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EQUILIBRIUM NH ACIDITY OF NITROGEN HETEROCYCLES

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The equilibrium acidity of the NH bonds of compounds is of theoretical and practical significance but has been investigated little [1]. Nitrogen heterocycles have been investigated little in this respect, and the pK_a values in water have only been obtained for a few of them [2, 3]. However, these values do not always correctly characterize the true acidity of the compounds (i.e., the acidity due to the internal structure) on account of the superimposition of the effects of specific solvation of the acids and the conjugate bases. A more reliable idea of the true acidity is given by the pK values determined in an aprotic polar solvent (DMSO). Scales of pK values as applied to many CH and OH acids with various structures in DMSO have already been established [4-8]. However, measurements of NH acidity in this solvent have been limited mainly to derivatives of aniline containing an electronegative group [COOR, C(O)R, etc.] at the nitrogen atom [9-11]. We therefore considered it expedient to determine the pK values in DMSO for a series of nitrogen heterocycles and some of their derivatives belonging to the NH-acid type, in which considerable variation in acidity can be achieved without the addition of acidifying groups at the nitrogen atom.

The equilibrium NH acidity of the heterocycles was studied by a transmetallation method [4], based on the spectrophotometric determination of the equilibrium constants (K_{eq}) for the reactions of the NH acids with potassium-substituted CH acids (indicators), the pK values of which are known. The investigated compounds, the employed CH indicators, the K_{eq} values, and the pK values referred to 9-phenylfluorene as standard CH acid (pK 18.5) are given in Table 1.

From comparison of the obtained data with published pK_a values (Table 2) it is seen that the equilibrium NH acidity of the heterocycles is higher in water than in DMSO. (This conclusion still holds if our results are referred to Bordwell's absolute scale [5], i.e., if the pK_{DMSO} values are reduced by 0.6-1.2 logarithmic units). The increase in acidity differs and is more significant for pyrrole, pyrazole, and imidazole than for the corresponding benzo derivatives (cf. ΔpK_1 in Table 2). This results in a tendency for the strength of the NH acids to level out in water compared with DMSO and, in some cases, even a reversal in the order of acidity (e.g., see carbazole and pyrazole).

The most likely reason for the differences in the pK_a and pK_{DMSO} values is stabilization of the N-anions in water on account of the formation of hydrogen bonds with the solvent. The degree of this specific solvation and its stabilizing effect must in all probability weaken with decrease in the true protophilicity of the N-anion, and for this reason replacement of the solvent has a more significant effect on the acidity of monocyclic NH acids than on the acidity of their benzo derivatives (cf. also indole and carbazole).

Other effects can make a specific contribution to the differentiation between the strength of the investigated NH acids. Thus, the formation of H bonds between the heterocycle and the solvent can lead to a decrease in the strength of the NH acids in DMSO, which is more protophilic than water [5]. The lower polarity of DMSO has a similar effect. On the

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TABLE 1. Equilibrium NH Acidity of Nitrogen Heterocycles in DMSO at 298°K

№	Compound	Indicator (pK)[a]	K_{eq}[b]	pK[c]
I	Pyrrole	Fluorene	0,41±0,03 (4)	23,3
II	Phenothiazine	The same	1,4±0,4 (5)	22,8
III	3,5-Dimethylpyrazole	9-Benzylfluorene (21.8)	0,58±0,13 (6)	22,0
IV	Indole	The same	2,9±0,6 (6)	21,3
V	Pyrazole	2-Cyanofluorene (18.9)	0,031±0,001 (3) 0,017±0,001 (3)	20,4
VI	2-Methylimidazole	9-Phenylfluorene (18.5)	0,04±0,01 (3)	19,9
VII	Carbazole	" "	0,08±0,02 (6)	19,6
VIII	3,5-Dimethyl-4-chloropyrazole	" "	0,30±0,04 (3)	19,0
IX	Imidazole	" "	0,39±0,06 (5)	18,9
X	Indazole	" "	0,47±0,03 (6)	18,8
XI	2-Phenylimidazole	" "	3,2±0,2 (3)	18,1
XII	4-Bromopyrazole	" "	32±3 (3)	17,0
XIII	Benzimidazole	Diphenylacetonitrile (18.3)	29±2 (3)	16,8
XIV	2-Phenylbenzimidazole	Ethyl p-nitrophenylacetate (15,1)	0,084±0,006 (3)	16,2
XV	1,2,4-Triazole	The same	0,53±0,05 (4)	15,4
XVI	Benzotriazole	p-Nitrophenylacetonitrile (13,1)	3,2±0,1 (6)	12,6
XVII	2-Phenyl-4,5-dibromoimidazole	9-Methoxycarbonylfluorene (11,5)	2,9±0,2 (3)	11,0
XVIII	2,4,5-Tribromoimidazole	9-Cyanofluorene (9,6)	57±4 (6)	7,8

