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Theoretical Calculations of pKa Values for Substituted Carboxylic Acid

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Abstract: Six different calculation methods have been used for studying ten derivatives of carboxylic compounds. Semi-empirical methods (AM1 and PM3), Hartree Fock (HF/STO-3G and HF/3-21G), and Density Function Theory (DFT/STO-3G and DFT/6-31G) were employed to calculate many theoretical physical parameters. The calculated data were correlated with experimental values of pKa using different regression types (enter, stepwise and simple regression). Depending on the Fisher values, (HF/STO-3G) was considered as the best method to predict the pKa data compare to the (PM3) method using enter method. While (HF/3-21G) method had higher values of Fisher compared with (PM3) using (stepwise) and (simple) methods. So, Multiple linear regression was performed to obtain the prediction values using (enter) compare with (stepwise), and the two methods are the best compared with simple regression. The acid strength was affected by the type of substituent, with electron-withdrawing substituents lowering the pKa (increase the acidity of the carboxylic acid versus electron releasing groups increasing it (decreasing the acidity of the carboxylic acid).

Keywords: pKa, DFT, Hartree-Fock, Semi-empirical, Carboxylic acid

Introduction

The dimer form is shown in the carboxylic acid in the solid and liquid phase by an association between two molecules by inter-molecular hydrogen bonding. The term pKa of the carboxylic acid can be determined depending on the equation:

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^{\ominus} + H_3O^{\oplus}$$

$$Ka = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]}$$

$$pKa = -logKa \text{ ------ (1)}$$

Or by the dissociation constant (Ka) of the following reaction:

$$BH \rightleftharpoons B^{\ominus} + H^{\oplus}$$

$$Ka = \frac{[H^+][B^-]}{[BH]} \text{ ------ (2)}$$

In chemistry, the term (Ka) is called the acid dissociation constant, which means the value of the acid strength. So, the stronger acid refers to larger values of (Ka).

The (pKa) value can be evaluated depending on the (⊗G) in temperature (T) to form the equation (3), and after that, the equation may be rearrangement to form the equation (4):

$$\Delta G = -RTlnK_a \text{ ------- (3)}$$

$$pK_a = \frac{\Delta G}{2.303RT} \text{ ---------- (4)}$$

Where (R) is a gas constant (1.98 cal.mol-1.k-1), (T) is the absolute temperature (298.0 K). The strongest acid forms a weak conjugate base and acid respectively. The weak acid dissociates into strong acid and base respectively.

$$\underset{\text{Strong Acid}}{HCl} \rightleftharpoons \underset{\text{Weak Conjucated Base}}{H^{\oplus} + Cl^{\ominus}}$$

$$\underset{\text{Weak Acid}}{NH3} \rightleftharpoons \underset{\text{Strong Conjucated Base}}{NH4^{\oplus} + H^{\ominus}}$$

Soft acid means that having a low positive charge, low electro-negativity, and high polarizabilities like sulphur and halogen. While, the hard acid is having a high positive charge, high electro-negativity, and low polarizability like hydrogen atoms [1,2]. Many compounds of carboxylic acid are used as drugs (aspirin)[3], fruits (lemons), and nature (lactic acid as the source of milk)[4].

Many derivatives have been obtained directly by a relationship between the experimental values with the computed theoretical physical parameters [5]. The thermodynamic cycle in the gas and the solvation energy for the reactant and the product are important to find the pKa by regression between the experimental with calculated parameters theoretically [6-8].

The pKa values have been determined, estimated, and predicted by HPLC [9] beside theoretical calculations methods [10-12] like simple regression [13], and quantitative structure-activity relationship (QSAR) [14]. Also, UV-Vis spectroscopy was used for pharmaceutical compounds [15], RNA[16], and DNA[17]. Previously, the derivatives of the carboxylic acid were calculated theoretically in the aqueous solution. Density function theory (DFT) and polarized continuum model (PCM) were used to predict the pKa values in the different thermodynamic cycles [18]. The quantum procedure is very important which is used in the drug [19], use of (QSPR) for predicted of pyridine series [20], determination of solubility at types of solvation [21], and lipophilicity [22]. This research aims to use different methods of the theoretical calculations AM1, PM3, HF/STO-3G, HF/3-21G, DFT/STO-3G, and DFT/6-31G to calculate and predict the pKa values. Many physical parameters were determined like HOMO, LUMO, zero-point energy, thermal energy, enthalpy, thermal free energy, total energy, entropy, heat capacity, and heat of formation.

