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UV Photoelectron Spectroscopic Study of Substituent Effects in Quinoline Derivatives

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The molecular and electronic structure of eight substituted quinolines has been investigated by HeI/HeII photoelectron spectroscopy, Green's function calculations, and comparison with the spectra of related compounds. The correlation between nitrogen lone pair ionization energies and basicity in 18 substituted quinolines is discussed. The influence of different substituents has been quantified via the scheme that is based on experimental energy shifts. The relationships between nitrogen ionization energies, pK_a values, and medicinal activity are also discussed.

Introduction

Quinoline compounds are of considerable interest because some of them have medicinal properties. For instance, the quinoline structural unit is common to antimalarial drugs (Scheme 1).

It is not surprising that the search for new antimalarial drugs is focused on quinoline derivatives. Kaschula et al.[1] have studied the mechanism of biological action for a series of 7-substituted 4-alkylaminoquinolines (Chart 1). They established that aminoquinolines accumulate in food vacuoles of the parasite via pH trapping. The accumulation leads to an increase of pH in these organelles which interferes with the parasite's ability to metabolize and utilize hemoglobin from the victim's erythrocytes. The trapping ability depends on the pK_a values of the available protonation sites in quinolines. The pK_a values are in turn related to the electron-donating ability and electronic structure of substituted quinolines. The nature of substituents which are likely to enhance drug activity was suggested as being moderately electron-withdrawing and strongly lipophilic.[1]

In view of the mechanism of biological action of antimalarials, a comprehensive analysis of the electronic structure of substituted quinolines would be useful. Unfortunately, some antimalarials such as quinine decompose on melting, which makes them unsuitable for photoelectron spectroscopic analysis. We have therefore studied those substituted quinolines that contain halogen or amino groups since these two groups appear to be important for medicinal properties (Scheme 1).

The presence of substituents affects pK_a values, which in turn affect medicinal activity. Strongly electron-withdrawing substituents (especially at the 2-position) decrease electron density on the ring nitrogen and

SCHEME 1

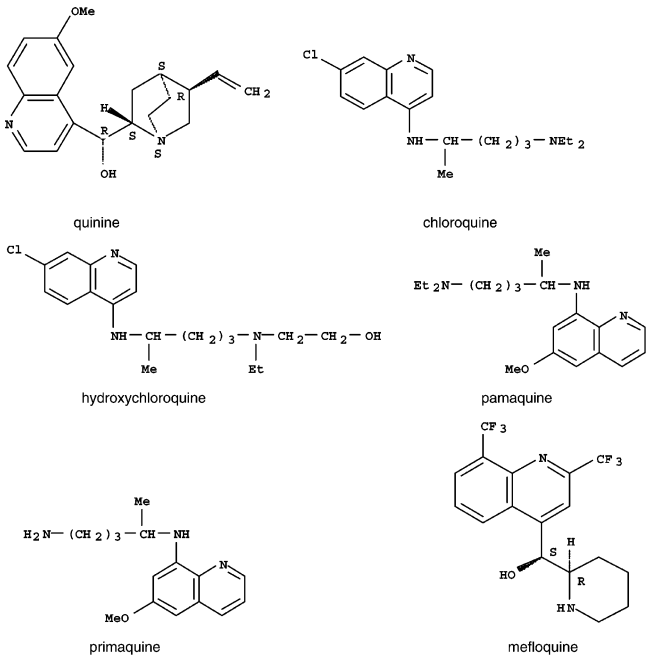
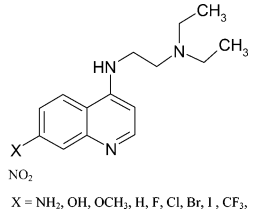


CHART 1. 7-Substituted 4-Aminoantiplasmodials



(1) Kaschula, C. H.; Egan, T. J.; Hunter, R.; Basilico, N.; Parapini, S.; Taramelli, D.; Pasini, E.; Monti, D. *J. Med. Chem.* **2002**, *45*, 3531.

