ACIDIC PROPERTIES OF N-HETARYLACETIC ACIDS AND INDUCTIVE
CONSTANTS OF N-HETARYL SUBSTITUENTS

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The inductive constants of the corresponding heterocyclic fragments were calculated on the basis of data on the pK_a values obtained by potentiometric titration of derivatives of indole, carbazole, 3-methylcarbazole, tetrahydrocarbazole, 6-methyltetrahydrocarbazole, and phenothiazine. The σ_R^0 constant of the 9-carbazolyl group was also calculated. The enthalpy and entropy of acidic dissociation were calculated from data on the effect of the temperature on the pK_a of 9-carbazolylacetic acid. It is shown that the entropy contribution to the free energy of dissociation of 9-carbazolylacetic acid predominates.

The determination of the inductive characteristics (σ^* and σ_I constants) of the X radicals from the pK_a values of the corresponding acetic acids XCH_2COOH has long been known [1] but has been used relatively rarely to measure the inductive constants of N-hetaryl groups. The inductive constants of the corresponding heterocyclic fragments were recently determined from data on the pK_a values of a series of 1-indolyl-, 9-carbazolyl- [2], and tetrazolylacetic acids [3]. In view of the relative simplicity of the methods for the synthesis of N-hetarylacetic acids and the accuracy in the measurement of the pK_a values this method may find wide application for the determination of such fundamental characteristics of N-hetaryl groups as the inductive constants. However, the following factors must be evaluated for the correct use of this method.

The dissociation constants of carboxylic acids are determined to a greater degree by the entropy factors than by the enthalpy factors [4]. The thermodynamics of acid–base dissociation have not been determined for N-hetarylacetic acids, and one cannot assert a priori that they will be subject to the same thermodynamic principles as are known acids. The inductive constants obtained from the pK_a values of N-hetarylacetic acids therefore cannot be assumed to be reliable without a thermodynamic analysis.

We measured the thermodynamic pK_a values of a number of acids (I, II, IIa,b, and IV) in 56% (by volume) ethanol at $25 \pm 0.05°C$ by potentiometric titration (Table 1).

II-III a X = H; b X = CH_3
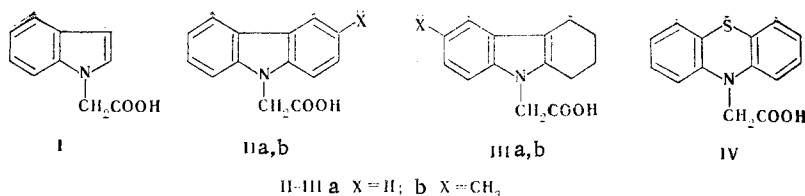
From the known expressions

$$\sigma^* = 8.18 - 1.35\, pK_a \text{ [5]} \tag{1}$$

$$\sigma_I = \sigma^*/6.23 \text{ [1]} \tag{2}$$

we calculated the inductive constants, which are presented in Table 1.

The pK_a values of acids I and IIa differ somewhat from the values obtained in [2], but the measurements made in the present research are more accurate, as demonstrated by the smaller deviation of the measured pK_a values of phenylacetic acid (5.44) from the value obtained in [6] (5.47).

TABLE 1. pK$_a$ Values of N-Hetarylacetic Acids in 56% (by volume) Aqueous Ethanol at 25°C and Inductive Constants of N-Hetaryl Fragments

Compound	pK_a	σ^*	σ_I
I	4,54±0,03	2,05±0,03	0,33±0,01
II a	4,64±0,01	1,92±0,02	0,31±0,03
II b	4,99±0,03	1,45±0,02	0,23±0,03
III a	4,77±0,02	1,74±0,03	0,28±0,02
III b	5,05±0,04	1,36±0,03	0,22±0,04
IV	5,01±0,02	1,42±0,03	0,23±0,02