Computational Procedure

Different methods at various basis sets have been used to accurately and predication of the pKa values. AM1, PM3, HF/STO-3GHF/3-21G, DFT/STO-3G, and DFT/6-31G were applied to study the acid-base physical properties of the substituent carboxylic acid. The calculations were performed by Chem-Office Ultra Program (16.0.0.82) package. Gaussian (98W) was used to find the thermodynamic parameters. Firstly, the energy of all the compounds was minimized with a molecular mechanic to reach the best stable form and less steric energy. Later, the global minima in the gas phase were obtained. SPSS software was used in the statistical methods especially, enter, stepwise, and simple regression methods.

Results and Discussion

pKa values for different substituted carboxylic acids were selected in Table 1 [23].

Table 1. Experimental pKa value for compounds set (A1)

No.	Set (A1)	pKa	No.	Set (A1)	pKa
1	$C_4H_9OCH_2CO_2H$	3.69	6	$CHCCH_2COOH$	3.32
2	CH_3CHCH_3-OCH_2CO_2H	3.69	7	$C_6H_5OCH_2CO_2H$	3.12
3	$C_3H_7OCH_2CO_2H$	3.65	8	$ClCH_2CO_2H$	2.81
4	$C_2H_5OCH_2CO_2H$	3.60	9	$CH_3CHClCO_2H$	2.80
5	$CH_3OCH_2CO_2H$	3.54	10	CH_3COCO_2H	2.50

Many theoretical parameters are evaluated like highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), zero energy (Z.E), thermal energy (En.), the energy of enthalpy (Enth.), the free energy (Free En.) (ΔG), total energy (T.E), entropy (S), and heat of formation (ΔHf).

Semi-empirical Method:

The quantum parameters calculated have been shown in tables 2-4 using semi-empirical, Hartree-Fock, and Density function theory.

Table 2. Physical properties for A1 compounds using AM1 and [PM3]

No.	HOMO (e.V)	LUMO (e.V)	Z.E (a.u)	En. (a.u)	Enth. (a.u)
1	-0.413 [-0.410]	0.039 [0.037]	0.182 [0.176]	0.193 [0.187]	0.194 [0.188]
2	-0.408 [-0.409]	0.041 [0.038]	0.153 [0.148]	0.163 [0.158]	0.163 [0.159]
3	-0.413 [-0.410]	0.039 [0.037]	0.154 [0.148]	0.163 [0.158]	0.164 [0.159]
4	-0.414 [-0.410]	0.039 [0.037]	0.125 [0.120]	0.133 [0.129]	0.134 [0.130]
5	-0.415 [-0.411]	0.038 [0.036]	0.096 [0.092]	0.103 [0.099]	0.104 [0.100]
6	-0.409 [-0.407]	0.032 [0.032]	0.073 [0.071]	0.079 [0.078]	0.080 [0.079]
7	-0.352 [-0.371]	0.001 [-0.011]	0.151 [0.146]	0.161 [0.156]	0.162 [0.157]
8	-0.423 [-0.410]	0.005 [0.004]	0.053 [0.052]	0.059 [0.058]	0.060 [0.059]
9	-0.418 [-0.408]	0.005 [0.002]	0.082 [0.080]	0.088 [0.087]	0.089 [0.088]
10	-0.411 [-0.407]	-0.002 [0.002]	0.073 [0.071]	0.079 [0.078]	0.080 [0.079]

Table 2. Continued

No.	Free En. (a.u)	T.E Kcal .mol	C.V Cal/ mol.K	S Cal/ mol.K	- Hf Kcal.mol
1	0.142 [0.136]	121.29 [117.80]	36.25 [37.98]	109.03 [109.72]	0.25 [0.236]
2	0.116 [0.110]	101.99 [99.46]	32.20 [33.81]	100.59 [103.39]	0.24 [0.228]
3	0.116 [0.111]	102.42 [99.45]	31.54 [33.11]	101.01 [101.93]	0.24 [0.227]
4	0.090 [0.085]	83.54 [81.08]	26.84 [28.26]	92.90 [94.15]	0.23 [0.219]
5	0.064 [0.060]	64.90 [62.74]	21.98 [23.32]	84.18 [85.25]	0.22 [0.211]
6	0.043 [0.041]	49.87 [49.04]	20.25 [20.90]	78.93 [79.67]	0.06 [0.071]
7	0.112 [0.110]	101.16 [98.06]	35.01 [36.02	105.03 [98.15]	0.16 [0.158]

