ELECTROCHEMICAL STUDY OF ACID-BASE PROPERTIES OF SOME 2,5-DIHYDRO-1,3,4-THIADIAZOLES IN AQUEOUS-ETHANOLIC SOLUTIONS*

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The dissociation constants K_a for spherically crowded 2′- and 2,5-substituted thiadiazolines and their protonated forms in 45% (v/v) aqueous-ethanolic solutions (ionic strength m = 0.1) were determined using the pH-metric method. All the thiadiazoles are weak bases. Some of them showed also weak acidic properties. The formation enthalpies have been calculated using the MNDO method. On the basis of the obtained results the mechanism of the protonation process is discussed.

Key words: Acidity; Basicity; Thiadiazoles; Dissociation constant; Substituent effect; Semiempirical calculations.

Compounds 2,5-dihydro-1,3,4-thiadiazoles (Δ^3-1,3,4-thiadiazolines) easily accessible as the products of [2+3] cycloaddition of diazomethane and its derivatives to thiocarbonyl compounds, represent a relatively little known class of five-membered sulfur–nitrogen heterocycles, which have recently found numerous important applications in the synthesis of sulfur-containing heterocycles[1]. The stability of thiadiazoles is known to depend greatly on the type and the position of substituents in the ring. Bulky alkyl substituents stabilize thiadiazole ring and enable their isolation as crystalline, analytically pure substances[2].

Under elevated temperature conditions 1,3,4-thiadiazoles extrude nitrogen and as reactive intermediates appear thiocarbonyl ylides which are recognized to be highly reactive sulfur-centred 1,3-dipoles[3]. According to Mloston and Huisgen 1,3,4-thiadiazole

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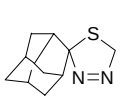
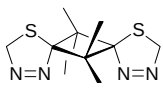
ring easily undergoes deprotonation at carbon atom C2 in the presence of bases and the generated carbanion is in equilibrium with a ring-opened form[4].

There are many papers concerning thermally or photochemically mediated conversions of thiadiazoles but to our knowledge no data are available on their acid-base properties. This aspect of thiadiazoles chemistry seems to be very crucial in explanation of their behaviour in polar solvents and on the electrode surface[5,6].

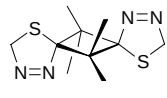
In the present work we describe the determination of protonation constants obtained in series of various substituted thiadiazoles **1a–1e**. The determination was carried out in aqueous-ethanolic solutions with ionic strength $m = 0.1$, using a potentiometric method. The semiempirical calculations were performed to determine the preferred site of protonation of thiadiazoles.

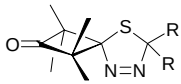


1a



cis/trans **1b**





1c-1e

1	R
c	H
d	CH_3
e	$(CH_3)_3C$

Unlike compounds **1a–1c** which contain two hydrogen atoms in the heterocyclic ring, thiadiazoles **1d** and **1e** are much more crowded having two methyl or two *tert*-butyl substituents at C2 carbon atom.

EXPERIMENTAL

2,5-Dihydro-1,3,4-thiadiazoles **1a–1d** were synthesized from corresponding thioketones by treatment with diazomethane (**1a**, **1b**), 2-diazopropane (**1c**) or di(*tert*-butyl)diazomethane (**1d**) and purified using previously described methods: Spiro[adamantane-2,2′-(2,5-dihydro-1,3,4-thiadiazole)] (**1a**, ref.[7]), 6,6,12,12-tetramethyl-4,11-dithia-1,2,8,9-tetraazadispiro[4.1.4.1]dodeca-1,8-diene (**1b**, ref.[8]), 1,1,3,3-tetramethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**1c**, ref.[9]), 1,1,3,3,7,7-hexamethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**1d**, ref.[10]), and 7,7-di(*tert*-butyl)-1,1,3,3-tetramethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**1e**, ref.[11]). Thiadiazole **1a** was isolated as an inseparable mixture of *cis* and *trans* isomers (*cis*/*trans* ratio is about 90 : 10). The structures of the isolated compounds were confirmed by spectroscopic methods. The stock solutions were prepared by dissolving the thiadiazoles in triply distilled water and ethanol 45% (v/v).

Standard solutions of HNO_3 and NaOH carbonate-free were prepared and standardized as recommended in ref.[12]. Solution of 0.1 M KNO_3 was used to control ionic strength. All reagents were analytically pure products of POCh-Gliwice.