TABLE 2. Dependence of the pK$_a$ of Acid IIa on the Temperature in 56% (by volume) Aqueous Ethanol

pK_a	4,49	4,58	4,64	4,72	4,78
Temperature, °K	293,15	296,15	298,15	300,15	302,15

Data on the effect of the temperature on the pK$_a$ of acid IIa are presented in Table 2. Satisfactory linear dependence of the pK$_a$ on the temperature (r = 0.99) is observed in the presented temperature series. The thermodynamic parameters of the dissociation of acid IIa in aqueous ethanol solution at 298.15°K were determined from the data obtained: ΔG° = 26.48, ΔH° = 55.1, and TΔS° = 81.58 kJ/mole. The results make it possible to speak of predominance of the entropy contribution to the free energy of dissociation of acid IIa; thus from the point of view of thermodynamics this acid behaves like known carboxylic acids [7], and "inclusion" of N-hetarylacetic acids in the $\sigma^*(\sigma_I)$—pK$_a$ correlation is consequently justified. One's attention is directed to the more significant (in absolute value) enthalpy and entropy components as compared with other acetic acids [4]. At present it is difficult to reliably interpret this anomaly because of the small amount of data on the thermodynamics of the acidic dissociation of N-hetarylacetic acids.

A comparison of acids IIa and IIIa shows that hydrogenation of one carbazole ring leads to a certain decrease in the acidic properties. This effect can be explained in two ways. First, from the point of view of the electronic effects in the tetrahydrocarbazolyl group relative to the carbazolyl group the degree of delocalization of the p electrons of the nitrogen atom over the aromatic system decreases, which leads to an increase in the electron density on this atom; second, replacement of the phenylene group by an electron-donor cyclohexene group also increases the electron density on the nitrogen atom. Thus the resonance and polar factors, by acting in the same direction, cause a decrease in the —I effect of the tetrahydrocarbazolyl group, which is also reflected in a decrease in the dissociation constant of acid IIIa. In addition, the decrease in the acidic properties on passing from acid IIa to acid IIIa may also be due to an increase in the steric shielding of the carboxy group on the part of the more bulky (than the phenylene ring) cyclohexene ring. It is known that steric shielding, by decreasing the energy of solvation of the anions, also decreases the acidic properties of carboxylic acids [4].

The lower strength of acid IV as compared with acid II is in agreement with the greater donor properties of phenothiazine [8], i.e., it is satisfactorily explained by electronic factors. Nevertheless, in this case one observes a certain amount of indeterminacy in the evaluation of the obtained value of the σ_I constant of the N-phenothiazinyl group, since the phenothiazine molecule, in contrast to the carbazole molecule, is nonplanar [8], and the steric factors that affect the solvation of both the acids and anions are consequently different for acids IV and IIa. In addition, N-substituted phenothiazines can exist in four different conformations [9], the electronic characteristics of which undoubtedly differ somewhat. The conformation in which acid IV exists is unknown, and one should therefore approach the value of the σ_I constant obtained with caution. It must be noted that the latter fact is an organic "threshold" that is peculiar to any method for the determination of the electronic characteristics of conformationally flexible phenothiazines.

TABLE 3. NH Acidities of Nitrogen Heterocycles and Inductive Constants of N-Hetaryl Groups

Heterocycle	pK_a [11]	σ_I
Pyrrole	23,3	0,24 [10]
Phenothiazine	22,8	0,23
Indole	21,3	0,33
Pyrazole	20,4	0,26 [10]
Carbazole	19,6	0,31
Imidazole	18,9	0,46 [10]
1-Tetrazole	4,89 [16]	0,65 [3]

