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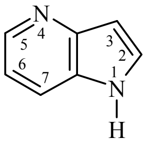
CORRELATIONS OF THE PHYSICOCHEMICAL PARAMETERS OF AZAINDOLES WITH THEIR REACTIONS

J. A. Kereselidze, Z. V. Pachuliya, T. Sh. Zarkuya, and Sh. A. Samsoniya

Using the AM1 semiempirical quantum method the enthalpies of formation, ionization energies, electron affinities, energy differences between highest occupied and lowest unoccupied orbitals, atomic charges, bond orders, and dipole moments have been calculated for 4-, 5-, 6-, and 7-azaindoles. A correlation has been built up between the calculated physicochemical parameters and the Hammett para-substituent and inductive constants. The 1H to 7H proton transfer in 7-azaindole has been quantitatively described.

Keywords: azaindoles, dipole moments, atomic charges, correlations, proton transfer, semiempirical quantum-chemical calculations, bond orders, ionization potentials, electron affinities, enthalpies of formation.

The electronic structure and reactivity of azaindoles have been the subject of many reviews [1-4] and original investigations [5-10]. Formally, azaindoles are the products of replacing one of the benzene ring carbon atoms with a nitrogen atom [1, 11].



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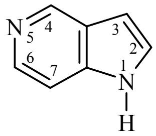

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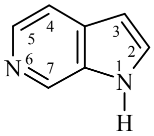

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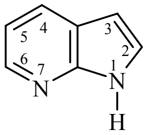

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A systematic investigation of the effect of a substituent in the pyridine ring on the properties of azaindoles has not been carried out and only isolated examples have been discussed [12-16]. With the aim of a systematic study of the effect of a substituent in the pyridine ring on the reactivity of azaindoles we have used the semiempirical AM1 quantum-chemical method to calculate their enthalpies of formation (ΔH), ionization energies (I), electron affinities (A), energy differences between highest occupied and lowest unoccupied orbitals (ΔE), atom charges (q_i), bond orders (P_{ij}), and dipole moments (μ) (see Table 1).

The calculated results for the unsubstituted azaindoles and for indole are given in Table 1.

It is notable that the dipole moment value agrees well ($\Delta\mu/\mu < 10\%$) with experimental data for indole [17] and 7-azaindole [18]. From Table 1 it is clear that the stability for the compounds studied decreases in the order:

5-azaindole > 6-azaindole > 4-azaindole > 7-azaindole

I. Javakhishvili State University, Tbilisi 0128, Georgia; e-mail: keres@tsu.edu.ge. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1062-1072, July, 2006. Original article submitted October 11, 2005; revision submitted April 9, 2006.

TABLE 1. Calculated Parameters for Indoles and Azaindoles

Parameter	Indole	4-Azaindole	5-Azaindole	6-Azaindole	7-Azaindole
ΔH, kJ/mol	248.7	311.8	302.2	307.2	315.6
I, eV	8.4	8.9	8.7	8.8	8.8
A, eV	0.3	0.5	0.6	0.5	0.5
$\Delta\Delta E$, eV	8.7	9.4	9.3	9.3	9.3
μ, Δ	1.89	3.68	3.87	3.28	1.44
$-q_1$	0.212	0.210	0.211	0.204	0.203
$-q^N$		0.094	0.161	0.130	0.147
$-q_2$	0.081	0.075	0.085	0.070	0.076
$-q_3$	0.200	0.182	0.180	0.204	0.192
P_{23}	1.642	1.641	1.649	1.628	1.637

i.e. the least stable is the 7-azaindole (315.6 kJ/mol). On the basis of the data in the Table a series of changes in the calculated parameters for indole and azaindole can be constructed.

The authors of [19] used a π-electron quantum-chemical approximation to calculate the ionization potentials and electron affinities of indole and azaindoles and obtained a series of changes. In particular, according to their data, the ionization potentials increase in the order:

indole < 5-azaindole < 7-azaindole < 6-azaindole < 4-azaindole

which is in good agreement with our results (see Table 1). However the values of the electron affinities are positioned in a rather different order.

