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# QUANTUM-CHEMICAL STUDY OF THE CH ACIDITIES OF METHYL DERIVATIVES OF FIVE-MEMBERED AROMATIC HETEROCYCLES

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The CNDO/2 (complete neglect of differential overlap) method was used for the study of the possibility of the quantum-chemical description of the electronic effects of substituents and heteroatoms on the CH acid properties of an extensive series of methyl derivatives of five-membered aromatic heterocycles. It is shown that the trend of the change in the relative rate constants of deuterium exchange of the methyl derivatives of furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrazole, imidazole, oxa- and thiadiazoles, and tetrazole corresponds in most cases to the changes in the deprotonation energies ($\Delta E = E_{\text{Het-CH}_2^-} - E_{\text{Het-CH}_3}$) and the charges on the hydrogen atoms of the methyl groups undergoing attack by the base. The factors responsible for violation of the indicated simple conformity are discussed.

Studies made in recent years have shown that within the limits of a series of similarly constructed compounds, the CNDO/2 (complete neglect of differential overlap) method can be successfully applied for the description of the kinetic and equilibrium acidities of carboxylic acids (for example, see the data on the CH acidities of substituted benzenes [1], some five- and six-membered nitrogen-containing heterocycles [2-4], methanes [5], ethylenes [6], phenylacetylenes [1], methyl derivatives of aromatic compounds [1], saturated rings [7, 8], etc.). In a continuation of our research on the relationship between the electronic structure and the lability of hydrogen atoms in organic compounds of different classes, we made a quantum-chemical examination of the CH acid properties of an extensive series of methyl derivatives of five-membered aromatic heterocycles. As in [5, 7, 9], we used the deprotonation energies ($\Delta E = E_{\text{Het-CH}_2^-} - E_{\text{Het-CH}_3}$) and the charges on the hydrogen atoms ($q_H$) undergoing attack by the base as the theoretical reactivity indices. The $\Delta E$ values were calculated for "planar" and pyramidal configurations corresponding to the model of complete detachment of a proton in the carbanion transition state. The experimental geometry of the corresponding unsubstituted heterocycles [9] was used as the basis of the calculation of the investigated series of methyl derivatives in most cases; the parameters of the idealized geometry recommended by Pople and Gordon [10] were used for

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TABLE 1. Relative Rate Constants for Deuterium Exchange and Quantum-Chemical Characteristics of the Deuterium Exchange of Methyl Derivatives of Five-Membered Heteroaromatic Compounds

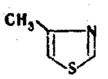
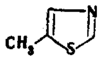
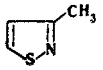
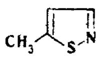
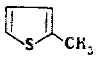
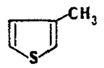
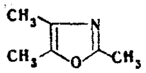
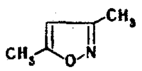
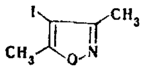
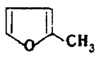
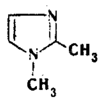
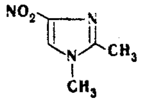
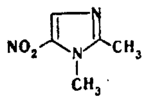
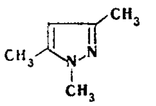
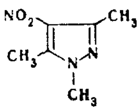
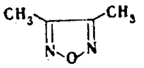
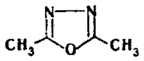
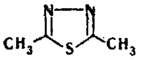
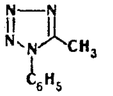
| Compound No. | Compound | Position | lg $f^a$ | $\Delta E^b$, eV | $q_H{}^c$, av |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| 1 |  | 2 | 8,9 | 25,4598<br>(23,9315) | 0,9776 |
| 2 |  | 4 | 5,3 | 26,7244<br>(25,2944),<br>$25,6613^d$ | 0,9866<br>$0,9799^d$ |
| 3 |  | 5 | 6,6 | 25,8235<br>(24,6401),<br>$25,8131^d$ | 0,9894<br>$0,9916^d$ |
| 4 |  | 3 | 6,8 | 25,7244<br>(24,3048),<br>$25,3867^d$ | 0,9846<br>$0,9798^d$ |
| 5 |  | 4 | 2,3 | 26,2189<br>(25,4800),<br>$25,7452^d$ | 0,9961<br>$0,9896^d$ |
| 6 |  | 5 | 8,5 | 26,4974<br>(24,1368),<br>$26,5484^d$ | 0,9877<br>$0,9812^d$ |
| 7 |  | 2 | 1,9 | 25,7550<br>(24,5795),<br>$25,7775^d$ | 0,9884<br>$0,9810^d$ |
| 8 |  | 3 | −1,1 | 26,1988<br>(25,3639),<br>$25,7194^d$ | 0,9956<br>$0,9892^d$ |
| 9 |  | 2 | 7,6 | 25,4111<br>(24,0436) | 0,9731 |
| 10 |  | 4 | No exchange | — | 0,9932 |
| 11 |  | 5 | 1,4 | 26,0428 | 0,9880 |
| 12 |  | 3 | $(5,7)^e$ | 25,7069<br>(25,0229) | 0,9857 |
| 13 |  | 5 |  | 26,0946<br>(24,3730) | 0,9762 |
| 14 |  | 3 | 7,3 | $25,7902^f$<br>(24,6468) | $0,9810^f$ |
| 15 |  | 5 | 10,8 | $25,4279^f$<br>(24,0145) | $0,9735^f$ |
| 16 |  | 2 | 0,9 | 26,0063<br>(24,8582) | 0,9824 |
| 17 |  | 2 | 8,3 | 25,9792<br>(24,9001) | 0,9820 |
| 18 |  | 2 | 13,5 | 25,0723<br>(23,8800) | 0,9721 |

