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POLYNUCLEAR BRANCHED TETRAZOLE SYSTEMS.

3*. ACIDITY OF α,ω-DITETRAZOL-5-YLALKANES

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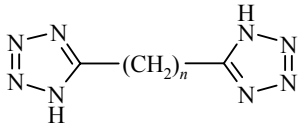
α,ω-Ditetrazol-5-ylalkanes with 1 to 5 methylene groups in the alkyl fragment display the properties of dibasic heterocyclic NH acids with pK_a values lying in the range 3.4-6.1. The pK_a values of these compounds are in a linear dependence on the values of the dielectric permeability of the medium, on the chemical shifts of the signals of the endocyclic carbon atom, and of the carbon atom of the α-methylene group in the ^{13}C NMR spectra.

Keywords: α,ω-ditetrazol-5-ylalkanes, 1,3-dipolar cycloaddition, acidity, potentiometry, NMR spectroscopy.

It is known that multibasic carboxylic acids are efficient ligands for binding metal ions into stable complexes [2]. The search for compounds possessing similar or greater complex-forming activity is an urgent problem. The polynuclear heterocyclic systems are extremely promising in this aspect. They are analogs of multibasic carboxylic acids in which the carboxyl groups are replaced by tetrazol-5-yl fragments. The NH-tetrazole ring possesses acidity close to a carboxyl group and is able to form stable complexes with metal ions. Comparison of the complex-forming ability of standard complexones containing carboxyl fragments in their structure, and their tetrazol-5-yl analogs in relation to ions of copper, cobalt, and nickel showed a preference for these heterocyclic derivatives [3]. The complex-forming activity of ligands may also be assessed from their acid-base properties [2].

Previously we synthesized polynuclear 2-(tetrazol-5-yl)ethyl compounds and investigated their acidic properties [1, 4]. Nonetheless the significant differences in the structure and in the solubility of these compounds does not permit a structure–property or property–property dependence to be reached correctly.

In the present work, using 1,3-dipolar cycloaddition of alkylammonium azides to dinitriles of dicarboxylic acids, ditetrazol-5-ylalkanes **1-5** with the number of methylene groups in the aliphatic fragment from 1 to 5 have been synthesized. Their acidic properties have been investigated. The 5,5'-ditetrazole **6** has been considered as a model compound.



1–**6**

1 n = 1, **2** n = 2, **3** n = 3, **4** n = 4, **5** n = 5, **6** n = 0

* For Part 2 see [1].

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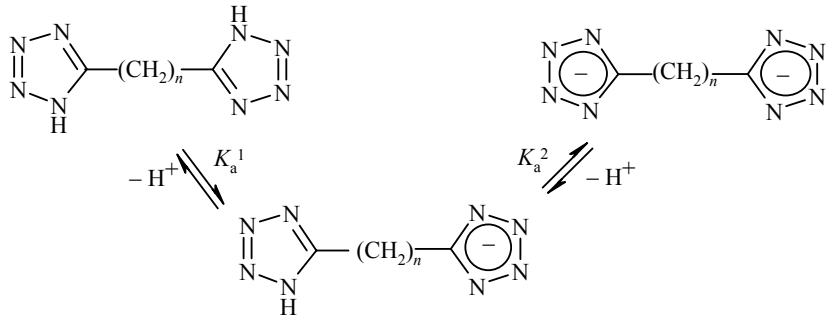
The values of pK_a^1 and pK_a^2, characterizing the acidity of the dibasic aliphatic carboxylic acids, have been known for a fairly long time [5]. The acid–base properties of only 5,5'-ditetrazole **6** were investigated quantitatively among the dibasic tetrazoles [6].

The acid dissociation of α,ω-ditetrazol-5-ylalkanes **1-5** occurs stepwise with the formation of the corresponding mono and dianions.



As follows from the data of Table 1, the pK_a values of compounds **1-5**, determined by potentiometric titration, are in the range 3.4-6.1 (for water). The acidity of these compounds therefore proved to be close to the acidity of the corresponding dibasic aliphatic carboxylic acids [5]. However clear correlation dependencies linking the values of pK_a^1 and pK_a^2 of tetrazoles **1-6** and the corresponding dicarboxylic acids failed to be exposed.

On increasing the number of bridge methylene groups (n) a tendency towards an increase in the pK_a value is seen (Fig. 1). However it may be observed from Figure 1 that at $n > 5$ these changes of pK_a value become insignificant. We note that at $n = 5$ the value of ΔpK_a, calculated as the difference between the acidity constants for the first and second stages ($\Delta pK_a = pK_a^2 - pK_a^1$), approaches the value of log 4, a statistical effect determined by the difference in the number of acidity centers at the first and second stages, although not equal to it. This fact may indicate the weak mutual electronic influence of the tetrazole rings [7].

