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Article

Theoretical investigation of pKa values for selected Aromatic Phenolic derivatives:A Comparative study using DFT and Hartree-Fock Computational approaches

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Abstract: This study aims to theoretically calculate the acidity functions of a series of phenolic compounds using two computational methods, namely the Hartree–Fock (HF) method and Density Functional Theory (DFT), with the)6-31G(basis set for both methods. A comparison between the two methods was conducted by theoretically calculating the thermodynamic functions (ΔS, ΔH, and ΔG) and energy-related parameters, including the (HOMO , LUMO energies, hardness, chemical potential, and global electrophilicity index)using Gaussian 09W. The pKa values were determined through statistical analysis of the experimental pKa values of these compounds in relation to the theoretically calculated parameters. The results showed that the HF method provided the best performance, with a correlation coefficient of (R^2 = 0.989) between the experimental pKa values and the global electrophilicity index (ω). This was followed by the DFT method, which yielded a correlation coefficient of (R^2 = 0.977) between the experimental pKa values and the chemical potential (μ).

Keywords: Quercetin; Cisplatin; Cardiotoxicity; Oxidative stress; Inflammation; Antioxidant defense.

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1. Introduction

In recent years, computational chemistry has made significant advanced through the use of quantum mechanical methods, particularly (HF) and (DFT)]1[. These methods provide reliable predictions of electronic and thermodynamic properties while requiring less computational time and lower costs than experimental studies[2]. Acidic properties are important characteristics for evaluating the behavior of organic compounds as they directly influence their chemical and physical properties, stability and interactions in various applications including pharmaceutical and environmental fields[3]. Phenolic compounds have received considerable attention in theoretical and computational chemistry because they contain a hydroxyl group directly attached to aromatic ring[4]. This structural feature can strongly influence their electronic and structural properties through factors such as the nature and position of substituent, resonance effect and inductive effects[5]. Consequently, predicting ionization constants using theoretical methods has become an essential area of reach as it helps establish a relationship between molecular structure and chemical activity[6].

Density Functional Theory (DFT)

Density Functional Theory (DFT) is a theoretical framework that aims to describe and understand atomic and electronic behavior based on the principles of quantum mechanics[7]. Accordingly, it is widely employed to calculate physical and chemical properties and to provide insight into various molecular phenomena. (DFT) is one of the most widely used computational methods because of its applicability to a wide range of molecular systems with relatively high computational efficiency[8]. The theory is primarily concerned with determining the electronic properties of a molecule in its ground state, which can be described in terms of its electron density.

One of the major advantages of(DFT) is its ability to account for electron-correlation effects more accurately than the Hartree–Fock (HF) method, in which electron correlation is not explicitly considered[9]. This feature contributes to the reliability and effectiveness of (DFT), making it a widely accepted and valuable approach in theoretical and computational chemistry research[10]. With the continuous development of computer technology and computational software, the number of studies and applications employing (DFT) has increased considerably. The applications of (DFT) are not restricted to the calculation of molecular energies; they also include the determination of the forces acting on individual atoms. By optimizing the molecular geometry and determining the structural changes required to minimize these forces, an equilibrium structure corresponding to a stable molecular configuration can be obtained[11].

Hartree - Fock (HF) Method

The Hartree - Fock method is one of the most important methods used in theoretical chemistry and quantum chemistry [12]. It is used to study the electronic structure of molecules and atoms by solving the Schrödinger equation approximately according to the self-consistent field principle [13]. This method is based on representing the electronic wave function by a Slater determinant, which satisfies the Pauli exclusion principle and takes into account the electron exchange effect [14]. However, it does not fully describe the electron correlation energy [15]. Nevertheless, it is characterized by accuracy and computational efficiency and serves as an essential starting point for other methods, in addition to being used as a basis for comparison with the results of Density Functional Theory (DFT) [16]. The (HF) method is widely used to calculate total energies, perform geometry optimization, and estimate molecular and electronic properties [17]. Therefore, it is considered a fundamental method in computational, quantum, and theoretical chemistry [18].

