoke, but rather try to avoid it [4,6]. Nevertheless, a number of relatively recent studies have demonstrated lung tumor induction in both rats and mice exposed to cigarette smoke; whereas in the older literature, tumors of the hamster larynx were produced [5,6].

The concept of tobacco development, composition and toxicity is a very rich area of study [7]. In recent years, a lot of effort has been devoted to the evaluation of by-products of tobacco burning and the potency of cigarette smoking [7]. However, the shortfalls in describing the toxic compound formation mechanism during tobacco burning and challenges of developing model compounds which can burn under conditions representing actual cigarette smoking with respect to heating rate, temperature distribution, variation in oxygen concentration, and residence time, impede this undertaking [8].

2. Computational Chemistry and Molecular Modeling

The term computational chemistry is largely used when a mathematical technique is sufficiently well developed that it can be automated for operation on a computer [9]. Molecular modeling is one of the

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most valuable and essential tool that is used by chemists in molecular design and it describes the generation, manipulation and representation of 3-dimensional structures [10]. Computational techniques that are represented by molecular modeling usually play a critical role in the process of molecular design, which makes these computational techniques important steps of a successful modeling procedure [9].

Quantum mechanics gives a mathematical account of the behavior of electrons that has never been found to be wrong [9]. However, the quantum mechanical equations have never been solved exactly for any chemical system other than the hydrogen atom [9]. Thus, the entire field of computational chemistry is constructed around approximate solutions, some of which are more accurate than any known experimental data [9,11]. Quantum chemical calculations of thermodynamic data have developed beyond the level of simply reproducing experimental values, and can now make accurate predictions for molecules whose experimental data are unknown [12]. The target is usually set as ± 2 kcal mol⁻¹ for energy [12].

3. Experimental Section

3.1. Materials

SE01 brand of cigarettes was purchased from vendors and used without further treatment.

3.2. Characterization of molecular products

SE01 cigarette was burned and the smoke was allowed to pass through a transfer line in flowing nitrogen (pyrolysis gas). The pyrolysis effluent was collected in 1mL methanol in crimp top vials for 5 minutes. A Varian GC hyphenated to a mass selective detector (MSD) was used to determine quantitative yields of propanol and phenol. 1 μ L of sample was injected into a GC column (HP-5MS, 30m x 250 μ m x 0.5 μ m). The temperature of the injection port was set at 150 °C and temperature programming was applied at a heating rate of 15°C for 10 minutes, holding for 1 minute at 200 °C, followed by a heating rate of 25 °C for 4 minutes, and holding for 3 minutes at 300 °C. The focus of this experiment was to monitor the evolution of propanol and phenol at various pyrolysis temperatures. Electron Impact ionization energy of 70eV was used. The compounds were identified using National Institute of Science and Technology software (NIST, USA). This was further confirmed by comparing the peaks and retention times of the

components with those of standards. The experimental pyrolysis temperature was varied from 200 °C to 700 °C in increments of 100 °C.

4. Computational Methodology

All calculations have been conducted with the *Gaussian 03* computational platform [13]. *Ab initio* calculations including correlation effects have been made by using the DFT level of theory with the 6-31++G(d,p) basis set. The frequency calculations also provide thermodynamic quantities such as zero-point vibrational energy (ZPVE), temperature corrections, and absolute entropies [14]. The optimized geometries and molecular orbitals (MOs) of molecular components were used in frequency calculations in order to determine their global energies and subsequently establish their global minima. Change in enthalpy was computed between the enthalpies of formation of the reactant (neutral compound) and its corresponding free radical. QSAR in HyperChem computational code was used to estimate the toxicity indices of propanol, phenol and their corresponding free radicals (propanoxy and phenoxy radicals) [15].

5. Results and Discussions

5.1. Pyrolysis

This is a process by which a biomass material such as tobacco is thermally decomposed in the absence of oxygen [16]. The basic phenomenon that takes place during pyrolysis is initiation of pyrolysis reactions due to increased temperature, leading to the release of volatiles and the formation of char [16, 17]. This study explored the experimental release of propanol and phenols from a common cigarette brand sold in Kenya (SME01), as well as perform theoretical enthalpy, and electronic calculations using Gaussian 03 computational platform.