TABLE 1 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| 19 |  | 2 | 13,5 | 24.9566<br>(23,6427) | 0,9708 |
| 20 |  | 3 | 1,2 | 26.2675 | 0,9883 |
| 21 | | 5 | 3,9 | 25,8725 | 0.9865 |
| 22 |  | 3 | 7,7 | 25.7097 | 0.9749 |
| 23 | | 5 | 13,1 | 24,2354 | 0,9509 |
| 24 |  | 3,4 | 8,0 | 25.8915[g]<br>(24,8150) | 0,9826[g] |
| 25 |  | 2,5 | 10,9 | 25.5328[h]<br>(24,2422) | 0,9723[h] |
| 26 |  | 2,5 | 11,5 | 25.4148<br>(24,1189) | 0.9763 |
| 27 |  | 2 | 11,6 | 25,7107 | 0.9729 |

[a] Log $f$ = log k − log $k_0$, where k and $k_0$ are rate constants for deuterium exchange of the methyl groups in the investigated compound and in toluene, respectively, referred to standardized conditions (0.57 N $C_2H_5OK + C_2H_5OD$, 25°C). The log k values were taken from [11]; log $k_0 = -15.9$ [12].

[b] These are the $\Delta E$ values for the pyramidal and (in parenthesis) planar carbanion models.

[c] These are the average $q_H$ values for the three hydrogen atoms of the methyl group.

[d] Within the spd approximation.

[e] This is the average value of the rate constants for the 3 and 5 positions.

[f] For 3,5-dimethyl-4-chloroisoxazole.

[g] For 3-methylfurazan.

[h] For 3-methyloxadiazole.

the substituents. In the calculation of the carbanions all of the angles (except those pertaining to the extracyclic $CH_2^-$ group in the "planar" model) were assumed to be the same as in the corresponding starting CH acid. The calculations were made with a BÉSM-6 computer from a program composed in the department of quantum chemistry of Leningrad State University.

The results of the calculation are presented in Table 1. Data on the relative rates of isotopic exchange of the hydrogen atoms of the methyl groups (log $f$), calculated from data from our previous study [11] relative to toluene [12] as the standard compound, are also presented in Table 1.

As seen from Table 1 and Figs. 1 and 2, both indices ($\Delta E$ and $q_H$) together accurately convey the trend of the change in the kinetic CH acidity:

$$\lg f = 255 - 9.6\Delta E_{pyr} \quad (r = 0{,}954,\ n = 14), \tag{1}$$

$$\lg f = 143 - 5{,}5\Delta E_{pl} \quad (r = 0{,}910,\ n = 11), \tag{2}$$

$$\lg f = 455 - 455 q_H \quad (r = 0{,}943,\ n = 15), \tag{3}$$

thereby demonstrating the effectiveness of the quantum-chemical interpretation of the reactivity both within the

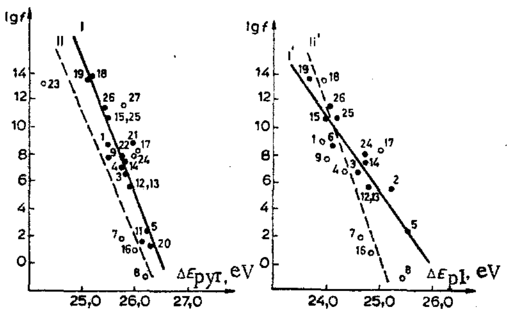


Fig. 1

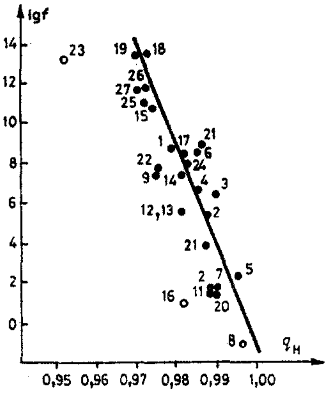


Fig. 2

Fig. 1. Relationship between log *f* and ΔE: I, I') azoles; II, II') toluenes (the numbering corresponds to that in Table 1; O) denotes compounds that are not included in the correlation treatment).