To estimate the influence of solvation effects on the acid dissociation of ditetrazoles **1-5** in water–organic solvent systems we have established the dependency of pK_a^1 and pK_a^2 values on the dielectric permeability of the medium in the system methanol–0.1 N aqueous $NaNO_3$ solution with a methanol content from 0 to 50 wt.% (Table 2). Values of the correlation parameters of the linear dependencies of pK_a^1 and pK_a^2 on $1/\varepsilon$ are shown in Table 3.

According to Tables 2 and 3 the values of the solvation coefficients (a, b) for all the compounds **1-5** investigated are approximately equal. This circumstance permits the suggestion of a related character for the solvation of each compound in the given binary solvent [8].

TABLE 1. Thermodynamic Acid Dissociation Constants of α,ω-Ditetrazol-5-ylalkanes **1-5** and 5,5'-Ditetrazole **6** at the First and Second Stages

Compound	n	pK_a^1	pK_a^2
1	1	3.42±0.01	5.30±0.02
2	2	4.42±0.03	5.74±0.03
3	3	4.95±0.01	5.94±0.02
4	4	5.17±0.02	6.09±0.03
5	5	5.23±0.01	6.10±0.03
6	0	1.41 [6]	4.25 [6]

TABLE 2. Acid Dissociation Constants of α,ω-Ditetrazol-5-ylalkanes **1-5** in Media of Various Dielectric Permeability

Compound	n_{CH2}	0*		10*		20*	
		pK_a^1	pK_a^2	pK_a^1	pK_a^2	pK_a^1	pK_a^2
1	1	3.32±0.01	5.20±0.02	3.32±0.02	5.19±0.02	3.34±0.02	5.23±0.02
2	2	4.31±0.03	5.64±0.03	4.29±0.05	5.66±0.03	4.32±0.02	5.68±0.02
3	3	4.85±0.01	5.83±0.02	4.86±0.01	5.91±0.01	4.88±0.01	5.94±0.02
4	4	5.07±0.02	5.99±0.03	5.08±0.02	6.03±0.02	5.10±0.02	6.03±0.02
5	5	5.12±0.01	5.99±0.02	5.13±0.01	6.01±0.02	5.16±0.01	6.04±0.03

Compound	n_{CH2}	30*		40*		50*	
		pK_a^1	pK_a^2	pK_a^1	pK_a^2	pK_a^1	pK_a^2
1	1	3.37±0.01	5.30±0.02	3.41±0.02	5.37±0.02	3.51±0.04	5.47±0.03
2	2	4.36±0.01	5.74±0.02	4.44±0.02	5.84±0.01	4.49±0.01	5.84±0.02
3	3	4.90±0.01	5.98±0.01	4.92±0.01	6.00±0.01	4.98±0.01	6.10±0.01
4	4	5.12±0.01	6.05±0.01	5.15±0.02	6.11±0.03	5.24±0.02	6.24±0.01
5	5	5.18±0.01	6.07±0.03	5.25±0.02	6.14±0.03	5.33±0.01	6.26±0.02

* Methanol content (wt. %) in the system methanol–0.1 N aqueous $NaNO_3$ solution.

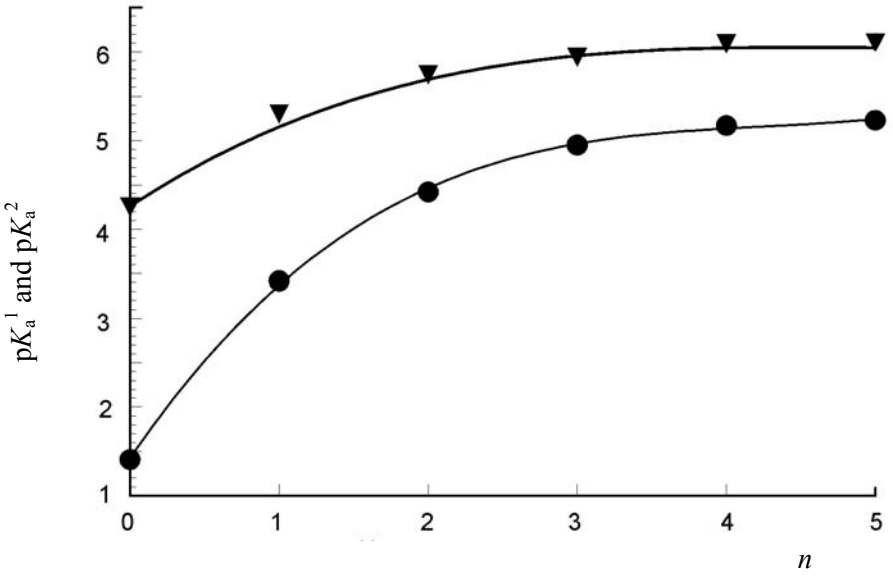


Fig. 1. Dependency of the acidity constant of ditetrazoles **1-6** on the number (*n*) of methylene groups.