Measurements of pH were carried out with Mera Elwro N-512 pH-meter and combined glass electrode type OP-08708P with accuracy of 0.01 pH units. The pH-meter was standardized against aqueous buffers POCh-Gliwice. The requisite readings were corrected for solvent contents using the relation $pH = pH^* - \delta$, where pH^* represents a pH-meter reading and δ is the correction factor for hydrogen ion concentration in the water–ethanol mixture used for measurement[13,14].

All experiments were carried out at the temperature of 277 ± 0.1 K. The solutions were deaerated by oxygen-free argon and titrations were performed under argon atmosphere.

RESULTS AND DISCUSSION

The potentiometric titrations of 2,5-dihydro-1,3,4-thiadiazoles (Th) in aqueous-ethanolic 45% (v/v) solutions containing c of Th and $3c$ of HNO_3 (where c is the concentration of each component within the range of 10^{-3}–10^{-4} mol l^{-1}) with ionic strength m = 0.1 were carried out with 0.1 M NaOH solution. The mixed water–ethanol solvent was used due to the insolubility of the thiadiazoles in pure water. Typical titration curves are presented in Fig. 1.

As can be seen from the Fig. 1 the potentiometric curves show three (**1a**, **1c**, **1d** and **1e**) and four (**1b**) acid-base equilibria. First, second and in the case of **1b**, **1d** and **1e** third end-point in titration curves correspond to the neutralization of acid added, free and bounded to thiadiazole. This indicates that protons are consumed by the thiadiazole. Therefore the acid-base equilibria correspond to the protonation of thiadiazoles. The next equilibria at the pH higher than pH of the supporting electrolyte are probably associated with the deprotonation of the thiadiazole molecules.

Dissociation constants were calculated numerically using PKAS (ref.[15]) and MINIGLASS (ref.[16]) algorithms. The calculation was performed according to the following scheme:

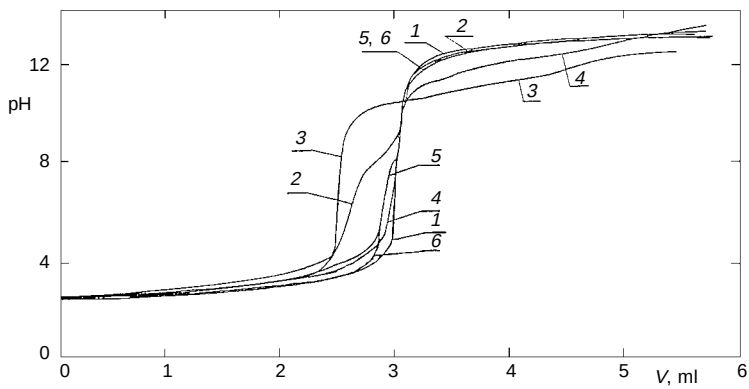


FIG. 1

Titration curves of 50 ml aqueous-ethanolic solutions of 5.2 . 10^{-3} M HNO_3 (*1*) and + 1.9 . 10^{-3} M Th: *2* Th = **1a**, *3* Th = **1b**, *4* Th = **1c**, *5* Th = **1d** and *6* Th = **1e** with 0.0902 M NaOH solution, T = 277 K, m = 0.1 (0.1 M KNO_3)

First, the logarithms of protonation constants are evaluated on the basis of pH for half values of $\bar{n}$, where $\bar{n}$ is the average number of bonded protons. This set of protonation constants is used for calculation of pH_i^{cal}, $S_i = (pH_i^{cal} - pH_i^{exp})$ and S_i^2, at each of the experimental points. The calculations are based on the Newton–Raphson method, using the iteration equation

$$\ln ([H^+]_{a+1}) = \ln ([H^+]_n) \exp\left(- \frac{F_n}{\partial F_n / \partial \ln ([H^+]_n)} \right), \qquad (1)$$

where

$$F_n = \frac{\sum_{i=1}^{N} (i[H^+]_n^i K_i)}{1 + \sum_{i=1}^{N} ([H^+]_n^i K_i)} - \frac{(N-a)C_{H_NL} - [H^+]_n + [OH^-]_n}{C_{H_NL}} . \qquad (2)$$

N is the number of protonation constants, C_{H_NL} is concentration of the acid, a is a fraction titrated at each point, K_i are total protonation constants, n is a number of steps in the iteration cycle.

In the next step, the values of S_i^2 obtained for all curve points are summed. The result, which is the measure of the calculated curve fitting to the experimental one, is the criterion for breaking calculations. The S_i values for each experimental curve segment are summed and, according to Motekajtis and Martell[15] suggestion, the average values are used as corrections to protonation constants. The corrected values of the constants are next used for evaluation of the new calculated curve. This procedure is repeated until the assumed convergence between the curves is reached.

