ACID-BASE PROPERTIES OF FIVE-MEMBERED NITROGEN-CONTAINING HETEROCYCLES (REVIEW)

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The acid-base properties of five-membered nitrogen-containing heterocycles with one, two, three, and four nitrogen atoms in the ring are discussed. The factors that determine the properties of these compounds as acids and bases are analyzed. The problems that arise in comparing the basicities of heterocycles, the protonation of which is described by different acidity scales are stressed. A significant amount of space is allotted to an examination of the acid-base properties of nitrogen-containing heterocycles in the gas phase and to the use of quantum-chemical methods in the study of the protolytic equilibria of these compounds.

The participation of nitrogen-containing heterocycles in various chemical transformations depends to a significant extent on the ability of these compounds to give up or add a proton. For processes in which the first step is ionization of the substrate this factor is of decisive significance. The study of the kinetics and mechanism of such reactions is impossible without a knowledge of the constants of the protolytic equilibria of the reagents that participate in them. In addition to this, information regarding the acidity and basicity constants of heterocyclic systems makes it possible to quantitatively characterize their electronic structures. Finally, the study of the ionization of heterocycles is also of independent significance, since "it may serve as the touchstone for the development of the structural theory of solvation" [1].

Voluminous literature has been devoted to the examination of the acid-base properties of five-membered nitrogen-containing heterocycles. However, the available data have been scattered over various sources and have not been previously practically systematized. In this review we discuss the results of investigations of the acid-base properties of five-membered rings with one, two, three, and four nitrogen atoms in the ring obtained using modern physicochemical methods and by the methods of quantum chemistry and published in the last ten years.

Five-membered nitrogen-containing heterocycles are NH acids, the dissociation constants of which vary over the range of ~18 orders of magnitude. When these compounds are dissolved in media with sufficient acidity, they act as bases (Table 1).

The acid-base properties of nitrogen-containing heterocycles are determined to a significant extent by the amount of nitrogen atoms in the ring. The acidity increases as nitrogen atoms accumulate in the molecule. Thus the dissociation constant increases by a factor of $\sim 10^{12}$ on passing from pyrrole to tetrazole. The basicity changes in the opposite order. In the examined series of compounds tetrazole is a weaker base than imidazole by a factor of $\sim 10^{10}$. Pyrrole, which is virtually as weak a base as tetrazole, deviates from this series.

The data on the NH acidities of nitrogen-containing heterocycles have been obtained mainly in dilute aqueous solutions and solutions of organic solvents and are therefore quite easy to compare. At the same time, one should bear in mind that the protonation of some nitrogen-containing heterocycles occurs in rather concentrated solutions of mineral acids, where one must resort to the apparatus of acidity functions to determine the equilibrium constants. This circumstance leads to substantial difficulties in comparing the basicities of the investigated compounds. The pK_{BH^+} values calculated using acidity functions that do not coincide with one another cannot be compared with one another, since a weaker base will not

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TABLE 1. Acid-Base Properties of Five-Membered Nitrogen-Containing Heterocycles in Solutions and in the Gas Phase

Compound	pK_a (in water)	pK_{BH^+}[*1]	*PA*	
			acidity	basicity
Pyrrole	17.51	−3.80	360.7	208.9
Pyrazole	14.21	2.52	—	212.8
Imidazole	14.17	7.0	364.0[*2]	222.1
1,2,3-Triazole	9.26	1.17	—	—
1,2,4-Triazole	10.04	2.45	—	212.4
Tetrazole	4.89	−2.68[*3]	—	—
		−3.01[*4]	—	

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[*] In sulfuric acid in the case of pyrrole and tetrazole.

[*2] Results of quantum-chemical calculations.

[*3] PMR spectroscopy.

[*4] Laser Raman spectroscopy.

necessarily correspond to the more negative pK_{BH^+} value [2].

In addition to the actively continuing study of the acid-base equilibria of five-membered nitrogen-containing heterocycles in solutions, a great deal of attention has been directed to the investigation of these processes in the gas phase in the last decade [3]. Substantial advances in this direction have been made thanks to the use of such modern physicochemical methods as ionic cyclotron resonance and high-pressure mass spectrometry [4, 5]. An evaluation of the "true" acidities and basicities of a number of nitrogen-containing heterocycles has been given on the basis of a comparison of the acid-base properties in solutions and in the gas phase, and the free energies of solvation in water and in several organic solvents have also been calculated [3].

Quantum-chemical methods have been used more and more extensively in recent years in the study of protolytic equilibria. A systematic approach that includes the simultaneous examination of the results of quantum-chemical calculations and experimental data obtained in a study of the acid-base properties of five-membered nitrogen-containing heterocycles has been created by the forces of several groups of researchers [6-9]. The following procedures lie at the foundation of this approach: calculation of the energy (enthalpy) of the protolytic equilibrium ΔE_p (ΔH_p); experimental determination of the proton affinity (PA) in the gas phase; experimental determination of the equilibrium constant (K_a, K_{BH^+}) in solution; analysis of the empirical relationships between pK_a, pK_{BH}, PA, and ΔE_p (ΔH_p), as well as various quantum-chemical indexes. The successful use of this approach was demonstrated in a study of the acid-base properties of pyrazoles, imidazoles, and triazoles.