			]		
8	0.023 [0.022]	36.83 [36.46]	16.78 [17.46]	76.34 [76.83]	0.16 [0.159]
9	0.050 [0.048]	55.51 [54.84]	22.21 [23.14]	82.60 [83.44]	0.17 [0.171]
10	0.041 [0.040]	49.60 [48.99]	20.56 [21.42]	81.95 [81.41]	0.20 [0.208]

Table 3. Physical properties for A1 compounds using HF/STO-3G and [HF/3-21G]

	HOMO	LUMO	Z.E	En.	Enth
1	-0.325 [-0.424]	0.312 [0.193]	0.213 [0.193]	0.224 [0.204]	0.225 [0.205]
2	-0.322 [-0.423]	0.313 [0.192]	0.179 [0.162]	0.187 [0.171]	0.188 [0.172]
3	-0.325 [-0.425]	0.312 [0.192]	0.179 [0.163]	0.188 [0.172]	0.189 [0.173]
4	-0.326 [-0.425]	0.311 [0.192]	0.145 [0.132]	0.153 [0.140]	0.154 [0.141]
5	-0.328 [-0.427]	0.309 [0.191]	0.111 [0.102]	0.117 [0.108]	0.118 [0.109]
6	-0.330 [-0.416]	0.295 [0.173]	0.083 [0.077]	0.089 [0.083]	0.090 [0.084]
7	-0.270 [-0.341]	0.252 [0.125]	0.171 [0.159]	0.180 [0.168]	0.181 [0.169]
8	-0.356 [-0.451]	0.260 [0.112]	0.061 [0.056]	0.066 [0.061]	0.067 [0.062]
9	-0.350 [-0.446]	0.260 [0.109]	0.094 [0.086]	0.101 [0.093]	0.102 [0.094]
10	-0.321 [-0.424]	0.212 [0.081]	0.082 [0.076]	0.089 [0.082]	0.090 [0.083]

Table 3. Continued

	FreeEn.	T.E	C.V	S	- Hf
1	0.176 [0.156]	140.3 [128.0]	33.40 [34.51]	102.8 [102.3]	452.96 [456.2]
2	0.144 [0.127]	117.6 [107.6]	29.80 [30.65]	94.5 [94.1]	414.38 [417.4]
3	0.144 [0.128]	118.0 [108.1]	29.17 [29.98]	95.72 [95.0]	414.38 [417.4]
4	0.112 [0.099]	95.8 [88.0]	24.95 [25.45]	88.52 [87.7]	375.80 [378.6]
5	0.080 [0.071]	73.7 [68.1]	20.62 [20.88]	81.18 [80.2]	337.22 [339.7]
6	0.053 [0.047]	55.8 [52.1]	19.50 [19.35]	77.95 [77.6]	299.52 [301.7]
7	0.134 [0.123]	112.7 [105.9]	31.88 [32.29]	97.32 [96.5]	525.39 [529.2]
8	0.031 [0.026]	41.4 [38.6]	16.14 [16.49]	75.52 [75.1]	678.80 [683.2]
9	0.063 [0.055]	63.3 [58.4]	21.26 [21.64]	81.88 [80.6]	-717.38 [-722.0]
10	0.052 [0.046]	55.5 [51.7]	20.01 [19.76]	79.81 [77.5]	-336.03 [-338.6]

Table 4. Physical properties for A1 compounds using DFT/STO-3G and [DFT/6-31G]