[a] The pK values of the indicators were taken from [4, 6]. [b] The number of determinations is given in parentheses. [c] $pK = pK_{indicator} - \log K_{eq}$; a statistical correction was not made.

other hand, the lower solvation energy of the proton [5] and also specific interaction between the proton-donating solvent and the heterocycles capable of behaving as bases should help to reduce the acidity in water. In view of the possibility of mutual compensation of the above-mentioned effects it must be supposed that the differentiating action of the medium on the equilibrium NH acidity of the heterocycles is largely due to specific solvation of their anions in water. This is favored indirectly by the similarity between the above-mentioned relationships of differentiation and those observed with replacement of the DMSO by a weakly polar aprotic solvent such as 1,2-dimethoxyethane (DME).

The pK values for the series of heterocycles measured in DME by the transmetallation method (with Li^+ as counterion) in relation to the same standard are given in Table 2. From comparison of the pK_{DMSO} and pK_{DME} values it follows that the relative acidity of the investigated compounds is higher in DME than in DMSO. Here, as in aqueous solution, the same tendency for the NH acidity to level out is observed in DME. In particular, the difference in the acidity of imidazole and pyrazole is small, and the latter was a stronger NH acid than carbazole. At the same time it is well known that the main role in the increase of the relative strength of the CH and NH acids with replacement of DMSO by DME is played by interionic interaction [4, 9, 12], which (like specific solvation) stabilizes the anion in a weakly polar medium.

Owing to the absence of additional stabilization of the N-anions in DMSO the pK scale in this solvent is more differentiated than in water or DME and more correctly reflects the dependence of the acidity of the heterocycles on the structure of molecules. We will consider the obtained results in this respect (Table 1).

The weakest NH acid in the series of investigated compounds is pyrrole. With the introduction of one and then two more nitrogen atoms into the molecule of this heterocycle the acidity of the imino group increases appreciably [cf. compound I with V, IX, XV], and the electron-withdrawing effect of the aza group at position 2 is weaker than that at position 3; the pK value of pyrazole is 1.5 logarithmic units higher than that of imidazole. It is interesting to note that the energy for the removal of the proton of the imino group in pyrazole, calculated by the CNDO/2 method, is 0.1 eV (2.3 kcal/mole) higher than the analogous value for imidazole, and this agrees well with the experimental result (1.5 pK units are equivalent to 2 kcal/mole). Although such good agreement must be regarded as accidental

TABLE 2. Effect of the Medium on the Equilibrium NH Acidity of Heterocycles[a]

№	Compound	pK_a	pK_{DMSO}	ΔpK_1[b]	pK_{DME}[c]	ΔpK_2[b]
I	Pyrrole	17,5	23,3	5,8	18,2	5,1
IV	Indole	17,0	21,3	4,3	16,7	4,6
VII	Carbazole	16,7	19,6	2,9	15,3	4,3
V	Pyrazole	14,2	20,4	6,2	12,9	7,5
X	Indazole	13,8	18,8	5,0	—	—
IX	Imidazole	14,2	18,9	4,7	13,2	5,7
XIII	Benzimidazole	12,9	16,8	3,9	—	—

[a] Acidity in water (pK_a) according to published data [3], acidity in DMSO (pK_{DMSO}) and in 1,2-dimethoxyethane (pK_{DME}). [b] $\Delta pK_1 = pK_{DMSO} - pK_a$; $\Delta pK_2 = pK_{DMSO} - pK_{DME}$. [c] The pK_{DME} values were calculated on the basis of the following experimental data (compound No., indicator, and average K_{eq} value): (I) 2-cyanofluorene (pK 18.3 [4]), 1.3; (IV) diphenylacetonitrile (pK 16.2 [4]), 0.30; (V), (VII), (IX) ethyl p-nitrophenylacetate (pK 13.1 [6]), 0.006, 1.6, and 0.75 respectively.

owing to the approximate nature of the calculations, based on a series of assumptions about the geometric parameters of the N-anions, it nevertheless indicates that in this case there are no discrepancies between theory and experiment.