PYRROLES

It is expedient to begin our discussion of the acid-base properties of five-membered nitrogen-containing heterocycles with an examination of the protolytic equilibria in the gas phase. It is customary to assume that one can determine the "true" acidity (basicity), which is not affected by solvation factors, in the gas phase [10]. The acidity (basicity) in the gas phase is determined by the free energy $\Delta G^0 = \Delta H^0 - T\Delta S$ of the corresponding protolytic equilibrium

$$\text{Het-H} \overset{K_a}{\rightleftharpoons} \text{Het}^- + \text{H}^+;$$

$$\text{Het-H} + \text{H}^+ \overset{K_{BH^+}}{\rightleftharpoons} \text{HetH}_2^+.$$

Since the entropy of an acid-base equilibrium in the gas phase usually does not exceed 9-12 J/mole·deg, free energy ΔG^0 is assumed to be equal to the change in enthalpy ΔH^0 [11]. The change in enthalpy of a protolytic equilibrium taken with the opposite sign is called the proton affinity PA (proton affinity). The proton affinity is calculated from experimental data obtained by means of such methods as ionic cyclotron resonance or high-pressure mass spectrometry. The proton affinity is a quantitative criterion of comparison of the acidities (basicities) of compounds in the gas phase.

The first research involving the quantitative study of the protolytic equilibria of various organic compounds in the gas phase was carried out about 20 years ago [3, 11]. The first data on the acidity of pyrrole in the gas phase were obtained considerably later by means of high-pressure mass spectrometry [12]. The acidity of pyrrole was evaluated from the difference between the energy of the >N–H bond (DH) and the electron affinity or the >N: radical (EA), which was found to be equal to 41.9 kcal/mole. The PA calculated from the expression PA = (DH − EA) + IP, where IP is the ionization potential of the hydrogen atom, is 355.5 kcal/mole. According to later refined data [13], ΔG^0 = 363 kcal/mole and PA = 360.7 kcal/mole for pyrrole. Unfortunately, experimental data on the acidities of substituted pyrroles in the gas phase are not available. For this reason, it is impossible to evaluate the effect of substituents on the PA values of pyrroles. One also cannot indicate how the acidity will change on passing from pyrrole to pyrazole or imidazole, since the acidities of the latter in the gas phase have not been studied.

The acidities of pyrroles in solutions have been investigated in quite some detail. Pyrrole itself is a weak acid with pK_a = 17.5 in water [14]. The acidity of pyrrole decreases substantially to pK_a = 23.05 on passing from water to DMSO [15]. In the case of an extensive series of compounds it has been shown [16] that the acidities of substituted pyrroles in DMSO are determined chiefly by the inductive effect of the substituents and depend little on the ability of the latter to enter into conjugation with the electron system of the heteroring. A good correlation between the pK_a values of pyrroles and the σ_I substituent constants was found. Similar conclusions were obtained in a study of the acidities of 2-substituted 5-(trifluoroacetyl)pyrroles [17]. Benzannelation has only a slight effect on the acidity of pyrrole – the pK_a of indole in water is 16.97 [18]. The effect of functional groups on the acidities of indoles has been studied in quite some detail. In the case of a series made up of 20 monosubstituted indoles it has been shown that a correlation dependence with ρ = 1.75 is observed between the pK_a values of these compounds and substituent constants σ [18].

The basicities of pyrroles have been investigated by many authors. Data obtained in recent years in a study of the basicities of pyrroles in the gas phase are of particular interest. This is associated with the fact that pyrrole in solutions has an anomalously low basicity. Pyrrole (pK_{BH^+} = −3.8) [14] is a significantly weaker base than pyrazole (pK_{BH^+} = 2.52) [19] or imidazole (pK_{BH^+} = 7.0) [20], since in the protonation of pyrrole the proton adds to the α-carbon atom of the ring rather than at the nitrogen atom, as in the case of other nitrogen-containing heterocycles [14, 21].

It is assumed that the pyrrolium cation that is formed in this case has a higher thermodynamic stability than the tautomer with a proton attached to the nitrogen atom. It is important that a similar dependence is also observed in the gas phase: the PA of pyrrole [5, 22], pyrazole, and imidazole [23] are, respectively, 208.9, 212.8, and 222.1 kcal/mole. It follows from this that the basicity of pyrrole in solution is determined primarily by the electronic structure and, to a lesser extent, by the energy of solvation of the pyrrolium ion.

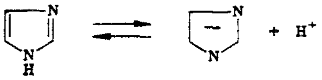
Because of the lack of systematic studies, one cannot yet evaluate the effect of substituents on the gas-phase basicities of pyrroles. It is known only that the PA of 2,5-dimethylpyrrole is 218.4 kcal/mole [24], while a correlation between the proton affinity and the protonation energy is observed for pyrrole and indole [25].