No.	HOMO	LUMO	Z.E	En.	Enth
1	-0.125 [-0.271]	0.126 [-0.003]	0.196 [0.181]	0.206 [0.192]	0.207 [0.192]
2	-0.123 [-0.269]	0.129 [-0.002]	0.163 [0.151]	0.172 [0.161]	0.173 [0.162]
3	-0.125 [-0.272]	0.125 [-0.003]	0.164 [0.152]	0.173 [0.161]	0.174 [0.162]
4	-0.126 [-0.272]	0.125 [-0.004]	0.133 [0.123]	0.140 [0.131]	0.141 [0.132]
5	-0.129 [-0.274]	0.121 [-0.005]	0.101 [0.094]	0.108 [0.101]	0.109 [0.102]
6	-0.155 [-0.277]	0.100 [-0.014]	0.075 [0.071]	0.081 [0.077]	0.082 [0.078]
7	-0.143 [-0.246]	0.072 [-0.021]	0.156 [0.148]	0.165 [0.158]	0.166 [0.159]
8	-0.171 [-0.297]	0.084 [-0.037]	0.055 [0.052]	0.060 [0.057]	0.061 [0.058]
9	-0.165 [-0.293]	0.083 [-0.047]	0.086 [0.081]	0.093 [0.087]	0.094 [0.088]
10	-0.141 [-0.269]	0.025 [-0.098]	0.074 [0.070]	0.081 [0.077]	0.081 [0.078]

Table 4. Continued

No.	FreeEn.	T.E	C.V	S	- Hf
1	0.158 [0.143]	129.1 [120.5]	34.6 [36.4]	101.4 [104.9]	455.6 [461.3]
2	0.129 [0.116]	108.1 [101.2]	30.9 [32.4]	93.7 [95.8]	416.7 [422.0]
3	0.129 [0.116]	108.5 [101.5]	30.1 [31.7]	94.3 [97.5]	416.7 [422.0]
4	0.100 [0.090]	88.0 [82.6]	25.5 [26.9]	86.6 [89.8]	377.9 [382.7]
5	0.071 [0.063]	67.6 [63.8]	20.8 [22.1]	79.0 [81.6]	339.0 [343.4]
6	0.044 [0.040]	50.7 [48.5]	21.0 [21.1]	78.9 [78.7]	301.2 [305.1]
7	0.120 [0.112]	103.5 [99.2]	34.3 [35.2]	97.5 [98.5]	528.4 [535.1]
8	0.026 [0.022]	37.8 [36.3]	16.8 [17.1]	75.1 [76.4]	-680.6 [-688.57]
9	0.054 [0.049]	58.1 [55.0]	22.2 [22.6]	82.2 [83.0]	-719.4 [-727.88]
10	0.042 [0.040]	50.5 [48.4]	21.4 [20.8]	82.2 [79.6]	-337.8 [-342.27]

The Binary Statistical

The binary correlation between the determined physicochemical parameters based on the different theoretical calculations with the experimental data was statistically and shown in Tables 5-10.

Table 5. Binary correlation between the parameters using (AM1)

	pKa	HOMO	LUMO	Z.E	En.	Enth.
pKa	1					

HOMO	-0.02	1				
LUMO	0.94	-0.32	1			
Z.E	0.72	0.38	0.52	1		
En.	0.72	0.38	0.51	1.00	1	
Enth.	0.72	0.38	0.51	1.00	1.00	1

Table 5. Continued

	FreeEn.	T.E	C.V	S	Hf
Free En.	1				
T.E	1.00	1			
C.V	0.98	0.98	1		
S	0.99	0.99	1.00	1	
Hf	-0.61	-0.61	-0.51	-0.57	1

Table 6. Binary correlation between the parameters using (PM3)

	pKa	HOMO	LUMO	Z.E	En	Enth
pKa	1					
HOMO	-0.19	1				
LUMO	0.85	-0.63	1			
Z.E	0.72	0.25	0.38	1		
En.	0.72	0.25	0.38	1.00	1	
Enth.	0.72	0.25	0.38	1.00	1.00	1

Table 6. Continued

	Free En	T.E	C.V	S	Hf
Free En.	1				
T.E	1.00	1			
C.V	0.99	0.99	1		
S	0.99	0.99	0.97	1	
Hf	-0.56	-0.56	-0.50	-0.62	1

Table 7. Binary correlation between the parameters using HF/STO-3G

	pKa	HOMO	LUMO	Z.E	En.	Enth.
pKa	1					
HOMO	0.17	1				
LUMO	0.96	-0.10	1			
Z.E	0.73	0.52	0.55	1		
En.	0.73	0.52	0.55	10.00	1	
Enth.	0.73	0.52	0.55	1.00	1.00	1

