Determination of *p*Ka Values of Some New Triazole Derivatives Using Different Methods

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The protonation constant values of 12 new triazole derivatives have been determined by potentiometric and spectrophotometric methods. Potentiometric and spectrophotometric methods were used in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures at 25°C with an ionic strength of 0.10 M. The calculation of the stoichiometric protonation constants was carried out using a PKAS computer program. In spectrophotometric method, the electronic absorption spectra of these triazole derivatives at various pH values at 200-400 nm intervals were recorded. The calibration of the electrode system was done potentiometrically by Gran's method. Data were calculated using the linearization method with Henderson-Hasselbach equation. The obtained results are in good accordance with potentiometric values. In addition, these triazole derivatives were studied in non-aqueous media (isopropyl alcohol, t-butyl alcohol, N,N-dimethyl formamide and acetonitrile) by potentiometric method according to half neutralization method. The half neutralization potential values and the corresponding pKa values were determined for all cases. The effect of solvents composition on the stoichiometric protonation constants are discussed.

Keywords: potentiometric method, spectrophotometric method, protonation constant

The *p*Ka of compound is an important property in both the life sciences and chemistry, since the propensity of a compound to donate or accept a proton is fundamental to understand many chemical and biochemical processes [1-3]. The *p*Ka value of a molecule also determines the amount of protonated and non-protonated forms at a specific *p*H and shows the equilibrium state of the chemical system [4]. Depending on the extent of solvent interactions with the associated and dissociated forms, the equilibrium can be shifted toward the acid or the conjugate base side [5]. In biochemistry, the information about the *p*Ka values of ionizable groups in a protein is essential for understanding its functional mechanism at moleculer level [6]. Many biological systems use proton-transfer reactions to perform communication between the extra cellular and intracellular media and the rate of the proton – transfer reaction depend, among many other factors, on the *p*Ka value of the species involved [7].

There have been a number of systematic studies on the basicity and acididity in different media using different techniques [8-20], but unfortunately very few have dealt with triazoles. It is well known that two major factors influence the basicity or acidity of a molecule [21-24], namely, structural and solvent effects. In most molecules there are two or more structural effects and it is usually difficult to assess how much each effect contributes to the basicity or acidity of a molecule. Moreover, it is sometimes extremely difficult to differentiate between structural and solvent effects. The considerable biological importance of triazoles has stimulated much work on these derivatives [25-29]. Some naturally occurring substances of pharmacological interest have been found to possess a triazole ring in their structure [30-32].

Lambert Beer's law has been tested extensively and in the absence of chemical complications, usually holds for concentrations below 10^{-2} M. At higher concentrations, the absorbance concentrations relation may be non-linear but the concentration can still be determined with the help of a calibration curve. A wide range of concentrations can be determined through appropriate choice of the optical path length and the measurement of wavelength [33]. Protonation constant of weak acidic compounds can be determined by several different methods. The potentiometric, chromatographic, electrophoretic methods also have been used widely [34].

The exact role of these derivatives in the mode of action as antibiotic or antitumor drugs remains obscure [35]. In addition, these derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, anti-inflammatory, antioxidant and anti-HIV properties [36-41]. An acceptable representation of the structure of a 1,2,4-triazole must take into consideration its amphoteric nature; the mobility of the imino hydrogen atom; more stability, aromatic character and substitution pattern of the nucleus and the physical evidence that suggests its considerably polar nature. 1,2,4-Triazole is readily soluble in polar solvents and only slightly soluble in nonpolar solvents, the solubility in the latter being increased by substitution of the nitrogen atom.

Experimental part

In this study, 12 different triazole derivatives [3-(4-bromobenzyl)-4-(4-methylphenyl) - 4,5 - dihydro - 1*H* - 1,2,4 -triazol-5-one (**1**), 3-(4-bromobenzyl)-4-(4-hydroxyphenyl) - 4,5 - dihydro - 1*H* -1,2,4-triazol-5-one (**2**), 3-(4-bromobenzyl)-4-(4-fluoro phenyl)-4,5-di hydro-1*H*-1,2,4-triazol-5-one (**3**), 3-(4-bromobenzyl)-4 -(4-acetylphenyl) - 4,5 - dihydro - 1*H* - 1,2,4 -triazol-5-one (**4**), 3-(4-bromobenzyl)-4-(4-phenoxy phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**5**), 3-methyl-4-(4-*tert*-butylphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**6**), 3-phenyl-4-(4-*tert*-butylphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**7**), 3-benzyl-4-(4-*tert*-butylphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**8**), 3-ethyl-4-(4-*tert*-butyl phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**9**), 3-(4-methylbenzyl)-4-(4-*tert*-butylphenyl) - 4,5-dihydro-1*H*-1,2,4-triazol-5-one (**10**), 3-(4-chlorobenzyl)-4-(4-*tert*-

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butylphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**11**), 3-(3-methylbenzyl)-4-(4-*tert*-butyl phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**12**) (fig. 1)] were synthesized according to new method of microwave-assisted synthesis in Rize University Organic Chemistry Research Laboratory and all products are synthesized according to the reported procedures [42].