Judged by the dipole moment values the 5-azaindole must be the most and the 7-azaindole the least polar. On the basis of a comparison of the series of changes in dipole moment and the charge on the pyrrole nitrogen atom in the azaindoles it seems that they change in parallel. Hence it can be proposed that the value of the dipole moment of the azaindole depends to a certain degree on the value of the charge on the pyrrole nitrogen atom q_1^N.

From an analysis of the value of the charges on the $C_{(2)}$ and $C_{(3)}$ atoms (q_2 and q_3) it is apparent that position 3 is an electrophilic center both in indole and in the azaindoles as might be expected [20]. In addition, the highest reactivity towards electrophilic substitution occurs in indole and 6-azaindole. From the series for q_3 it is evident that 5-azaindole is less inclined towards electrophilic substitution at position 3 as had been shown experimentally [2]. It should be noted here that the bond order P_{23} changes in parallel with the value of the charge on atom $C_{(2)}$ (q_2). Hence we can propose that the basic q_2 charge contributes to the P_{23} value.

As evident from the series of changes in the ΔE values an electron transfer reaction must be typical of indole. For azaindoles this reaction is less likely because of the broader energy gap ΔE.

A major part of the work was connected with correlating the physicochemical characteristics of the azaindoles substituted in the pyridine ring with the Hammett σ_p substituent constant and with the inductive constants σ_I.

The results of the correlation analysis of the dependence of the atomic charges for the 4-, 5-, 6-, and 7-azaindoles on the values of the Hammett σ_p para substituent constant and the inductive constant σ_I allow us to make several conclusions.

The value of the charge on the $C_{(2)}$ atom (q_2) for the 4-substituted 5-, 6-, and 7-azaindoles depends inversely on σ_p (Fig. 1). Hence electron donor substituents in the pyridine ring facilitate and electron acceptor substituents hinder the process of electrophilic substitution in position 2 of the azaindoles. For these dependences the reaction constant $\rho < 0$ and the correlation coefficient is $r \sim 0.98$.

The dependence of q_2 on the inductive constant σ_I in the 4-substituted 5- and 6-azaindoles and 6-substituted 4- and 5-azaindoles has a downward parabolic form (Fig. 2). The dependence of the charge on atom $C_{(3)}$ for the 6-substituted 4-azaindole has an upward parabolic form (Fig. 3). Moreover, electron-donor substituents in position 6 decrease and electron-acceptors increase the charge at position 3.

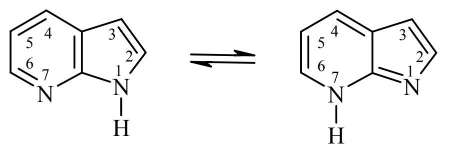
In the azaindoles, as in indoles, the bond order P_{23} predetermines to a marked degree the ratio of the products of electrophilic substitution at positions 2 and 3. From the correlation analysis of the dependence of P_{23} on the effect of the substituent in the pyridine ring it is evident that for 4-substituted 6- and 7-azaindoles and 6-substituted 4-, 5-, and 7-azaindoles P_{23} depends on σ_p inversely (Fig. 4) and for 5-substituted 6- and 7-azaindoles in parallel (Fig. 5). For 6-substituted 4- and 5-azaindoles and 4-substituted 6-azaindole the dependence of P_{23} on σ_I has a downward parabolic form (Fig. 6).

The next physicochemical parameter for which correlation analysis was carried out showed that the ionization energy correlated with the energy of the highest occupied molecular orbital of the azaindole. The value of I for all substituted azaindoles varied in parallel with the σ_p constant (Fig. 7) but the dependence on the σ_I constant has a parabolic form (Fig. 8). According to data in [21] in the series of 4- and 7-azaindoles the effect on a substituent on the ionization energy is due mainly to an inductive effect. Overall, for all of the azaindoles electron donor substituents decrease the ionization potential and electron acceptors increase it.

The difference in energy between the highest occupied and lowest unoccupied orbitals ΔE correlate only with the inductive constant σ_I. The dependence of ΔE on σ_I for all of the 4-, 5-, and 6-azaindoles has a parabolic form (Fig. 9).

The dependence of the dipole moment μ for the 5- and 6-azaindoles on the σ_I constant has a parabolic form (Fig. 10) which is typical of other nitrogen-containing heterocyclic compound [22].

It is known that 7-azaindole can exist in two tautomeric forms 1H (a) and 7H (b) as shown by spectroscopic methods [23, 24].