Table 7. Continued

	Free En.	T.E	C.V	S	Hf
Free En.	1				
T.E	1.00	1			
C.V	0.97	0.98	1		
S	0.98	0.99	0.99	1	
Hf	0.19	0.18	0.12	0.09	1

Table 8. Binary correlation between the parameters using HF/3-21G

	pKa	HOMO	LUMO	Z.E	En.	Enth.
pKa	1					
HOMO	0.08	1				
LUMO	0.98	-0.03	1			
Z.E	0.73	0.43	0.60	1		
En.	0.72	0.43	0.60	1.00	1	
Enth.	0.72	0.43	0.60	1.00	1.00	1

Table 8. Continued

	Free En.	T.E	C.V	S	Hf
Free En.	1				
T.E	1.00	1			
C.V	0.98	0.99	1		
S	0.99	0.99	0.99	1	
Hf	0.19	0.18	0.09	0.08	1

Table 9. Binary correlation between the parameters using DFT/STO-3G

	pKa	HOMO	LUMO	Z.E	En.	Enth.
pKa	1					
HOMO	0.76	1				
LUMO	0.93	0.54	1			
Z.E	0.74	0.78	0.57	1		
En.	0.73	0.77	0.56	1.00	1	
Enth.	0.73	0.77	0.56	1.00	1.00	1

Table 9. Continued

	Free En.	T.E	C.V	S	Hf
Free En.	1				
T.E	1.00	1			
C.V	0.95	0.96	1		
S	0.95	0.96	0.99	1	
Hf	0.18	0.17	0.11	0.08	1

Table 10. Binary correlation between the parameters using DFT/3-21G

	pKa	HOMO	LUMO	Z.E	En.	Enth.
pKa	1					
HOMO	0.29	1				
LUMO	0.92	0.18	1			
Z.E	0.72	0.61	0.60	1		
En.	0.72	0.61	0.60	1.00	1	
Enth.	0.72	0.61	0.60	1.00	1.00	1

Table 10. Binary Continued

	Free En.	T.E	C.V	S	Hf
Free En.	1				
T.E	1.00	1			
C.V	0.98	0.98	1		
S	0.99	0.99	0.99	1	
Hf	0.18	0.17	0.11	0.06	1

Later, pKa values were correlated with the calculated parameters using different types of statistical regression like enter, stepwise and simple methods.

AM1 Method
[Enter Regression]:
pKa = 4.633 + 5.063 (HOMO) + 19.354 (LUMO) + 8.215 (Free Energy) – 0.054 (C.V) + 0.012 (S) + 0.504 (Hf)
(R= 0.990 , St. error = 0.105, F= 25.35)

[Stepwise Regression]:
pKa = 5.415 + 24.266 (LUMO) + 6.674 (HOMO)
(R= 0.983 , St. error = 0.090, F= 102.693)
[Simple Regression]:
pKa = 2.748 + 21.991 (LUMO)
(R= 0.940 , St. error = 0.159, F= 60.36)

PM3 Method:
[Enter Regression]:
pKa = 11.940 + 23.196 (HOMO) + 16.575 (LUMO) + 27.402 (Free Energy) – 0.196 (C.V) + 0.043 (S) + 1.211 (Hf)
(R= 0.983 , St. error = 0.137, F= 14.66)

[Stepwise Regression]:
pKa = 11.221 + 26.971 (LUMO) + 21.039 (HOMO)
(R= 0.964 , St. error = 0.131, F= 46.40)

[Simple Regression]:
pKa = 2.864 + 18.725 (LUMO)
(R= 0.849 , St. error = 0.245, F= 20.71)

HF/STO-3G Method:
[Enter Regression]:
pKa = 1.868 + 3.259 (HOMO) + 9.881 (LUMO) + 4.675 (Free Energy) – 0.021 (C.V) - 0.002 (S) + 1.93x10-4 (Hf)
(R= 0.999 , St. error = 0.027, F= 378.51)

[Stepwise Regression]:
pKa = 1.472 + 12.239 (LUMO) + 5.138 (HOMO)
(R= 0.992 , St. error = 0.061, F= 226.79)

[Simple Regression]:
pKa = -0.102 + 11.893 (LUMO)
(R= 0.956, St. error = 0.136 , F= 85.01)