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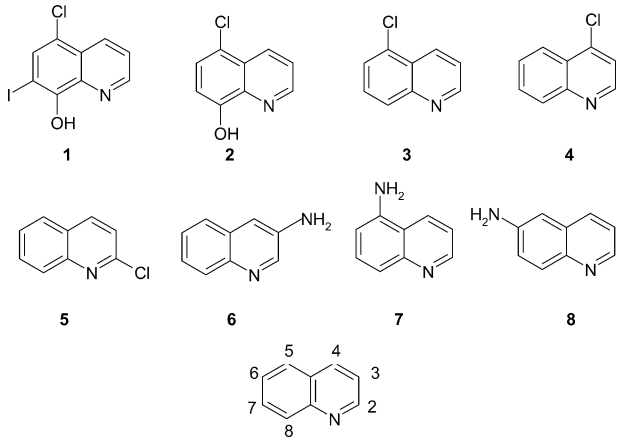
CHART 2



therefore make the molecule less prone to electrophilic attack. Strongly electron-donating substituents have the opposite effect, while the influence of alkyl and aryl groups is small.[2]

The electronic structures of some quinolines, including the parent molecule, have been investigated previously by UV photoelectron spectroscopy (UPS) and semiempirical MO calculations. The compounds studied were quinoline,[3] heptaquinoline,[3] alkylquinolines[4] and some isomeric methoxy, methyl, hydroxyl, and haloquinolines.[5]

Experimental and Theoretical Methods

The samples of 5-chloro-7-iodo-8-hydroxyquinoline (**1**), 5-chloro-8-hydroxyquinoline (**2**), 5-chloroquinoline (**3**), 4-chloroquinoline (**4**), 2-chloroquinoline (**5**), 3-aminoquinoline (**6**), 5-aminoquinoline (**7**), and 6-aminoquinoline (**8**) were obtained commercially and used without further purification after confirming their identity by measuring melting points and mass spectra (Chart 2).

The sample inlet temperatures were 160, 100, 50, 50, 60, 130, 160, and 150 °C for **1**−**8**, respectively. These temperatures were necessary to obtain sufficient vapor pressures in the ionization region. The absence of sharp, distinct peaks belonging to dissociation products such as N_2, CO_2, CO, and HI suggested that sample did not decompose at elevated temperatures. To test this suggestion further we examined the remainder of the sample after taking the UPS spectrum visually and by measuring its mass spectrum. Again, no sign of decomposition was observed. The positive outcome of such tests represents a necessary (though not sufficient) condition to prove the lack of decomposition.

Quantum chemical calculations were performed with the Gaussian 03 program.[6] Full geometry optimization was performed using the DFT method at the B3LYP/6-31G* level. Subsequently, a single-point calculation was performed with the Outer Valence Green's Function (OVGF) method.[7] The method enables one to obtain vertical ionization energies without recourse to Koopmans' approximation. Franck−Condon principle states that vertical transitions are the most probable and they correspond to the total energy difference between the molecular ground state and corresponding molecular ion of the same geometry. OVGF method describes vertical ionization energy because the method includes perturbation expansion of the molecular wave function which contains self-energy correction terms. These terms describe various many-body effects (correlation and reorganization energies) which are present in the molecule and ion.

The HeI and HeII photoelectron spectra of **1**−**8** were recorded and calibrated with small amounts of Xe gas which was added to the sample flow. The spectral resolution in the HeI and HeII spectra was 25 and 70 meV, respectively, when measured as fwhm of the $^2P_{3/2}$ Ar^+ line. The resolution in the HeII spectra was always inferior to that of HeI, which implies that some bands that are well resolved in HeI may be unresolved in the corresponding HeII spectrum. In consequence, the measured relative band intensities and intensity ratios sometimes refer to a combined intensity of two bands rather than to that of a single band.

The spectral bands were, when necessary for intensity measurements, simulated by asymmetric Gaussian profiles.[8] This allowed the deconvolution and estimate of intensity of individual bands to be made. Baseline corrections were also employed. Baseline parameters were determined from the data near the baseline and an exponential baseline function was used (i.e., band intensity $\sim 1/E_k$; where E_k is the photoelectron kinetic energy). This baseline function was recommended by the manufacturer for the spectrometer used in this work. The assignment of spectra of large molecules can often be facilitated by measuring band intensities at various photon energies. The empirical relative intensity ratio for the ith band was calculated as: $RI_i = \{B_i^{HeII}\Sigma_i B_i^{HeI}\}/\{B_i^{HeI}\Sigma_i B_i^{HeII}\}$ where B_i stands for the band intensity of the ith band in the HeI or HeII spectrum and the index of summation runs through the bands of interest. In our spectra the bands of interest were ring π-ionizations, nitrogen, and substituent lone pairs. RI values (presented in Table 1) correspond to experimental HeII/HeI intensity ratios of a particular band, normalized by the total intensity for the group of bands. The normalization was necessary because absolute band intensities could not be measured. RI values are presented as an aid in the spectral assignment. It is well established that, e.g., chlorine lone pair ionizations show a very pronounced