Values of the dissociation constants were determined for two identical samples of each compound for 20 points on titration curves for each titration interval. An average square error of measurements did not exceed 0.02 pH unit. The pK_a values of the dissociation constants are given in Table I.

The pK_a values have a conditional character because in a mixed water–organic solvent the change in the value of dielectric constant and in the solvating ability can influence the acidity of an acid BH^+ or the basicity of a base B according to the solvent composition[13,14,17,18]. It is known that pK_a values increase with increasing content of organic solvent[19].

The program MOPAC ver. 6.00 (ref.[20]), using the MNDO semiempirical method, was used to carry out theoretical calculations. In order to establish the mechanism of protonation process, we calculated enthalpies of formation of compounds **1a–1e** and the corresponding single-protonated systems. In Tables II–VI heat of formation and protonation enthalpies for investigated compounds are given.

TABLE I

Values of dissociation constants pK_a of the thiadiazoles **1a–1e** in aqueous-ethanolic solution 45% (v/v) ethanol at m = 0.1

Compound	Potentiometry						Voltammetry		
	acid addition method				direct method				
	H_4B^{2+}	H_3B^{+}	H_2B	HB^{-}	H_2B	HB^{-}	H_4B^{2+}	H_3B^{+}	HB^{-}
1a		7.40 ± 0.02	>11					7.3	
1b	3.19 ± 0.03	3.47 ± 0.03	9.66 ± 0.02	10.16 ± 0.03	9.53 ± 0.02	10.00 ± 0.03	3.5	6.7	
1c	2.87 ± 0.03	3.45 ± 0.03	10.23 ± 0.02		10.18 ± 0.03			7.1	10.5
1d	3.24 ± 0.03	3.97 ± 0.03						5.9	
1e	<2								

The species with more than one proton bound to the investigated thiadiazoles were also calculated. However, the heats of formation of these species, except **1b**, are not energetically convenient.

The protonation reaction is as follows:

$$B + H_5O_2^+ \leftrightarrow BH^+ + 2\,H_2O \qquad (A)$$

and the total heat of reaction (*A*)

$$\Delta H_{f_{Th}} + \Delta H_{f_{H_5O_2^+}} + \Delta H_p = \Delta H_{f_{Th-H^+}} + 2\,\Delta H_{f_{H_2O}}\ , \qquad (3)$$

where *B* is investigated compound, $\Delta H_{f_{Th}}$ the enthalpy of formation of thiadiazole molecule, $\Delta H_{f_{H_5O_2^+}}$ the enthalpy of formation of hydroxonium ion (ΔH_f = 275.81 kJ mol^{-1}), ΔH_p the enthalpy of the protonation, $\Delta H_{f_{Th-H^+}}$ the enthalpy of the formation of the protonated thiadiazole molecule, $\Delta H_{f_{H_2O}}$ the enthalpy of the formation of water (ΔH_f = –254.85 kJ mol^{-1}).

We decided to use the enthalpy of the formation of proton hydrated with two water molecules which is, according to the literature[21,22], a sufficient approximation.

All the calculations were carried out for isolated systems. Hence, the obtained results do not depend on the nature of the solvent. For the same reason one cannot use directly these results for description of processes occurring in solvent. However, there is a possibility of comparing the obtained results for the same group of compounds in isolated system and transposing them into the solvent.

CONCLUSION

The data presented in Tables II–VI can be summarized as follows:

1. The positive values of the protonation enthalpy show that Brønsted conjugated bases are weak. The differences in protonation enthalpies of the investigated com-

TABLE II
The formation enthalpies and the protonation enthalpies of spiro[adamantane-2,2′-(2,5-dihydro-1,3,4-thiadiazole)] (**1a**)

Protonated atom	ΔH_f kJ mol^{-1}	ΔH_p kJ mol^{-1}
–	72.55	–
1	880.15	22.09
2	877.76	19.87
3	923.45	65.40

pounds are small. This suggests that the values of their dissociation constants could be also similar.

2. The preferred position of protonation seems to be one of the nitrogen atoms; however, in compounds **1c**, **1d** and **1e** protonation of oxygen cannot be excluded. The obtained values of ΔH_p for **1d** are 47.70 kJ mol^{-1} for N1, 37.74 kJ mol^{-1} for N2 and –54.94 kJ mol^{-1} for the oxygen. The values of the protonation enthalpy of oxygen in the carbonyl group calculated by MNDO method could be lower than the experimental values, *ca* 40 to 100 kJ mol^{-1} (ref.[22]). So, if the hypothetic acid would be dibasic, the protonation surely affects one of the nitrogen atoms (in particular N2) and the oxygen atom.