2. Methodology

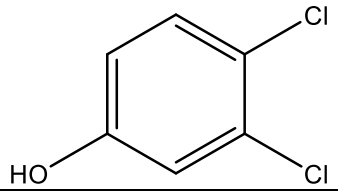
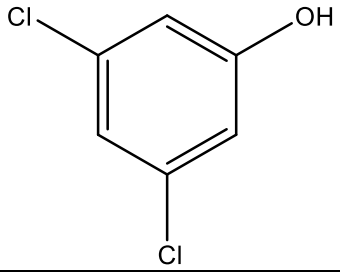
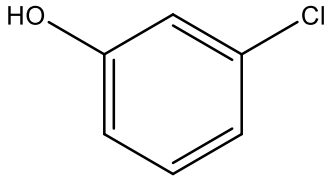
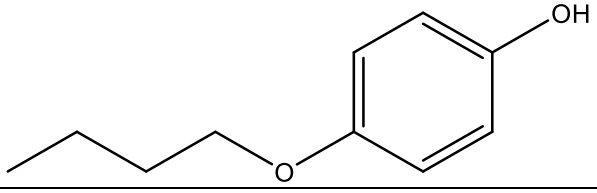
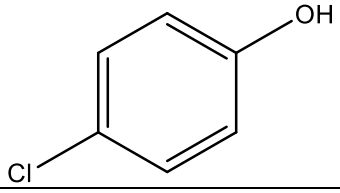
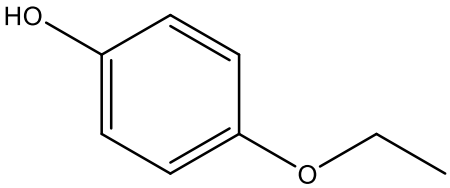
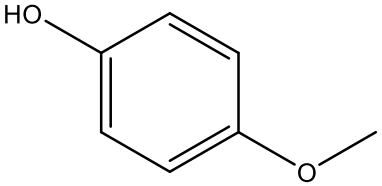
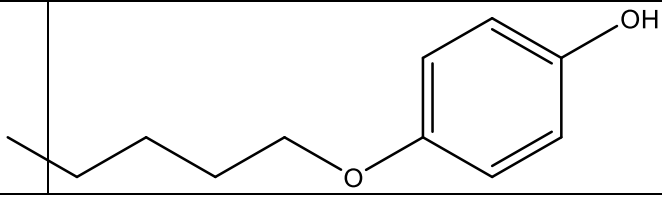
Scientific Background

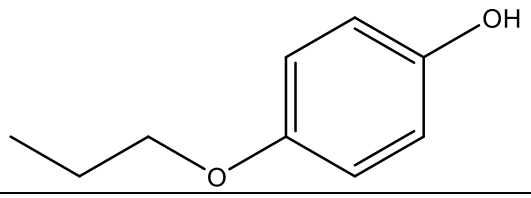
In this research, the programs (Chem.Office), (Gaussian program Gauss View 6.0.16), and (Gaussian 09W) were used [19]. The (Gaussian 09W) program has a distinctive feature, namely, its extensive amount of information in the field of computational and theoretical chemistry [20]. The pKa values were obtained from the theoretically calculated variables, namely, the thermodynamic functions (ΔH, ΔG, ΔS) and the energy-related functions (HOMO, LUMO, hardness, chemical potential, and global electrophilicity index).

The calculation steps in the (Gaussian 09W) program are as follows: first, the molecular structure is drawn in the (Chem.draw) program, and then the compound is transferred to the (Chem.3D) program and saved as an (Input File) . Next, the (Gauss View 6.0) program is opened, and the file saved in the (Chem.3D) program in the form of an (Input File) is opened . Then, the (Calculate) button is selected, followed by (Gaussian Calculation Setup). From the (Job Type) button, (Optimization) is selected, and then

(Minimum) is selected to obtain the lowest energy, at which point the compound is more stable and the optimal sterochemical conformation is otained . Next, from the (Method) button, the theoretical method is selected and the (Basis Sets) are specified . After that, (Submit) is selected, and the calculation is performed in the (Gaussian 09W) program. Upon completion, the results are saved using (Notepad).