5.2. Experimental results

The evolution of propanol and phenol was monitored using GC-MS and the results presented in Fig 1. It is evident that the yields of both propanol and phenol peaked at about 400 °C and decreased significantly to a yield intensity of approximately 9.2×10^7 and 1.2×10^6 GC area counts, respectively, at 700 °C. It is remarkable that propanol was evolved at higher yields throughout the entire pyrolysis temperature in comparison to phenol. At 400 °C for instance, propanol was about three times higher than phenol.

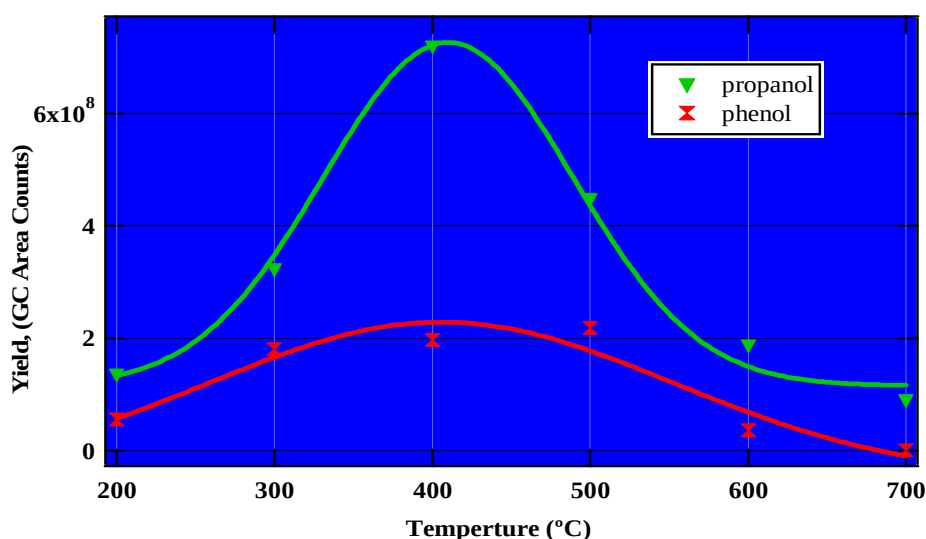


Fig.1: Yields (GC-Area counts) of propanol and phenol from the combustion of SME01 cigarette brand.

Fig. 1 above demonstrates that propanol and phenol are formed in low yields between 200 and 300 °C. Similarly, between 600 and 700 °C, the yields of the two molecular products (propanol and phenol) decreased significantly, however, it should be noted that at high temperature zones, most molecular products of cigarette smoking are converted to more lethal polycyclic aromatic hydrocarbons (PAHs) such benzo[a]pyrene and cyclopentafused PAHs [18]. The latter compounds are well established cancer causing compounds [18]. The fact that, propanol, phenol and possibly other toxic molecular by-products from combustion of tobacco are released in low yields at low temperatures is a pointer that the development of modern cigarettes should be smoked at low temperatures to minimize high doses of tobacco toxins. Optimum temperatures are therefore critical in tobacco and cigarette development.

5.3. Free radical formation

Recent developments in free radical studies have revealed that many neuronal diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis as well as other problems such as aging, diabetes, cardiovascular disease, prematurity in babies and cancer, are linked to oxidative stress [19]. At high temperatures, hydrogen may be abstracted from the molecules (propanol and phenol) forming reactive

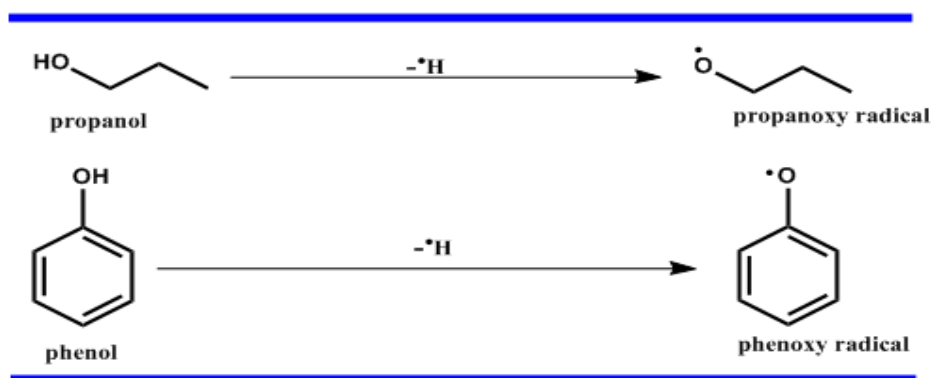
free radicals, Scheme 1. The free radicals are responsible for the reactions that lead to formation of other combustion byproducts such as aldehydes, olefins, and PAHs. Their thermo-chemical properties are therefore of paramount importance in this study. Their sum of electronic and thermal enthalpies was calculated using DFT with B3LYP/6-311++(d,p) level of theory and tabulated in Table 1, *vide infra*.

