EXPERIMENTAL AND THEORETICAL STUDY OF THE BASICITY OF AZOLES AND THEIR ANALOGS*

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The thermodynamic ionization constants of 30 imidazole, pyrazole, triazole, and thiazole derivatives and their structural analogs were determined by potentiometric titration in acetonitrile. The effect of individual structural factors on the basicity of the azole molecules is discussed. It is demonstrated that the best theoretical basicity index is the magnitude of the electrostatic energy of interaction (ε) of the unshared pair of the nitrogen atom being protonated with the system of π charges. The ε values were calculated by means of the MO self-consistent-field (MO SCF) method with the Pariser-Parr-Pople approximation and by the simple Hückel method. The $pK_a-\varepsilon$ correlation equations obtained make it possible to predict the pK_a values of azoles with an average accuracy of ~ 0.5 pK_a units for acetonitrile solutions and 0.3 units for aqueous solutions.

The literature contains much data with respect to the acid-base properties of azoles [2,3]. However, most of the measured ionization constants of the conjugate acids of azoles were obtained for aqueous or water-containing solutions and are concentration constants. In addition, the data for different groups of compounds pertain to different measurement conditions and are not always comparable one with another.

The tasks of the present study were as follows: determination of the thermodynamic ionization constants of the conjugate acids of a systematic series of azoles in a nonaqueous solvent (acetonitrile) and correlation of the pK_a values obtained with the parameters of the electronic structures of the investigated compounds. Azole compounds of the I-IX types and their structural analogs (X-XII) were studied.

The pK_a values of the azoles and their analogs, which are presented in Table 1, lead to the following qualitative conclusions.

1. Annelation of the benzene rings to the imidazole ring lowers the basicity substantially (the basicity constants decrease by almost three orders of magnitude in the series of unsubstituted compounds I-VI)

2. A substituent in the meso position of the azole ring [compounds of the benzimidazole (II) and benzothiazole (IX) types] has an even sharper effect on the basicity. The correlation of the ionization constants in reaction series II, IX with the σ substituent constants is shown in Fig. 1; this correlation is satisfied under the condition of comparison of the electron-acceptor substituents with the nucleophilic σ^- constants. This indicates considerable polarization of the unprotonated forms of the azole molecules via a mechanism caused by an increased contribution of structures of the XIII and XIV types, the role of which in compounds of this type with a strong electron acceptor in the 2-position has been previously noted [4].

The point corresponding to compound 8 in reaction series II deviates sharply from the correlation line (Fig. 1). This may be associated with the possibility of protonation of the nucleophilic center in the nitro group of XIV and, consequently, with dropping out of compound 8 from the reaction series.

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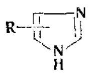
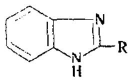


I



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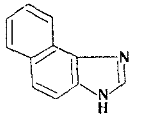

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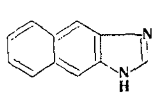

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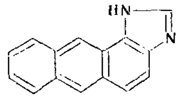

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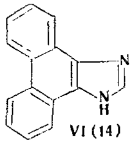

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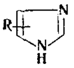

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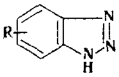

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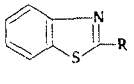

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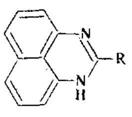
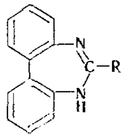


X



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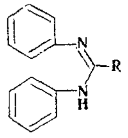
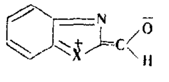


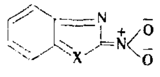
XII

I R=H (1), 4,5-$(CH_2)_4$(2), 4,5-$(C_6H_5)_2$ (3), 2-NH_2-4,5-$(C_6H_5)_2$ (4);
II R=H (5), CH_3(6), NH_2 (7), NO_2 (8)*, C_6H_5 (9), CHO (10)*; VII R=H(15), 4,5-benzo (16);
VIII R=H (17), 4,5-benzo (18); IX R=H (19), CH_3 (20), NH_2 (21), C_6H_5 (22), CHO (23);
X R=H (24), CH_3 (25), C_6H_5 (26); XI R=CH_3(27), C_6H_5 (28); XII R=CH_3(29), C_6H_5 (30)

3. The inclusion of an amidine grouping in six-membered (X) and seven-membered (XI) rings or its occurrence in a noncyclic structure (XII) has comparatively little effect on the basicity. However, when this grouping is included in a five-membered imidazole ring, the basicity decreases appreciably (III and IV with two benzene rings, as in X-XII). A discussion of this regularity in terms of resonance stabilization of the amidine group in different rings was presented in [1,5].



XIII



XIV

In order to establish the quantitative correlation of the basicity constants of the investigated compounds with the parameters of their electronic structure, we calculated the π-electron energies and charge distributions of unprotonated and protonated forms of compounds 1-30. The calculated dipole moments in almost all cases coincide quite well with the experimental values, which attests to the correctness of the calculated electron distribution (see Table 1).