TABLE 3. Statistical Parameters of the Correlation Dependency of the Acid Dissociation Constants of α,ω-Ditetrazol-5-ylalkanes on the Reciprocal Dielectric Permeability of the Medium

Com-pound	$pK_a^1 = a\,(1/\varepsilon) + b$				$pK_a^2 = a\,(1/\varepsilon) + b$			
	a	*b*	*r*	*s*	*a*	*b*	*r*	*s*
1	35±6	2.84±0.09	0.95	0.02	55±6	4.46±0.09	0.98	0.03
2	39±6	3.78±0.09	0.96	0.02	44±6	5.07±0.09	0.96	0.03
3	34±2	4.54±0.04	0.98	0.01	45±5	5.28±0.08	0.97	0.02
4	30±5	4.67±0.07	0.95	0.02	43±8	5.43±0.13	0.93	0.03
5	40±5	4.59±0.07	0.97	0.02	50±6	5.33±0.10	0.97	0.03

It was shown previously by the authors of [9] that for 5-substituted tetrazoles a linear dependency exists between the chemical shift of the signals of the endocyclic carbon atom of the tetrazole ring in the ^{13}C NMR spectra and pK_a. We have also found analogous correlation dependencies (1), (2) for the sizes of pK_a^1 and pK_a^2 of compounds **1-5**.

$$pK_a^1 = (0.528 \pm 0.048) \times \delta(C^5_T) - (77.302 \pm 7.481),\ r = 0.99,\ s = 0.14,\ n = 5 \quad (1)$$

$$pK_a^2 = (0.233 \pm 0.023) \times \delta(C^5_T) - (30.274 \pm 3.633),\ r = 0.98,\ s = 0.07,\ n = 5 \quad (2)$$

Different correlation dependencies (3) and (4) were also made apparent for tetrazoles **1-5**, linking the acid dissociation constants at the first and second stages with the values of the chemical shift of the signals of the carbon atom of the α-methylene groups.

$$pK_a^1 = (0.515 \pm 0.018) \times \delta(C_{\alpha\text{-}CH2}) - (6.410 \pm 0.378),\ r = 0.99,\ s = 0.05,\ n = 5 \quad (3)$$

$$pK_a^2 = (0.227 \pm 0.015) \times \delta(C_{\alpha\text{-}CH2}) + (0.975 \pm 0.318),\ r = 0.99,\ s = 0.04,\ n = 5 \quad (4)$$

The established correlation ratios may be used, with a high degree of confidence, for predicting on the basis of NMR spectroscopic data the acid–base properties of compounds belonging to the α,ω-ditetrazol-5-ylalkane series.

The values of pK_a^1 and pK_a^2 obtained in the present study enable selection of such values of the pH of the medium at which only undissociated molecules, monoanions, or dianions, predominantly exist. This has a decisive value in processes of complex-formation (tetrazolate anions form more stable chelate complexes with metal ions), and may also be valuable when assessing the reactivity of compounds of this type.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (300 and 75 MHz respectively) in DMSO, internal standard was the solvent signal. The IR spectra were recorded on a Shimadzu FTIR 8400 instrument in KBr disks. Elemental analysis was carried out on a Hewlett-Packard 185B C,H,N analyzer. Melting points were determined on a PTP type of instrument with a heating rate of 1°C/min in the melting range. Potentiometric titration was carried out on a pH 121 potentiometer (electrodes: glass EVL-1M3, silver chloride ESL-63-07T4.1). All potentiometric measurements were made at 25°C. Values of pK_a were calculated according to [8].

