Comparative Study of CBS-Q Calculated and Experimental pKa Values for Fluoro-Acetoxy Derivative

Mustafa Lawar1,2*, Safia Elbadwe3,4, Ismail Yalçın5, Kayhan Bolelli5, Hakan Sezgin Sayiner6 and Fatma Kandemirli7

1Higher Institute of Medical Professionals, Absalim, Tripoli, Libya.
2Department of Genetic and Bioengineering, Kastamonu Universitesi Faculty of Engineering and Architecture, Kastamonu, Turkey.
3Department of Statistics, Faculty of Science, Tripoli University, Tripoli, Libya.
4Department of Modes, School of Natural and Applied Science, Atılım University, Ankara, Turkey.
5Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Ankara, Turkey.
6Department of Infectious Diseases, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey.
7Department of Biomedical, Kastamonu Universitesi Faculty of Engineering and Architecture, Kastamonu, Turkey.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOCS/2019/v6i218991

Editor(s):
(1) Dr. Fahmida Khan, National Institute of Technology Raipur, Chhattisgarh, India.

Reviewers:
(1) Elmeliani M’hammed, University Oran 1, Algeria.
(2) Hidetaka Kawakita, Saga University, Japan.
(3) Dr. Collins U. Ibeji, University of Nigeria, Nsukka, Nigeria.
(4) Joseph C. Sloop, Georgia Gwinnett College, USA.

Complete Peer review History: http://www.sdiarticle3.com/review-history/47995

Original Research Article

Received 28 February 2019
Accepted 07 May 2019
Published 18 May 2019

ABSTRACT

The pKa values were calculated for some acetoxy group molecules using CBS-Q method which is one of the Complete Basis Set methods to find accurate energies. The acetoxy group molecules were also planned by Quantitative Structure Activity Relationship (QSAR) to study their effect on paraoxonase1 activity.

*Corresponding author: E-mail: alawermustafa@gmail.com;
The results of this study showed a strong relationship, \((R^2=0.99)\) between the calculated and experimental pKa, also showed correlations between the activity of the enzyme and some of the studied descriptors. Moreover, the results of the study revealed that by using the SPSS program, there is a correlation between LUMO, Softness, Nucleofugality and Electrofugality as dependent variables and Cal. pKa as an independent variable.

**Keywords:** Acetoxy; QSAR; pKa; HOMO and LUMO.

### 1. INTRODUCTION

In this study, we have calculated pKa value for acetoxy group using CBS-Q method which is one of the Complete Basis Set methods to find accurate energies [1-5]. Acetoxy derivatives thought to be molecules that may activate paraoxonase1 (PON1). We used the following thermodynamic cycles as [6].

#### 1.1 Cycle 1

The thermodynamic cycle 1 were given at Scheme 1.

Theoretical pKa values are commonly obtained by using the thermodynamic cycles. Experimental solvation free energy of \(H^+\) was used to calculate pKa value in thermodynamic cycles.

\[ \text{pKa} = \frac{\Delta G_{\text{aq}}}{2.303RT} \quad (1) \]

\[ \Delta G_{\text{aq}} = \Delta G_{\text{gas}} + \Delta \Delta G_{\text{solv}} \quad (2) \]

In this cycle, \(\Delta G_{\text{gas}}\) can be calculated as in Eq.3

\[ \Delta G_{\text{gas}} = G_{\text{gas}}(H^+) + G_{\text{gas}}(B^-) - G_{\text{gas}}(BH) \quad (3) \]

Since proton electronic energy is zero, \(H_2\) gas \((H^+)\) has been obtained by adding up the translational energy \((E = 3/2RT)\) and \(PV = RT\). This value reported 1.48 kcal/mol at 298 K. Entropy, \(S(H^+)\), was calculated by the Sackur–Tetrode equation for gas-phase monoatomic species, so \(TS = -7.76\) kcal/mol at 298 K and 1 atm. Then \(G_{\text{gas}}(H^+)\) equals -6.28 kcal/mol [7].