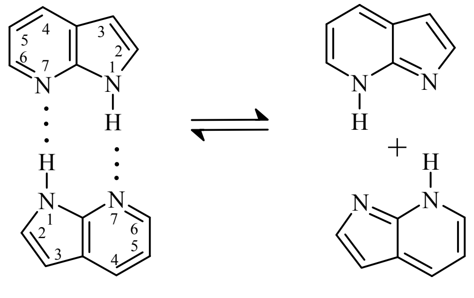


4 **4a**

ΔH = 315.6 kJ/mol ΔH = 382.5 kJ/mol

The difference in the enthalpy of formation of the 7-azaindole **4** and the 7H-azaindole **4a** is 66.9 kJ/mol and this points to an endothermic process for the transfer of proton 1 to 7.

It is assumed that this process occurs *via* a dimer mechanism [25] which was also used for constructing an energy diagram using the reaction coordinate approach (Fig. 11). From Fig. 11 it is apparent that the enthalpy of activation $\Delta\Delta H^{\#}$ = 83.6 kJ/mol and the enthalpy of reaction $\Delta\Delta H$ = 69.8 kJ/mol. The latter value agrees well with the difference in enthalpy of formation of the separate tautomers (66.9 kJ/mol).



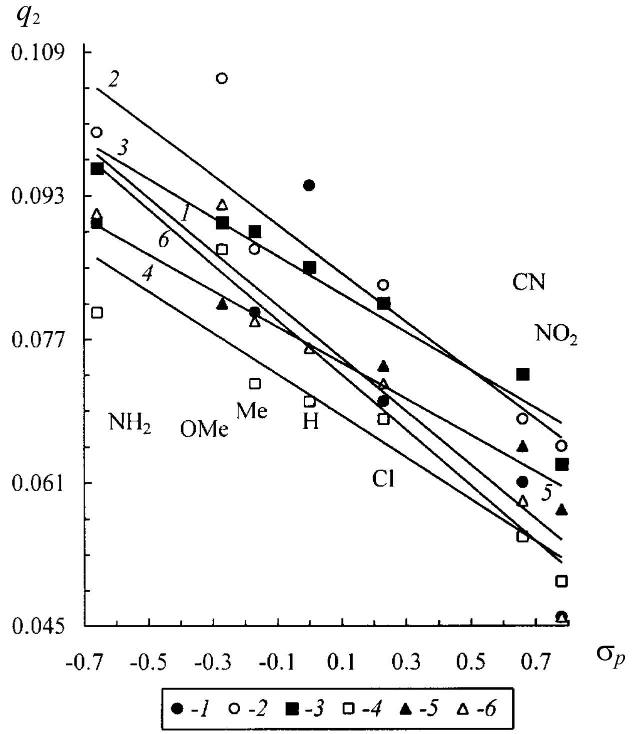


Fig. 1. Dependence of q_2 on σ_p for 6-substituted 4-azaindole (1), 5-azaindole (3) and 7-azaindole (6); 4-substituted 5-azaindole (2), 6-azaindole (4), and 7-azaindole (5).