(2) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Amsterdam, 2000; pp 176−178.
(3) Van den Ham D. M. V.; van der Meer, D. *Chem. Phys. Lett.* **1972,** *15*, 549.
(4) Moomaw, W. R.; Kleier, D. A.; Markgraf, J. H.; Thoman, J. W.; Ridyard, J. N. A. *J. Phys. Chem.* **1988**, *92*, 4892.
(5) Ahmed, A. A.; Julliard, M.; Chanon, F.; Chanon, M.; Gracian, F.; Pfister-Guillouzo, G. *Spectrochim. Acta A* **1997**, *53*, 335.
(6) Gaussian 03, Revision B.05: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 2003.
(7) Cederbaum, L. S.; W. Domcke, W. *Adv. Chem. Phys.* **1977**, *36*, 205.
(8) Lichtenberger, D. L.; Copenhaver, A. S. *J. Electron Spetrosc. Relat. Phenom.* **1990**, *50*, 335.

TABLE 1. Vertical Ionization Energies ($E_i \pm 0.05$ EV), Empirically Derived Band Assignments (MO type), Calculated Ionization Energies (GF/eV), and Experimental Ratios of Relative HeII/HeI Band Intensities (RI)[a−c]

compd	band	E_i	MO type	GF	RI
1	X	(8.03)	π_5	7.99	1.28
	A	(9.03)	π_4	8.95	0.93
	B	9.63	n_N	9.90	0.53
	C−D	(10.2)	σ_I, π_I	10.02, 10.11	1.33
	E	10.62	π_3	10.57	1.33
	F−G	11.37	π_{Cl}, σ_{Cl},	11.45, 11.50	0.65
	H	11.98	n_O	12.33	0.81
2	X	8.2	π_5	7.91	1.58
	A	9.33	π_4	9.0	1.6
	B	10.05	n_N	10.14	1.22
	C	10.45	π_3	10.38	1.40
	D	10.95	π_{Cl}	11.04	0.91
	E	11.33	σ_{Cl}	11.34	0.26
	F	12.0	n_O	12.0	
3	X	(8.58)	π_5	8.28	1.28
	A−B	9.3, 9.5	π_4, n_N	8.91, 9.53	1.8
	C	10.58	π_3	10.32	1.21
	D−E	11.35	π_{Cl}, σ_{Cl}	11.21, 11.26	0.63
4	X	(8.65)	π_5	8.36	1.35
	A−B	9.3, 9.5	n_N, π_4	8.90, 9.56	1.70
	C	10.32	π_3	10.01	1.06
	D−E	11.43	π_{Cl}, σ_{Cl}	11.38, 11.57	0.74
5	X	(8.75)	π_5	8.50	1.22
	A	9.2	π_4	8.73	1.22
	B	9.9	n_N	9.80	1.33
	C	10.95	π_3	10.64	0.83
	D−E	11.35	σ_{Cl}, π_{Cl}	10.94, 11.14	0.83
6	X	8.0	π_5	7.52	0.94
	A	8.65	π_4	8.30	0.85
	B	9.35	n_N	9.70	0.95
	C	9.95	π_3	9.90	0.92
	D	11.0	n_{NH2}	11.21	1.20
7	X	7.9	π_5	7.46	1.27
	A	8.95	π_4	8.58	1.12
	B	9.3	n_N	9.20	1.12
	C	10.05	π_3	10.03	1.05
	D	10.75	n_{NH2}	10.80	0.86
8	X	7.85	π_5	7.45	0.87
	A	8.7	π_4	8.36	1.19
	B	9.1	n_N	9.08	1.19
	C−D	10.35	π_3, n_{NH2}	10.41, 10.43	1.04

[a] Average RI values for bands which could be resolved in HeI, but not in HeII spectra; adiabatic ionization energies are given in parentheses and have an uncertainty of 0.03 eV. [b] The bands were simulated by asymmetric Gaussian band shapes as suggested in ref 8, and the variable bandwidths were in the range 0.1−0.3 eV. [c] Where adiabatic energies only are given they are the same as the band maxima, which in other cases correspond to vertical ionization energies.

decrease in band intensity on going from HeI to HeII radiation,[11] i.e., their HeII/HeI ratios are smaller than for other orbitals such as nitrogen lone pairs or π-orbitals.

Results and Discussion

(A) Electronic Structure. The analysis of the photoelectron spectra is summarized in Table 1.

The arguments used in the assignments include the following general, empirical considerations:

(a) The assignment of the photoelectron spectrum of quinoline is well established[3] from the analysis of the "perfluoro-effect" and reveals four bands with ionization energies <11 eV.

They are three π-orbitals (out of the total of five occupied π-orbitals) and a single σ-orbital (nitrogen lone pair). We can thus expect to observe four similar bands in the spectra of substituted quinolines. In addition, bands from ionizations of orbitals localized on substituents will appear.