Since pKa determination employs the standard free deprotonation energy in solution, 1 M aqueous phase calculations also uses a reference state of 1 M and gas-phase free deprotonation energies are calculated to a reference state of 1 atm, gas-phase free energy difference, \(\Delta G_{\text{gas}}\), must be referred to 1 M by taking into account the factor RT\(\ln 24.46\).

\[ \Delta G_{\text{gas}}(1\text{M}) = \Delta \Delta G_{\text{gas}}(1\text{atm}) + RT\ln 24.46 \quad (4) \]

The calculation of \(\Delta \Delta G_{\text{solv}}\) were obtained with the Eq.5

\[ \Delta \Delta G_{\text{solv}} = \Delta G_{\text{solv}}(H^+) + \Delta G_{\text{solv}}(B^-) - \Delta G_{\text{solv}}(BH) \quad (5) \]

This work is aimed to study the quantum chemical descriptors of acetoxy derivatives, calculate pKa and compared to the experimental pKa for the same compounds that may activate paraoxonase1.

\[ \Delta G_{\text{aq}} \]

\[ \Delta G_{\text{solv}}(BH) \]

\[ \Delta G_{\text{solv}}(B^-) \]

\[ \Delta G_{\text{solv}}(H^+) \]

\[ \Delta G_{\text{aq}} \]

\[ \Delta G_{\text{solv}}(BH) \]

\[ \Delta G_{\text{solv}}(B^-) \]

\[ \Delta G_{\text{solv}}(H^+) \]

\[ \text{BH}_{(\text{aq})} \]

\[ \text{BH}_{(\text{aq})} \]

\[ \text{B}^-_{(\text{aq})} \]

\[ \text{B}^-_{(\text{aq})} \]

\[ \text{H}^+_{(\text{aq})} \]

\[ \text{H}^+_{(\text{aq})} \]

\[ \text{Scheme 1. Thermodynamic cycle 1 interrelationship between the gas phase and solution thermodynamic parameters} \]
2. MATERIALS AND METHODS

2.1 Molecules of Study

Khersonsky, Tawfik [8] studied a group of molecules including these 7 molecules of study. CBS-Q was used for the calculation of pKa, these calculations have been used for gas and water phase calculations of acetoxy derivatives. All calculations were performed using Gaussian 09W program [9].

2.2 Calculation Methods

All calculations were performed on Intel core-i7 Sony laptop Computer, using Gaussian 09W program [9]. The CBS-Q method has been used for all gas and water phase calculations for acetoxy molecules. All calculation results have no imaginary frequency at gas and water phase.

The CBS-Q method is one of the effective methods of The Complete Basis Set Methods which were developed by Petersson and coworkers [10,11,5]. The CBS methods include some corrections for ab-inito calculation errors. These methods use relatively large basis sets for the structure calculation, medium-sized basis sets for the second-order correlation correction, and small-sized basis sets for higher order correlation corrections. Thus the CBS methods can compute energies for the molecules very accurately [12,13,10,11].

3. RESULTS AND DISCUSSION

The pKa values for the 7 acetoxy derivatives were calculated, thermodynamic data for those molecules were calculated in the case of syn-periplanar position and in antiperiplanar position, these data are presented in Tables 2 and 3.

The calculated pKa for the syn-periplanar -position compounds were near to the experimental pKa, and when testing the correlation between them, a significant relationship has been observed, as presented by Fig. 1.

While in antiperiplanar-position the calculated pKa was little bit far from experimental one, but also it gave a good relationship.

Moreover, the quantum chemical calculations have been carried out at the CBS-Q level of theory using Gaussian-09 series of program package. Some descriptors for the same molecules like $E_{\text{HOMO}}$, $E_{\text{LUMO}}$, Energy gap, Hardness, Softness, Electronegativity, Chemical potential, Electrophilicity index, Electrofugality, and Nucleofugality were calculated, as shown in Table 4.