Voluminous literature has been devoted to the study of the basicities of pyrroles in solutions of mineral acids [14]. As we have already noted, pyrrole is a weak organic base, while the pK_{BH^+} values of 1-methyl- and 3-methylpyrrole are −2.9 and −1.0, respectively. Of the three isomeric monomethylpyrroles, 2-methylpyrrole has the greatest basicity with pK_{BH^+} = −0.2. The basicity increases even more when several methyl groups are introduced into the pyrrole ring – the pK_{BH^+} value of 2,3,4,5-tetramethylpyrrole is 3.7. Virtually the same value (3.75) was also found for 3,5-dimethyl-4-ethylpyrrole [26]. The enthalpy and entropy of protonation of this compound are ΔH = 38.2 kJ/mole and ΔS = −44.8 J/mole·K. It is interesting that α-protonated pyrrolium ions that are quite stable under ordinary conditions are formed in the reaction of di- and tri-tert-butylpyrrole with tetrafluoroboric acid [27]. As compared with pyrrole, 1-phenylpyrrole is a weaker base: pK_{BH^+} = −5.8. At the same time, benzannelation has little effect on the basicity: the pK_{BH^+} value of indole is −3.5 [28]. It should be noted that the basicities of indoles have been studied in quite some detail. It has been shown that the protonation of indole and substituted indoles takes place at the $C_{(3)}$ atom of the pyrrole ring [28-32]. It is interesting that carbazole (pK_{BH^+} = −6.0) is protonated at the nitrogen atom [14].

In closing our discussion of data on the basicities of pyrroles we should dwell on some problems that arise in the study of the protonation of these compounds. The principal problem with which one must deal in this case is the well-founded selection of an acidity function that is suitable for the description of protonation equilibria. Acidity functions H_0 and H_M are currently usually employed in the study of the basicities of pyrroles [14, 33]. Acidity function H_I has been proposed for evaluation of the basicities of indoles [28]. It has also been noted that the protonation of 2-acetylpyrroles is not described by any of the known acidity functions [21]. It should be noted that, as a result of the impossibility of using one acidity function for the description of the protolytic equilibria of pyrroles, the basicity constants of these compounds obtained by means of different acidity scales cannot be compared with one another. This circumstance ultimately creates considerable difficulties in the study of the kinetics and mechanisms of the reactions of pyrroles that take place in solutions of acids.

PYRAZOLES AND IMIDAZOLES

As we have already noted, the acidities of pyrazoles and imidazoles in the gas phase have not been studied. A theoretical examination of the acidity of imidazole was recently accomplished by means of a quantum-chemical method (ab initio, STO, 4-31G) [34].



It was found that the change in the enthalpy of equilibrium (1) ΔH^0 = 364 kcal/mole. Unfortunately, one cannot draw a valid conclusion regarding the acidity of imidazole in the gas phase and compare the gas-phase acidities of imidazole and other five-membered nitrogen-containing heterocycles only on the basis of the calculated data.

The acidities of pyrazole and imidazole in water and several organic solvents have been studied by a number of authors [18, 20, 35]. It was shown that pyrazole and imidazole are weak acids but stronger than pyrrole: the pK_a values in water are 14.21 and 14.17, respectively. It is interesting that the acidities of these compounds in water are virtually the same; however, in DMSO imidazole (pK_a = 18.9) is a stronger acid than pyrazole (pK_a = 20.4) [35]. The reason for this may be the more effective specific solvation of the pyrazolate anion in water due to the formation of hydrogen bonds [36].

Systematic data on the effect of substituents on the acidities of pyrazole and imidazole are not available. Substituents that have electron-acceptor properties increase the acidities of these compounds. For example, the pK_a values for 3-acetyl- and 4-nitropyrazole in water are, respectively, 11.85 and 9.67 [37]. Similar regularities were found in a study of the acidities of 4-bromopyrazole and 2-phenyl- and 2,4,5-tribromoindazole in DMSO [35]. The presence of phosphorus-containing substituents in the imidazole molecule has a particularly appreciable effect on the acidity [38]. Thus the following exponents of the acidity constants were found for tris[4,5-dipropyl-2-imidazolyl]phosphine in 80% ethanol: pK_a^1 = 2.55, pK_a^2 = 4.36, and pK_a^3 = 6.67.

The existence of a correlation between the $\Delta\nu_{NH}$ values and the Hammett substituent constants was observed in a study of the acidities of 2,4,5-triarylimidazole derivatives (a total of ~30 compounds) by IR spectroscopy [39]. Benzannelation has only a slight effect on the acidity of pyrazole: the pK_a of indazole in water is 13.8 [18]. The acidity increases to a somewhat greater extent in the benzannelation of imidazole: the pK_a to benzimidazole is 12.9 [18]. As expected, the acidity of benzimidazole decreases on passing from water to DMSO [35] and acetonitrile [40]: pK_a = 16.8 and 25.6, respectively. It was shown that the pK_a values of 2-substituted benzimidazoles correlate with the σ_M substituent constants [9].