5.4. Computational details

The current work was explicitly carried out with *Gaussian 03* system of programs using DFT and the diffuse-polarized basis set, 6-311++G(d,p). To calculate the energy change for formation of a compound or a radical from its constituents, the following thermodynamic equation was employed [20].

$$\Delta rH^0 = \sum (\epsilon_0 - H_{corr})_{products} - \sum (\epsilon_0 - H_{corr})_{reactants} \quad (1)$$

Where, ΔrH^0 is change in enthalpy of the reaction, H_{corr} is zero-point correction to the thermal enthalpy and ϵ_0 is the sum of electronic and thermal enthalpies



Scheme 1. Formation of propanoxy and phenoxy radicals from propanol and phenol respectively.

Table 1 reports the enthalpies for propanol, phenol, and their corresponding free radicals calculated at the density functional level of theory. The general trend was that there was no significant variation in thermal energy with temperature for either the propanol, phenol or their analogous free radicals. Nonetheless, it was observed that

propanoxy and phenoxy radicals had lower negative enthalpy values as compared to those of molecular parent compounds (propanol and phenol).

Table 1: Thermo-chemical data for molecular compounds and their corresponding radicals.

Temp. (K)	Enthalpy (Hartrees/molecule)			
	propanol	Propanoxy radical	phenol	Phenoxy radical
373	-194.30	-193.65	-307.54	-306.90
473	-194.30	-193.64	-307.54	-306.90
573	-194.29	-193.64	-307.53	-306.89
673	-194.29	-193.63	-307.53	-306.89
773	-194.28	-193.63	-307.52	-306.88
873	-194.27	-193.62	-307.51	-306.87
973	-194.27	-193.61	-307.50	-306.86
1073	-194.26	-193.61	-307.49	-306.86
1173	-194.25	-193.60	-307.49	-306.85
1273	-194.24	-193.59	-307.48	-306.84

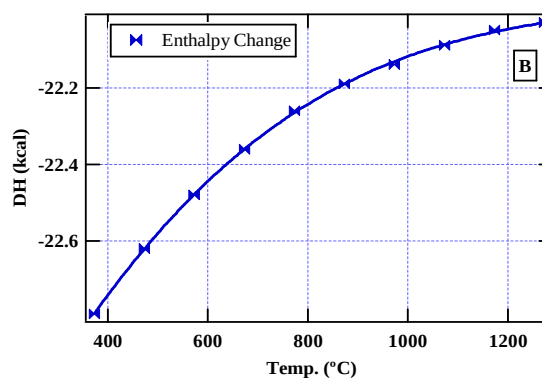
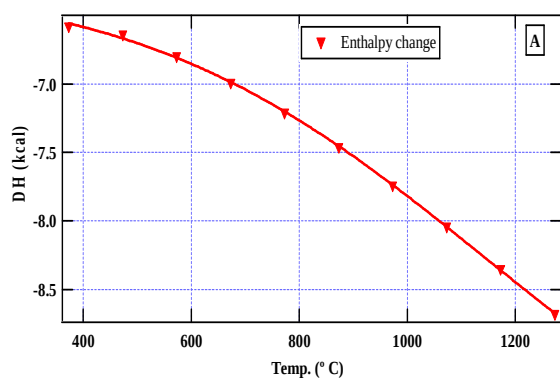
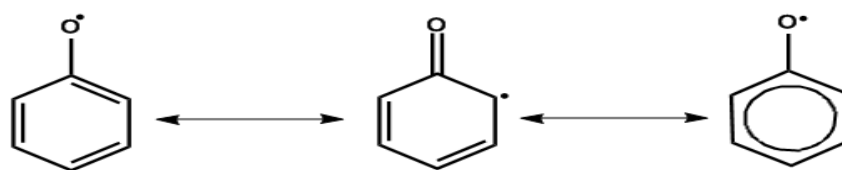
Fig.2: Enthalpy changes as a function of temperature: **A.** propanol-propanoxy radical and **B.** phenol-phenoxy radical enthalpy changes.