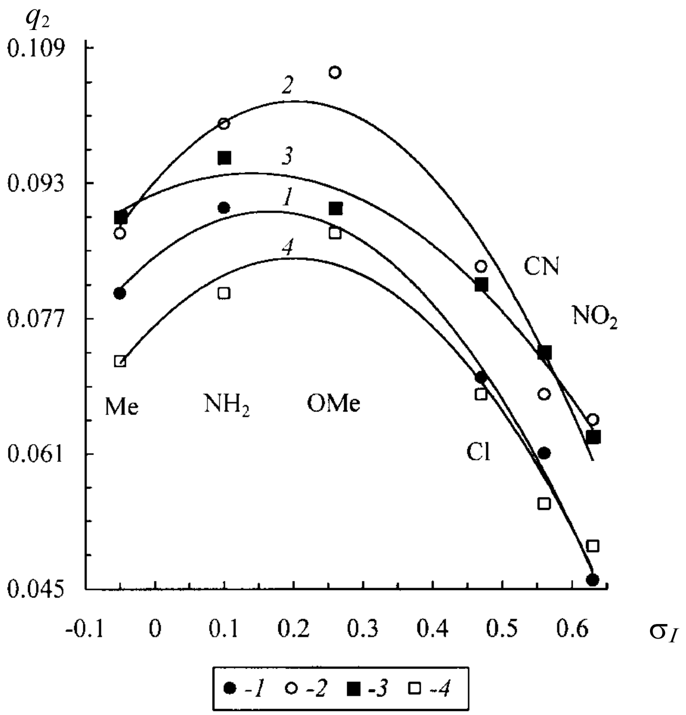


Fig. 2. Dependence of q_2 on σ_I for 6-substituted 4-azaindole (1) and 5-azaindole 3); 4-substituted 5-azaindole (2) and 6-azaindole (4).

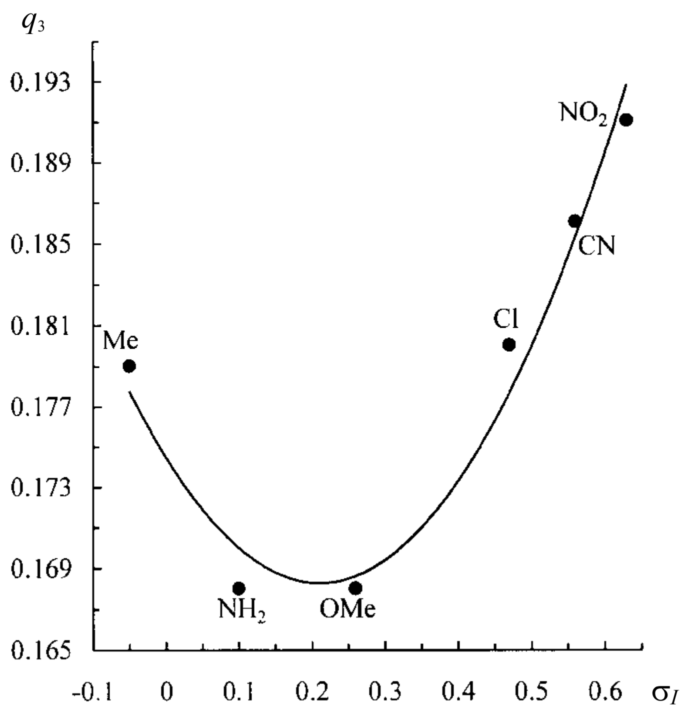


Fig. 3. Dependence of q_3 on σ_I for 6-substituted 4-azaindole.

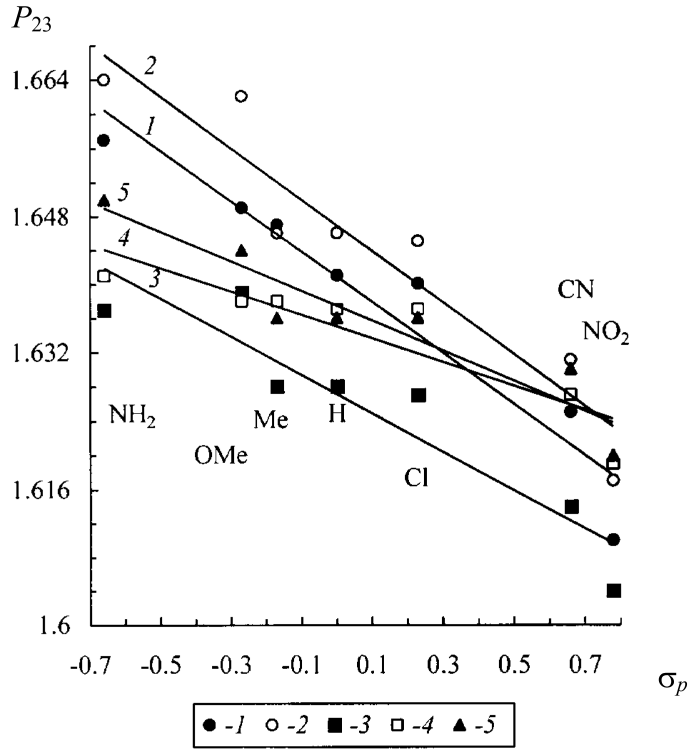


Fig. 4. Dependence of P_{23} on σ_p for 6-substituted 4-azaindole (1), 5-azaindole (2), and 7-azaindole (5); 4-substituted 6-azaindole (3) and 7-azaindole (4).