$E_{\text{HOMO}}$ is associated with the ability of a molecule to donate an electron, the high $E_{\text{HOMO}}$ value indicates the tendency of the molecule to donate electrons to an appropriate acceptor molecule with lower energy MO [14-18]. HOMO and LUMO

<table>
<thead>
<tr>
<th>Mol. No.</th>
<th>Name</th>
<th>Structure</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trifluoroethyl acetate</td>
<td><img src="image1" alt="Structure" /></td>
<td>12.4</td>
</tr>
<tr>
<td>2</td>
<td>2,2-difluoroethyl acetate</td>
<td><img src="image2" alt="Structure" /></td>
<td>13.3</td>
</tr>
<tr>
<td>3</td>
<td>2-fluoroethyl acetate</td>
<td><img src="image3" alt="Structure" /></td>
<td>14.2</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl acetate</td>
<td><img src="image4" alt="Structure" /></td>
<td>16.1</td>
</tr>
<tr>
<td>5</td>
<td>Propyl acetate</td>
<td><img src="image5" alt="Structure" /></td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Butyl acetate</td>
<td><img src="image6" alt="Structure" /></td>
<td>16.1</td>
</tr>
<tr>
<td>7</td>
<td>Isopropyl acetate</td>
<td><img src="image7" alt="Structure" /></td>
<td>17.1</td>
</tr>
</tbody>
</table>
### Table 2. Calculated pKa to the experimental pKa of some acetoxy derivatives compounds (syn-periplanar-positions)

<table>
<thead>
<tr>
<th>Mol. No.</th>
<th>Structure</th>
<th>CH2-g (kcal/mol)</th>
<th>gp-an (kcal/mol)</th>
<th>CH2-aq (kcal/mol)</th>
<th>aq-an (kcal/mol)</th>
<th>Cal. pKa</th>
<th>Exp. pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure" /></td>
<td>-604.71715</td>
<td>-604.179206</td>
<td>-604.724876</td>
<td>-604.269088</td>
<td>10.15</td>
<td>12.40</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure" /></td>
<td>-505.531756</td>
<td>-504.597594</td>
<td>-505.540674</td>
<td>-505.083327</td>
<td>10.87</td>
<td>13.30</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure" /></td>
<td>-406.353085</td>
<td>-405.807454</td>
<td>-406.360854</td>
<td>-405.901682</td>
<td>11.71</td>
<td>14.20</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>-307.193869</td>
<td>-306.638776</td>
<td>-307.200251</td>
<td>-306.737631</td>
<td>13.29</td>
<td>16.10</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure" /></td>
<td>-346.42217</td>
<td>-345.867373</td>
<td>-346.428935</td>
<td>-345.966237</td>
<td>13.33</td>
<td>16.10</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure" /></td>
<td>-385.650767</td>
<td>-385.096011</td>
<td>-385.657331</td>
<td>-385.19437</td>
<td>13.45</td>
<td>16.10</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure" /></td>
<td>-346.426101</td>
<td>-345.870991</td>
<td>-346.432491</td>
<td>-345.968931</td>
<td>13.72</td>
<td>17.10</td>
</tr>
</tbody>
</table>

#### Fig. 1. The relationship between the calculated and experimental pKa in the syn-periplanar position

\[
y = 1.206x + 0.133 \\
R^2 = 0.985
\]

