# MO SELF-CONSISTENT-FIELD (SCF) CALCULATIONS OF QUINOLINE AND ITS DERIVATIVES.

## 3.* PROTONATION ENERGIES AND BASIC PROPERTIES

Z. P. Bruvers and I. V. Zuika

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The basic properties ($pK_{NH^+}$) of quinoline and its amino-, methoxy-, and S-methyl-substituted derivatives (substitution in the 2–8 positions of the quinoline ring) are compared with the bond energy [$E(N_{het}H)$], the charge on the nitrogen atom ($q_N$), and the protonation energy ($E_p$) calculated within the CNDO/2 approximation with partial optimization of the geometry of the molecules.

In a continuation of our studies of the electron structures and properties of quinoline derivatives in the present research we examined the changes in the basis properties ($pK_{NH^+}$) in the quinoline series and for its S-methyl, methoxy, and amino derivatives. The following parameters were selected for the characterization of the $pK_{NH^+}$ values of these compounds: 1) the energy of protonation of the molecule $E_p = E^+ - E^\circ$, where $E^+$ is the total energy of the protonated form, and $E^\circ$ is the total energy of the neutral molecule; 2) the charge on the heterocyclic nitrogen atom ($q_N$) in the neutral molecule; 3) the energy of the bond between the proton and the heterocyclic nitrogen atom.

We calculated 2-, 3-, 4-, 5-, 6-, 7-, and 8-amino, methoxy-, and S-methylquinolines, as well as 5-fluoro- and 5-chloro-8-S-methylquinoline by the CNDO/2 method [2] with partial optimization of the geometry of the molecules (the C—S bond length ranged from 1.75 to 1.78 Å, the C—O bond length ranged from 1.36 to 1.38 Å, and the C—N bond length ranged from 1.39 to 1.45 Å). The S-methylquinolines were calculated within the sp and spd bases of

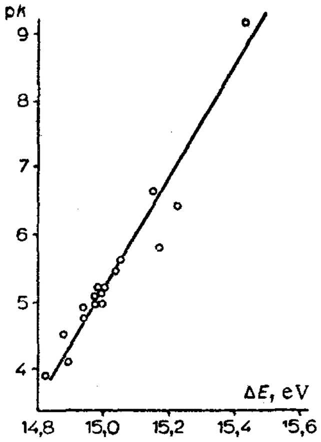

Fig. 1

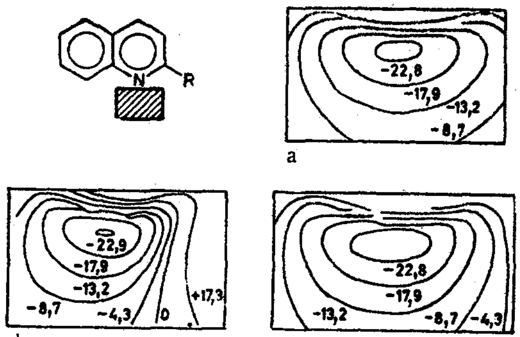

Fig. 2

Fig. 1. Dependence of the $pK_{NH}$ + values on the $E_p$ values of quinoline and its derivatives.

Fig. 2. Electrostatic potential in the region of protonation of quinoline (a) and 2-methoxy- (b) and 2-aminoquinoline (c).

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*See [1] for communication 2.

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TABLE 1. Protonation Energies ($E_p$), Charges on the Nitrogen Atom ($q_N$), Bond Energies [$E(N_{het}H)$], and Basic Properties of Quinoline and Its Derivatives

