TAUTOMERISM AND ACID–BASE PROPERTIES OF TETRAZOLES (REVIEW)

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The prototropic tautomerism and acid–base properties of tetrazoles are discussed in this review. Major attention is directed to the factors that determine the state of the tautomeric equilibria, the acidities and basicities of tetrazoles, and the reactivities of tetrazoles. The available data are interpreted from the point of view of quantum-chemical calculations and modern concepts regarding the behavior of weak organic bases in solutions of acids.

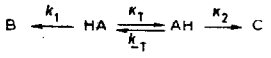
The considerable interest in the chemistry of tetrazoles [1-5] is associated with the application of these compounds in medicine [6, 7], biology [8], analytical chemistry [9], the manufacture of polymeric materials [10], agriculture [11], etc. In this connection, numerous transformations and the physicochemical properties of tetrazole and its derivatives have been investigated. Studies devoted to the investigation of prototropic tautomerism as one of the important factors that determine the structure and reactivity of tetrazoles constitute a significant part of the research in this area. Another important problem that is directly associated with prototropic tautomerism and to which too little attention has been paid for a long time is the behavior of tetrazoles in solutions of acids and bases. A study of the kinetics and mechanisms of the reactions of tetrazole and substituted tetrazoles that occur in solutions of acids and bases is impossible without a knowledge of the constants of the protolytic equilibria of these compounds. In addition, a study of the ionization of heterocyclic compounds makes it possible to obtain valuable information regarding the transmission of the electronic effects of substituents in such systems and regarding their structures. Important advances in this area have been made in the last 5–10 yr, during which period the systematic study of the tautomerism and acid-base properties of tetrazoles with the application of modern physicochemical methods and the methods of quantum chemistry was begun.

Prototropic Tautomerism of Tetrazoles

Tetrazole and 5-substituted tetrazoles can exist in two tautomeric forms, viz., the 1-H and 2-H forms:

A large amount of literature has been devoted to the study of the prototropic tautomerism of tetrazoles, and data through 1973 have been correlated by Elguero and Katritzky [12]. The results obtained mainly in recent years will be examined below.

Various methods can be used to investigate the tautomeric equilibria of tetrazoles. However, because of the peculiarities of the structure of the tetrazole ring, chemical methods and the determination of the basicities are not applicable for these ends. In the study of tautomeric equilibria by chemical methods it is assumed that different tautomeric forms undergo reaction with the same reagent to give isomeric products B and C:



Then, under the condition that k_1 and k_2 are much larger than k_T and K_{-T} and in the case of the complete conversion to B and C, the K_T value can be calculated from the ratio of the concentrations of B and C. This method is not applicable to tetrazoles, since the ambident tetrazolate anion, which is common to both tautomeric forms, rather than the individual tautomers, participates in reactions with electrophilic reagents [13].

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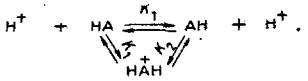
The tautomeric equilibrium constant can be determined if the basicity constants of the individual tautomers (K_1 and K_2) are known:



However, in connection with the fact that measurement of the basicities of the tautomers is impossible in most cases, the basicity constants of fixed tautomers (usually the methylated derivatives) are used to ascertain the K_T values, in which case the following two assumptions are made: The two tautomeric forms give a common anion when they are protonated, and alkylation has little effect on the basicities of the investigated tautomers. Unfortunately, this simple and efficient method is not suitable for tetrazoles, since the 1-H and 2-H tautomers do not form a common anion when they are protonated.

Physical and physicochemical methods such as the method of dipole moments, NMR and IR spectroscopy, correlation analysis, and some other methods find broad application in the study of the prototropic tautomerization of tetrazoles. One of the most widely used methods for the study of the tautomeric equilibria of tetrazoles is a comparison of the experimental and calculated dipole moments of the individual tautomers. The dipole moments of 1-H- and 2-H-tetrazoles calculated from the usual vector additive scheme [14] are, respectively, 5.26 and 2.04 D. The dipole moments obtained by means of an improved vector additive scheme [15], which differs with respect to the more accurate allowance for the geometry and polarities of the bonds of the molecule under consideration, are 5.16 and 2.38 D. Calculations of the dipole moments by means of quantum-chemical methods give values that are close to those obtained by additive schemes. Thus, the dipole moments of the 1-H and 2-H tautomers calculated by the ab initio method in [16] are, respectively, 5.17 and 2.54 D. The dipole moments of tetrazole found experimentally in benzene [12] and dioxane [17] are 5.10 and 4.96 D. A comparison of the experimental values of the dipole moments with the calculated values for 1-H and 2-H tetrazoles provides evidence that the tautomeric equilibrium for tetrazole itself is shifted to favor the 1-H tautomer. Finally, it must be noted that the dipole moments of tetrazole and C-deutero- and N-deuterotetrazoles determined by means of the Stark effect from data from the microwave spectra of these compounds are 2.19, 5.30, and 2.14 D, respectively [18]. It follows from this that tetrazole and N-deuterotetrazole exist in the gas phase primarily in the form of the 2-H tautomer, while the 1-H form predominates for C-deuterotetrazole. These results to a certain extent contradict the data obtained by other authors. At the same time it is apparent that because of the closeness of the energies of the 1-H and 2-H tautomers, the determination of their individuality by means of spectral methods is fraught with considerable difficulties and requires additional experimental verification.