Fig. 2. Relationship between log *f* and $q_H$ (the numbering of the points corresponds to that in Table 1; O denotes compounds that are not included in the correlation treatment).

"isolated molecule" approximation and within the delocalization approximation for the prediction of the CH acid properties of azoles. The approximately identical character of the correlations does not make it possible to form a judgement regarding the preferableness of one of the indices used; to the same extent, it is not possible on the basis of the data obtained in this research to make an unambiguous choice between the two investigated models of the transition state.

As in the previous calculations of CH acidity [5, 7], expansion of the basis through inclusion in it of the d orbitals of sulfur has little effect on the calculated deprotonation energies.

In Fig. 1 one's attention is drawn to the shift of the correlation lines that characterize the CH acidity in the series of azoles relative to the lines for substituted toluenes.* This apparently should be considered to be the result of the overall effect of mainly two complicating factors:

a) All of the calculations were made for isolated molecular systems and essentially characterize the CH acidity in the gas phase. However, the experimental rate constants pertain to the conditions under which the process was carried out in a polar solvent, in which the effect of specific solvation of the nitrogen-containing heterocycles may have an appreciable effect on their position in the general scale of carboxylic acids [13-16].

b) The dependence of the electron repulsion integrals on the nature of the basis atomic orbitals is ignored in the CNDO/2 method; according to the results of a recent theoretical analysis [4, 8], this is one of the fundamental reasons for the inadequate description of the CH acidities of nitrogen-containing heterocycles within the framework of this method. The fact that five-membered rings that do not contain a nitrogen heteroatom (Nos. 7, 8, and 16 in Fig. 1) deviate appreciably from correlation lines I and I' and are grouped about lines II and II'k, which convey the trend of the change in the rate constants for deuterium exchange in substituted toluenes, also constitutes evidence that it is precisely the presence of a nitrogen heteroatom that is responsible for the indicated deviations.

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*Correlation lines II and II' in Fig. 1 were constructed on the basis of our results, and partially, the reported results of calculation of the ΔE values and data on the rate of deuterium exchange of substituted toluenes [1, 16]. The corresponding equations have the form $\log f = 218.0-8.3\ \Delta E_{pyr}$ and $\log f = 280.6-11.2\ \Delta E_{pl}$.

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# ISOTOPIC HYDROGEN EXCHANGE IN METHYL DERIVATIVES OF FIVE-MEMBERED AROMATIC HETEROCYCLES

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and E. Ya. Konyakhina

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The kinetics of isotopic exchange of the hydrogen atoms of the methyl groups in an alcohol solution of potassium ethoxide were studied for an extensive series of methyl derivatives of azoles and di-, tri-, and tetrazoles. The electronic effect of one or several heteroatoms and substituents on the rate of deuterium exchange of five-membered heterocycles is satisfactorily conveyed by the correlation relationship previously established for a series of substituted toluenes and six-membered heteroaromatic compounds ($\rho_{25°} = 7.6$). The limitations that exist in a number of cases are discussed in connection with the peculiarities of the electron-density distribution in five- and six-membered heterocycles.

In our previous research [1] we established that the trend of the change in the intensity of the bands of C–H stretching vibrations in the IR spectra ($A^{1/2}_{CH}$) and the chemical shifts of the protons of the methyl group in the PMR spectra ($\delta^{CH_3}$) of methyl derivatives of azoles and di-, tri-, and tetrazoles containing polar substituents in the heteroaromatic ring is determined by the sum of additive contributions made to the $A^{1/2}$ and $\delta$ values by one or several heteroatoms and substituents. The possibility of their examination within the framework of a single reaction series with the corresponding methyl derivatives of six-membered aromatic and heteroaromatic compounds was demonstrated, and, in addition, the applicability of a quantum-chemical treatment of the changes in the $\delta$ and $A^{1/2}$ values was investigated.

In order to study the possibility of the extension of a similar approach for the description of the electronic effects on the characteristics of the reactivities of five-membered aromatic heterocycles, in the present research we found comparable (with one another) rate constants of basic deuterium exhcnage of an extensive series of methyl derivatives of thiazole, oxazole, isoxazole, pyrazole, imidazole, oxa- and thiadiazoles, triazole, and tetrazole, and we also made a correlation analysis of the experimental data obtained. In a subse-

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State Institute of Applied Chemistry, Leningrad 197198. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1196-1201, September, 1977. Original article submitted June 16, 1976; revision submitted November 26, 1976.