(b) Relative band intensities in the spectrum give information about the number of ionizations present within each band. When the spectrum of a molecule is measured first at the HeI and then at the HeII photon energy, relative band intensities will be different in the two spectra. The intensity changes can be rationalized qualitatively via the photon energy dependence of the atomic photoionization cross-sections for various orbitals. The HeII/HeI cross-section ratios for C2p, O2p, N2p, I5p, and Cl3p orbitals are 0.31, 0.64, 0.45, 0.10, and 0.05, respectively.[9] The ratios indicate that orbitals with substantial halogen character will exhibit strong and distinct variations in band intensities and consequently be readily identifiable in the spectra. The remaining orbitals, however, cannot be distinguished on that basis, because their HeI−HeII atomic cross-section differences are not sufficiently large.

(c) The band profiles also provide insight into the nature of the orbitals. Sharp, narrow bands correspond to the ionization from strongly localized, nonbonding orbitals as suggested by the Franck−Condon principle.

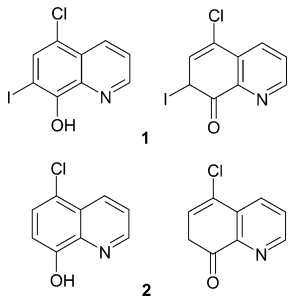
(d) The comparison was made between GF energies and the experimental, vertical ionization energies.

(e) Finally, a "composite molecule" method, i.e., comparison with the spectra of related molecules was used when arguments a−c could not provide definitive assignments.

Assignments for each group of molecules studied in this work are given in the paragraphs below.

Quinolines with Several Substituents (1 and 2). The spectra of **1** and **2** are shown in Figure 1 and their assignment is given in Table 1. The intensities of the sharp bands at 11.37 eV in **1** and at 11.33 eV in the spectrum of **2** vary strongly with photon energy. On the basis of general empirical considerations mentioned earlier, we conclude that these bands correspond to chlorine lone pair ionizations. Comparison with the spectra of related molecules containing similar functional groups, i.e., chlorobenzene,[10] iodobenzene,[10] phenol,[10] and chloro-4-iodobenzene[11] helps to identify which bands in **1** and **2** are of chlorine, which are of iodine and which of oxygen lone-pair type (OH group). The conclusions drawn from these empirical considerations are supported by the results of GF calculations.

1 and **2** can exist in the keto and enol tautomeric forms shown below.



(9) Yeh, J. J. *Atomic Calculation of Photoionization Cross-sections and Asymmetry Parameters*; Gordon and Breach: Langhorne 1993; pp 27−33, 49, 85, 121.

(10) Kimura, K.; Katsumata, S.; Achiba, Y.; Yamazaki, T.; Iwata, S. *Handbook of HeI Photoelectron Spectra of Fundamental Organic Molecules*; Japan Scientific Societies Press: Tokyo 1981; pp 190−191, 193−194.

(11) Novak, I.; Potts, A. W. *J. Phys. Chem. A* **1998**, *102*, 3532.

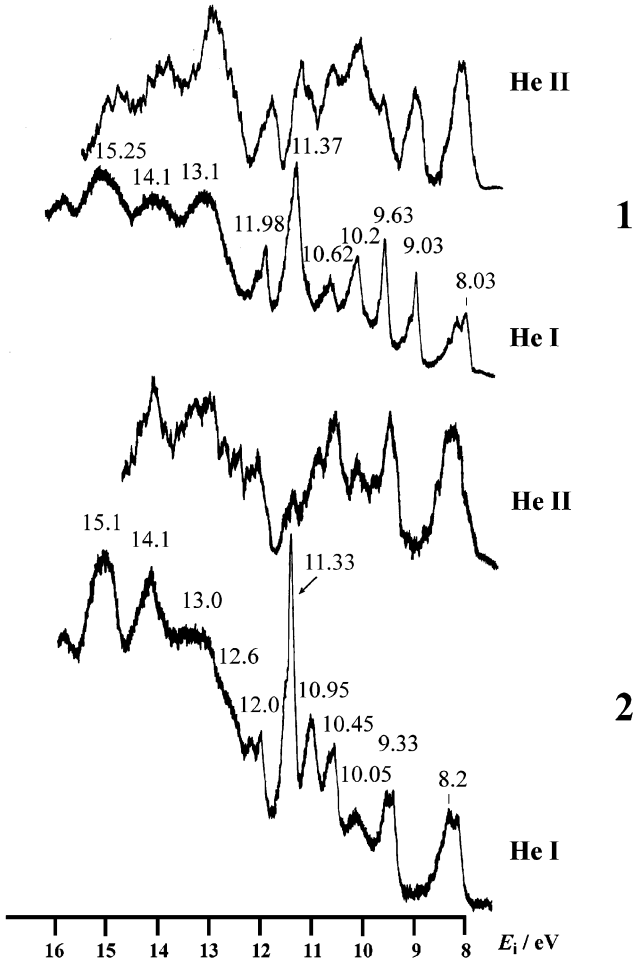


FIGURE 1. HeI/HeII photoelectron spectra of **1** and **2**.

