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QUANTUM-CHEMICAL INVESTIGATION OF THE DEPENDENCE OF pK_a ON THE CALCULATED ENERGY OF PROTON REMOVAL FOR CERTAIN DERIVATIVES OF INDOLE AND PHENOL

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The total energies of derivatives of N-hydroxyindole, indole, and phenol, and of their corresponding anions have been estimated with the aid of ab initio calculations on the 3-21G basis. The energies of proton removal were calculated from the difference in total energies of the appropriate anions and molecules. By comparing the calculated energies of proton removal with experimental values of pK_a (acidity characteristic) a practically linear dependence was shown for the acidity characteristic on the energy of proton removal for the series of compounds investigated. An empirical formula has been proposed expressing the dependence of pK_a on the energy of proton removal, which makes it possible to predict pK_a in this series by carrying out calculations of the energy of proton removal (transfer).

Keywords: N-hydroxyindole, indole, anion, 3-21G basis, depronation, acidity, *ab initio* calculations.

Investigations of the acid–base properties of derivatives of indole and phenol are of significant interest, since pK_a values and the regularities of acidity change in series of these compounds are extremely important for predicting their reactivity and their pharmaceutical potential. In view of the analogy in chemical behavior of indole and phenol derivatives (properties of the proton in N-H and O-H bonds), we placed them in one series for a theoretical study of their proton-donating ability.

The problem of the present investigation is the calculation of the energy of proton removal for certain derivatives of indole and phenol and clarification of the dependence of pK_a on this value. Such an approach may permit prediction of pK_a values for new derivatives of phenol or indole and thereby facilitate prediction of their chemical and biological properties.

In the present work we have investigated the changes in deprotonation energy in a series of derivatives of indole (N-hydroxyindole) and phenol.

$$\text{R–OH} \rightarrow \text{R–O}^- + \text{H}^+,$$

where R is an indole or diphenyl group having various substituents in the series. It is necessary to mention that similar investigations have been carried out using predictions by the CDLAP method [1].

However if a particular fragment is absent from the molecules studied assessment becomes impossible using the predictions of the CDLAP method. Consequently we chose one of the standard *ab initio* quantum-chemical methods [2] with a comparatively small orbital basis 3-21G and without calculating solvation spheres,

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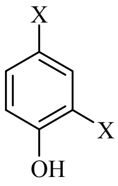
which we consider a compromise, in view of the limited resources of the usual personal computer and the significant errors on using alternative (rapid) semiempirical quantum-chemical methods for describing OH and H bonds [3-5].



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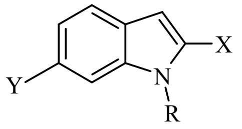

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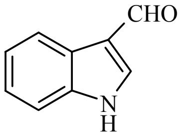

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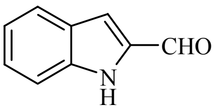

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1 X = H, **2** X = NO_2, **3** R = H, X = H, Y = H, **4** R = OH, X = H, Y = H,
5 R = OH, X = COOMe, Y = H, **6** R = OH, X = H, Y = NO_2

The values of the total energies of molecules and of the anions corresponding to them were calculated with complete optimization of the geometry by the RHF/3-21G method [6] using the Gaussian 98 program [6]. For a more adequate assessment of the electronic structure and energy characteristics of the anions being studied we also used the 3-21G$^+$ basis with the addition of diffuse functions enabling a more precise description of the behavior of the unshared electron pairs. All the structures optimized by us correspond to minima on the potential energy surface.

The differences between the calculated total energies of the anions and of the molecules corresponding to them served as assessments of the energy of deprotonation (proton removal).

The values of pK_a calculated by us and from the literature are given in Table 1. The experimental values of pK_a for N-hydroxyindole and N-hydroxy-2-methoxycarbonylindole are absent from Table 1 because the determination of pK_a for N-hydroxyindole proved to be impossible due to its chemical instability [7], and specific experimental difficulties were encountered with N-hydroxy-2-methoxycarbonylindole.

The following stage of our work was the prediction of values of unknown pK_a for which it was necessary to make more precise the dependence of pK_a on the energy of proton removal. On constructing the appropriate graph we discovered that it is represented by a practically straight line, i.e. it is described by the function $Y = kX + b$, which we subsequently calculated in the selection of an empirical formula for the relationship indicated above.

In the formula p$K_a = kE + b$ the coefficients k and b were calculated by the least squares method, starting from the series of calculated data (Table 1), after which the empirical dependence of pK_a on the deprotonation energy E acquires the form:

$$pK_a = 0.10197E - 18.8614 \qquad (1)$$

Substituting the values of E calculated for N-hydroxyindole and N-hydroxy-2-methoxycarbonylindole in formula (1), we found that the unknown pK_a values must be equal to 12.96 and 10.08 respectively. The values of pK_a found by the proposed empirical formula additionally confirm our preliminary conclusion on the fact that the acidity of the series of indole and phenol derivatives increases with the reduction in the energy of proton removal. This is seen in Table 1, in which the found pK_a values for N-hydroxyindole and N-hydroxy-2-methoxycarbonylindole are also included. Deviations from linearity in the graph constructed by us are explained by the none quivalence of the conditions of calculating the deprotonation energies and the experimental determination of the given pK_a values. Calculation of the energies was carried out without allowing for solvation spheres, though the pK_a values given by us were determined in aqueous medium.

TABLE 1. Total Energies (E) of Molecules and Corresponding Anions, Proton Removal Energies (ΔE), Calculated and Experimental Acidity Characteristics (pK_a)

Compound	E, a. e.		ΔE, kcal/mol	pK_a
	molecule	anjon		
1	-303.86010	-303.38878	295.753	9.94 [8]
2	-708.42775	-708.08489	215.145	4.01 [9]
3	-359.45470	-358.90625	344.152	16.97 [10]
4	-433.82650	-433.32916	312.081	12.96*
5	-659.21191	-658.75096	283.825	10.08*
6	-636.12020	-635.70449	260.858	6.9 [7]
7	-471.55161	-471.05719	310.249	12.36 [10]
8	-471.54512	-471.04621	313.066	14.00 [11]

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* Value of pK_a found using formula (1).

A smooth reduction in the energy for proton removal was noted in the series indole → 2-formylindole → N-hydroxyindole → 3-formylindole → phenol → N-hydroxy-2-methoxycarbonylindole → N-hydroxy-6-nitroindole → 2,4-dinitrophenol. An increase in acidity occurs synchronously in this series with the change in energy of deprotonation, which is obvious from the pK_a values given in Table 1.

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