Of all the five-membered nitrogen-containing heterocycles, the basicities of pyrazoles and imidazoles in the gas phase have been investigated in greatest detail. The proton affinity of pyrazole determined by high-pressure mass spectrometry is 212.8 kcal/mole [23].

Several different PA have been presented for imidazole: 219.8 [19], 222.1 [23], and 224.9 kcal/mole [24]. However, regardless of which of the indicated PA one should acknowledge as most reliable for imidazole in the gas phase, just as in solutions, imidazole is a stronger base than pyrazole. These data provide a basis for assuming that the relative stabilities of pyrazolium and imidazolium ions are retained on passing from solution to the gas phase. Consequently, the medium does not have a substantial effect on the character of charge delocalization in these ions. Of the substituted imidazoles, the basicities of 1- and 4-methyl-substituted compounds in the gas phase were studied: PA = 228.0 and 224.8 kcal/mole, respectively [23, 41].

The problem of the site of addition of the proton in the substrate inevitably arises in investigating the protonation of compounds that have several potential basicity centers. This problem has been solved successfully for imidazole by comparing the experimentally found enthalpy of protonation with the ΔH^0 value calculated by a quantum-chemical method for processes that lead to the formation of protonated structures with the proton attached to the nitrogen atoms in the 1 and 3 positions of the imidazole ring [23]; it was established that in imidazole the proton adds to the nitrogen atom in the 3 position of the heteroring. It should be added that the basicities of mono-, di-, tri-, and tetramethyl-substituted pyrazoles and imidazoles were recently studied by means of a quantum-chemical method (ab initio, STO-3G) [8]. It was shown that a correlation is observed between the protonation energy ΔE_p and the orbital energy N_{1S} and, most important, that in all of the investigated series methylimidazoles are stronger bases than the isomeric methylpyrazoles.

The first research involving the quantitative evaluation of the basicities of pyrazoles and imidazoles in solutions was carried out in the middle of the 1950s and at the start of the 1960s [42, 43]. The basicities of more than 100 substituted pyrazoles and imidazoles were determined somewhat later in the course of systematic investigations [44, 45]. The data obtained in these studies are presently considered to be the most reliable.

The following indexes of the basicity constants were found for pyrazole [44] and imidazole [20] in water: pK_{BH^+} = 2.52 and 7.0, respectively. The basicity constant of imidazole decreases by a factor of approximately six when the temperature is increased from 10°C to 40°C [46]. The thermodynamic parameters of the ionization of imidazole are ΔH^0 = 37.05 kJ/mole and ΔS = 9.8 J/mole·K [20]. It should be noted that the basicities of pyrazole and imidazole in water have been studied by many researchers [20, 44, 46-49] and that the pK_{BH^+} values obtained in these studies virtually coincide. The basicity of imidazole increases substantially on passing from water to acetonitrile [6, 50].

In comparing pyrazole and imidazole one's attention is directed to the exceptionally large difference in the basicities of these compounds. Until recently, no explanation for this had been found. The solution of the problem was found by comparing the total energies of the neutral and protonated forms of imidazole and pyrazole calculated by means of the MNDO method [51]. It was found that the charge in the imidazolium cation is delocalized to a greater extent than in the pyrazolium cation.

The basicities of pyrazoles and imidazoles in solutions depend substantially on the nature of the substituents and their position in the ring and vary over a wide range. Thus the basicity constant decreases by a factor of ~10^5 on passing from 4-methyl- to 4-nitropyrazole: pK_{BH^+} = 3.09 and −1.96, respectively [44]. 1-(p-Nitrophenyl)-4-nitropyrazole is an even weaker base: pK_{BH^+} = −4.43 [52]. A similar pattern is also observed for substituted imidazoles: thus the pK_{BH^+} values of 2-methyl- and 4-nitroimidazole are, respectively, 8.02 and −0.81 [46, 53]. With respect to their basicities, halo- and phenyl-substituted pyrazoles and imidazoles occupy an intermediate position between the methyl and nitro derivatives. As in the case of pyrrole, the benzannelation of pyrazoles and imidazoles leads to a decrease in the basicities: the pK_{BH^+} values of indazole [47] and benzimidazole [54] are, respectively, 1.39 and 5.69. The effect of substituents on the basicities of indazole and benzimidazole was studied in [19, 47, 55].

It has been shown [50] that substituted pyrazoles and imidazoles are significantly stronger bases in acetonitrile than in water.

Correlation relationships between the pK_{BH^+} values and the substituent constants have been established for substituted pyrazoles and imidazoles by a number of researchers. This problem was examined in detail in a recently published review [56].

In concluding our discussion of the data on the basicities of pyrazoles and imidazoles we must note that quantum-chemical methods were used successfully in the study of these compounds. It was established that the energy of the electrostatic interaction (ε) of the unshared pair of electrons of the nitrogen atom undergoing protonation with the system of π charges is the best theoretical basicity index [6]. It was later shown [7] for a large series of substituted pyrazoles and imidazoles (a total of 22 compounds) that a correlation is observed between the pK_{BH^+} values and the orbital energy of the unshared pair of the nitrogen atom, which is the basicity center. All of the investigated compounds are grouped into three series: those that do not contain a methyl group in the α position, those that contain one methyl group, and those that contain two methyl groups.