The study of the prototropic tautomerism of tetrazoles by NMR spectroscopy is complicated by the fact that the cleavage of the existing bond and the formation of a new N–H bond are rather fast processes as compared with the rate of recording of the spectrum. For this reason it is impossible to record the NMR spectra of the individual tautomers, and it is necessary to use model compounds to determine the tautomeric equilibrium constants. In this case the tautomeric equilibrium constant can be calculated by means of the expression

$$K_T = \frac{\delta - \delta_{1\text{-H}}}{\delta_{1\text{-H}} - \delta_{2\text{-H}}},$$

where δ is the observed averaged chemical shift, and $\delta_{1\text{-H}}$ and $\delta_{2\text{-H}}$ are the chemical shifts of the corresponding model tautomers. In recent studies [19, 20] it was shown by ^{13}C NMR spectroscopy in the case of a series of 5-substituted tetrazoles that the tautomeric equilibrium in the dimethyl sulfoxide (DMSO)–water system is shifted to favor the 1-H tautomer, regardless of the nature of the substituent attached to the ring carbon atom. The same conclusion follows from a comparison of the $J(^{13}C-H)$ spin–spin coupling constants for tetrazole and 1- and 2-methyltetrazoles [21]. According to the ^{13}C NMR data, the nature of the solvent does not have an appreciable effect on the state of the tautomeric equilibria of tetrazoles [22]. Tetrazole exists primarily in the 1-H form in solvents such as DMSO, dimethylformamide (DMF), acetone, and water.

Interesting information regarding the tautomeric composition in the crystalline state was obtained in an examination of the IR and Raman spectra of tetrazole and its derivatives [23]. The authors showed that the calculated vibrational spectrum of the 1-H tautomer coincides satisfactorily with the experimental spectrum of tetrazole. These data are in agreement with the results of a study of the tautomerism of tetrazoles obtained by other methods.

The applicability of the Hammett equation for the description of the acid–base properties of 5-substi-

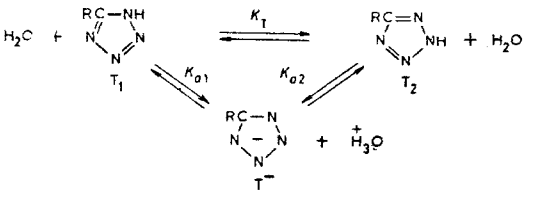
tuted tetrazoles may serve as a useful criterion in the estimation of the tautomeric equilibria of these compounds. The correlation of the pK_a values with the electronic constants of the substituents means that the investigated tetrazoles exist as individual tautomeric forms if the acidity constants of the tautomers differ appreciably. This condition is evidently observed in the usual case, since, for example, the basicity constants of the isomeric 1- and 2-methyl-5-phenyl tetrazoles differ by a factor of ~10 [24]. The good correlation between the pK_a values and the electronic constants of the substituents observed for several series of 5-substituted tetrazoles [25, 26] constitutes evidence that the indicated compounds exist primarily in one tautomeric form.

Thus, on the basis of the data obtained by various physical and physicochemical methods it may be assumed that tetrazole and 5-substituted tetrazoles exist primarily in the 1-H form. Charton's assertion [27] that the 2-H form predominates in the tautomeric equilibrium should be considered to be erroneous, since he arrived at this conclusion on the basis of an analysis of the correlation dependences of the pK_a values of 5-substituted tetrazoles on the substituent constants. A well-reasoned criticism of this approach is presented by Elguero and Katritzky [12].

Acidities of Tetrazoles

Tetrazoles are heterocyclic NH acids, the pK_a values of which range from 1 to 7 pH units. The dissociation constants of ~200 tetrazoles with various structures are presently known. The data obtained prior to 1965 are presented in an earlier review [1].

