Abstract: An investigation employing the semiempirical molecular orbital MNDO method in the program package of the HyperChem 7.5 software to calculate \( \Delta H(M) \), \( \Delta H([M+H]^+) \) and local proton affinities (PAs) as well as the charge distributions for the two highly electronnegative hetero atoms (\( O_1 \) and \( N_1 \)) in six quinolone derivatives have been undertaken. The MNDO calculated values of PAs for the quinolone derivatives at site \( O_1 \) and at site \( N_1 \) indicate that the average energy separation between PA values at two respective sites is equal to about 164 kJ.mol\(^{-1}\). This allows the authors to conclude that the protonation at site \( O_1 \) is a more favoured process than at \( N_1 \). This conclusion can be explained as resulting from the presence of unsaturated carbonyl (C = O) double bond and ion pair electrons of the oxygen atom, which increase the influences of the protonation at \( O_1 \) site, which is known to be a good proton acceptor. The preferential protonation at site \( O_1 \) for the studied molecules have been confirmed by the calculated \( \Delta H([M+H]^+) \) values at sites \( O_1 \) and \( N_1 \).

Keywords: semiempirical molecular orbital MNDO calculations, proton affinities, and quinolone derivatives.

1. Introduction

Nitrogen heterocycles molecules are an important feature in the chemical structures of many natural products, and often impart specific biological properties. An important class of such compounds is the quinolones and its antibacterial derivatives, which are widely used as prescribed drugs because of their safety, good tolerance, and broad antibacterial spectrum with low resistance [1-4]. The majority of quinolones in clinical use belong to the subset fluoroquinolones, which have a fluorine atom attached to the central ring system, typically at the C-6 or C-7 positions.

Protonation is a simple chemical reaction process. The attachment of the proton H\(^+\) to a molecule is quantified by its proton affinity (PA). An extensive number of papers describing computational studies of PA have appeared in the chemical literature [5]. The widespread interest in the basicity and accompanying proton affinity of molecules is not surprising due to the important role of the proton transfer reaction in organic chemistry and biochemistry. The resulting protonated molecules are frequently a pivotal intermediate that guides the succeeding steps of the overall process [5-8]. Knowledge of the intrinsic basicity of a compound in the gas phase is central to the understanding of its reactivity. It has now been well established that electronic structure calculations provide accurate gas-phase proton affinities as well as valuable information on the structures of the base and its conjugate acid. Another advantage of determining proton affinities computationally is that absolute rather than relative values of the proton affinity are obtained [5-8]. It is worth noting that many authors used semiempirical methods for calculating proton affinity for molecules [9-11].

In the present work we have studied six quinolone derivatives: Quinolone (I), 1-methyl quinolone (II), 1-ethyl quinolone(III), 1-cyclopropyl quinolone(IV), 3-carboxylic- quinolone(V), and 6- fluoroquinolone (VI) (Scheme 1) using the semiempirical quantum chemical MNDO method. These six quinolone derivatives were used as a synthetic antibacterial compounds having two basic nitrogen \( N_1 \) and oxygen \( O_1 \) sites. The aim of the study is to investigate the gas phase protonation of the quinolone derivatives in order to gain information about their basicities and the nature of the protonation sites i.e. the proton affinity corresponding to protonation on either nitrogen (\( N_1 \)) or oxygen (\( O_1 \)) was calculated. Furthermore, the effect of substituents in the quinolone molecule on the proton affinities of quinolone derivatives are also discussed.

2. Computational Method:

All semiempirical quantum chemical calculations have been performed with the version of the HyperChem 7.5 software package [12]. The MNDO method [13] was used after optimization of geometries to calculate \( \Delta H \) values for M and \([M+H]^+\) as well as the charge distribution for nitrogen and oxygen atoms. Also, the proton affinity at the two hetero atoms (nitrogen and oxygen) was calculated. The use of a semiempirical method for the present type of calculations can give great insight into structure and reactivity of such large molecules [14]. We chose to carry out the present calculations by the MNDO method for the following reasons: (a) It is a well tested semiempirical molecular orbital (MO) method [15] and its accuracy for predicting \( \Delta H \) (see for example Ref. 16) values seems to be sufficient for the present study, (b) The data reported for a large number of compounds prove that the MNDO method achieves better agreement with experimental than MINDO-3 [17] (c) The results of many authors (for example Ref. 18-20) for positive ions indicate that using MNDO and AM1 methods lead to geometries and energies close to that obtained at high level of ab initio theory with, of course, a minute fraction of the computation effort.

3. Results and Discussion:

The essential structural formulas of the quinolone molecule and its derivatives were given in scheme 1 while Figure 1 shows the numbering system of these molecules. Investigation of the calculated charge distribution of neutral, ionized and protonated quinolone derivatives ( Table 1) indicate that the average for the most negative values of charge distribution for the heteroatoms (\( N_1 \) and \( O_1 \)) in the
six studied molecules are ≈ -0.290 (N₁) and ≈ -0.313 (O₁₁).
These values of the charge distribution indicate that the six quinolone derivatives are protonated at the heteroatoms (N₁ and O₁₁).