We have performed DFT and AM1 calculations to estimate the relative abundance of these forms at the temperature of the experiment. The calculation of total energy differences (corrected for ZPE) between the tautomers shows that the enol form is more stable than the keto form by 38.8 and 53.9 kJ/mol for **1** and **2**, respectively. The corresponding AM1 values are 46.7 and 42.4 kJ/mol. Assuming that the population of tautomers is governed by a Boltzmann distribution, the keto/enol ratio becomes $\leq 10^{-5}$, which implies that the presence of keto form can be neglected under the experimental conditions.

Chloroquinolines (3−5). The spectra of **3**−**5** (Figure 2) can be assigned by comparison with the spectra of quinolin,[3] chloropyridines,[12] and 2-chloro-4-methylquinoline.[5] The reference spectra serve to identify the position of chlorine lone pair bands. The identification of chlorine lone pairs can be also be made by noticing that the bands at 11.35, 11.43, and 11.35 eV in **3**−**5**, respectively**,** exhibit a considerable drop in intensity on going from HeI to HeII. This is typical of chlorine lone pair ionizations, to which these bands can thus be attributed. The band at 11.35 eV in **5** shows a smaller drop in intensity than the corresponding bands in **3** and **4**. This is due to a strong overlap with the neighboring π_3-orbital ionization, the intensity of which increases with increasing photon

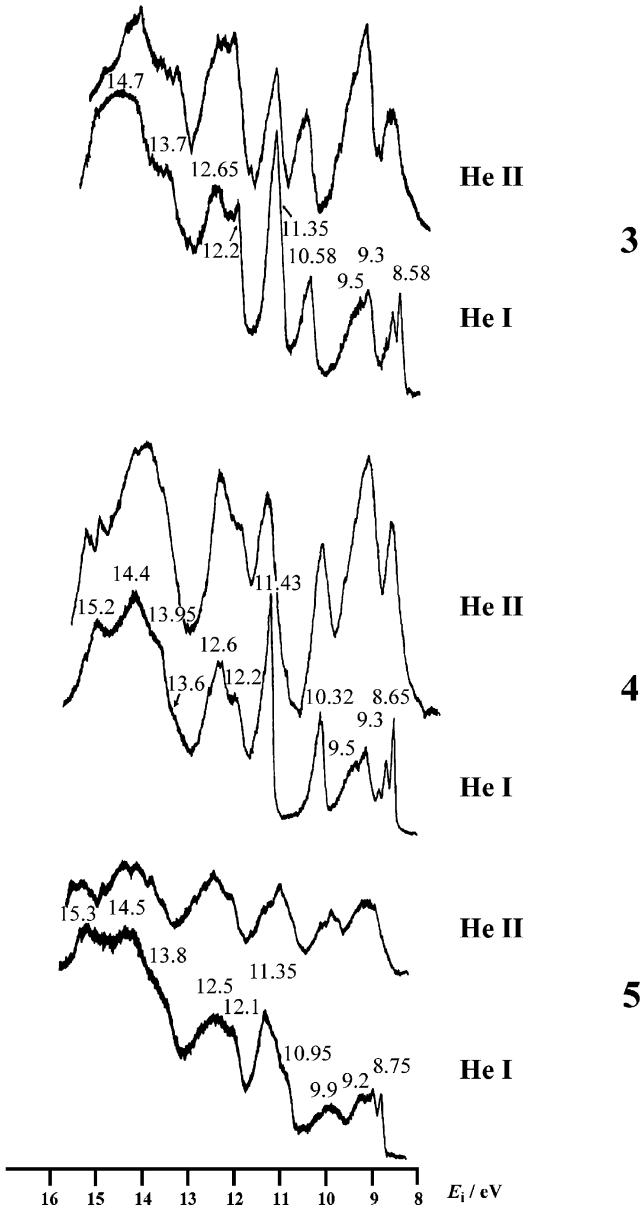


FIGURE 2. HeI/HeII photoelectron spectra of **3**−**5**.

energy. The comparison of the spectra of **3**−**5** with the spectrum of quinoline[3] and GF calculations then leads to the assignment of the remaining bands in the 8−12 eV region to ionizations from π-orbitals and quinoline nitrogen lone pairs.

