Semiempirical Calculations of the Proton Affinities of Some Quinolone Derivatives

M. A. Rabbih, S. M. A. Mamoun and Ezzat T. M. Selim
Atomic and Molecular Physics Unit, Nuclear Physics Dept., N.R.C., Atomic Energy Authority, Abuzable 13759, Egypt.
mamoun_sarhan@yahoo.com

Abstract: An investigation employing the semiempirical molecular orbital MNDO method in the program package of the HyperChem 7.5 software to calculate $\Delta H_f(M)$, ΔH_f $[M+H]^+$ and local proton affinities (PAs) as well as the charge distributions for the two highly electronegative hetero atoms (O_{11} and N_1) in six quinolone derivatives have been undertaken. The MNDO calculated values of PAs for the quinolone derivatives at site O_{11} 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_{11} 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_{11} site, which is known to be a good proton acceptor. The preferential protonation at site O_{11} for the studied molecules have been confirmed by the calculated ΔH_f $[M+H]^+$ values at sites O_{11} 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 fluoroquinoles, 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 (Π), 1-ethyl quinolone(III), 1-cyclopropopyl quinolone(IV), 3-carboxylic- quinolone(V), and 6- fluoroquinolone (VI)) (Scheme 1) using the semiemiperical quantum chemical MNDO method. These six quinolone derivatives were used as a synthetic antibacterial compounds having two basic nitrogen N_1 and oxygen O_{11} 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_{11}) was calculated. Furthermore, the effect of substituents in the quinolone molecule on the proton affinities of quinolone derivatives are also discussed.

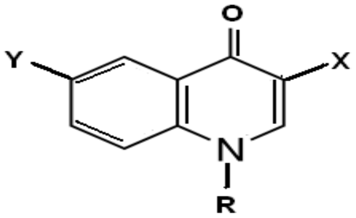
2. Computational Method:

All semiemperical 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 ΔH_f 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 semiemperical 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 semiemperical molecular orbital (MO) method [15] and its accuracy for predicting ΔH_f (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_{11}) in the six studied molecules are ≈ -0.290 (N_1) and ≈ -0.313 (O_{11}). These values of the charge distribution indicate that the six quinolone derivatives are protonated at the heteroatoms (N_1 and O_{11}).

Investigation of the calculated PA values (Table 2) at sites N_1 and O_{11} for the six studied molecules indicate that the six proton transfer reactions have average value of PAs (for the six molecules) at site O_{11} equal to 936 k J. mol^{-1} while at site N_1 is equal to 771 k J. mol^{-1} . Therefore, the average energy separation between PA values at site O_{11} and at site N_1 is equal to about 164 k J. mol^{-1}. Hence, the authors conclude that the protonation at site O_{11} (for the six molecules) is the most favoured process than that at N_1. 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 O_{11} which is known to be a good proton acceptor.



Molecules	R	X	Y
I	H	H	H
II	CH_3	H	H
III	C_2H_5	H	H
IV	c-C_3H_5	H	H
V	H	COOH	H
VI	H	H	F

Scheme 1. Essential structure of quinolone and its derivatives

The calculated ΔH_f $[M+H]^+$ values (Table 2) at site N_1 are equal to 774,795,778,887,452 and 598 k J. mol^{-1}, while at site O_{11} 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 O_{11} are more stable than those at site N_1 confirming that the protonation at O_{11} 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 N_1 and 3- and 6-carbon positions of the quinolone derivatives on the proton affinities are observed. The substituents –CH_3, -C_2H_5, and C-C_3H_5 have negligible effect on the proton affinity values at N_1 and O_{11} positions, while the substituents –COOH and F at C_3 and C_6 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 –CH_3, -C_2H_5 and C-C_3H_5 groups are electron donors.

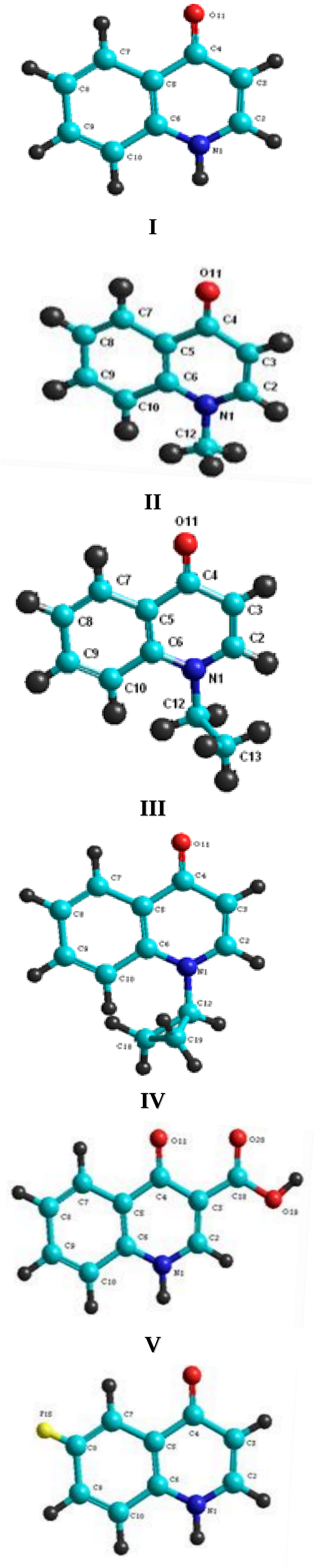

I
II
III
IV
V
IV

Figure 1. The numbering system of a quinolone molecule and its derivatives

Table 1. The calculated charge distribution (coulomb) of neutral, ionized and protonated quinolone and its derivatives using the MNDO method.