Fig. 2 predicts remarkable results on the thermo-chemical behavior of propanol and phenol towards the formation of their respective free radicals. Whereas the enthalpy change for the formation of propanoxy radical from propanol (Fig. 2A) is accompanied by increase in exothermicity with increase in temperature while that of formation of phenoxy radical from phenol is accompanied by decrease in exothermicity with increase in temperature. Nonetheless, the high negative enthalpy changes during the conversion of phenol to phenoxy radical is an indication that phenoxy radical is readily formed from phenol. On the other hand, the low negative enthalpy values during the formation of propanoxy radical from propanol suggests that formation of propanoxy radical from propanol is not readily favored. This is characteristic of the structures of propanoxy and phenoxy radicals.

The phenoxy radical is viewed as most stable compared to the propanoxy radical because it exhibits various resonance structures as shown in Scheme 2. Propanoxy radical has only one structure and thus cannot exhibit resonance behavior. However, propanoxy radical being unstable has a short life-time and therefore very reactive. This makes it biologically hazardous because it is capable of reacting more readily with DNA, lipids, other biological compounds such as microsomes, and RNA. Nevertheless, phenoxy radical is a well-established biological pollutant [21]. It is classified as a persistent free radical that has long life-times and can react with biological molecules in the body to cause serious cellular damage and subsequent oxidative stress and cancer [21,22].



Scheme 2. Resonance structures of phenoxy radical.

5.5. Toxicity indices

The relative toxicities of the compounds under study were explored using the QSAR method incorporated in the HyperChem computational software program [15]. The logarithm of octanol-water partition coefficient is an important parameter in determining the relative toxicity of compounds [23]. It predicts the lipophilicity and hydrophobicity of a pollutant. Lipophilicity correlates with many biological activities such as mutagenicity and carcinogenicity [9,23]. QSAR modeling establishes an attractive approach to preliminary assessment of the impact on environmental health by a primary pollutant and the set of transformation products that may be persistent and toxic to the environment [24].

Table 2: QSAR toxicity indices for propanol, phenol, and their corresponding free radicals.

Compound/Radical	P	Log P
propanol	8.71	0.94
Propanoxy radical	512.86	2.71
phenol	3.72	0.57
Phenoxy radical	97.72	1.99

It is clear from Table 2 above that propanoxy radical is about 513 more soluble in water than in octanol and therefore highly hydrophilic. This supports the thermo-chemical data that propanoxy radical is indeed very reactive towards biological systems (Fig. 3A). This is because, biological systems are considered hydrophilic and inadvertently polar. High lipophilicity correlates more strongly with biological activity, which translates to more oxidative stress and extensive cellular injury [23]. Phenoxy radical on the other hand is about 98 times more soluble in water than

in octanol and subsequently also very reactive in contact with biological systems. Lipophilic compounds can cross biological barriers which contain lipids, for example, cell or microsomal membranes and skin stratum consequently causing cell aberrations and subsequent oxidative stress and cancer [23,25,26]. The molecular products, propanol and phenol, are less polar and less soluble in water. Their water-octanol coefficients were estimated to be 8.71 and 3.72, respectively (Table 2). This suggests that they are more soluble in octanol and therefore highly hydrophobic. Low toxicity index does not imply that a compound is less toxic but may react with non-polar biological

components such as lipids and eventually cause cell alterations leading to cancer and gene mutation.

5.6. Molecular geometries

Geometrical parameters such as bond lengths and bond angles have a great influence on the strength of the bonds involved and consequently the potential energy surface. The stronger the molecular bond of a compound, the higher the vibrational frequency. The potential energy surfaces of the molecular products and radicals have been conducted in detail using DFT with B3LYP/6-31G++(d,P) level of theory. Fig. 3 reports the optimized structures investigated in this study.