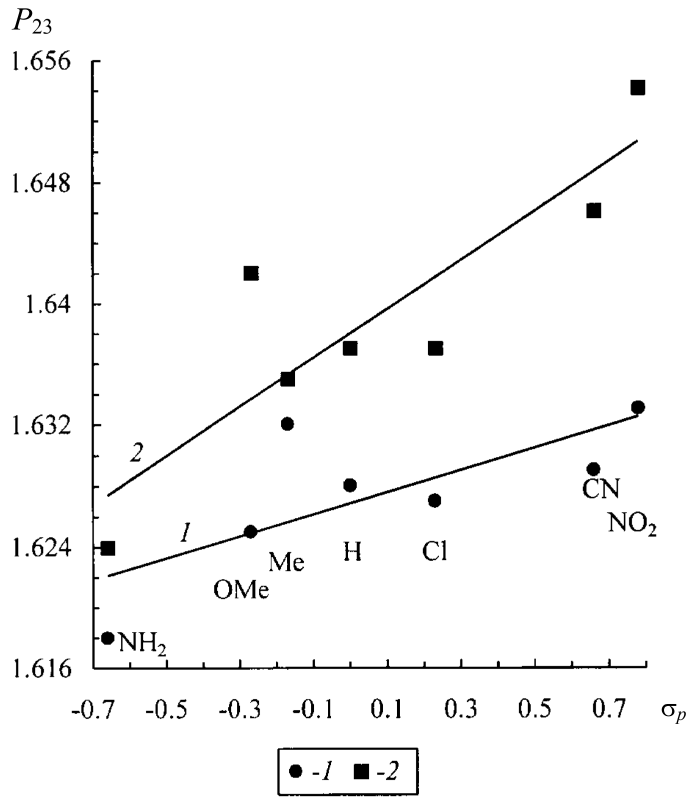


Fig. 5. Dependence of P_{23} on σ_p for 5-substituted 6-azaindole (1) and 7-azaindole (2).

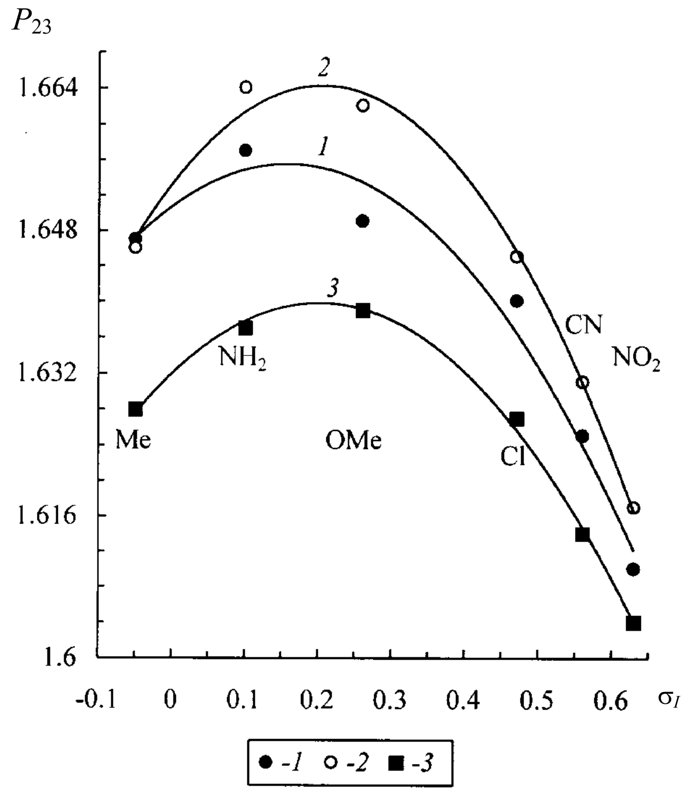


Fig. 6. Dependence of P_{23} on σ_I for 6-substituted 4-azaindole (1) and 5-azaindole (2); 4-substituted 6-azaindole (3).