HF/3-21G Method:
[Enter Regression]:
pKa = 2.471 + 0.876 (HOMO) + 8.992 (LUMO) + 3.233 (Free Energy) -3.13x10-4 (C.V) - 0.007 (S) - 2.16x10-4 (Hf)
(R= 0.999 , St. error = 0.029, F= 334.76)

[Stepwise Regression]:
pKa = 1.551 + 8.871 (LUMO) + 0.013 (C.V)
(R= 0.998 , St. error = 0.030, F= 937.47)

[Simple Regression]:
pKa = 1.741 + 9.782 (LUMO)
(R= 0.984, St. error = 0.083, F= 241.94)

DFT/STO-3G Method:
[Enter Regression]:
pKa = 4.480 - 6.669(HOMO) + 7.118 (LUMO) + 10.836 (Free Energy) + 0.025 (C.V) – 0.046 (S) + 0.001 (Hf)
(R= 0.999 , St. error = 0.025, F= 441.23)

[Stepwise Regression]:
pKa = 3.551 + 9.681 (LUMO) + 8.802 (HOMO)
(R= 0.980 , St. error = 0.098, F= 86.51)

[Simple Regression]:
pKa = 2.066 + 12.202 (LUMO)
(R= 0.934, St. error = 0.166, F= 54.32)

DFT/3-21G Method:
[Enter Regression]:
pKa = 3.863 - 7.300 (HOMO) + 8.295 (LUMO) + 13.439 (Free Energy) - 0.001 (C.V) – 0.035 (S) + 0.001 (Hf)
(R= 1.000 , St. error = 0.014, F= 1321.25)

[Stepwise Regression]:
pKa = 3.862 + 8.291 (LUMO) + 0.001 (H.F) + 13.433 (Free Energy) - 7.352 (HOMO) – 0.035 (S)
(R= 1.000 , St. error = 0.012 , F= 2111.15)
[Simple Regression]:
pKa = 3.589 + 13.217 (LUMO)
(R= 0.923, St. error = 0.178, F= 46.36)

Equation (5) was obtained from the difference between the calculated and the experimental pKa values. This equation gives an identification to choose the best method to predict the experimental values.

$$\Delta pKa = pKa_{exp.} - pKa_{calc.} \text{-----(5)}$$

Tables 11-16 were shown the predicted pKa and experimental value based on six methods of calculations using different types of regression methods like enter, stepwise and simple regression.

Table 11. Predicted pKa values using AM1 in different regression methods

No.	pKa Exp.	Enter	Stepwise	Simple
1	3.69	3.70	3.61	3.61
2	3.69	3.65	3.68	3.64
3	3.65	3.64	3.61	3.61
4	3.6	3.59	3.61	3.61
5	3.54	3.51	3.57	3.59
6	3.32	3.36	3.46	3.45
7	3.12	3.08	3.09	2.77
8	2.81	2.71	2.71	2.86
9	2.8	2.74	2.75	2.86
10	2.5	2.62	2.62	2.71
R		0.991	0.984	0.940
*St. error		0.063	0.084	0.159
F		417.1	236.9	60.26

* Standard error

Table 12. Predicted pKa values using PM3in different regression methods

Comp. No.	Enter	Stepwise	Simple
1	3.77	3.59	3.56
2	3.66	3.66	3.59
3	3.69	3.59	3.56
4	3.63	3.60	3.57
5	3.50	3.56	3.55
6	3.39	3.52	3.47
7	3.14	3.09	2.64
8	2.79	2.69	2.94
9	2.69	2.71	2.92

10	2.68	2.71	2.90
R	0.983	0.964	0.850
St. error	0.084	0.123	0.244
F	236.2	105.0	20.8

Table 13. Predicted pKa values using HF/STO-3G in different regression methods

Comp. No.	Enter	Stepwise	Simple
1	3.72	3.62	3.61
2	3.69	3.65	3.62
3	3.67	3.62	3.60
4	3.63	3.61	3.60
5	3.57	3.57	3.58
6	3.33	3.39	3.41
7	3.14	3.17	2.90
8	2.80	2.82	2.99
9	2.84	2.86	2.99
10	2.52	2.42	2.42
R	0.999	0.992	0.957
St. error	0.016	0.056	0.135
F	6724.2	526.6	86.2