With allowance for prototropic tautomerism, the dissociation of tetrazoles can be represented as



where K_{a1} and K_{a2} are the dissociation constants of the 1-H and 2-H tautomers, and T^- is the tetrazolate anion.

In general form the expression for the observed dissociation constant has the form $K_{obs} = [T^-] \cdot [\overset{+}{H}_3O]/([T_1] + [T_2])$; however, since the tautomeric equilibria for 5-substituted tetrazoles are essentially shifted to favor the 1-H tautomer, $K_{obs} = [T^-] \cdot [\overset{+}{H}_3O]/[T_1] = K_{a1}$. Thus, the acidities of tetrazole and 5-substituted tetrazoles are actually estimated from the degree of dissociation of the 1-H tautomer, which can be calculated by means of the equation $pK_a = pH + \log I + \Delta$ or its modification $pK'_a = mpH + \log I$, where $[T_1]/[T_2]$ is the ionization ratio, and Δ is the correction for the ionic strength of the solution.

Although Bershtein and Kaminskii [28] are of the opinion that the use of the second equation for the determination of the dissociation constant does not make it possible to uncover a "tendency for a regular decrease in the pK_a values as the pH of the medium changes," there is evidently no fundamental difference in the treatment of the experimental data by means of these equations. At the same time, the practice of studying the acid–base properties of weak organic bases [29] provides a basis for the assumption that the magnitude of slope m is the most objective criterion of the applicability of the selected acidity scale (pH). If slope m differs only slightly from unity, the index of the dissociation constant is determined by division of the free term of the equation by slope m: $pK_a = pK'_a/m$. Thus, it might be expected that the numerical pK_a values obtained by these and other methods should not differ and will coincide with the pH values at the half-neutralization point. The validity of this assumption was demonstrated in the case of a study of the acidities of tetrazole and a series of substituted 5-phenyltetrazoles [26].

The dissociation constants of tetrazoles can be determined by means of methods such as conductometric and potentiometric titration, as well as by UV spectrophotometry. The latter two methods are used more often than the others.

Most of the data on the acidities of tetrazole and 5-substituted tetrazoles were obtained in aqueous and aqueous alcohol solutions. Several examples of the study of the acidities of tetrazoles in solution in 1,1,3,3-tetramethylguanidine are also known [30]. When the dissociation constants of 5-substituted tetrazoles in aqueous and aqueous alcohol solutions are compared, 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

pK_a values of 5-phenyltetrazole in water [31] and 50% and 76% methanol [32] are, respectively, 4.38, 4.54, and 4.89. However, it is surprising that the acidity of tetrazole in water [26] (pK_a 5.00) and in solution in 1,1,3,3-tetramethylguanidine [30] (pK_a 4.53) does not change as markedly as one might have expected on the basis of the difference in the dilectric permeabilities and the solvating capacities of these solvents. Unfortunately, the acid–base properties of tetrazoles in nonaqueous solvents have received very little study, and it is therefore impossible to estimate the effect of the nature of the solvent on the acidities of these compounds.

Systematic data on the effect of the temperature on the dissociation of tetrazole and 5-substituted tetrazoles are not available, although it might be assumed that the dissociation constants of tetrazoles would change only slightly with the temperature. The thermodynamic parameters of the dissociation were measured for tetrazole and some 5-substituted tetrazoles in water at 25°C [31]. The ΔH^0 and ΔS^0 values for the dissociation of tetrazole are 3.1 kcal/mole and −12.1 cal/mole-deg. Close values were also obtained for other investigated compounds.

The nature of the substituent attached to the ring carbon atom has a decisive effect on the acidities of tetrazoles. Tetrazole itself [26] is an acid with medium strength. As expected, the dissociation constants of 5-alkyltetrazoles [31, 33] change only slightly as the alkyl chain becomes longer. Thus, the pK_a values of 5-methyl- and 5-(n-octyl)tetrazoles are, respectively, 5.63 and 5.73. The dissociation constants of the simplest 5-alkyltetrazoles [30] correlate with the σ^* substituent constants, and the ρ value is very low (0.17). The acidities undergo an increase of approximately two to three orders of magnitude on passing to amino group-protonated 5-alkylaminotetrazoles [34]. 5-Trifluoromethyltetrazole is a strong acid (pK_a 1.14) [35]; this is associated with the substantial electron-acceptor effect of the trifluoromethyl group. A similar picture is also observed for 5-dinitromethyltetrazole [36]. Insofar as one can judge from the available data, 5-trifluoromethyltetrazole is the strongest acid of all of the investigated compounds of this series.