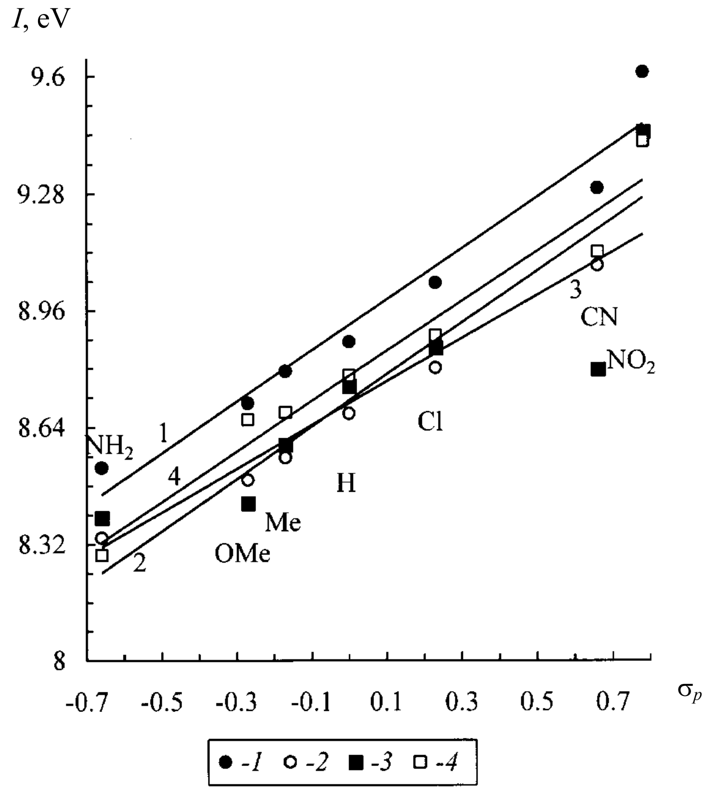


Fig. 7. Dependence of *I* on σ_p for 5-substituted 4-azaindole (1); 7-substituted 5-azaindole (2) and 6-azaindole (3); 4-substituted 7-azaindole (4).

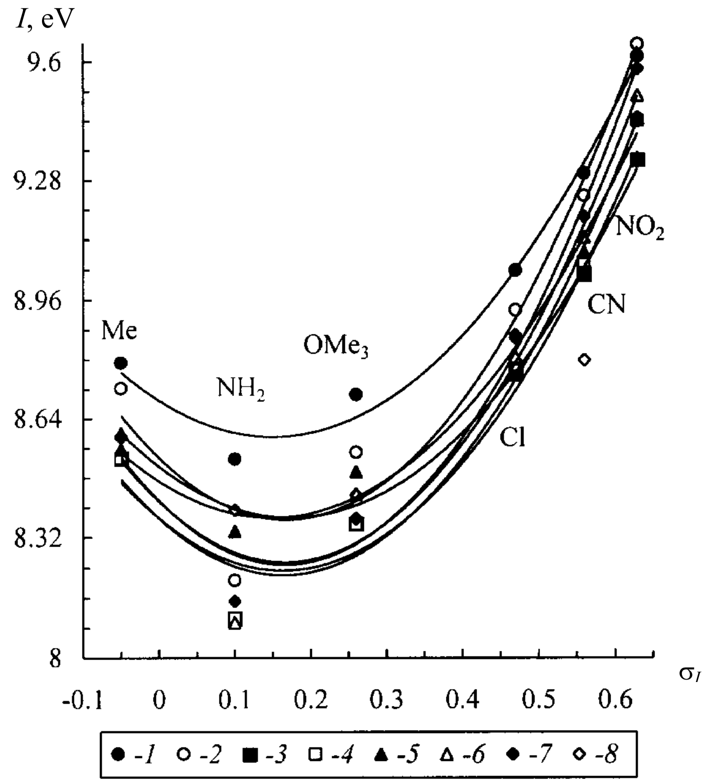


Fig. 8. Dependence of *I* on σ_I or 5-substituted 4-azaindole (1), and 6-azaindole (7); 6-substituted 4-azaindole (2) and 5-azaindole (4); 4-substituted 5-azaindole (3) and 6-azaindole (6); 7-substituted 5-azaindole (5) and 6-azaindole (8).