Table 14. Predicted pKa values using HF/3-21G in different regression methods

Comp. No.	Enter	Stepwise	Simple
1	3.71	3.71	3.63
2	3.66	3.66	3.62
3	3.66	3.65	3.63
4	3.61	3.59	3.62
5	3.55	3.52	3.61
6	3.34	3.34	3.44
7	3.13	3.08	2.97
8	2.79	2.77	2.85
9	2.83	2.80	2.81
10	2.50	2.53	2.54
R	0.999	0.998	0.984
St. error	0.019	0.026	0.082
F	4551	2378	246.4

Table 15. Predicted pKa values using DFT/STO-3G in different regression methods

Comp. No.	Enter	Stepwise	Simple
1	3.67	3.67	3.60
2	3.65	3.71	3.63
3	3.60	3.66	3.59
4	3.57	3.65	3.59
5	3.53	3.59	3.55
6	3.30	3.15	3.28
7	3.08	2.99	2.94
8	2.78	2.86	3.09
9	2.82	2.90	3.08
10	2.48	2.55	2.37
R	0.999	0.981	0.933
St. error	0.019	0.091	0.167
F	4653	199.4	53.9

Table 16. Predicted pKa values using DFT/6-31G in different regression methods

Comp. No.	Enter	Stepwise	Simple
1	3.57	3.62	3.54
2	3.57	3.61	3.55
3	3.52	3.56	3.54
4	3.48	3.52	3.53
5	3.45	3.49	3.52
6	3.23	3.27	3.40
7	2.97	3.02	3.31
8	2.65	2.68	3.09
9	2.62	2.65	2.96
10	2.40	2.44	2.28
R	0.998	0.998	0.924
St. error	0.028	0.030	0.178
F	2061	1798.3	46.3

While (figures 1-3) have been shown the fisher values for the theoretical methods in enter, stepwise and simple regression.

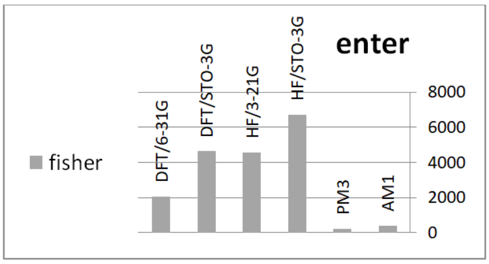

Fig 1. Fisher values for all methods using enter regression

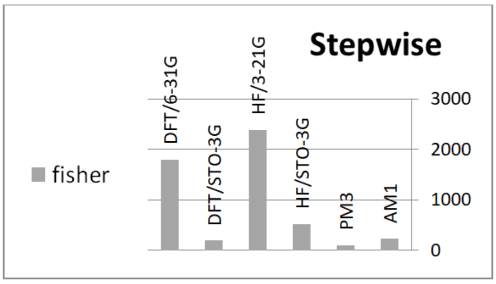

Fig 2. Fisher values for all methods using stepwise regression

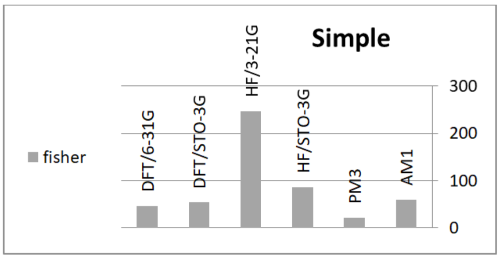

Fig 3. Fisher values for all methods using simple regression

4. Conclusion

From the obtained results, the correlation coefficient (R) sometimes gives the relation between the experimental and the theoretical calculated. But, not give the real meaning to compare between these values The results show a good linear relationship between experimental pKa values and the calculated and can draw the correlation between calculated and experimental pKa values of studied carboxylic acids and showing it in figure and the average error is less than 0.01 and 0.07 pKa units where the data are nearest between them (~0.93 to ~0.99). So, the standard error or the Fisher values from this research showed an excellent correlation and good parameters to describe the system. The results confirm that the acid strength depends on the type of the group substituent. Electron withdrawing groups attached to the carboxylic acid lead to greater acidity than electron releasing groups because of their anion stabilizing capability. Also, it showed that the pKa values of carboxylic acids can be calculated using (HF/STO-3G) method with acceptable accuracy.

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