3. The enthalpies of protonation of the isomers of **1b** do not differ substantially (by *ca* 2 kJ mol^{-1}). Similarly to **1a**, the protonation takes place only on one nitrogen atom in each ring.

The comparison of the experimental by determined dissociation constants with the calculated results suggests following conclusions:

1. Dissociation constants K_{a_1} of **1a**, **1d** and **1e**, K_{a_1} and K_{a_2} of **1b** are associated with the protonation equilibrium of nitrogen atoms in thiadiazole rings.

TABLE III

The formation enthalpies and the protonation enthalpies of *cis*- and *trans*-6,6,12,12-tetramethyl-4,11-dithia-1,2,8,9-tetraazodispiro[4.1.4.1]dodeca-18-diene (**1b**)

Protonated atom	ΔH_f^{cis}, kJ mol^{-1}	ΔH_f^{trans}, kJ mol^{-1}	ΔH_f, kJ mol^{-1}	
			cis	*trans*
–	–297.32	–297.11	–	–
1	1 114.41	1 116.50	31.38	33.89
2	1 126.96	1 111.19	27.57	28.58
3	1 169.05	1 167.25	86.23	84.64
1,2	2 255.39	2 256.77	387.06	388.65
1,3	2 407.81	2 409.90	539.49	541.79
1,1′	2 234.51	2 236.56	366.18	368.44
1,2′	2 204.42	2 200.95	336.10	332.84
1,3′	2 287.02	2 285.80	418.69	417.69
2,3	2 398.52	2 397.64	530.12	529.53
2,2′	2 180.16	2 178.82	311.83	310.70
2,3′	2 253.46	2 253.46	386.73	388.86
3,3′	2 339.15	2 339.57	470.83	417.45

2. Dissociation constants K_{a_2} of **1c**, **1d** and **1e** are associated with the protonation processes on the oxygen atom in the carbonyl group, as indicated also by the voltammetric investigation of these compounds. It was found that the electrode reaction of the carbonyl group is preceded by the chemical reaction with participation of proton[23].

TABLE IV
The formation enthalpies and the protonation enthalpies of 1,1,3,3-tetramethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**1c**)

Protonated atom	ΔH_f, kJ mol^{-1}	ΔH_p, kJ mol^{-1}
–	–16.07	–
1	815.63	47.70
2	807.18	37.74
3	866.72	97.28
4	824.37	–65.65

TABLE V
The formation enthalpies and the protonation enthalpies of 1,1,3,3,7,7-hexamethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**1d**)

Protonated atom	ΔH_f, kJ mol^{-1}	ΔH_p, kJ mol^{-1}
–	–42.01	–
1	774.12	31.38
2	765.13	21.63
3	789.44	45.94
4	701.32	–42.17

TABLE VI
The formation enthalpies and the protonation enthalpies of 7,7-di-*tert*-butyl-1,1,3,3-tetramethyl-8-thia-5,6-diazaspiro[3.4]oct-5-en-2-one (**1e**)

Protonated atom	ΔH_f, kJ mol^{-1}	ΔH_p, kJ mol^{-1}
–	90.67	–
1	891.99	15.82
2	884.87	8.70
3	909.10	32.93
4	828.56	–47.61

3. The dissociation constants K_{a_2} for **1a**, K_{a_3} and K_{a_4} for **1b** and K_{a_3} for **1c** express possibly the deprotonation equilibria. Deprotonation of thiadiazoles associated with the ring-opening in solutions of bases was reported by Mloston and Huisgen[4]. This gives rise to thiol anions[4]. We have confirmed the phenomenon by voltammetric investigations of 2,5-dihydro-1,3,4-thiadiazoles (refs[5,6,24]). During the electrode reactions of compounds **1a**, **1b** and **1c** on HMDE in alkaline solutions formation of electroactive mercury salts was observed[5,6,24]. Similar behaviour of substances containing a thiol group was described in many previous papers[25–32].

To check acid properties of the thiadiazole, the aqueous-ethanolic 45% (v/v) solutions of thiadiazole in 0.1 M KNO_3 were titrated with 0.0988 M NaOH solution. The titration curves of **1b** and **1c** are presented in Fig. 2. The titration curves of compounds **1d** and **1e** do not differ from the titration curve of the supporting electrolyte. It indicates that the molecule of sterically crowded derivative **1d** and **1e** (without acidic H-atom at C2) are stable and have not shown acid properties. Also the results obtained in voltammetric experiments suggest that deprotonation of thiadiazoles takes place only with compounds having two hydrogen atoms at carbon C2 (ref.[24]). The values of dissociation constants K_a were calculated by the method reported in literature[33] and the results are summarized in Table I.