Aminoquinolines (6−8). The molecules in this class contain a single amino group substituted at different ring positions. Their spectra (Figure 3) can be assigned by comparison with the spectra of quinoline,[3] aniline,[10] and aminopyridines[13] and by GF calculations. Amino nitrogen lone pairs in aniline and aminopyridines have ionization energies of 10.8 and 11.16−11.65 eV, respectively. This information suggests that the bands at 11.0, 10.75, and 10.35 eV in the spectra of **6**−**8** correspond to nitrogen lone pair ionizations. The HeII/HeI intensity variations in the spectra of **6**−**8** are not sufficiently pronounced to

(12) Murrell, J. N.; Suffolk, R. J. *J. Electron Spectrosc. Relat. Phenom.* **1972/73**, *1*, 471.

(13) Kobayashi, T.; Nagakura, S. *J. Electron Spectrosc. Relat. Phenom.* **1974**, *4*, 207.

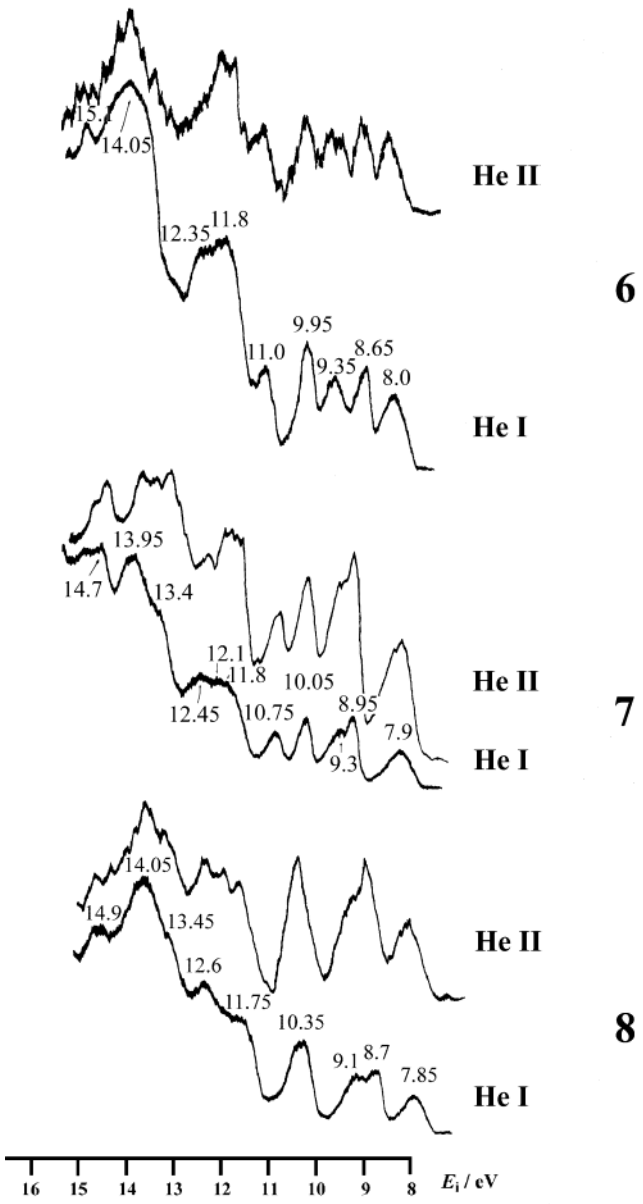


FIGURE 3. HeI/HeII photoelectron spectra of **6**−**8**.

identify amino groups, but GF results allow us to assign the remaining bands to π-orbitals and quinoline nitrogen lone pairs.

(B) Substituent Effects. Valence ionization energies can be used to gain insight into how substituents affect the electronic structure of quinoline and how they affect pK_a values of their conjugate acids. The ionization energies are measured in the gas phase so a more appropriate comparison would be with experimental gas-phase proton affinities rather than pK_a values. However, proton affinity values are not available. We have collated all available experimental data regarding ionization energies of substituted quinolines and their basicity and summarized them in Table 2. In some cases, there is a discrepancy between reported pK_a values, therefore we have listed all the available data. Based on the data in Table 2, it appears that pK_a values are quite sensitive to changes in the ionization energy even though the electronic structure is not the sole influence governing basicity.[4] Comparable changes in nitrogen lone pair ionization energies do not lead to comparable changes in pK_a values when quinolines with different substituents are compared. However, within the class of homologues/isomers, the lower the ionization energy of a nitrogen lone pair, the higher its basicity (larger pK_a). In aminoquinolines, for example, this trend is exhibited by both quinoline nitrogens which are protonated first and by amino nitrogens, which are protonated second.[14] As a rule, the nitrogen site with larger pK_a value is protonated first, i.e., it is protonated at lower acidity.