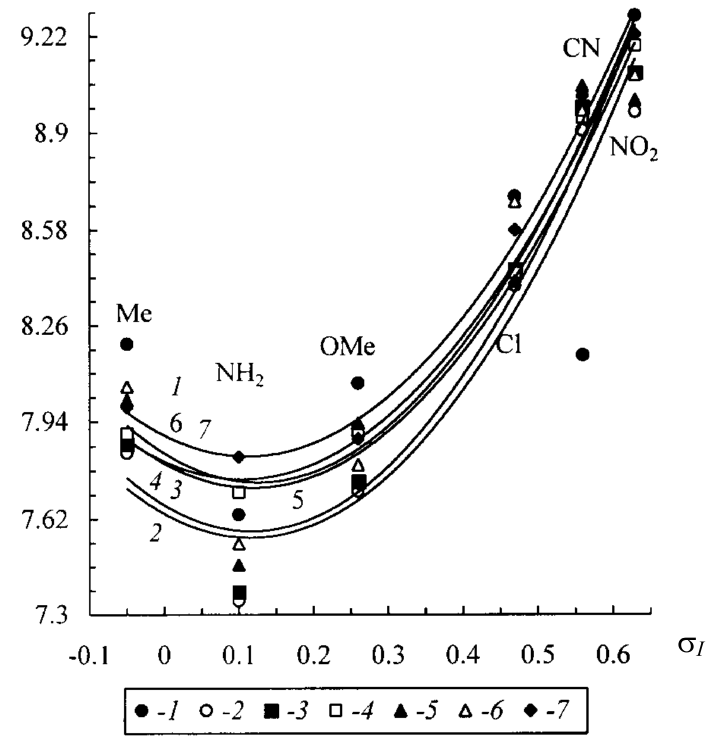


Fig. 9. Dependence of Δ*E* on σ_I for 6-substituted 4-azaindole (1) and 5-azaindole (3); 4-substituted 5-azaindole (2) and 6-azaindole (5); 7-substituted 5-azaindole (4) and 6-azaindole (7); 5-substituted 6-azaindole (6).

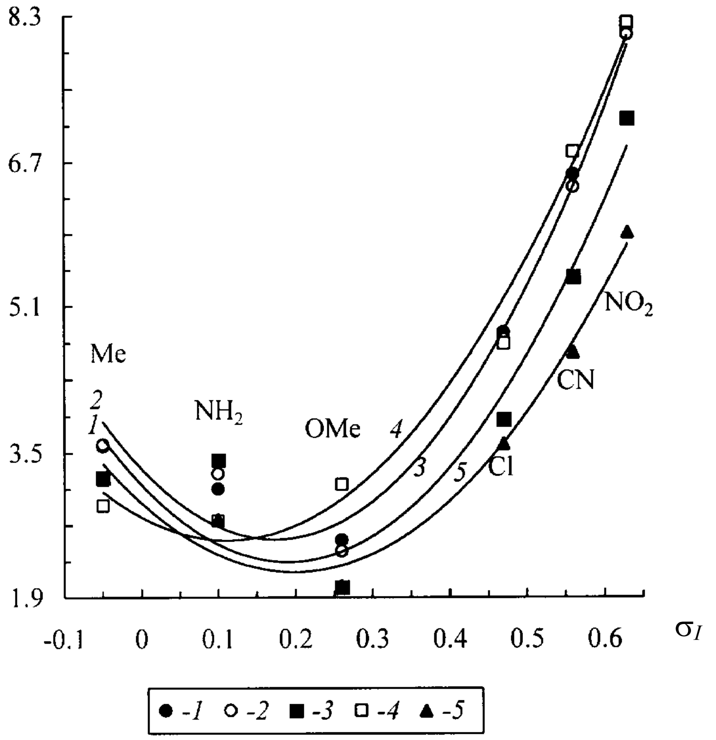


Fig. 10. Dependence of μ on σ_I for 4-substituted 5-azaindole (1) and 6-azaindole (3); 6-substituted 5-azaindole (2); 5-substituted 6-azaindole (4); 7-substituted 6-azaindole (5).