TRIAZOLES

The acid-base properties of triazoles have not been adequately studied. This is especially surprising since the reactions of triazoles in which the first step is ionization of the substrate have been investigated in very great detail. Data on the acidities of triazoles in the gas phase evidently are not available. In most cases the acidities of these compounds have been investigated in water. Data on the acidities in DMSO and aqueous ethanol are available. The pK_a values of 1,2,3- and 1,2,4-triazole in water are, respectively, 9.26 and 10.04 [19]. As expected, the acidity of 1,2,4-triazole decreases on passing from water to DMSO: pK_a = 15.4 [35]. Because of the lack of systematic studies, it is difficult to evaluate the effect of the nature of the substituents and isomerism on the acidities of 1,2,3-triazoles on a quantitative level. It is known that the introduction of a phenyl group into the 4 position of the triazole ring leads to an appreciable increase in the acidity: the pK_a value of 4-phenyl-1,2,3-triazole is 7.68 [57]. The acidity increases to an even greater extent under the influence of substituents such as a bromo [58] or cyano group [57]: the pK_a values of 4,5-dibromo- and 4,5-dicyano-1,2,3,-triazole are, respectively, 5.37 and 2.53. Nonionized carboxy, nitro, and phenylsulfonyl groups have a similar effect [58-60]. Benzannelation also leads to an increase in the acidity: the pK_a value of benzotriazole in water is 8.2 [57], whereas it is 12.6 in DMSO [35]. In a study of the thermodynamics of the ionization of 1,2,3-triazole and some 4,5-disubstituted 1,2,3-triazoles [58], it was shown that it is impossible to explain the change in the enthalpy of ionization of these compounds by means of a simple electrostatic model, while electrostatic factors evidently make a definite contribution also to the change in the entropy of ionization.

The acidities of 3(5)-substituted 1,2,4-triazoles change in conformity with the electronic effects of the substituents: the pK_a values of 3-amino- and 3-nitro-1,2,4-triazole are, respectively, 11.5 and 6.05 [19, 61]. The introduction of two electron-acceptor substituents into the triazole ring increases the acidity to an even greater extent: the pK_a of 3,5-dichloro-1,2,4-triazole is 5.20 [19]. It was observed that substituents in the 3 and 5 positions of the heteroring affect the acidities of 3,5-disubstituted tetrazoles differently [62]. The acidities of 5-substituted 3-azido-1,2,4-triazoles were studied in 80% ethanol [63]. However, because of the lack of data on the acidities of these compounds in water, it is difficult to evaluate the effect of the nature of the solvent on the state of the acid-base equilibrium. The existence of a correlation of the pK_a values with the substituent constants has been shown for a series of 3-substituted 1,2,4-triazoles, as well as 5-substituted 3-azido-, 3-bromo-, and 3-nitro-1,2,4-triazole [62]. In the opinion of Pevzner and coworkers [62], the inductive effect plays the predominant role in the transmission of the electronic effect of substituent R to the $N_{(1)}$ reaction center.

The basicity of 1,2,3-triazole in the gas phase has not been studied. Data on the basicity of 1,2,4-triazole in the gas phase were published only in 1986 [23]. The proton affinity for this compound determined by means of high-pressure mass spectrometry was found to be 212.4 kcal/mole. The experimental PA was compared with the enthalpies of protonation of 1,2,4-triazole at the $N_{(2)}$ and $N_{(4)}$ atoms calculated by a quantum-chemical method (ab initio, MP 2/6-31G). It was shown that the nitrogen atom in the 4 position is the most probable basicity center in 1,2,4-triazole.

In comparing the results of studies of the basicities of five-membered nitrogen-containing heterocycles in the gas phase it must be noted that the basicities decrease in the order imidazole, pyrazole, 1,2,4-triazole; the same order is also observed when one compares the basicities of these heterocycles in aqueous solutions.