| Compound | $E(N_{het}H)$, eV | $E_n$, eV | $-q_N$ | $pK_{NH^+}$ |
|---|---|---|---|---|
| Quinoline | 26,46 | 14,99 | 0,162 | 4,94 |
| 2-Amino | 26,57 | 15,40 | 0,222 | 7,34 |
| 3-Amino | 26,43 | 14,98 | 0,143 | 4,95 |
| 4-Amino | 26,56 | 15,44 | 0,196 | 9,17 |
| 5-Amino | 26,48 | 15,04 | 0,167 | 5,46 |
| 6-Amino | 26,45 | 15,05 | 0,156 | 5,63 |
| 7-Amino | 26,50 | 15,16 | 0,173 | 6,65 |
| 8-Amino | 26,40 | 14,89 | 0,156 | 3,99 |
| 2-Methoxy | 26,43 | | | 3,17 |
| 3-Methoxy | 26,42 | 14,94 | 0,139 | 4,88 |
| 4-Methoxy | 26,58 | 15,23 | 0,191 | 6,45 |
| 5-Methoxy | 26,50 | 14,98 | 0,168 | 5,20 |
| 6-Methoxy | 26,45 | 14,97 | 0,155 | 5,06 |
| 8 Methoxy | 26,41 | 14,99 | 0,145 | 5,14 |
| 2-S-Methyl | 26,53 | | | 3,71 |
| 3-S-Methyl | 26,44 | 15,02 (14,83)* | 0,149 | 3,88 |
| 4-S-Methyl | 26,58 | 15,31 (15,15) | 0,183 | 5,81 |
| 5-S-Methyl | 26,49 | 15,09 (14,88) | 0,166 | 4,50 |
| 6-S-Methyl | 26,46 | 15,10 (14,94) | 0,158 | 4,75 |
| 7-S-Methyl | 26,51 | 15,17 (15,00) | 0,171 | 5,20 |
| 8-S-Methyl | 26,36 | 15,04 (15,12) | 0,153 | 3,50 |
| 5-Fluoro-8-S-methyl- | 26,40 | 14,38 | 0,157 | 2,67 |
| 5-Chloro-8-S-methyl- | 26,40 | 14,80 | 0,154 | 2,27 |

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*For an spd basis of the AO of the sulfur atom.

the AO of the sulfur atom. The starting geometry of the molecules was taken from [3]. The protonation energy ($E_p$), the charge on the nitrogen atom ($q_N$), the energy of the NH bond, and the $pK_{NH^+}$ values [4-6] of substituted quinolines are presented in Table 1. Of the calculated parameters of the molecules, only $E_p$ (for S-methylquinolines with allowance for the d orbitals of the sulfur atom) correlates satisfactorily with the $pK_{NH^+}$ values (Fig. 1). $\Delta E$ (kcal/mole) = $2.74\Delta pK_{NH^+}$ ($R = 0.967$). Allowance for the solvation energy within the framework of an electrostatic model in this series of related compounds has virtually no effect on the correlation of $E_p$ with $pK_{NH^+}$.

In the case of 3-, 4-, 5-, 6-, and 7-substituted quinolines the $pK_{NH^+}(E_p)$ values are determined primarily by the nature of the interaction of the substituent with the ring. Substantial deviations between the $pK_{NH^+}$ and $E_p$ values (Table 1) are noted in the case of 2-methoxy- and 2-S-methylquinolines, and the decrease in the $pK_{NH^+}$ value as compared with the $pK_{NH^+}$ value of quinoline evidently is not determined by these effects of the substituents. The decrease in the $pK_{NH^+}$ value may be associated with steric hindrance to protonation on the part of the substituent in the 2 position. According to electrostatic-potential maps in the protonation region (Fig. 2), the influence of this effect in, for example, 2-methoxyquinoline, is substantially greater than in the case of 2-aminoquinoline. In the latter compound the $E_p$ value correlates satisfactorily with the $pK_{NH^+}$ value (2-methoxy- and 2-S-methylquinoline were excluded).

In contrast to 3-substituted quinolines (substituted in the meta position relative to the nitrogen atom), in 8-substituted quinolines a hydrogen bond (HB) makes a contribution to the $pK_{NH^+}$ and $E_p$ values. According to the results of the calculation, the energy of the hydrogen bond in the neutral form of 8-aminoquinoline is 3.5 kcal/mole (calculated with allowance for the change in the p–π conjugation of the $NH_2$ group with the ring), as compared with 1.5 kcal/mole in the protonated form. The weaker hydrogen bond in the latter is the reason for the decrease in the $pK_{NH^+}$ ($E_p$) value of this compound as compared with 3-aminoquinoline. The increase in the $pK_{NH^+}$ ($E_p$) value of 8-methoxyquinoline as compared with 3-methoxyquinoline is due to the presence of a hydrogen bond only in the protonated form of the former. According to the results of the calculation, the hydrogen bond in the protonated form of 8-S-methylquinoline does not differ substantially from that in 8-methoxyquinoline [E(S...H) and E(O...H) are 0.314 and 0.308 eV] and also leads to an increase in $E_p$ as compared with 3-S-methylquinoline. As in the case of 2-methoxyquinoline, the decrease in the $pK_{NH^+}$ value of 8-S-methylquinoline is evidently associated with steric hindrance.

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