However, it was found that the magnitudes of the π-electron charges on the protonation center as well as the differences in the total π-electron energies of the conjugate acids and bases correlate poorly with the experimental pK_a values. As in a number of previous studies [10-12], a better measure of the basicity was found to be the energy of electrostatic interaction of the unshared pair of the nitrogen atom undergoing protonation with the system of π charges calculated with the Pariser-Parr-Pople (PPP) approximation

$$\varepsilon^{PPP} = -2 \sum_{\mu}' q_{\mu} \gamma_{\mu N}, \tag{1}$$

which can be considered to be a measure of the affinity of the base for a proton. In expression (1), q represents the charges on the atoms, while $\gamma_{\mu N}$ are the electron repulsion integrals. The calculated ε values are presented in Table 1, while their correlation with the pK_a values is given in Fig. 2.

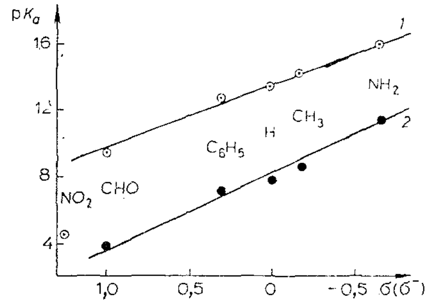


Fig. 1. Correlation of the pK_a values (in acetonitrile) of 2-substituted benzimidazoles (1) and benzothiazoles (2) with the σ substituent constants.

As seen from Fig. 2, the data for compounds of the I-VIII types of the azole series lie satisfactorily on a single line (only imidazole itself deviates markedly). However, thiazole derivatives (IX) and X-XII do not lie on the correlation line for the azoles. Independent linear $pK_a-\varepsilon$ dependences, which are approximately parallel to the azole line,

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*N-Methyl derivative.

TABLE 1. Thermodynamic Ionization Constants of Azoles and Their Analogs (in acetonitrile at 25°C), Dipole Moments (μ), and Proton Affinity Energies (ε), Calculated by the Pariser-Parr-Pople Method

Compound	pK_a	ε, eV	μ_{calc}, D*	μ_{exp}, D[7,8]
1	14,99	3,69	4,00	3,99
2	16,21	4,26	4,05	3,98
3	13,43	3,57	4,21	4,39
4	15,89	4,33	4,23	—
5	13,25	3,52	3,84	4,03
6	14,20	3,83	4,02	4,65
7	15,95	4,34	4,37	—
8	4,52	1,79	4,66	—
9	12,65	3,51	3,80	3,63
10	9,56	2,60 †	2,91 †	3,37
11	12,76	3,50 †	4,00 †	4,04
12	12,92	3,50	3,80	—
13	12,75	3,49 †	4,08 †	—
14	12,31	3,48	3,78	4,11
15	9,21	2,87	2,47	2,21
16	7,50	2,55	2,89	1,83
17	7,81	2,51 ‡	4,43	4,07
18	7,86	2,60 ‡	4,51	—
19	7,84	3,17	1,70	1,45
20	8,67	3,54	1,83	—
21	11,41	3,92	1,10	—
22	7,16	3,42	1,63	—
23	3,79	2,48 †	2,51 †	2,84
24	13,58	3,24	3,86	3,18
25	14,70	3,60	4,27	3,25
26	13,44	3,17	4,64	3,48
27	15,67	4,72	2,77	—
28	13,93	4,39	2,91	2,67[9]
29	15,51	3,75	—**	—
30	14,66	3,50	—**	—

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*The μ_{calc} value was calculated as the sum of the π and σ components. The μ_σ values were calculated as in [6].

†The ε and μ values for the more stable geometrical isomers or tautomers are presented.

‡The ε values were calculated for protonation of the nitrogen in the 3 position. The $\varepsilon_{2=N}$ values are about 1 eV lower.

**The dipole moments were not calculated in view of the indeterminacy of the molecular conformation.

TABLE 2. Correlation of the Basicities of Azoles by Indexes (1) and (2)

Solvent	Correlation of ε^{PPP}					Correlation of ε^{HMO}				
	n*	ε_0	A	r	s	n*	ε_0	A	r	s
Acetonitrile	18	−1,901	4,708	0,985	0,503	10	−1,617	2,082	0,974	0,611
Water	10	0,497	2,832	0,968	0,301	18	−4,039	3,797	0,964	0,337

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*This symbol represents the number of compounds included in the correlation.

can be projected for IX and X. This circumstance is probably due to the differences in the solvation of the different types of compounds, which can have a substantial effect on the basicity [13].