The basicities of 1,2,3- and 1,2,4-triazoles in aqueous solutions have been studied by a number of researchers. The pK_{BH^+} values obtained in [19, 57] differ only slightly and are, respectively, 1.17 and 2.45. At the same time, the information available regarding the effect of substituents on the basicity of 1,2,3-triazole is extremely limited. The introduction of a methyl group into the 1 position of the heteroring leads only to a slight increase in the basicity constant: the pK_{BH^+} value of 1-methyl-1,2,3-triazole is 1.25 [19]. Annelation of the triazole ring with a pyridine ring decreases the basicity appreciably: the pK_{BH^+} value of 5-amino-6-cyano-1,2,3-triazolo[4,5-b]pyridine is −0.06 [64]. The basicities of substituted 1,2,4-triazoles have been studied to a considerably better extent. 1-Methyl-1,2,4-triazole is an appreciably stronger base than unsubstituted triazole: pK_{BH^+} = 3.20 [19]. The basicity increases to an even greater extent when two methyl or two amino groups are introduced into the ring: the pK_{BH^+} values of 3,5-dimethyl- and 3,5-diamino-1,2,4-triazole are, respectively, 3.68 and 4.43 [65]. Substituents such as an azido or nitro group, the presence of which in the 3(5) position of the ring leads to a sharp decrease in the basicity constant, have a very strong effect on the basicity of 1,2,4-triazole. The pK_{BH^+} values of 3-azido- and 3-nitro-1,2,4-triazole are −0.24 and −3.7, respectively [61, 63]. It is interesting that the introduction of a methyl group into the 1 position of the heteroring actually does not affect the index of the basicity constant: the pK_{BH^+} value of 1-methyl-3-nitro-1,2,4-triazole is −3.56 [61]. However, if the methyl group is in the 5 position of the ring, the basicity constant increases somewhat: the pK_{BH^+} value of 3-nitro-5-methyl-1,2,4-triazole is −2.93 [61]. An analysis of the transmission of the electronic effects of substituents to the basicity center was made for two series of 3-substituted 1,2,4-triazoles and 5-substituted 3-azido-5-R-1,2,4-triazoles using two-parameter correlation equations [62]. In conclusion, it must be noted that in studies of the basicities of triazoles, the protonation of which occurs in aqueous solutions of acids, various researchers have used various acidity functions [61, 66, 67], usually H_0 and H_A, to calculate the pK_{BH^+} values. This means that comparison of the basicities of triazoles with respect to the pK_{BH^+} values is possible only for those compounds, the protonation of which is described by any one acidity function.

TETRAZOLES

In the series of nitrogen-containing heterocycles under discussion in this review tetrazoles have extremal acid-base properties. The high acidity of tetrazole (Table 1) is explained by the stability of the tetrazolate anion, which has pronounced aromatic character. At the same time, the tetrazolium ion, which is formed in the protonation of tetrazole in the 4 position, has weak aromatic character, as evidenced by the nonequivalent values of the multiplicity indexes of the bonds [68, 69]. The low stability of the tetrazolium ion is evidently the reason for the low basicity of tetrazole (Table 1).

The acidities of tetrazoles in the gas phase have not been studied. Most of the data on the acidities of these compounds have been obtained in aqueous and aqueous alcohol solutions. The known pK_a values of 5-substituted tetrazoles lie in the −0.8...7 range [70, 71]. Data on the acidities of tetrazoles in the DMSO–water system [72] and in solution in 1,1,3,3-dimethylguanidine [73] are available. 5-Phenyltetrazole, the acidity of which has been studied in acetone, acetonitrile, nitromethane, and DMSO, has been investigated in greater detail in this respect [74].

In comparing the dissociation constants of 5-substituted tetrazoles in water and organic solvents it is apparent that, as expected, a decrease in the dielectric permeability of the solvent leads to a decrease in the dissociation constant. Thus, for example, the dissociation constant of 5-phenyltetrazole in water is greater by a factor of $\sim 10^3$ than in acetone. However, it is surprising that the pK_a value of tetrazole on passing from water to 1,1,3,3-tetramethylguanidine (pK_a 4.86 and 4.53, respectively) does not change as markedly as one might have expected on the basis of the difference in the dielectric permeabilities and solvating capacities of these solvents. Unfortunately, systematic studies of the acid-base properties of tetrazoles in nonaqueous solvents have not been made. For this reason, it is difficult to evaluate more rigorously the effect of the nature of the solvent on the acidities of these compounds. The available data on the effect of the temperature on the acidities of tetrazole and 5-substituted tetrazoles are extremely limited. On the basis of the available experimental data it may be concluded that the dissociation constants of tetrazoles change only slightly over the 20-45°C range [74]. According to the data of the authors of the review, the thermodynamic parameters of the dissociation of tetrazole, 5-methyltetrazole, and 5-trideuteromethyltetrazole calculated from the dependence of the pK_a values on the temperature are as follows, respectively: ΔH^0 = 53, 53, and 50 kJ/mole, and ΔS^0 = 0.09, 0.07, and 0.06 J/mole·K. The nature of the substituent attached to the ring carbon atom has a decisive effect on the acidities of tetrazoles. Tetrazole itself is an acid of medium strength with pK_a = 4.86. The dissociation constants of 5-alkyltetrazoles change only slightly with lengthening of the alkyl chain [75, 76]. Thus the pK_a values of 5-methyl and 5-octyltetrazole are, respectively, 5.63 and 5.73. The dissociation constants of the simplest 5-alkyltetrazoles correlate with the σ^* substituent constants; ρ has a very low value – 0.17 [73]. The acidity increases by approximately two to three orders of magnitude on passing to 5-alkylaminotetrazoles protonated at the amino group [77]. Replacement of protium by deuterium in the methyl group of 5-methyltetrazole has virtually no effect on the acidity constant of this compound: $K_H/K_D = 0.9$ [71]. The presence of electron-acceptor substituents such as the trifluoromethyl [70] or tetrazolyl [78] group at the endocyclic carbon atom leads to a sharp increase in the acidities of the corresponding tetrazoles. A similar pattern is observed for 5-dinitromethyl- [70] and 5-nitrotetrazole [79]; as far as one can judge from the available data, 5-nitrotetrazole ($pK_a = -0.83$) is the strongest NH acid of all of the compounds of this series. With respect to their acidities, 5-chloro-, 5-bromo-, and 5-iodotetrazole are comparable to the corresponding haloacetic acids [70]. The dissociation constants of these compounds correlate with the σ_M substituent constants [80]. 5-Aryltetrazoles are stronger acids than 5-alkyltetrazoles. The pK_a values of 5-aryltetrazoles vary from 4.7 for 5-(p-methoxyphenyl)tetrazole to 3.19 for 5-(o-nitrophenyl)tetrazole [81]. 5-(o-Methoxyphenyl)tetrazole, for which an anomalously high value ($pK_a = 7.02$) was recorded, constitutes an exception [81]. This is evidently due to an $N_{(1)}$–H...O bond. A good correlation between the pK_a values and the electronic constants of the substituents is observed for 5-aryltetrazoles [72, 81]. Finally, data on the acidities of tetrazoles with more complex substituents attached to the endocyclic carbon atom – 1-(5-tetrazolyl)-3,5-diaryl- and 3-(5-tetrazolyl)-1,5-diarylformazans – are available [82, 83].