Successive annellation of the pyrrole ring with one and two benzene rings is accompanied by an increase in NH acidity [cf. compound I with IV, VIII]. On the average the contribution from this structural effect amounts to 2 pK units, as shown by the good linear relation between the pK values of compounds I, IV, V, IX, XI (pK') and those of their benzene derivatives IV, VII, X, XIII, XIV (pK") respectively:

$$pK'' = 1.01pK' - 2.1;\ S = 0.25;\ r = 0.995.$$

On the basis of this equation and the pK value of compound XVI it is possible to determine the acidity of 1,2,3-triazole in DMSO approximately (pK $\sim$ 14.7).

The increase in the stability of the N-anions during annellation of the benzene ring with the heterocycle is in all probability due to an increase in the degree of p,π-conjugation between the heteroatom and the aromatic hydrocarbon fragment. It is clearly the weakening of the conjugation resulting from disruption in the coplanarity of the molecule which gives rise to the decrease in the equilibrium NH acidity (by 5.5 pK units) in the transition from carbazole to diphenylamine (pK in DMSO 25.1 [9]). This probably also gives rise to the lower acidity of phenothiazine (II) compared with carbazole, since the introduction of a sulfur atom into the five-membered ring in itself helps to increase the NH acidity, if this change in structure is not due to the appearance of additional steric hindrances to p,π-conjugation (e.g., the acidity of indoline is 1.7 pK units lower than the acidity of 3,4-dihydro-2H-benzo-1,4-thiazine [13]). It can be seen, however, that the role of conjugation in the stabilization of the N-anions is not so significant as in the case of carbanions. Thus, the difference between the pK values of diphenylmethane and fluorene amounts to 9.6-10 pK units [5], and this is almost twice the corresponding difference for their NH analogs (5.5 pK units).

The equilibrium NH acidity of imidazole and its derivatives VI, XI, XVII, XVIII is described very well by a linear relation between the pK values and the sums of the σ_m constants of the substituents, irrespective of the positions which they occupy in the heterocycle:

$$pK = 18.9 - 9.5\Sigma\sigma_m;\ S = 0.25;\ r = 0.9991.$$

An analogous relationship was found as applied to the acidity of the pyrazoles III, V, VIII, XII:

$$pK = 20.6 - 8.8\Sigma\sigma_m;\ S = 0.4;\ r = 0.987.$$

Since there are no π-acceptor groups apart from the phenyl among the investigated substituents, it is difficult to judge to what extent the obtained relationships are general. However, we note that they are consistent with the conclusion of Charton [14], who demonstrated that the basicity of substituted 1-methylimidazoles (i.e., the acidity of positively charged NH acids) in water corresponds best to correlation of the pK_α values with the σ_m constants of the most varied substituents situated at positions 2, 4, and 5 of the heterocycle.