Studied Compounds

COMP.	Structure
3,4-Dichlorophenol	
3,5-Dichlorophenol	
3-Chlorophenol	
4-Butoxyphenol	
4-Chlorophenol	
4-Ethoxyphenol	
4-Methoxyphenol	
4-Pentoxyphenol	

4-Propoxyphenol	

3. Results and Discussion

Table 1. Values of the Energy Functions Using the (DFT/6-31G) Method.

COMP.	HUMO	LUMO	ω	μ	ŋ
3,4-Dichlorophenol	0.23582-	0.02755-	0.083262	-0.13169	0.104135
3,5-Dichlorophenol	0.24616-	0.02779-	0.085919	-0.13698	0.109185
3-Chlorophenol	0.23448-	0.01468-	0.07061	-0.12458	0.1099
4-Butoxyphenol	0.20077-	0.00220-	0.051867	-0.10149	0.099285
4-Chlorophenol	0.22606-	0.01603-	0.069761	-0.12105	0.105015
4-Ethoxyphenol	0.20177-	0.00292-	0.052675	-0.10235	0.099425
4-Methoxyphenol	0.20256-	0.00391-	0.053649	-0.10324	0.099325
4-Pentoxyphenol	0.20054-	0.00200-	0.051655	-0.10127	0.09927
4-Propoxyphenol	0.20121-	0.00257-	0.052263	-0.10189	0.09932

Table 2. Values of the Thermodynamic functions Using the (DFT/6-31G) Method.

COMP.	ΔH	ΔG	ΔS
3,4-Dichlorophenol	0.094645	0.052444	88.818
3,5-Dichlorophenol	0.094579	0.052230	89.132
3-Chlorophenol	0.103194	0.064343	81.768
4-Butoxyphenol	0.237065	0.184533	110.563
4-Chlorophenol	0.103266	0.064394	81.813
4-Ethoxyphenol	0.176825	0.131538	95.316
4-Methoxyphenol	0.146773	0.105106	87.697
4-Pentoxyphenol	0.267151	0.210969	118.246
4-Propoxyphenol	0.206943	0.157944	103.125

Table 3. pKa Values Using the (DFT/6-31G) Method.

COMP.	Theor. pKa	Ex. pKa	ΔpKa
3,4-Dichlorophenol	8.6632113	8.65	0.013211
3,5-Dichlorophenol	8.378403	8.22	0.158403
3-Chlorophenol	9.0457374	9.11	-0.06426
4-Butoxyphenol	10.289149	10.26	0.029149
4-Chlorophenol	9.2360582	9.46	-0.22394
4-Ethoxyphenol	10.242848	10.25	-0.00715
4-Methoxyphenol	10.194931	10.27	-0.07507
4-Pentoxyphenol	10.300724	10.13	0.170724
4-Propoxyphenol	10.267344	10.27	-0.00266

Figure 1. Correlation between the Experimental and Theoretical pKa Values Using the (DFT/6-31G) Method