α,ω-Ditetrazol-5-ylalkanes (general procedure using ditetrazol-5-ylmethane **1** as an example). A mixture of malononitrile (12.0 g, 182 mmol), sodium azide (26.0 g, 400 mmol), and dimethylamine hydrochloride (32.6 g, 400 mmol) in DMF (70 ml) was maintained at 107-112°C for 12 h. The reaction mixture was then filtered, and the solvent evaporated in vacuum. The residue was dissolved in distilled water (50 ml) and acidified with dilute hydrochloric acid to pH 1. The precipitated solid was filtered off, washed with water, and dried. Compound **1** (23.5 g, 85%) of mp 210°C was obtained. After purification by reprecipitation with active carbon and recrystallization from 2-propanol colorless crystals of mp 214°C were obtained. IR spectrum, ν, cm^{-1}: 2800-3200 (NH), 1567, 1452, 1432, 1405, 1273, 1242, 1197, 1105, 1076. ^1H NMR spectrum, δ, ppm: 4.75 (2H, s, $C\underline{H}_2CN_4H$); 15.55 (2H, br. s, $CN_4\underline{H}$). ^{13}C NMR spectrum, δ, ppm: 152.5 (tetrazole); 19.1 ($\underline{C}H_2CN_4H$). Found, %: C 23.80; H 3.32; N 73.14. $C_3H_4N_8$. Calculated, %: C 23.69; H 2.65; N 73.66.

1,2-Di(tetrazol-5-yl)ethane (2). Yield 16.4 g (82%); mp 244°C (2-propanol). IR spectrum, ν, cm^{-1}: 2800-3200 (NH), 1586, 1455, 1414, 1261, 1118, 1114, 1102, 1062, 1002. ^1H NMR spectrum, δ, ppm: 3.39 (4H, s, $C\underline{H}_2CN_4H$); 16.06 (2H, br. s, $CN_4\underline{H}$). ^{13}C NMR spectrum, δ, ppm: 154.9 (tetrazole); 20.9 ($\underline{C}H_2CN_4H$). Found, %: C 29.11; H 3.45; N 67.22. $C_4H_6N_8$. Calculated, %: C 28.92; H 3.64; N 67.44.

1,3-Di(tetrazol-5-yl)propane (3). Yield 6.1 g (73%); mp 198°C (2-propanol). IR spectrum, ν, cm^{-1}: 2800-3200 (NH), 1579, 1454, 1430, 1418, 1407, 1280, 1256, 1208, 1110, 1082, 1056. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.16 (2H, q, *J* = 7.5, $C\underline{H}_2CH_2CN_4H$); 2.98 (4H, t, *J* = 7.5, $C\underline{H}_2CN_4H$); 15.9 (2H, br. s, CN_4H). ^{13}C NMR spectrum, δ, ppm: 155.5 (tetrazole); 24.8 ($\underline{C}H_2CH_2CN_4H$); 22.2 ($\underline{C}H_2CN_4H$). Found, %: C 32.74; H 4.09; N 62.27. $C_5H_8N_8$. Calculated, %: C 33.33; H 4.48; N 62.19.

1,4-Di(tetrazol-5-yl)butane (4). Yield 15.3 g (87%); mp 204°C (2-propanol). IR spectrum, ν, cm^{-1}: 2800-3200 (NH), 1578, 1457, 1448, 1424, 1321, 1305, 1260, 1204, 1127, 1109, 1085, 1053. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.74 (4H, q, *J* = 7.5, $C\underline{H}_2CH_2CN_4H$); 2.92 (4H, t, *J* = 7.5, $C\underline{H}_2CN_4H$); 15.9 (2H, br. s, $CN_4\underline{H}$). ^{13}C NMR spectrum, δ, ppm: 155.8 (tetrazole); 26.4 ($\underline{C}H_2CH_2CN_4H$); 22.4($\underline{C}H_2CN_4H$). Found, %: C 36.96; H 4.93; N 57.51. $C_6H_{10}N_8$. Calculated, %: C 37.11; H 5.19; N 57.70.

1,5-Di(tetrazol-5-yl)pentane (5). Yield 10.4 g (68%); mp 142°C (2-propanol). IR spectrum, ν, cm^{-1}: 2800-3200 (NH), 1576, 1464, 1452, 1426, 1407, 1352, 1318, 1298, 1254, 1231, 1185, 1110, 1083, 1059. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (2H, q, *J* = 7.5, $C\underline{H}_2CH_2CH_2CN_4H$); 1.73 (4H, q, *J* = 7.5, $C\underline{H}_2CH_2CN_4H$); 2.87 (4H, t, *J* = 7.5, $C\underline{H}_2CN_4H$); 15.8 (2H, br. s, $CN_4\underline{H}$). ^{13}C NMR spectrum, δ, ppm: 155.9 (tetrazole); 27.7 ($\underline{C}H_2CH_2CH_2CN_4H$); 26.6 ($\underline{C}H_2CH_2CN_4H$); 22.6 ($\underline{C}H_2CN_4H$). Found, %: C 40.52; H 6.43; N 54.38. $C_7H_{12}N_8$. Calculated, %: C 40.38; H 5.81; N 53.81.

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