The acidities of 5-chloro-, 5-bromo-, and 5-iodotetrazoles [37] are comparable to the acidities of the corresponding haloacetic acids. The dissociation constants of these compounds correlate [25] with the σ_m substituent constants. 5-Phenyltetrazoles are stronger acids than the unsubstituted alkyl derivatives. The pK_a values of these compounds range from 4.70 for 5-(p-methoxyphenyl)tetrazole to 3.19 for 5-(o-nitrophenyl)tetrazole [26]. 5-(o-Methoxyphenyl)tetrazole [26], for which an anomalously high pK_a value of 7.02 was established, constitutes an exception. This is evidently associated with the existence of a hydrogen bond between the hydrogen atom attached to the nitrogen atom in the 1 position of the ring and the oxygen atom of the methoxy group.

A good correlation between the dissociation constants and the σ^0 substituent constants is observed for substituted 5-phenyltetrazoles [26] (Fig. 1).

$$pK_a = -(1.27 \pm 0.09)\sigma^0 + (4.40 \pm 0.06);$$

$$r = 0.99;\ n = 6;\ s = 0.09.$$

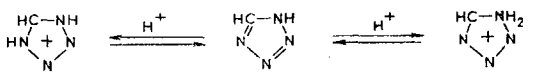
The dissociation constants of substituted 1-(5-tetrazolyl)-3,5-diarylformazans [38] vary over a range of ~1.5 pH units depending on the nature of the substituent in the phenyl ring. At the same time, the dissociation constants for 3-(5-tetrazolyl)-1,5-diarylformazans differ only slightly.

In conclusion, one cannot fail to note that the pK_a values of 5-substituted tetrazoles are comparable to the pK_a values of the corresponding carboxylic acids. This conclusion is not unexpected, since the negative charge in the tetrazolate anion, as in the case of the carboxylate anion, is markedly delocalized. This follows from an analysis of the molecular diagrams of the anions of tetrazole and 5-substituted tetrazoles [40].

Finally, it is very important that the data on the acid–base properties of tetrazoles make it possible to make a quantitative study of the reactivities of these compounds in, for example, processes such as alkylation, addition to the multiple bonds, and many others.

Basicities of Tetrazoles

Tetrazoles are weak organic bases and are protonated when they are dissolved in acids. The site of addition of the proton to the ring is difficult to predict, since the tetrazole ring has several potential basic centers.



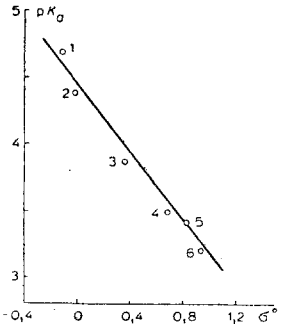


Fig. 1. Dependence of the pK_a values of substituted 5-(R-phenyl)tetrazoles on the σ^0 substituent constants: 1) R = p-OCH_3; 2) R = o-CH_3; 3) R = m-Cl; 4) R = m-NO_2; 5) R = p-NO_2; 6) R = o-NO_2.

The nitrogen atom in the 1 or 4 position may be the protonation center in the tetrazole ring, since the distribution of the electron density over the tetrazole ring is maximal at these atoms [40, 41] (Fig. 2). It is also possible that the site of protonation of tetrazoles depends on the nature and position of the substituent in the ring. To a first approximation, it may be assumed that the protonation of tetrazoles is described by the Brønsted equation. In this case, with allowance for the proportionality of the acidity scales, the protolytic equilibrium constant (K_{BH^+}) can be calculated from the expression

$$pK_{BH^+} = mH_0 + \lg I,$$

where I is the ionization ratio.

One of the most important stages in the study of the basicities of weak organic bases is the solution of the problem as to which acidity function (H_0, H_A, or H_X) describes the protonation of this class of compounds. The problem essentially reduces to an examination of the ratios of the activity coefficients of the protonated and unprotonated forms of the bases (f_{BH^+}/f_B). When the f_{BH^+}/f_B ratios for anilines and the investigated compounds change identically (when the Hammett postulate is observed), slope m is unity. This means that the compounds of this class are protonated in the same way as Hammett bases. When the Hammett postulate is violated, slope m differs substantially from unity, and a different acidity function must be used in place of H_0 to describe the protonation.