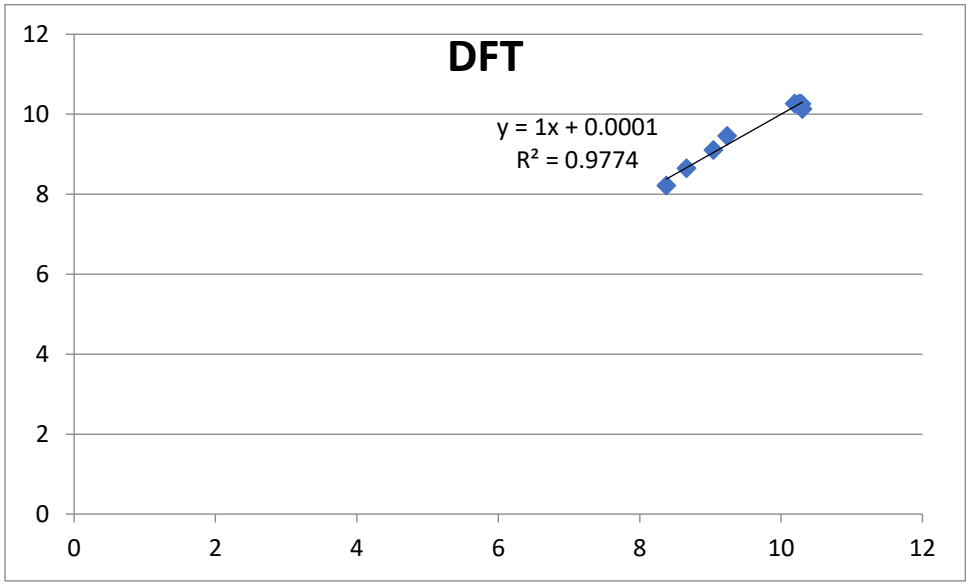


Table 4. Values of the Energy Functions Using the (HF/6-31G) Method

COMP.	HUMO	LUMO	ω	μ	ŋ
3,4-Dichlorophenol	-0.33371	0.10391	0.030168	-0.1149	0.21881
3,5-Dichlorophenol	-0.34386	0.10266	0.032573	-0.1206	0.22326
3-Chlorophenol	-0.33037	0.11861	0.024969	-0.10588	0.22449
4-Butoxyphenol	-0.29705	0.12979	0.016385	-0.08363	0.21342
4-Chlorophenol	-0.32175	0.11835	0.023501	-0.1017	0.22005
4-Ethoxyphenol	-0.29803	0.12909	0.016705	-0.08447	0.21356
4-Methoxyphenol	-0.29897	0.12806	0.017101	-0.08546	0.213515
4-Pentoxyphenol	-0.29681	0.12999	0.016301	-0.08341	0.2134
4-Propoxyphenol	-0.29749	0.12941	0.016544	-0.08404	0.21345

Table 5. Values of the Thermodynamic functions Using the (HF/6-31G) Method.

COMP.	ΔH	ΔG	ΔS
3,4-Dichlorophenol	0.101158	0.059885	86.866
3,5-Dichlorophenol	0.101098	0.059668	87.197
3-Chlorophenol	0.110186	0.072040	80.287
4-Butoxyphenol	0.251984	0.200405	108.556
4-Chlorophenol	0.110281	0.072119	80.320
4-Ethoxyphenol	0.188260	0.143675	93.837
4-Methoxyphenol	0.156534	0.115398	86.578
4-Pentoxyphenol	0.283827	0.228779	115.859
4-Propoxyphenol	0.220117	0.172029	101.210

Table 6. pKa Values Using the (HF/6-31G)) Method.

COMP.	Theor. pKa	Ex. pKa	
3,4-Dichlorophenol	8.5689916	8.65	-0.081
3,5-Dichlorophenol	8.2733923	8.22	0.05339
3-Chlorophenol	9.2079873	9.11	0.09799
4-Butoxyphenol	10.263012	10.26	0.00301
4-Chlorophenol	9.3883937	9.46	-0.0716
4-Ethoxyphenol	10.223698	10.25	-0.0263
4-Methoxyphenol	10.175089	10.27	-0.0949
4-Pentoxyphenol	10.273406	10.13	0.14341
4-Propoxyphenol	10.243502	10.27	-0.0265

Figure 1. Correlation between the Experimental and Theoretical pKa Values Using the (HF/6-31G) Method.