Data on the basicities of tetrazoles in the gas phase are not available. At the same time, tetrazoles, being weak bases as compared with other five-membered nitrogen-containing heterocycles, have been studied in greatest detail. Voluminous information regarding the behavior of these compounds in sulfuric, perchloric, nitric, and trifluoroacetic acids is available [70, 71]. A detailed study of the basicities of tetrazoles with various structures in aqueous solutions of sulfuric and perchloric acids showed that the protonation of these compounds is described by the H_0 acidity function [70, 71]. The X acidity scale was used along with the H_0 acidity function in calculating the pK_{BH^+} values for some tetrazoles; results that virutally coincide were obtained in all cases [84].

Depending on the electronic nature of the substituents and their position in the ring the pK_{BH^+} values of tetrazoles lie in the –2...–9 range. It was shown by laser Raman spectroscopy that in 17.2...37.0% H_2SO_4 tetrazole forms a complex with the hydrated proton of the type proposed by Khaldna [85]:

$$T\cdot sH_2O + H^+\cdot xH_2O \rightleftarrows T\cdots H^+\cdot nH_2O + (s+x-n)H_2O.$$

Protonation of tetrazole occurs in 37.0...61.1% H_2SO_4: $pK_{BH^+} = -3.01$. The introduction of a methyl group into the 1 or 2 position of the ring has virtually no effect on the basicity of tetrazole. At the same time, 5-methyltetrazole is an appreciably stronger base than tetrazole: $pK_{BH^+} = -1.83$. 1- and 5-Aryltetrazoles are weaker bases than the corresponding alkyl derivatives. The pK_{BH^+} values of these compounds lie in the –3.18...–3.99 and –1.88...–3.88 ranges, respectively [70]. 5-Trifluoromethyltetrazole, 1,1'-diphenylditetrazolyl, and 5-nitrotetrazole are the weakest bases in the tetrazole series: $pK_{BH^+} = -7.0$, -7.47, and -9.26, respectively [79, 86]. A linear dependence over a broad range of changes in the exponents of the corresponding constants is observed between the pK_{BH^+} and pK_a values of 5-substituted tetrazoles; this makes it possible to quantitatively evaluate the acid-base properties of 5-substituted tetrazoles with the most diverse structures [79]. As compared with monosubstituted tetrazoles, the basicities of disubstituted tetrazoles have been studied in greater detail. The basicity constants of a large series of 5-substituted 1- and 2-methyltetrazoles, 1- and 2-methyl-5-aryltetrazoles, and 1-aryl-5-methyltetrazoles in aqueous sulfuric acid were determined by UV and PMR spectroscopy [87-90]. It was shown that the pK_{BH^+} values of 1-phenyl-5-methyltetrazoles correlate with the σ_I substituent constants and the pK_{BH^+} values of isomeric 1- and 2-methyl-5-aryltetrazoles correlate with the σ constants [87, 90]. These data are in good agreement with the results obtained for tetrazole and monosubstituted tetrazoles. Only cycloalkanotetrazoles, for which very high pK_{BH^+} values (1.74...1.81) were found, regardless of the number of methylene groups in the ring [91]. It may be assumed that the pK_{BH^+} values obtained in studies of the protolytic equilibria in formic acid pertain not to protonation, but rather to one of the types of equilibria associated with the formation of ion pairs.