Molecule	Charge on O_{11}			Charge on N_1		
	Neutral	Charged	Protonation at O_{11}	Neutral	Charged	Protonation at N_1
I	-0.321	-0.166	-0.188	-0.283	-0.042	0.087
II	-0.321	-0.170	-0.190	-0.316	-0.072	0.024
III	-0.322	-0.171	-0.191	-0.309	-0.063	0.028
IV	-0.319	-0.187	-0.192	-0.278	-0.138	0.079
V	-0.283	-0.141	-0188	-0.277	-0.050	0.080
VI	-0.312	-0.161	-0.185	-0.279	-0.043	0.088

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

Molecules	$\Delta H_f(M)$ kJ.mole^{-1}	$\Delta H_f[M]^+$ kJ.mole^{-1}	$\Delta H_f[M+H]^+$ at O_{11} kJ.mole^{-1}	$\Delta H_f[M+H]^+$at N_1 kJ.mole^{-1}	P.A kJ.mole^{-1}
I	17	`770	611	774	At O_{11} = 937 At N_1= 774
II	50	790	635	795	At O_{11} = 946 At N_1= 787
III	26	766	612	778	At O_{11}= 946 At N_1= 783
IV	142	879	723	887	At O_{11} = 946 At N_1= 787
V	-338	439	271	452	At O_{11} = 920 At N_1= 741
VI	-175	594	435	598	At O_{11}= 920 At N_1= 757

References

[1] P. C. Appelbaum, P. A. Hunter, Int. J. Antimicrob. Agents 16, 5–15, 2000.

[2] Y. Mizuki, I. Fujiwara, T. Yamaguchi, J. Antimicrob. Chemother. 37 (Suppl. A), 41–55, 1996.

[3] P. Ball, J. Antimicrob. Chemother. 46, 17–24 ,2000 Topic T1.

[4] V. Snaz-Nebot, I. Valls, D. Barbero, J. Barbosa, Acta Chem. Scand. 51, 896–903,1997.

[5]A.Bagno and G. Scorrano , J. Phys.Chem, 100, 1536–1544, 1996.

[6]M. E. Maksic, M. Hodoscek, D. Kovacek, Z. B. Maksic and M. Primorac, J. of Molecular Structure (Theochem) 417, 131–143, 1997

[7]Y.R.Mishchuk, A. L. Potyagaylo and D.M. Hovorum J. of Molecular Structure (Theochem)552, 283-289, 2000.

[8]G. A. Deakyne, Int. J. Mass Spectrom. 227, 601–616, 2003.

[9] M. A. Rabbih, S. M. A. Mamoun, A. M. Hassan Rezk M.A.Fahmey and E.T.M.Selim, Journal of applied spectroscopy , under publication

[10] A. H. Htto, D. Prescher, E. Gey and S. Schrader, J. of Fluorine Chemistry 82, 55–71, 1997.

[11] J. F. Capitani, J. of Molecular Structure (Theochem), 332, 21–23, 1995.

[12] HyperChem ™ Release 7.5 Prof. for windows "Molecular Modelling System", HyperCube, User Evaluation copy, organization: evaluation copy, Dealer: copyright ©2002, HyperCube, Inc, Serial No. 99-999-9999999999

[13] M. J. S. Dewar and W. Thiel. Ground States of Molecules, 38. The MNDO Method. Approximations and Parameters, J. Am. Chem. Soc., 99, 4899–4907, 1977.

[14] W. Thiel, Adv. Chem. Phys., 93, 703, 1996.

[15]M. J. S.Dewar and W. Thiel, J. Am. Chem. Soc., 99, 4899, 1977.

[16] D. Higgins, C. Thomson and W. Thiel, J. Comput. Chem, 9, 702, 1988.

[17] V. I. Minikin, B. Ya. Simkin and R. M. Minyaev," Quantum Chemistry of Organic Compounds, Mechanisms of Reactions", Springer-Verlag, Berlin, Heidlberg, p.82,1990.

[18] G.P.Ford, J.Am.Chem.Soc.,108, 5104,1986

[19] J.Hrusak and M.Thaczyk, Org. Mass spectrum., 24, 989, 1989.

[20] S. Tobita, K. Nakajima, S. Tajima and A. Shigihara, Rap. Comm. Mass Spectrom. 4, 472, 1990.