It is apparent that this approach is somewhat simplified and does not make it possible to evaluate the "previous history" of strictly the protonation process; nevertheless, it was found to be extremely fruitful in the study of weak organic bases [42]. In a study of the basicity of tetrazole [43] in aqueous sulfuric acid solutions by means of PMR spectroscopy it was shown that the chemical shift of the proton attached to the ring carbon atom does not change at up to 37.0% H_2SO_4. At the same time, the signal of the C–H proton is shifted to weak field as the sulfuric acid concentration is increased further, and the dependence of δ_{C-H} on H_0 (H_0 is the Hammett acidity function) has the form of the sigmoid curve that is characteristic for Hammett bases. These changes in the chemical shift are observed in 37.0-61.1% H_2SO_4 and are associated with protonation of tetrazole. The pK_{BH^+} value of tetrazole is −2.68.

However, the use of PMR spectroscopy for the study of the protolytic equilibria of weak organic bases in a number of cases does not make it possible to establish the detailed features of the protonation mechanism. This information can be obtained by means of the methods of vibrational spectroscopy. The use of vibrational spectroscopy also makes it possible to follow the fine changes in the structures of the individual fragments of the investigated compounds. However, the low intensities of the lines in the Raman spectra require the use of solutions with high concentrations, and this limits the possibilities of this method. Raman spectroscopy with the use of a laser as the source of excitation makes it possible to overcome these difficulties [44]. Thus laser Raman spectroscopy was used in a study of the basicity of tetrazole in aqueous sulfuric acid solutions [45]. The Raman spectrum of tetrazole in dilute (up to 17%) solutions of sulfuric acid is virtually independent of the H_2SO_4 concentration and coincides with the spectrum of the powder. The positions and intensities of the lines of the spectrum change as the sulfuric acid concentration increases from 17.2 to 37.0%. The ν_1 band at 1259 cm^{-1} undergoes the greatest change. This line is related to the vibrations of the $N_2N_3N_4C$ fragment of the ring. Commencing with 37.0% H_2SO_4 one observes the appearance of the ν_2 line at 1310 cm^{-1}, which is related

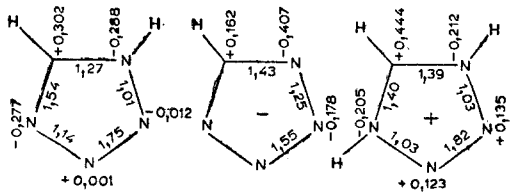


Fig. 2. Molecular diagrams of tetrazole, the tetrazolate anion, and protonated tetrazole.

to the vibrations of the same ring fragment of the protonated form of tetrazole. The dependences of the molar coefficients of scattering (V_1 and V_2) at the analytical ν_1 and ν_2 frequencies on H_0 have the form of sigmoid curves (Fig. 3). The specific character of the inflection for ν_1 (the maximum change in intensity occurs within the limits of 1 H_0 unit) constitutes evidence that equilibrium with the formation of a complex with a hydrated proton of the type proposed by Khaldna [46] is observed for tetrazole in 17.2–37.0% H_2SO_4:

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

The change in the intensity of the ν_2 band in 37.0–61.1% H_2SO_4 is associated with protonation of tetrazole. The pK_{BH^+} value found for tetrazole (−3.01) is in good agreement with the value obtained by PMR spectroscopy. According to the available data [43, 45], tetrazole is a Hammett base.

The determination of the site of addition of the proton in the tetrazole system has very great significance in the study of the mechanisms of the reactions of tetrazoles that take place in acidic media. There are several possibilities for the solution of this problem (for example, vibrational spectroscopy and correlation analysis). Vibrational spectroscopy has been used to determine the site of addition of a proton in tetrazole, and correlation analysis has been used in the study of the basicities of mono- and disubstituted tetrazoles. Since the protonation of tetrazole may occur via two pathways, the two most probable models of protonated tetrazole, viz., models with the proton attached to the ring nitrogen atoms in the 1 and 4 positions, were selected for the examination [45]. It was established that satisfactory agreement between the calculated and experimental spectra of protonated tetrazole is observed only for the model with the proton attached to the nitrogen atom in the 4 position. Hence, it follows that the nitrogen atom in the 4 position of the ring is evidently the protonation center in tetrazole.

The basicities of 1- and 5-substituted phenyltetrazoles have been studied quite thoroughly, while less study has been devoted to alkyltetrazoles. The selection of these compounds does not stem from any fundamental deliberations but is explained by the convenience in the examination of the UV spectra of phenyltetrazoles, since UV spectroscopy has been used in most cases for the study of the protonation of monosubstituted tetrazoles.