TABLE 2. Comparison of Nitrogen Lone Pair Ionization Energies (E_i/eV), Available pK_a Values (±0.02), and Orbital Energy Shifts ($\Delta\pi$/eV, ΔN/eV) in Substituted Quinolines[a,b]

molecule	E_i	pK_{a1}	pK_{a2}	$\Delta\pi$	Δn
quinoline (Q)	9.39[3]	4.81[20]			
2,3-diMe-Q	9.11[4]	5.99[4]		1.19	0.28
2,6-diMe-Q	9×10^5	5.46[15]		1.08	0.29
6-Me-Q	9.3[5]	5.22[16]		0.53	0.09
2-Me-4-MeO-Q	9.15[5]			1.83	0.24
4-Me-2-MeO-Q	9.4[5]			1.58	−0.01
6-OMe-Q	9.25[5]	5.03[16]		0.83	0.14
4-OMe-Q	9.2[5]	6.45[16]		1.43	0.19
2-Cl-4-Me-Q	9.7[5]			0.38	−0.31
3-Br-Q	9.65[5]	2.74[17]		−0.37	−0.26
3-NH_2-Q (**6**)	9.35,[b] 11.0*	−0.57[14]	4.96[14]	1.83	0.04
5-NH_2-Q (**7**)	9.3,[b] 10.75*	0.49[14]	5.63[14]	1.53	0.09
6-NH_2-Q (**8**)	9.1,[b] 10.35*	1.63[16]	5.59[16]	1.53	0.29
2-Cl-Q (**5**)	9.9[b]			−0.47	−0.51
4-Cl-Q (**4**)	9.5[b]	3.72[16]		0.16	−0.11
5-Cl-Q (**3**)	9.5[b]	3.65[16]		−0.03	−0.11
5-Cl-8-OH-Q (**2**)	10.05[b]	3.79,[20] (4.19[18])	9.29,[20] (8.95[18])	0.45	−0.66
5-Cl-7-I-8-OH-Q (**1**)	9.63[b]	2.96[19]	7.6[19]	0.73	−0.24
Heptafluoro-Q	11.4[3]			−2.72	−2.01

[a] Superscripts indicate references to experimental E_i and pK_a values; numbers with an asterisk correspond to amino nitrogen lone pair energies. pK_a values refer to conjugate acids of the respective amine bases. [b] E_i measured in this work.

To quantify the substituent effects we introduce variables $\Delta\pi$ and Δn, defined as follows

$$\Delta\pi = \sum_i [\pi_i(\mathrm{Q}) - \pi_i(\mathrm{RQ})]$$

and

$$\Delta n = 9.39 - n_{\mathrm{RQ}}$$

where 9.39 eV is the ionization energy of the nitrogen lone pair in quinoline (Q) and π_i(Q) and π_i(RQ) are ionization energies of the first three π-orbitals (π_5, π_4, and π_3) in Q and in substituted quinolines (RQ), respectively. The $\Delta\pi$ and Δn definitions are based on the notion of σ/π separation and are defined so that negative $\Delta\pi$ and Δn values imply a stabilizing effect by the substituent, while positive values imply a destabilizing effect. This is in accordance with standard thermodynamic usage. $\Delta\pi$ and Δn values are listed in Table 2. The values in Table 2 allow us to make a distinction between resonance and inductive substituent effects[2] and even to describe more complex cases when several different substituents are present simultaneously. Δn values (whether stabilizing or destabilizing) describe the presence of an inductive substituent effect. $\Delta\pi$ values reflect the presence of both

(14) Schulman, S. G. *J. Pharm. Sci.* **1971**, *60*, 371.

resonance and inductive effects. One must bear in mind that the magnitude of the effect depends on the topology of substitution, i.e., on a substituent's position on the ring as well as on the structure of the substituent.