### Table 3. Calculated pKa to the experimental pKa of some acetoxy derivatives compounds (antiperiplanar-positions)

<table>
<thead>
<tr>
<th>Mol. No.</th>
<th>CH2-g (kcal/mol)</th>
<th>gp-an (kcal/mol)</th>
<th>CH2-aq (kcal/mol)</th>
<th>aq-an (kcal/mol)</th>
<th>Cal. pKa</th>
<th>Exp. pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-604.7132</td>
<td>-604.105244</td>
<td>-604.720172</td>
<td>-604.2715</td>
<td>6.87</td>
<td>12.40</td>
</tr>
<tr>
<td>2</td>
<td>-505.528058</td>
<td>-504.999049</td>
<td>-505.534058</td>
<td>-505.0851</td>
<td>6.97</td>
<td>13.30</td>
</tr>
<tr>
<td>3</td>
<td>-406.346338</td>
<td>-405.811861</td>
<td>-406.354372</td>
<td>-405.90227</td>
<td>8.45</td>
<td>14.20</td>
</tr>
<tr>
<td>5</td>
<td>-346.416057</td>
<td>-345.871429</td>
<td>-346.423042</td>
<td>-345.96616</td>
<td>10.65</td>
<td>16.10</td>
</tr>
<tr>
<td>6</td>
<td>-385.645342</td>
<td>-385.10061</td>
<td>-385.652389</td>
<td>-385.19636</td>
<td>10.26</td>
<td>16.10</td>
</tr>
<tr>
<td>7</td>
<td>-346.470306</td>
<td>-345.877325</td>
<td>-346.429248</td>
<td>-345.97077</td>
<td>11.38</td>
<td>17.10</td>
</tr>
</tbody>
</table>
Table 4. calculated descriptors for the acetoxy derivative compounds (syn-periplanar -position)

<table>
<thead>
<tr>
<th>Mol. No.</th>
<th>HOMO (eV)</th>
<th>LUMO (eV)</th>
<th>Energy Gap (eV)</th>
<th>Hardness (eV)</th>
<th>Softness (eV')</th>
<th>Electro-negativity (eV)</th>
<th>Chemical potential (eV)</th>
<th>Electrophilicity index (ω)</th>
<th>Nucleofugality</th>
<th>Electr fugality</th>
<th>Cal. pKa</th>
<th>Exp. pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-12.5081</td>
<td>4.428144</td>
<td>16.93623</td>
<td>8.468114</td>
<td>0.059045</td>
<td>4.03997</td>
<td>-4.03997</td>
<td>0.963695</td>
<td>1.157782</td>
<td>9.237722</td>
<td>10.2</td>
<td>12.4</td>
</tr>
<tr>
<td>2</td>
<td>-12.3201</td>
<td>4.594951</td>
<td>16.915</td>
<td>8.457501</td>
<td>0.059119</td>
<td>3.86255</td>
<td>-3.86255</td>
<td>0.882016</td>
<td>1.248216</td>
<td>8.973317</td>
<td>10.9</td>
<td>13.3</td>
</tr>
<tr>
<td>3</td>
<td>-12.1377</td>
<td>4.761214</td>
<td>16.89895</td>
<td>8.449474</td>
<td>0.059175</td>
<td>3.68826</td>
<td>-3.68826</td>
<td>0.804977</td>
<td>1.341454</td>
<td>8.717974</td>
<td>11.7</td>
<td>14.2</td>
</tr>
<tr>
<td>4</td>
<td>-11.7905</td>
<td>5.11959</td>
<td>16.9101</td>
<td>8.455052</td>
<td>0.059136</td>
<td>3.33462</td>
<td>-3.33462</td>
<td>0.657909</td>
<td>1.549973</td>
<td>8.220897</td>
<td>13.3</td>
<td>16.1</td>
</tr>
<tr>
<td>5</td>
<td>-11.757</td>
<td>5.079589</td>
<td>16.83663</td>
<td>8.418317</td>
<td>0.059394</td>
<td>3.38727</td>
<td>-3.38723</td>
<td>0.662074</td>
<td>1.532505</td>
<td>8.20966</td>
<td>13.6</td>
<td>16.1</td>
</tr>
<tr>
<td>6</td>
<td>-11.7252</td>
<td>5.092379</td>
<td>16.81759</td>
<td>8.408793</td>
<td>0.059462</td>
<td>3.31641</td>
<td>-3.31641</td>
<td>0.653994</td>
<td>1.541977</td>
<td>8.174804</td>
<td>13.4</td>
<td>16.1</td>
</tr>
<tr>
<td>7</td>
<td>-11.7472</td>
<td>5.137006</td>
<td>16.88425</td>
<td>8.442127</td>
<td>0.059227</td>
<td>3.30512</td>
<td>-3.30512</td>
<td>0.646983</td>
<td>1.562925</td>
<td>8.173167</td>
<td>13.7</td>
<td>17.1</td>
</tr>
</tbody>
</table>