The basicity of 1-methyltetrazole in trifluoroacetic and nitric acids has been investigated by PMR spectroscopy, and it has been concluded that it exists in the protonated form in trifluoroacetic acid, although the basicity constant is not presented [47]. In the study of the protonation of 1-methyltetrazole in nitric acid [48] it was shown that this compound is a Hammett base and that the pK_{BH^+} value is −2.40. UV spectroscopy has been used successfully in the study of the basicities of substituted 1- and 5-phenyltetrazoles in aqueous sulfuric acid solutions [43, 49]. The absorption maxima are shifted in the electronic spectra of 1- and 5-phenyltetrazoles as the sulfuric acid concentration changes. The absence of an isobestic point in the spectra is a consequence of this. It is assumed that these phenomena are associated with the effect of the medium on the unprotonated and protonated forms of the base. Neglect of the effect of the medium during the treatment of the experimental data may lead to erroneous conclusions regarding the nature of the investigated compounds. Many researchers have frequently directed their attention to the importance of this stage in the study of the basicities of weak organic bases [29, 50]. A number of methods [28] that are recommended for use in the treatment of experimental data obtained by UV and PMR spectroscopy are presently known. The accuracy of the calculation of the ionization ratios and, in the final analysis, the solution of the problem of the affiliation of an investigated compound with a definite type of weak base depend on the choice of the method of treatment. Unfortunately, many cases in which completely different results were obtained for the same compounds, depending on the method of treatment of the experimental data, are known. It should be noted that the Stewart–Grenger method [51] was used as the most reliable method for the treatment of the data obtained in the study of the basicities of substituted 1- and 5-phenyltetrazoles. According to the available data, 1- and 5-phenyltetrazoles are Hammett bases, the pK_{BH^+} values of which range from −3.18 to −3.99 and −1.88 to −3.88 H_0

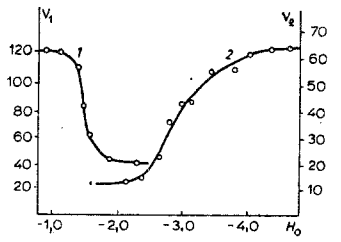


Fig. 3

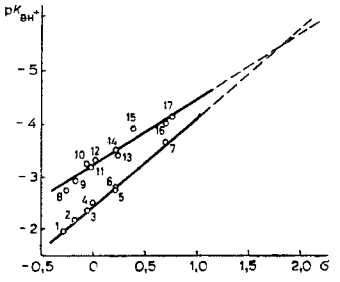


Fig. 4

Fig. 3. Dependence of the molar coefficients of scattering (V_1 and V_2) of tetrazole on H_0: 1) ν_1 1259 cm^{-1}; 2) ν_2 1310 cm^{-1}.

Fig. 4. Dependence of the pK_{BH^+} values of 1-methyl-5-(R-phenyl)tetrazoles (1-7) and 2-methyl-5-(R-phenyl)tetrazoles (8-17) on the σ substituent constants: 1) R = p-OCH_3; 2) R = p-CH_3; 3) R = m-CH_3; 4) R = H; 5) R = p-Cl; 6) R = p-Br; 7) R = m-NO_2; 8) R = p-OCH_3; 9) R = p-CH_3; 10) R = m-CH_3; 11) R = o-CH_3; 12) R = H; 13) R = p-Cl; 14) R = p-Br; 15) R = m-Br; 16) R = m-NO_2; 17) R = p-NO_2.

units, respectively. The basicities of some 5-phenyltetrazoles were also studied in perchloric acid [49]. It is interesting that the pK_{BH^+} values for 5-phenyl- and 5-(p-chlorophenyl)tetrazoles in sulfuric and perchloric acids are identical. At the same time, 5-(p-nitrophenyl)tetrazole is a somewhat weaker base in sulfuric acid than in perchloric acid: The pK_{BH^+} values are -3.88 and -3.40, respectively. The basicities of 5-phenyltetrazole in sulfuric acid at 25 and 60°C differ only slightly [49].

As in the case of disubstituted tetrazoles, the results of a correlation analysis of the basicity constants of these compounds as a function of the substituent constants were used for the determination of the site of addition of a proton in substituted 1- and 5-phenyltetrazoles. The validity of this approach is confirmed by the existence of a correlation between the effective charges on the nitrogen atoms in the 1 and 4 positions of the ring and the σ_p substituent constants for 1,5- and 2,5-disubstituted tetrazoles [40]. In fact, a good correlation between the pK_{BH^+} values and the σ^H substituent constants is observed for substituted 1-phenyltetrazoles:

$$pK_{BH^+} = -(0.85 \pm 0.05)\sigma^H - (3.59 \pm 0.05),$$

$$r = 0.96,\ n = 6,\ s = 0.09.$$

Since the electronic effects of the substituents in 1-substituted tetrazoles [23] are transmitted primarily in one direction, viz., from the N_1 atom to the N_4 atom through the N_2 and N_3 atoms, the correlation means that the site of addition of the proton is the nitrogen atom in the 4 position of the ring.