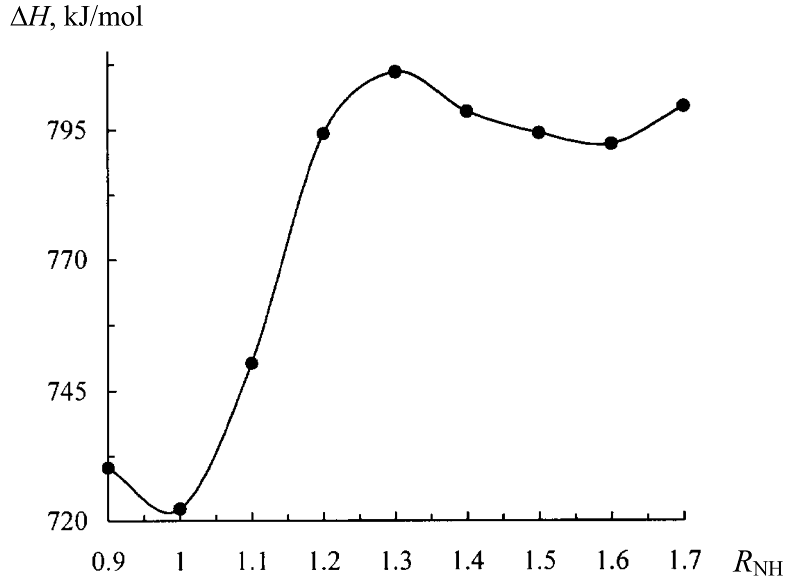


Fig. 11. Dependence of enthalpy (ΔH) on the reaction coordinates (R_{NH}) for the transfer process of proton 1 to 7.

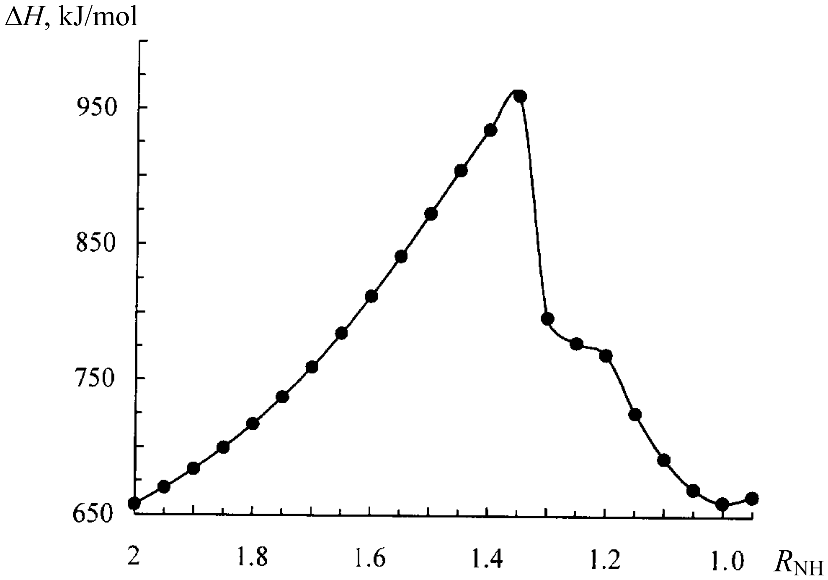


Fig. 12. Dependence of enthalpy (ΔH) on the reaction coordinates (R_{NH}) for the transfer process of proton 1 to 4.

From the data obtained a general conclusion can be made that the 1H to 7H rearrangement in 7-azaindole is an equilibrium process and is shifted toward the 7-azaindole. This is confirmed by the value of the equilibrium constant K_T, calculated by a method proposed by us before [26].

It is known that the transfer of a proton in azaindoles between the nitrogen atoms is only characteristic of 7-azaindole. With the aim of studying the possible realization of a transfer of the proton from 1 to 4 we have built up a model of two 4-azaindoles placed in parallel. In this model the protons of the pyrrole ring nitrogen are located above and below the pyridine nitrogen atoms at a distance of 2.0 Å. In the reaction coordinate approach (R_{NH}) an energy diagram was constructed for the transfer of proton 1 to 4 in 4-azaindole (Fig. 12) from which it is seen that the enthalpy of activation $\Delta\Delta H^{\#} = 302.4$ kJ/mol. This high energy barrier is evidently associated with steric strain in the proposed model.

From the correlation analysis carried out it can be concluded that the data obtained can serve as a quantitative description of the reactivity of the azaindoles investigated and also in the planning of a targeted synthesis of azaindole derivatives.

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