EXPERIMENTAL

The pK values of the heterocycles were determined for dilute solutions ($\leqslant 10^{-3}$ M) prepared in thoroughly dried DMSO and DME in fully sealed evacuated apparatus [4]. The spectrophotometric measurements were made on an SF-4A instrument. The investigated compounds were partly ready-made reagents purified by sublimation (III, mp 102-104°C; VI, 138-139°C) or by recrystallization from petroleum ether (IV, 51-52°C), benzene (IX, 87°C; XVI, 284-286°C), or alcohol (XIII, 168-170°C). The other compounds except pyrrole were synthesized by known methods: Phenothiazine (II, 181-182°C) was obtained by the reaction of diphenylamine with sulfur [15]. Pyrazole (IV, 68-70°C) was obtained by condensation of 1,1,3,3-tetraethoxypropane with hydrazine hydrate [16]. Carbazole (VII, 235-237°C) was obtained by dehydrogenation of tetrahydrocarbazole with chloranil [17]. 3,5-Dimethyl-4-chloropyrazole (VIII, 116-117°C) was obtained by chlorination of 3,5-dimethylpyrazole [18]. Indazole (X, 139-140°C) was obtained from anthranilic acid [19]. 2-Phenylimidazole (XI, 144-145°C) was obtained by decarboxylation of 2-phenylimidazole-4,5-dicarboxylic acid [20]. 4-Bromopyrazole (XII, 92-93°C) was obtained by bromination of pyrazole [21]. 2-Phenylbenzimidazole (XIV, 284-286°C) was obtained by cyclization of N-benzoyl-o-phenylenediamine [22]. 2-Phenyl-4,5-dibromoimidazole (XVII, 140°C) was obtained by bromination of 2-phenylimidazole [23]. 1,2,4-Triazole (XV, 118-120°C) was obtained by deamination of 4-amino-1,2,4-triazole [24]. 2,4,5-Tribromoimidazole (XVIII, 213-215°C) was obtained by bromination of imidazole [25]. The synthesized compounds were purified by recrystallization from alcohol (II, VII, XI, XIII, XIV), water (V, VIII, XII, XVIII), benzene (XV, XVII), and petroleum ether (X), and compounds VII and XI were first sublimed. The melting points of the purified compounds agreed with the published data within 1-2°C. The pyrrole (I) (bp 130-132°C at 760 mm Hg) was obtained from B. A. Trofimov (Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR), to whom the authors convey their sincere gratitude.

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PROTONATION OF DERIVATIVES OF PYRROLO(1,2-a)PYRAZINE AND PYRROLO(1,2-a)-PYRIMIDINE

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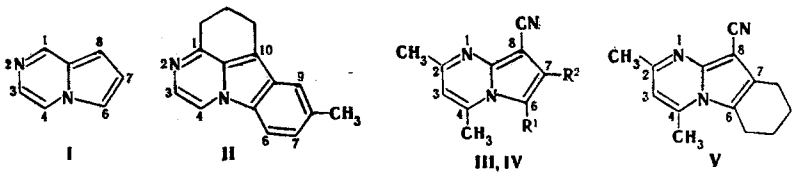
Study of the protonation of derivatives of 5- and 7-azaindoles [1, 2] has shown that the structure of the monocations of these compounds corresponds to a significant contribution of the quinonoid structure with transfer of the positive charge from the cation center – the nitrogen atom of the pyridine fragment, $N_{(5)}$ and $N_{(7)}$ respectively – to the pyrrole nitrogen atom $N_{(1)}$. Earlier [3] the predominance (~ 90%) of the para-quinonoid structure with transfer of the positive charge from the exocyclic amino group to the 4-aminopyridine cation has been established. The results of subsequent studies of the structure of the mono- and dications of the imidazo(4,5-b)pyrazines [4] compared with the results for the protonation of purine [5] suggested that the perturbation of the cation aromatic system, linked with delocalization of the positive charge, makes a considerable contribution to the stabilization energy of the protonated forms and to a significant degree determines the position of the mono-protonation center in polybasic heteroaromatic systems. From this point of view data relating to the structure of the protonated forms of ambi- and polydentate bases of the indolizine type and its aza analogs are of special interest.

We have studied the protonation of pyrrolo(1,2-a)pyrazine (I), 1,10-trimethylene-8-methylpyrazino(1,2-a)indole (II) and the 2,4-dimethyl-8-cyanopyrrolo(1,2-a)pyrimidines (III-V). Previously it has been established [6] that in CF_3COOH protonation of derivatives of pyrrole(1,2-a)pyrimidine, structurally analogous to compounds III-V, but not carrying sub-



I II III, IV V

III $R^1=R^2=CH_3$; IV $R^1=CH_3$, $R^2=C_2H_5$

stituents at $C_{(8)}$, occurs exclusively at $C_{(6)}$. The formation of cations, corresponding to proton addition to the carbon atom of the pyrrole ring in the α- and β'-positions to the bridgehead nitrogen, was also discovered when derivatives of pyrrolo(1,2-a)pyridazine were protonated under similar conditions [7, 8]; at the same time it was shown that only the α-form of the conjugate acid is thermodynamically stable in solution [8]. Moreover it is known that in a series of aza analogs of indolizine, containing a nitrogen atom of the "pyridine" type in the five-membered ring, N-protonation is always observed [9, 10]. These results suggest three possible structures of the conjugate acid of pyrrolo(1,2-a)pyrazine (I):

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