The ε value in expression (1) is not directly associated with the internal energy of the molecule but is determined by the distribution of the charges on the atoms. This distribution (in contrast to the energy characteristics) can be reproduced sufficiently closely to the more rigorous MO self-consistent-field (MO SCF) methods within the framework of the simple Hückel MO (HMO) method; this was achieved with the system of parameters used in the present study. In this connection, it can be expected that, like expression (1), expression (2), which was obtained with the HMO approximation, will also serve as a basicity criterion

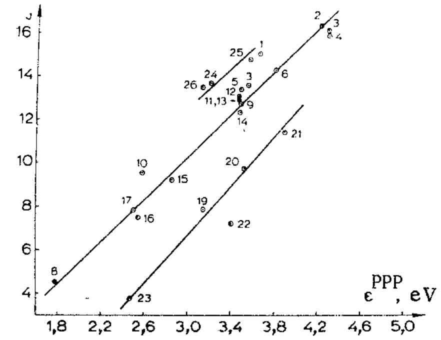

Fig. 2. Correlation of the pK_a values (in acetonitrile) with the ε^{PPP} values (the numbering of the points corresponds to the numbering of the compounds in Table 1).

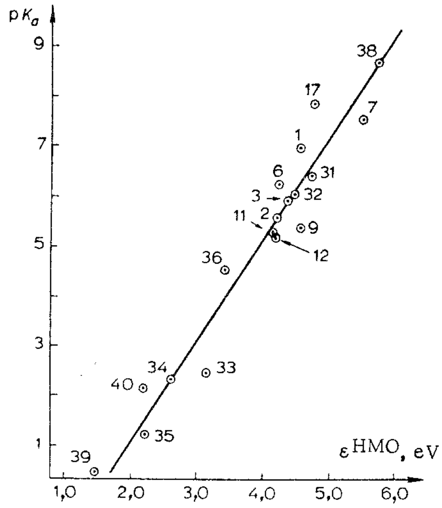

Fig. 3. Correlation of the pK_a values of azoles (in water) with the ε^{HMO} values. The numbering of points 1-30 corresponds to the numbering in Table 1. The remaining points are as follows: 31) 2-phenylimidazole; 32) 4-phenylimidazole; 33) pyrazole; 34) 1,2,4-triazole; 35) indazole; 36) 5-nitrobenzimidazole; 37) 2-methylimidazole; 38) 2-aminoimidazole; 39) N-methyl-2-nitroimidazole; 40) N-methyl-5-nitroimidazole.

$$\varepsilon^{HMO} = -2\sum_{\mu}\frac{q_{\mu}}{r_{\mu N}}, \qquad (2)$$

where $r_{\mu N}$ is the distance between the protonation center and the atom.*

In fact, as seen from the data in Table 2, the pK_a values of azoles, determined in acetonitrile, correlate with the ε^{HMO} values. Figure 3 also illustrates the possibility of the correlation of the ε^{HMO} values of a more extensive set of experimental data, which were obtained for the pK_a values of azoles in aqueous media and borrowed from reviews [2, 3, 14] and original papers [15, 16].

The correlation dependences obtained are presented in analytical form in Table 2, and the regression coefficients (r) and mean-square deviations (s) were calculated with inclusion in the equation of all, even appreciably deviant, points.

It follows from an examination of the above data that the use of correlations of the pK_a values of compounds of the azole series with the basicity indexes from Eqs. (1) and (2) makes it possible to predict the basicity constants of azoles with an accuracy of about 0.5 pK_a units for acetonitrile solutions and 0.3 units for aqueous solutions.

EXPERIMENTAL

Starting Compounds. Starting compounds of the I-IX types were obtained by the methods reviewed in [17-19]. Naphth[2,3-d]imidazole (compound 12) was furnished by A. F. Pozharskii, while anthraceno[1,2-d]imidazole (compound 13) was supplied by M. V. Gorelik. Compounds X-XII were obtained as described in [1, 9]. Prior to the measurements, all of the compounds were thoroughly purified, usually by recrystallization from a suitable solvent until the material had a constant melting point.

Ionization Constants. The ionization constants of the conjugate acids of bases 1-30 were determined in acetonitrile by the method in [20].

Quantum-Mechanical Calculations. The energies and π-electron structures of compounds 1-30 and their conjugate acids were calculated by means of the SCF MO methods with the Pariser-Parr-Pople (PPP) approximations and the approximations of the simple Hückel MO method. The geometries of the imidazole, thiazole, and pyrazole rings were taken in conformity with the experimental data. The benzene and perimidine rings in X were considered to be regular hexagons with 1.40-Å sides. We calculated the geometry of dibenzodiazepines XI in [9]. The starting parameters and the scheme of calculation via the PPP and HMO methods are the same as in previous papers [21, 22].

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*The $r_{\mu N}$ values was taken as equal to the covalent radius of nitrogen (0.63 Å). One should not expect close coincidence of the ε^{PPP} and ε^{HMO} values, since different electron repulsion potentials are used in expressions (1) and (2).

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