Table 5. calculated descriptors for the acetoxy derivative compounds (antiperiplanar-position)

<table>
<thead>
<tr>
<th>Mol. No.</th>
<th>HOMO (eV)</th>
<th>LUMO (eV)</th>
<th>Energy Gap (eV)</th>
<th>Hardness (eV)</th>
<th>Softness (eV')</th>
<th>Electro-negativity (eV)</th>
<th>Chemical potential (eV)</th>
<th>Electrophilicity index (ω)</th>
<th>Nucleofugality</th>
<th>Electr fugality</th>
<th>Cal. pKa</th>
<th>Exp. pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-12.6836</td>
<td>4.4488</td>
<td>17.132423</td>
<td>8.566212</td>
<td>0.058369</td>
<td>4.117387</td>
<td>-4.117387</td>
<td>0.98952</td>
<td>1.155239</td>
<td>9.390013</td>
<td>6.87</td>
<td>12.4</td>
</tr>
<tr>
<td>2</td>
<td>-12.5206</td>
<td>4.6831</td>
<td>17.203718</td>
<td>8.601859</td>
<td>0.058127</td>
<td>3.918743</td>
<td>-3.918743</td>
<td>0.892629</td>
<td>1.274816</td>
<td>9.112301</td>
<td>6.97</td>
<td>13.3</td>
</tr>
<tr>
<td>3</td>
<td>-12.3105</td>
<td>4.7901</td>
<td>17.100586</td>
<td>8.550293</td>
<td>0.058478</td>
<td>3.760235</td>
<td>-3.760235</td>
<td>0.826835</td>
<td>1.341747</td>
<td>8.62217</td>
<td>8.45</td>
<td>14.2</td>
</tr>
<tr>
<td>4</td>
<td>-11.8975</td>
<td>5.0572</td>
<td>16.950106</td>
<td>8.475053</td>
<td>0.058997</td>
<td>3.422403</td>
<td>-3.422403</td>
<td>0.691019</td>
<td>1.506142</td>
<td>8.350948</td>
<td>10.99</td>
<td>16.1</td>
</tr>
<tr>
<td>5</td>
<td>-11.9315</td>
<td>5.1596</td>
<td>17.091062</td>
<td>8.545531</td>
<td>0.05851</td>
<td>3.385939</td>
<td>-3.385939</td>
<td>0.670794</td>
<td>1.55762</td>
<td>8.329499</td>
<td>10.65</td>
<td>16.1</td>
</tr>
<tr>
<td>6</td>
<td>-11.9029</td>
<td>5.1724</td>
<td>17.075279</td>
<td>8.53764</td>
<td>0.058564</td>
<td>3.365259</td>
<td>-3.365259</td>
<td>0.663237</td>
<td>1.566799</td>
<td>8.297316</td>
<td>10.26</td>
<td>16.1</td>
</tr>
<tr>
<td>7</td>
<td>-11.7818</td>
<td>5.0573</td>
<td>16.839082</td>
<td>8.419541</td>
<td>0.059386</td>
<td>3.362265</td>
<td>-3.362265</td>
<td>0.671345</td>
<td>1.51885</td>
<td>8.243381</td>
<td>11.38</td>
<td>17.1</td>
</tr>
</tbody>
</table>
Table 6. Comparison between anti-periplanar and syn-periplanar positions highest $E_{\text{HOMO}}$, $E_{\text{LUMO}}$ and energy gap