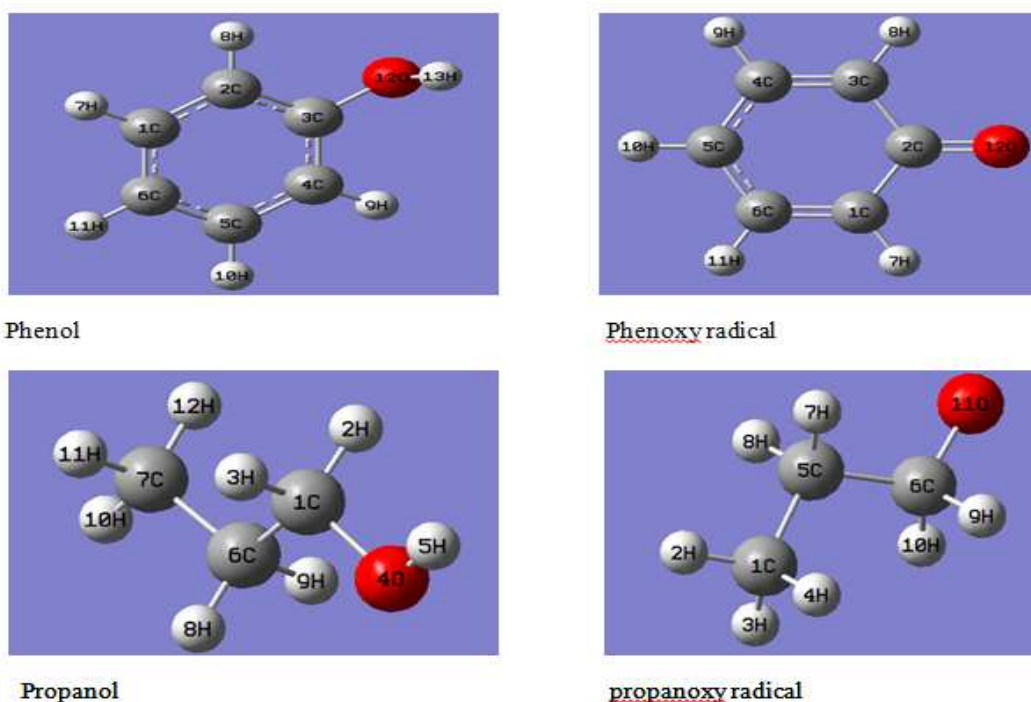


Fig. 3: Optimized geometries of phenol, propanol and their corresponding free radicals.

A geometry optimization will determine the potential energy minimum that is nearest to the input structure on the potential energy surface (PES) [11]. This search follows the potential energy surface such that it is continuously moving towards a lower energy [11]. The calculation will converge once a minimum energy point on the PES

has been reached. Since the fundamental objective is to find the global minimum on the molecular structure, it is imperative that the input structure is well selected [9]. The computed geometrical parameters such as bond lengths and bond angles are reported in Table 3, *vide infra*.

Table 3: Bond angles and bond lengths of optimized structures.

Compound /Radical	Bond angle (°)	Bond length (Å)
Phenol	H13O12C3 = 109.76	H9C4 = 1.08
	C2C1C6 = 120.31	H13O12 = 0.96
	H9C4C5 = 121.21	
Phenoxy radical		
	H7C1C2 = 117.08	O12C2 = 1.25
	H10C5C6 = 119.65	C2C3 = 1.45
	C3C4C5 = 120.28	
Propanol		
	H5 O4 C1 = 108.98	O4 C1 = 1.43
	H8 C6 C1 = 108.45	C6 H8 = 1.95
	H8C6 H1 = 106.66	
Propanoxy radical		
	O4 C1 H2 = 107.05	O4C1= 1.36
	C1C 5 H8 = 108.43	H8C5 = 1.09
	H8 C5 H7 = 106.65	

6. Conclusion

Tobacco use has always been a controversial subject with its increasing popularity on one side and the giving of evidence of clinical risks on one side. We have established from this study that propanoxy radical is not only very unstable but also very reactive towards polar compounds of biological nature hence making it a prime suspect for causing oxidative stress, cancer and respiratory problems such as emphysema and whizzing. Surprisingly, the investigation of propanol and propanoxy radical in cigarette smoke has not been studied before. Therefore this study is the first to explore the presence of propanol in mainstream cigarette smoking. This is critical in understanding the composition of cigarette smoke and its health problems. The enthalpy data indicate that the exothermicity process for converting phenol to phenoxy radical decreases with increase in temperature while that of propanol to propanoxy radical increases with increase in temperature.

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