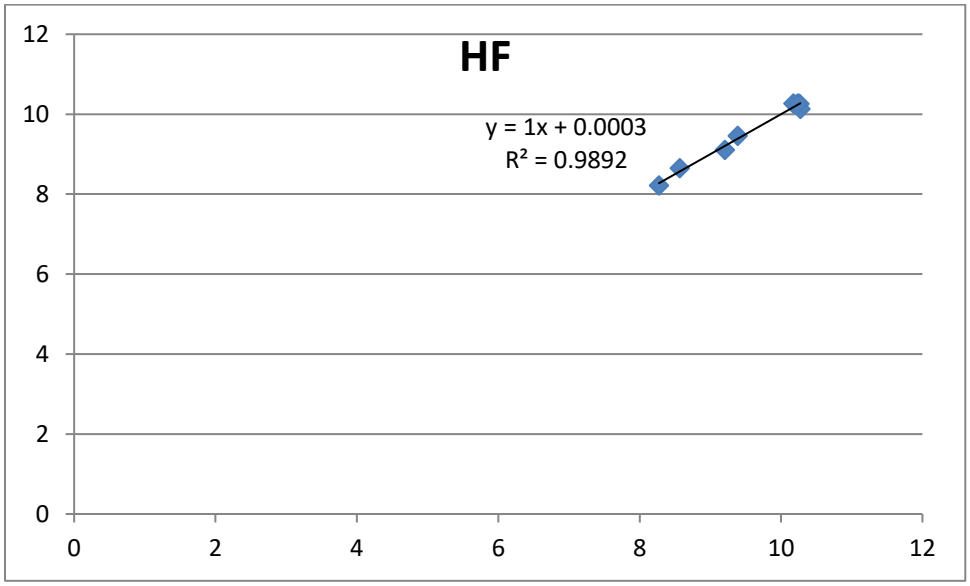


Table 7. Statistical Analysis Results for the (DFT/6-31G) Method.

Variables with Experimental pKa Values	R^2
pKa+HOMO	0.961
pKa+LUMO	0.955
pKa+ΔH	0.607
pKa+ΔG	0.636
pKa+ΔS	0.308
pKa+μ	0.977
pKa+ŋ	0.769
pKa+ω	0.976

Table 8. Statistical Analysis Results for the (HF/6-31G) Method.

Variables with Experimental pKa Values	R^2
pKa+HOMO	0.972
pKa+LUMO	0.955
pKa+ΔH	0.608
pKa+ΔG	0.633
pKa+ΔS	0.326
pKa+μ	0.987
pKa+ŋ	0.761
pKa+ω	0.989

The values of chemical hardness (η) were obtained from the following equation [21]:

$$\eta = (ELUMO - EHOMO)/2$$

The values of chemical potential (μ) were obtained from the following equation [22]:

$$\mu = (EHOMO + ELUMO)/2$$

The values of the global electrophilicity index (ω) were obtained from the following equation [23]:

$$\omega = \mu^2/2\eta$$

The theoretical pKa values were obtained from the following equations based on the results of the statistical analysis. For the (DFT/6-31G) method, the correlation coefficient ($R^2 = 0.977$) was obtained between the experimental pKa values and the chemical potential (μ) values. The theoretical pKa values were then the correlation coeffiecient according to the following equation:

$$pKa = 53.839(\mu) + 15.753$$

For the (HF/6-31G) method, the correlation coefficient ($R^2 = 0.989$) between the experimental pKa values and the global electrophilicity index (ω) values was obtained. The theoretical pKa values were then correlation coeffiecient(R) according to the following equation:

$$pKa = -122.913(\omega) + 12.273$$

The relationship between (Ka) and (pKa) is inverse because ($pKa = -\log\{Ka\}$) [24]. Thus, as the acidity of phenol increases, the pKa value decreases [25]. As the stability of the phenoxide ion ($C_6H_5O^-$) formed by the loss of a proton (H^+) increases, the acidity of phenols also increases [26]. Electron-withdrawing groups increase the acidity of phenols because they withdraw electron density from the ring and the oxygen atom, thereby stabilizing the negative charge on the phenoxide ion and making it more stable [27]. For example, (3,5-Dichlorophenol) has the highest acidity among the compounds used because it contains two chlorine groups, which are electron-withdrawing groups through the inductive effect.

In contrast, electron-donating groups make the phenoxide ion less stable because they donate electron density toward the ring and the oxygen atom . This decreases the stability of the phenoxide ion and, consequently, reduces acidity . For example, (4-Methoxyphenol) and (4-Propoxyphenol) contain electron-donating groups (Methoxy, Propoxy), respectively. Therefore, they are the least acidic compounds among those used, despite having the highest (pKa) values. This is because the relationship between acidity and (pKa) is inverse.

4. Conclusion

The findings of this study demonstrate that cisplatin induces significant cardiac oxidative and inflammatory damage in rats, accompanied by increased cardiac injury and oxidative stress markers and depletion of antioxidant defenses. Quercetin administration markedly reduced these alterations and improved the histological structure of cardiac tissue. Therefore, quercetin exhibited a clear protective effect against cisplatin-induced cardiotoxicity, mainly through attenuation of oxidative stress and inflammation.

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