<table>
<thead>
<tr>
<th>Mol. no.</th>
<th>$E_{\text{HOMO}}$</th>
<th>Mol. no.</th>
<th>$E_{\text{LUMO}}$</th>
<th>Mol. no.</th>
<th>Energy gap</th>
<th>Mol. no.</th>
<th>$E_{\text{HOMO}}$</th>
<th>Mol. no.</th>
<th>$E_{\text{LUMO}}$</th>
<th>Mol. no.</th>
<th>Energy gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-11.7252</td>
<td>7</td>
<td>5.137006</td>
<td>1</td>
<td>16.93623</td>
<td>7</td>
<td>-11.7818</td>
<td>6</td>
<td>5.1724</td>
<td>2</td>
<td>17.20372</td>
</tr>
<tr>
<td>7</td>
<td>-11.7472</td>
<td>4</td>
<td>5.11959</td>
<td>2</td>
<td>16.9150</td>
<td>4</td>
<td>-11.8975</td>
<td>5</td>
<td>5.1596</td>
<td>1</td>
<td>17.13242</td>
</tr>
<tr>
<td>5</td>
<td>-11.757</td>
<td>6</td>
<td>5.092379</td>
<td>4</td>
<td>16.9101</td>
<td>6</td>
<td>-11.9029</td>
<td>7</td>
<td>5.0573</td>
<td>3</td>
<td>17.10059</td>
</tr>
<tr>
<td>4</td>
<td>-11.7905</td>
<td>5</td>
<td>5.079589</td>
<td>3</td>
<td>16.89895</td>
<td>5</td>
<td>-11.9315</td>
<td>4</td>
<td>5.0527</td>
<td>5</td>
<td>17.09106</td>
</tr>
<tr>
<td>3</td>
<td>-12.1377</td>
<td>3</td>
<td>4.761214</td>
<td>7</td>
<td>16.88425</td>
<td>3</td>
<td>-12.3105</td>
<td>3</td>
<td>4.7901</td>
<td>6</td>
<td>17.07528</td>
</tr>
<tr>
<td>1</td>
<td>-12.5081</td>
<td>1</td>
<td>4.428144</td>
<td>6</td>
<td>16.81759</td>
<td>1</td>
<td>-12.6836</td>
<td>1</td>
<td>4.4488</td>
<td>7</td>
<td>16.83908</td>
</tr>
</tbody>
</table>
Fig. 2. The relationship between the calculated and experimental pKa in the antiperiplanar position

\[ y = 0.8965x + 6.6775 \]

\[ R^2 = 0.9627 \]

Fig. 3. Molecular structure, HOMO, LUMO & ESP of the 7 molecules
orbitals of the 7 molecules were obtained from the quantum chemical calculation by the DFT using cbs-q bases sets as shown in Fig. 1.

The highest $E_{\text{HOMO}}$ among the 7 syn-periplanar-molecules were: -11.7252 eV, -11.7472 eV, -11.757 eV, -11.7905 eV, -12.1377 eV, -12.3201 eV and -12.5081 eV, recorded with molecules: 6, 7, 5, 4, 3, 2 and 1, respectively. Whereas the $E_{\text{LUMO}}$ of these molecules were: 5.137006 eV, 5.11959 eV, 5.092379 eV, 5.079589 eV, 4.761214 eV, 4.594951 eV and 4.428144 eV, these values for 7, 4, 6, 5, 3, 2 and 1 molecules, respectively. The Energy Gap among these molecules were: 16.93623 eV, 16.9150 eV, 16.9101 eV, 16.89895 eV, 16.88425 eV, 16.83663 eV and 16.81759 eV, these for molecules 1, 2, 4, 3, 7, 5 and 6. As the molecules with smaller $E_{\text{HOMO}}$ - $E_{\text{LUMO}}$ energy gap lead to lower kinetic stability and higher chemical reactivity, so the molecules that have high activity are 1, 2, 4, 3, 7, 5 and 6 respectively [14].