It has been previously shown that there is an approximate linear correlation between the acidic properties of ring-substituted carbazoles and the pK_a values of the corresponding 9-carbazolylacetic acids [2]. A fundamental question arises as to whether the observed regularity between the σ_I constants of the N-hetaryl groups and the pK_a values of the corresponding heterocycles is general or is observed only within a single class of compounds (carbazoles). The acidities of the heterocycles and the σ_I constants are presented in Table 3. The available data for other related heterocyclic systems are also included to extend the series. The inductive constants for pyrrole, pyrazole, and imidazole were determined in [10] from data from the ^{13}C NMR spectra of N-phenylazoles. The σ_I constant found from the dissociation constant of 1-tetrazolylacetic acid [3] was used for the 1-tetrazolyl group. It follows from the data presented in Table 3 that a rather approximate qualitative correspondence ($r = 0.93$, $S_0 = 2.52$, $\rho = 38.69$) is observed between the pK_a and the σ_I constants; this correspondence indicates the following tendency: The most acidic heterocycle has the greatest $-I$ effect. The existence of this principle leads to the conclusion that in these heterocyclic systems the structural effects that ensure the degree of delocalization of the unbonded electrons attached to the nitrogen atom act in the same direction in the anions and neutral molecules. The observed deviations are due to both the different methods of determination of the σ_I constants and the significant contribution of the resonance effects and, in individual cases (phenothiazine), steric effects to stabilization of the anions of the heterocycle in NH acidic dissociation [11].

Correlation Eq. (3), which satisfactorily links the ^{13}C NMR chemical shifts of the terminal vinyl atoms of olefins XCH=CH$_2$ with the inductive and resonance constants of substituents X, is presented in [12]:

$$\Delta\delta C = 11.9\sigma_I + 63.5\sigma_R^0, \tag{3}$$

where $\Delta\delta C$ is the difference in the chemical shifts of ethylene and the vinyl derivative. Using the previously found σ_I constants and ^{13}C NMR chemical shifts of the vinyl C$_\beta$ atoms of 9-vinylcarbazole (101.8 ppm) [13] and 1-vinylindole (95.53 ppm) [14] one can evaluate the resonance characteristics for the 9-carbazolyl and 1-indolyl groups from Eq. (3). The σ_R^0 constants obtained in this way are -0.49 for the 1-indolyl group and -0.41 for the 9-carbazolyl group. The σ_R^0 constant for the 1-indolyl group (-0.44) was previously found in [15]. Considering the inaccuracies of correlation Eq. (3) the agreement between the resonance constants obtained by the two methods should be considered to be acceptable.

EXPERIMENTAL

The thermodynamic pK_a values of the N-hetarylacetic acids were determined by potentiometry as described in [2].

Acids I-IV were synthesized by reaction of the corresponding heterocycles with bromoacetic acid in DMSO or DMF by the method in [17]. The following acids were obtained [the number of the acid, the melting point, and the chemical shifts of the CH$_2$ groups (in parts per million in d$_6$-DMSO) are given]: I, 157-158, 5.20; IIa, 215-216, 5.40; IIb, 180-181, 5.35; IIIa, 144-145, 5.04; IIIb, 130-131, 4.97; IV, 145-146, 4.75.

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NUCLEOPHILIC SUBSTITUTION IN o-NITRO AZIDES OF THE PYRIDINE SERIES

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The reactions of 2-nitro-3-azidopyridine and 3-nitro-4-azidopyridine with amines and anionic nucleophiles, viz., sodium hydroxide, sodium alkoxides, the sodium salt of p-thiocresol, and potassium cyanide, were investigated. A possible reaction mechanism is proposed.

We have previously shown that nucleophilic substitution of the hydrogen atom in the α position of the pyridine ring to give the previously inaccessible 2-nitro-3,6-diaminopyridines occurs in the reaction of 2-nitro-3-azidopyridine with amines in aqueous solution. Pyrido-[2,3-c]furoxane is an intermediate in this reaction [1].

In a continuation of our research on nucleophilic substitution in pyridine we studied the reaction of 2-nitro-3-azidopyridine with anionic nucleophiles, viz., sodium hydroxide, sodium alkoxides, the sodium salt of p-thiocresol, and potassium cyanide, and the reaction of the isomeric 3-nitro-4-azidopyridine with amines and charged nucleophiles.

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