The tetrazole ring has two potential basicity centers. This is associated with the fact that the electron-density distribution in tetrazole has maxima at the nitrogen atoms in the 1 and 4 positions of the ring [69]. On the basis of a study of the vibrational spectrum of protonated tetrazole and an examination of the results of a correlation analysis of the basicity constants of several series of mono- and disubstituted tetrazoles it was concluded that the protonation center in tetrazoles is the nitrogen atom in the 4 position of the ring [70]. The authors of the review* arrived at the same conclusion when they compared the calculated values of the total energies of different forms of protonated tetrazole — forms with the proton attached to the nitrogen atoms in the 1 and 4 positions of the ring. Protonation of tetrazole at the nitrogen atom in the 4 position leads to a symmetrical structure with an energy gain of 50 kJ/mole, which is achieved through better conditions of delocalization of the positive charge in the system. These results provide a basis for the assumption that in the gas phase, just as in solutions, the addition of a proton in tetrazoles should occur at the nitrogen atom in the 4 position of the ring.

A substantial change in approaches to the study of the acid-base properties of five-membered nitrogen-containing heterocycles has occurred in the last two decades. An enormous amount of experimental data on the constants of the protolytic equilibria of these compounds has been accumulated. Fundamentally important data on the gas-phase acidities and basicities have been obtained. The advances in the application of quantum-chemical methods in the investigation of proton-transfer reactions are unquestionable [92]. More and more attention is being directed to the role of the acid-base transformations of five-membered heterocycles in the study of their reactivities [93-95] and biological activities [96, 97]. At the same time, it should be emphasized that many exceptionally important problems still remain unsolved. This primarily pertains to the problem of the effect of the nature of the solvents on the acid-base properties of five-membered nitrogen-containing heterocycles. The investigations dealing with this topic are rare, and the results obtained by the authors of these studies do not agree with one another in some cases [98]. Data on the constants of the protolytic equilibria in mixed solvents are not available. As before, the problem of the well-founded selection of a method for calculation of the ionization relationships in the study of the basicities of five-membered nitrogen-containing heterocycles in solutions of mineral acids remains unsolved. It might be assumed that in a number of cases the use of inadequate methods of treatment of the experimental data leads to the need to use different acidity functions to describe the protolytic equilibria. New methods of calculation of the pK_{BH^+} values of weak bases are virtually not used in investigating the basicities of five-membered nitrogen-containing heterocycles [2, 99-101]. In this connection attention should be directed to the method of calculation of pK_{BH^+} values using the X acidity scale [100]. This method has been successfully tested in studies of the basicities of compounds of various classes, including indoles [100] and tetrazoles [84].

Finally, it should be noted that although methods for the determination of acidities and basicities in the gas phase have recently been improved substantially, the proton affinities (even for such a well-studied compound as ammonia) that are presented in the most authoritative sources [11, 102, 103] differ by ~5 kcal/mole. This pertains to an even greater extent to heterocycles, the investigation of the acid-base properties of which in the gas phase is essentially just beginning. Thus it is absolutely clear that the scale of research involving the systematic study of the acid-base properties of five-membered nitrogen-containing heterocycles in the gas phase, despite the complex experimental technique used for these purposes, should be expanded substantially.

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^{1}H AND ^{13}C NMR SPECTRA, STEREOISOMERISM, AND CONFORMATIONAL STATES OF 3-PHENYL-5-ISOPROPOXYTETRAHYDRO-2-FURANONES

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The ^{1}H and ^{13}C NMR spectra of the diastereomers of 3-phenyl-5-isopropoxytetrahydro-2-furanone were obtained. The stereoisomerism and preferred conformational states of these diastereomers were established by means of the spectroscopic criteria found for 3,4-disubstituted sulfolanes and 1,1,3,4-tetrasubstituted silacyclopentanes. It is shown that for the cis isomer the equilibrium is shifted to favor pseudoequatorial conformers, whereas for the trans isomer it shifted to favor ae conformers with a preferred pseudoequatorial orientation of phenyl substituent.

The diastereomeric pair of 3-phenyl-5-isopropoxytetrahydro-2-furanone, in which the substituents are attached to carbon atoms separated by one CH_2 group, is a convenient subject for testing the efficiency of the spectroscopic criteria for the determination of the stereoisomerism of disubstituted five-membered heterocycles developed primarily in the investigation of the ^{1}H and ^{13}C NMR spectra of vicinally substituted five-membered cyclic compounds [1-3].

The ^{1}H NMR spectra of the ring protons of diastereomers I and II correspond to a four-spin ABKX system (Tables 1 and 2).

As analysis of the chemical shifts (CS) of the ring carbon atoms shown that the chemical shifts of the $C_{(2)}$ and $C_{(4)}$ nuclei, i.e., the carbon nuclei coupled with one substituent, of I are greater than the CS of the corresponding carbon nuclei of II. It is known that in disubstituted derivatives of cyclopentane and cyclohexane the carbon nuclei coupled with one substituent are more strongly shielded in the trans isomers if the substituted carbon atoms are separated by one methylene fragment [5, 6] as compared with the CS of the analogous atoms in the cis isomers. Consequently, II is the trans isomer, and I is the cis isomer. Since

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