Fig. 4. HOMO & LUMO for syn-periplanar-molecules

\[ y = 0.260x + 1.637 \]
\[ R^2 = 0.955 \]

Fig. 5. The correlation between calculated pKa and LUMO in case of syn-periplanar-position
Nucleofugality is defined as the propensity of an atom or group of them to depart bearing the bonding electron pair in a heterolytic cleavage process [17,18], the highest nucleofugality of the 7 molecules were: 1.562925, 1.549973, 1.541977, 1.532505, 1.341454, 1.248216 and 1.157782. these results for molecules: 7, 4, 6, 5, 3, 2 and 1. According to these values, those molecules have the activation activity to PON1. Fig. 6 represents the relationship between the calculated pKa and nucleofugality, which also confirmed by the results of the statistical analysis.

In case of antiperiplanar position, the calculated descriptors were presented in Table 5, the values were not far of the syn-periplanar -position case, but there was a rearrangement of the molecules, especially for the HOMO and LUMO, Energy Gap and nucleofugality as shown in Table 6, as well as Figs. 7 and 8.

![Graph](image1.png)

**Fig. 6. The correlation between calculated pKa and Nucleofugality in case of syn-periplanar – position**

![Graph](image2.png)

**Fig. 7. The correlation between calculated pKa and nucleofugality in case of trasposition**
3.1 Statistical Analysis

To detect whether there is a relationship or effect between the independent variable (Calculated pKa) and dependent variables (E_{HOMO}, E_{LOMO}, Hardness, Energy Gap, Softness, Electronegativity, Chemical potential, electrophilicity index(\omega), Nucleofugality and Electrfugality), and, which of these variables is more effective, multiple regression analysis has been used, as it is the standard method and used to enter all independent variables not excluding any variables.

Given the correlation matrix between all independent and dependent variables, it has been shown that the variables (E_{HOMO}, E_{LOMO}, Energy Gap, Softness, Hardness, Electronegativity and Chemical potential) have no correlation between them, so these variables would be excluded as they were not effective.

While the remaining independent variables (electrophilicity index (\omega), Nucleofugality, Electrfugality) were associated with the dependent variable, this is in case of syn-periplanar -position molecules.

The correlation coefficient, value between the dependent variable and the independent variables under study was $R = 0.999$ intermediate value indicating a relationship between these variables. The coefficient of determination $R^2 = 0.998$, which revealed that, the independent variables were able to explain 100% of the differences and changes in (Cal. pKa).

Anova test showed that there was a very strong relationship between the independent variable and dependent variables, which confirmed the high explanatory power of the statistically multiple linear regression model. From the
coefficients table, it can be concluded that the statistically independent variables and T-test at the significant level (P ≤ 0.05) had no significant effect on the multiple regression model, although there was a correlation between these variables and the independent variable.

Regression equation was obtained using non-standard beta (fixed limit) as follows:

Cal. pKa = -3.010+2.720 electrophilicity index(ω) + 10.259 Nucleofugality -.145 Electrofugality.

In case of antiperiplanarposition, the independent variables (LOMO, Softness, Nucleofugality, Electrofugality) was associated with the dependent variable. The value of the correlation coefficient between the dependent and independent variables under study was R = 0.682 intermediate value and indicated a relationship between these variables. The coefficient of determination R² = 0.465 this means that the independent variables were able to explain 47% of the differences and changes in (Cal. pKa).

Anova test showed that there was a relationship between the independent variable and dependent variables which confirmed the high explanatory power of the statistically multiple linear regression model. From the coefficients table, it can be concluded that the statistically independent variables and T-test at the significant level (P ≤ 0.05) had no significant effect on the multiple regression model, although there was a correlation between these variables and the independent variable.

4. CONCLUSION

This paper aimed to study the relation of calculated pKa with the experimental for 7 molecules and to study the effect of some descriptors on the above-mentioned molecules and their correlation with calculated pKa. The values of calculated pKa revealed that there was a strong relationship between the calculated and experimental pKa. The calculated values were nearby the experimental values of syn-periplanar -position molecules, calculation of pKa using other methods could be more close to the experimental. Extensive comparative studies by the other methods, rather than CBS-Q to confirm which is a more acceptable method.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