The basicity constants for substituted 5-phenyltetrazoles [49] correlate with the σ substituent constants:

$$pK_{BH^+} = -(1.80 \pm 0.03)\sigma - (2.24 \pm 0.03),$$

$$r = 0.98,\ n = 8,\ s = 0.15.$$

However, the interpretation of these data is fraught with certain difficulties, since the electronic effects of the substituents in 5-substituted tetrazoles [23] are transmitted via two pathways, viz., from the C atoms to the N_2 atom through the N_1 atom and from the C atom to the N_3 atom through the N_4 atom. Thus, on the basis of only the correlation of the pK_{BH^+} values with the σ substituent constants, one cannot unambiguously determine the site of addition of the proton in the tetrazole system. Nevertheless, considering the data obtained during a study of the protonation of tetrazole [43, 45] and 1-substituted tetrazoles [43], it may be assumed that the reaction center in the protonation of 5-phenyltetrazoles in the nitrogen atom in the 4 position of the ring.

As compared with monosubstituted tetrazoles, little study has been devoted to the basicities of disubstituted tetrazoles. The available data are in good agreement with the results obtained for tetrazole and monosubstituted derivatives. Only cylomethylenetetrazoles [52], for which very high basicity constants were found, regardless of the number of methylene links in the ring, were found, constitute an exception: The pK_{BH^+} values range from 1.74 to 1.81. It might be assumed that the pK_{BH^+} values obtained for these compounds pertain to one of the types of equilibria associated with the formation of ion pairs rather than to the protolytic

equilibrium. This assumption is not without foundation, since the protonation of cyclomethylenetetrazoles has been studied in formic acid by a conductometric method.

The basicities of 1,5- and 2,5-disubstituted tetrazoles [24, 43, 53, 54] in sulfuric acid have been studied by UV and PMR spectroscopy. The reaction series were selected in such a way that the change in the basicities of the investigated compounds could be followed as a function of the electronic properties and the position of the substituent in the ring and the site of addition of the proton in the tetrazole system could be determined. Substituted 1-phenyl-5-methyltetrazoles, as well as isomeric 1- and 2-methyl-5-phenyltetrazoles, are included in these reaction series. Data on the site of addition of the proton in substituted tetrazoles were obtained during a study of the basicities of these compounds. The protonation of 1-phenyl-5-methyltetrazoles in sulfuric acid is described by the Hammet acidity function. The basicity constants of these compounds correlate with the σ_I substituent constants:

$$pK_{BH^+} = -(1.17 \pm 0.08)\sigma_I - (1.96 \pm 0.07),$$

$$r = 0.95,\ n = 7,\ s = 0.11$$

It follows from this that the site of addition of the proton in 1-phenyl-5-methyltetrazoles is the nitrogen atom in the 4 position of the ring. It was noted above that the direction of protonation of tetrazoles possibly depends on the position of the substituent in the tetrazole ring. Valuable information in this respect was obtained during a study of the basicities of isomeric 1- and 2-methyl-5-phenyltetrazoles in sulfuric acid [24, 54]. It is apparent that the site of addition of the proton in isomeric 1- and 2-substituted tetrazoles should be determined by the electronic structure of the substrate. It has been demonstrated by means of quantum-chemical calculations by a semiempirical variant of the self-consistent-field (SCF) MO LCAO method within the Pariser–Parr–Pople (PPP) approximation that the greatest electron density in 1- and 2-methyltetrazoles is observed on the nitrogen atoms in the 1 and 4 positions of the ring [24, 40]. On the basis of this it might be assumed that the addition of a proton takes place at the same reaction center in the protonation of 1- and 2-substituted tetrazoles.