Fluorine substituents exert mostly inductive stabilization. This can be deduced from the fact that both Δn and $\Delta\pi$ values are large, negative, and of comparable magnitude. Other halogen substituents cause similar, albeit smaller, inductive stabilizations. Our scheme allows us to monitor sensitivity of different sites toward substitution. Thus, for example, one can conclude that the 2- and 3-positions are more sensitive to substitution than the 4-position, which agrees with an earlier suggestion based on chemical reactivity data.[2]

The presence of amino or methoxy substituents induces large, predominantly resonance destabilization ($\Delta\pi > \Delta n > 0$). Methyl substituents act in a similar manner, but their destabilizing effect is weaker and additive (compare 6-Me and 2,6-diMe-Q). The presence of different types of substituents leads to more complicated and interesting effects. However, our scheme still allows us to readily deduce the net effect. For example, in 2-Cl,4-Me-Q we can see how chlorine causes inductive stabilization ($\Delta n < 0$) and at the same time counteracts (weakens) the resonance destabilization induced by the methyl group. $\Delta\pi$ and Δn values in **1** and **2** have opposite signs. This is because halogens stabilize nitrogen lone pairs while the hydroxy group acts in the opposite sense by strongly destabilizing π-electron density.

(C) Medicinal Activity and the Electronic Structure. Some 4- and 8-substituted derivatives[21] possess antimalarial activity. This activity depends on the protonation of various basic nitrogen sites in the molecule.[1] The cell environment cannot tolerate excessive acidity so the active site(s) is(are) the one which can be easily protonated. In most of these derivatives (chloroquine, hydroxychloroquine, primaquine, and pamaquine) the substituent group is a secondary or tertiary amine located on the side chain (Scheme 1) whose nitrogens are likely to be protonated first. In compounds **6**−**8**, protonated quinoline nitrogens and primary amino nitrogens have pK_a values in the ranges of 4.96−5.63 and −0.57 to 0.49, respectively (Table 2).[14] These values are too low for nitrogen sites to be protonated under physiological conditions and such compounds would be medicinally inactive. Nonetheless, our results suggest that it is possible to distinguish the ionization energies for different types of nitrogen lone pairs by UPS measurements and correlate them with pK_a measurements and studies of medicinal activity.

The study of aminoquinolines reveals that pK_a variation of their conjugate acids obtained by shifting a NH_2 group around the quinoline nucleus amounts to $\Delta pK_{a2} = 0.67$. The corresponding change in NH_2 lone pair energy is $\Delta n = 0.65$ eV. Much larger variations in basicities ($\Delta pK_a = 2.08-2.37$) were achieved by varying substituents at the 7-position in a series of 7-substituted 4-aminoantiplasmodials.[1] In these antiplasmodials, pK_{a1} and pK_{a2} values for the conjugate acids of quinoline and tertiary amino nitrogens are in the ranges of 6.28−8.36 and 7.65−10.02, respectively.[1] While the mechanism of biological activity of 4-substituted quinolines is consistent with the weak-base-hypothesis,[21] the mechanism of 8-aminoquinolines is unknown except for the suggestion that it may involve a radical anion intermediate at the 8-amino group.[21] In any case, knowledge of the electronic structure would complement nicely basicity measurements in seeking leads for new antimalarial drugs. Another useful piece of information obtained from a UPS study concerns the influence of solvent on basicity. There is a good correlation between ionization energy changes and pK_a changes in substituted quinolines. This suggests that solvent effects do not influence relative basicity much within the same class of derivatives.

Summary

We have analyzed substituent effects in quinolines by using a scheme based on experimental ionization energy shifts. The scheme allows us to monitor and quantify the influence of different substituents on the electronic structure of the quinoline core. This information may be useful in the analysis of structure−activity relationships (SAR) of new quinoline derivatives with medicinal properties. The usefulness arises from the fact that medicinally active derivatives often contain several types of substituents, but pK_a measurements alone cannot explain the influence of a particular substituent type on overall basicity. However, it is precisely the knowledge regarding the influence of individual substituents on basicity that is required for designing better antimalarial agents.

Supporting Information Available: Coordinates and total energies for substituted quinolines. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Jia, Z.; Ramstad, T.; Zhong, M. *Electrophoresis* **2001**, *22*, 1112.
(16) Perrin, D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965; pp 243−247.
(17) Slater, B.; McCormack, A.; Avideef, A.; Comer, J. E. A. *J. Pharm. Sci.* **1994**, *83*, 1280.
(18) Janjić, T. J.; Pfendt, L. B.; Aleksić, M. B. *Talanta* **1992**, *39*, 55.
(19) Tan, K. Y.; Takacs-Novak, K. *Anal. Chim. Acta* **2001**, *434*, 157.
(20) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York, 1989; Vol. 6, 2nd Supplement, p 482.
(21) Williams, D. A.; Lemke, T. L. *Foye's Principles of Medicinal Chemistry*, 5th ed.; Lippincott Williams & Wilkins: Baltimore, 2002; p 876.