The values of dissociation constants calculated from the titration curves presented in Fig. 2 are consistent with previously determined dissociation constants of thiadiazole molecules (Table I).

In Table I, we also present the values of dissociation constants pK_a of thiadiazoles obtained by voltammetry[5,6,24]. As we can notice, all values of the dissociation constants obtained by voltammetric measurements for compounds **1a–1d** are similar and the values of dissociation constants of H_4B^{2+}, H_3B^+, H_2B and HB^- forms of compound **1b** obtained by potentiometric method are also very close each to other. It is in agreement

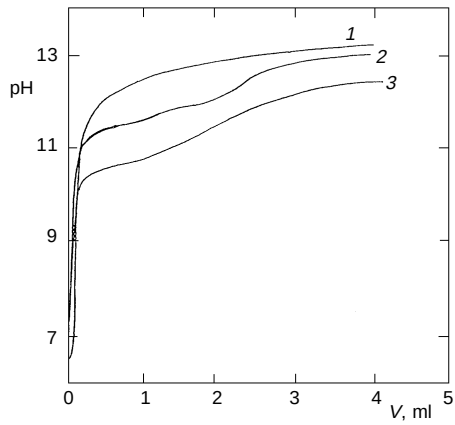
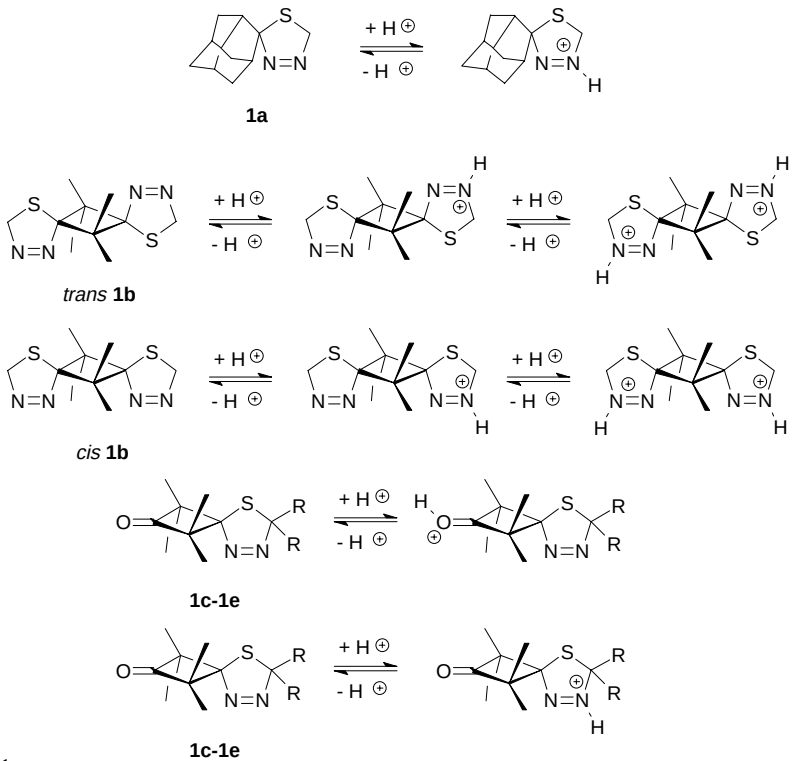


FIG. 2
Titration curves of 50 ml 2.0 M KNO_3 aqueous-ethanolic solutions (*1*) + 2 . 10^{-3} M Th: *2* Th = **1b** and *3* Th = **1c** with 0.0902 M NaOH solution, T = 277 K, m = 0.1

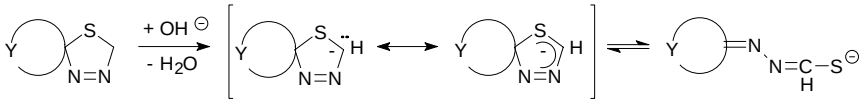
with the MNDO calculations. The same differences in dissociation constants of **1b** and **1c** obtained by both methods were observed (Table I).

These results suggest that protonation of thiadiazoles may take place both at the electrode surface and in the bulk of the solution. The differences of protonation constants of the investigated thiadiazoles obtained by the potentiometric method may result from differences in solvation processes of these compounds caused by the molecular structure[17,18].

On the basis of the above conclusions we propose the acid-base equilibria of the thiadiazoles under investigation in Schemes 1 and 2.



SCHEME 1



SCHEME 2

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