Investigation of the calculated PA values (Table 2) at sites N₁ and O₁₁ for the six studied molecules indicate that the six proton transfer reactions have average value of PAs (for the six molecules) at site O₁₁ equal to 936 k J. mol⁻¹ while at site N₁ is equal to 771 k J. mol⁻¹. Therefore, the average energy separation between PA values at site O₁₁ and at site N₁ is equal to about 164 k J. mol⁻¹. Hence, the authors conclude that the protonation at site O₁₁ (for the six molecules) is the most favoured process than that at N₁. This conclusion can be explained as due to the presence of unsaturated carbonyl(C═O)double bond (pyridine oxygen) and lone pair electrons of oxygen atom in the studied quinolones derivatives leading to increase the influences of the protonation site on O₁₁ which is known to be a good proton acceptor.

The calculated ΔH_f [M+H]^+ values (Table 2) at site N₁ are equal to 774,795,778,887,452 and 598 k J. mol⁻¹, while at site O₁₁ they are equal to 611,635,612,723,271 and 435 k J. mol⁻¹ for quinolone (Q), 1-methyl-Q-,1-ethyl-Q-,1-cyclopropylQ,3-carboxylic-Q- and 6-flouro-Q-, respectively. Investigation of these calculated ΔH_f values for the protonated molecules at the two sites indicates that the product ΔH_f [M+H]^+ ions at site O₁₁ are more stable than those at site N₁ confirming that the protonation at O₁₁ is the most favoured process. It is worth mentioning that the calculated ΔH_f [M+H]^+ values indicate that protonation causes change in the molecular geometry leading to change in the total energy content.

Finally, the effect of substituents at the N₁ and 3- and 6-carbon positions of the quinolone derivatives on the proton affinities are observed. The substituents –CH₃, -C₂H₅, and C₃C₃H₆ have negligible effect on the proton affinity values at N₁ and O₁₁ positions, while the substituents –COOH and F at C₃ and C₆ have reduced the PA values by about 20 kJ.mol⁻¹ at the two positions. Furthermore, the effect of substituents on quinolone heat of formation is to reduce ΔH_f (M) in 3-carboxylic-Q- (V) from 17 to -338 kJ.mol⁻¹ and in 6-flouro-Q- (VI) from 17 to -175 kJ.mol⁻¹. It is worth noting that –COOH group and F atom are electron acceptors while –CH₃, -C₂H₅ and C₃C₃H₆ groups are electron donors.
### Table 1. The calculated charge distribution (coulomb) of neutral, ionized and protonated quinolone and its derivatives using the MNDO method.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Charge on O₁₁</th>
<th>Charge on N₁</th>
<th>Protonation at O₁₁</th>
<th>Protonation at N₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-0.321</td>
<td>-0.166</td>
<td>-0.188</td>
<td>-0.283</td>
</tr>
<tr>
<td>II</td>
<td>-0.321</td>
<td>-0.170</td>
<td>-0.190</td>
<td>-0.316</td>
</tr>
<tr>
<td>III</td>
<td>-0.322</td>
<td>-0.171</td>
<td>-0.191</td>
<td>-0.309</td>
</tr>
<tr>
<td>IV</td>
<td>-0.319</td>
<td>-0.187</td>
<td>-0.192</td>
<td>-0.278</td>
</tr>
<tr>
<td>V</td>
<td>-0.283</td>
<td>-0.141</td>
<td>-0.0188</td>
<td>-0.277</td>
</tr>
<tr>
<td>VI</td>
<td>-0.312</td>
<td>-0.161</td>
<td>-0.185</td>
<td>-0.279</td>
</tr>
</tbody>
</table>

### Table 2. The calculated heat of formation values for neutral, charged, protonated and proton affinities of quinolone and its derivatives using the MNDO method.

<table>
<thead>
<tr>
<th>Molecules</th>
<th>ΔH(M) kJ.mole⁻¹</th>
<th>ΔH(M⁺) kJ.mole⁻¹</th>
<th>ΔH(M⁺H⁺) at O₁₁ kJ.mole⁻¹</th>
<th>ΔH(M⁺H⁺) at N₁ kJ.mole⁻¹</th>
<th>P.A kJ.mole⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17</td>
<td>770</td>
<td>611</td>
<td>774</td>
<td>At O₁₁ = 937</td>
</tr>
<tr>
<td>II</td>
<td>50</td>
<td>790</td>
<td>635</td>
<td>795</td>
<td>At O₁₁ = 946</td>
</tr>
<tr>
<td>III</td>
<td>26</td>
<td>766</td>
<td>612</td>
<td>778</td>
<td>At O₁₁ = 946</td>
</tr>
<tr>
<td>IV</td>
<td>142</td>
<td>879</td>
<td>723</td>
<td>887</td>
<td>At O₁₁ = 946</td>
</tr>
<tr>
<td>V</td>
<td>-338</td>
<td>439</td>
<td>271</td>
<td>452</td>
<td>At O₁₁ = 920</td>
</tr>
<tr>
<td>VI</td>
<td>-175</td>
<td>594</td>
<td>435</td>
<td>598</td>
<td>At O₁₁ = 920</td>
</tr>
</tbody>
</table>

### References