In fact, 1- and 2-methyl-5-phenyltetrazoles are Hammett bases. The pK_{BH^+} values of these compounds correlate with the σ substituent constants (Fig. 4):

$$pK_{BH^+} = -(1.63 \pm 0.06)\sigma - (2.43 \pm 0.02),$$

$$r = 0.99,\ n = 7,\ s = 0.05$$

and

$$pK_{BH^+} = -(1.25 \pm 0.11)\sigma - (3.19 \pm 0.04),$$

$$r = 0.97,\ n = 10,\ s = 0.11.$$

From a comparison of the reaction constants for 1-methyl-5-phenyltetrazoles and 5-phenyltetrazoles [49] it may be concluded that all of the compounds of the indicated reaction series are protonated at the nitrogen atom in the 4 position of the ring. At the same time, the reaction constants for 1- and 2-methyl-5-phenyltetrazoles differ. However, the certain decrease in the ρ value for the 2-substituted derivatives is associated with the peculiarities of the change in the indexes of the bonds in these compounds as compared with their 1-substituted analogs [24]. Consequently, the center of protonation in 2-methyl-5-phenyltetrazoles is the nitrogen atom in the 4 position of the ring. Lippman and co-workers [55] arrived at the same conclusion during a study of the PMR spectra of some protonated 2-substituted tetrazoles.

One's attention is drawn to the fact that 1-methyl-5-phenyltetrazoles are stronger bases than the isomeric 2-substituted derivatives over the investigated range of changes in the electronic properties of the substituents. At the same time, it follows from the presented correlations of the pK_{BH^+} values with the σ values that inversion of the basicities for the indicated reaction series should be observed as the electron-acceptor properties of the substituents in the phenyl ring become stronger. The σ_{inv} value can be calculated from the expression

$$\sigma_{inv} = \frac{pK_{BH^+}{}^1 - pK_{BH^+}{}^2}{\rho_1 - \rho_2},$$

where $pK_{BH^+}{}^1$ and $pK_{BH^+}{}^2$ are the basicity constants of 1- and 2-methyl-5- phenyltetrazoles, and ρ_1 and ρ_2 are the reaction constants for the investigated reaction series.

The protonation of substituted 1,5-diphenyltetrazoles is described by the H_0 acidity function; this follows from a detailed analysis of the dependence of the ionization ratios I on H_0 for all of the investigated

compounds of this series [43]. The pK_{BH^+} values of 1,5-diphenyltetrazoles lie in a relatively narrow interval (−2 to −4 H_0 units), particularly if one takes into account the broad range of the change in the electronic constants of the substituents, and correlate with the σ substituent constants, probably because of conjugation between the phenyl rings:

$$pK_{BH^+} = -(1.20 \pm 0.15)\sigma - (2.74 \pm 0.07),$$

$$r = 0.97,\ n = 7,\ s = 0.13.$$

The low value of the reaction constant ($\rho = -1.20$) constitutes evidence for the considerable distance of the substituent from the protonation center. The same principle is also observed for 1-phenyltetrazoles and 1-phenyl-5-methyltetrazoles, in which the site of addition of the proton is the nitrogen atom in the 4 position of the ring. However, the reaction constant increases to 1.80 as the substituent moves closer to the reaction center, as in the protonation of substituted 5-phenyltetrazoles [49].

Thus, on the basis of the available data it may be assumed that the protonation center in substituted 1,5-diphenyltetrazoles is the nitrogen atom in the 4 position of the ring. It should be noted that the basicity constants of mesoionic 2,3-diaryl-2H-tetrazolyl-5-thiolates [56] range from 1.12 to −2.05 H_0 units.

The considerable amount of available experimental data from the study of the basicities of tetrazoles makes it possible to form a judgment regarding several principles of the behavior of these compounds in solutions of acids. All of the investigated tetrazoles are undoubtedly Hammett bases. Despite the wide variation in the electronic properties of the substituents in tetrazoles, the maximum change in the basicity constants is only two orders of magnitude. The protonation center in tetrazole and substituted tetrazoles, regardless of the nature and position of the substituent in the ring, is the nitrogen atom in the 4 position of the ring, and this constitutes evidence for the stability of the tetrazole structure. These data are confirmed by quantum-chemical calculations of tetrazole and some substituted tetrazoles. Thus, the distribution of the electron density in 5-substituted tetrazoles is only slightly dependent on the electronic properties of the substituent attached to the ring carbon atom [40]. At the same time, a considerable decrease in the electron density on the ring nitrogen atoms occurs in the protonation of tetrazole, in which the proton adds to the N_4 atom (Fig. 2). This is evidently the reason for the fact that protonation has an appreciable effect on some properties of tetrazole, including the spectral characteristics. Thus, as we have already noted, the chemical shift of the C−H proton and the frequencies and intensities of the lines in the vibrational spectra change as a result of protonation. This makes it possible to determine the basicity constants of tetrazole and 1-methyltetrazole by PMR and Raman spectroscopy [43, 45, 48]. Finally, it should be noted that protonation of tetrazole and its derivatives [40] in the 4 position has little effect on the indexes of the multiplicity of the bonds, particularly the N_1-N_2 bond.

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