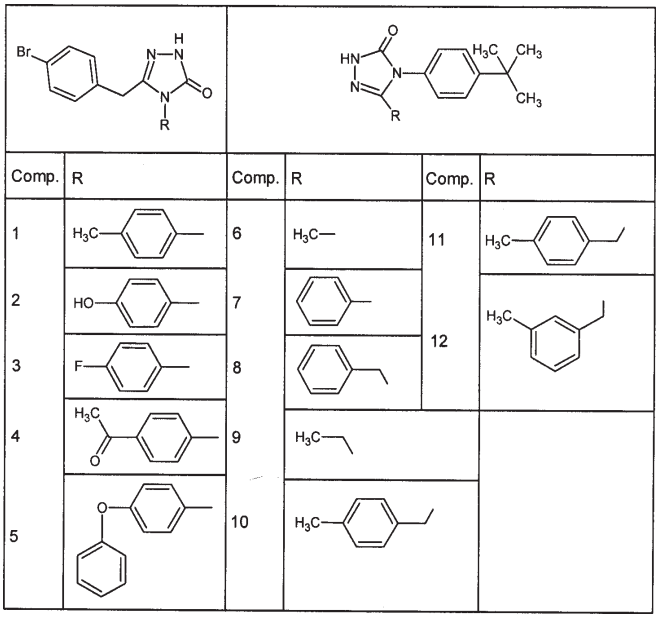

Fig. 1. Studied triazole derivatives

In potentiometric and spectrophotometric methods were used all stock solutions in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures were prepared in double-distilled conductivity water. Purified ethanol, dioxan and methanol were used for preparation of ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. All other chemicals used in this study were reagent grade purity. Stock solutions of strong acid and strong base had prepared by using analytical reagent-grade hydrochloric acid and sodium hydroxide, respectively. Acid solutions prepared in water were standardized by titration against primary standard sodium carbonate (Merck). Solutions of standard bases containing 0.10 M NaCl were prepared as ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 were potentiometrically standardized against hydrochloric acid solutions by use of Gran's plot techniques, allowing determination of dissolved carbonate impurity [43]. Primary Standard sodium chloride (Merck) was used to keep the ionic strength constant.

All potentiometric measurements were performed in an 80 mL jacketed titration cell thermostated at 25.0 ± 0.1°C and under nitrogen atmosphere in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. An Orion 720 A Model pH ionmeter, fitted with a combined pH electrode (Ingold) containing a filling solution of 0.01 M NaCl, was used for measuring the cell emf values. The potentiometric cell was calibrated before each experiment so that the hydrogen ion concentration rather than the activity was measured. For all the solvent mixtures examined, reproducible values of autoprotolysis constants Kw were calculated from several series of $[H^+]$ and $[OH^-]$ measurements at 0.10 M NaCl. The following solutions prepared in water and each of the solvent mixtures studied (total volume=50 mL) were titrated potentiometrically with CO_2-free standard 0.1 M NaOH dissolved in the corresponding solvents: (a) $2.5x10^{-3}$ M HCl (for cell calibration); (b) ($2.5x10^{-3}$ - $7.5x10^{-3}$ M) HCl + $1.5x10^{-3}$ M triazoles. During each titration the ionic strength was maintained at 0.1 M NaCl and a potential reading was taken after a suitable time (normally 2-3 min) for equilibration. The protonation constants of the triazoles were calculated by analyzing the titration data using the PKAS computer program developed by Motekaitis and Martell [44]. Potentiometric titration cell is given figure 2.

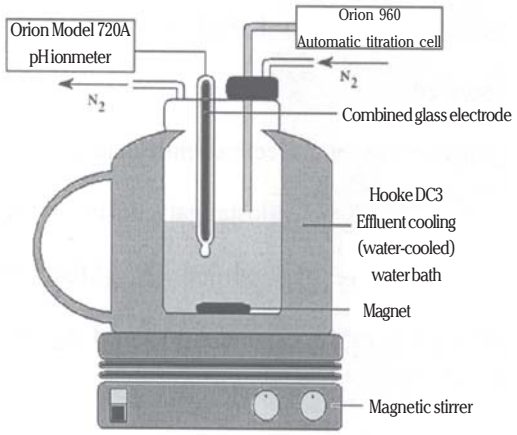

Fig. 2. Potentiometric titration cell

For spectrophotometric method in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures doubly distilled conductivity water was used as aqueous medium as well as for the preparation of ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. All other chemicals used in this investigation were reagent grade purity. Water conductivity was lower than 0.05 Scm^{-1}. Ethanol, dioxan and methanol were supplied by Merck. Potassium hydroxide (Merck), potassium chloride (Merck), hydrochloric acid (Merck) were used. While spectrophotometric measurements were done, solutions of individual triazole derivatives were prepared at a concentration of approximately 5.10^{-4} mol L^{-1}. All the solutions were prepared in 0.1 mol L^{-1} potassium chloride to adjust the ionic strength. The calibration of the electrode system was done potentiometrically by Gran's method [43]. Absorbance measurements were carried out by using a Shimadzu 2450 UV/Vis spectrophotometer. The absorbance measurements were carried out in two matching quartz 1.0 cm cells with a 1 mm path length. The emf measurements to evaluate the *p*H of the solution were performed with a model Orion 720 A pH meter with Ag/AgCl combined pH electrode system (± 0.1 mV). The pKa values of the different triazole derivatives were determined by means of the data obtained from spectrophotometric titrations in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures at 25°C±0.1 and in 0.1 mol L^{-1} ionic strength (NaCl). A suitable amount of a solution containing the compound to be analyzed at the required conditions of temperature, ionic strength and solvent composition was added to the pre-titrated background solution and small amounts of hydrochloric acid solutions were then added. The spectral data were obtained by adding 0.05 mL NaOH which changed the *p*H in the range of 3.0-10.0. These amounts should be high enough to provoke a measurable change in the *p*H of the test solution. At each *p*H, UV/Vis spectra were recorder with 1 nm resolution in order to obtain different spectra around the maximum λ for each triazole derivatives. After each addition, the potential was allowed to stabilize and the potential value was used to calculate the *p*H of the solution using the value of E^o

calculated in the calibration step. After each addition of titrant and after waiting for the potential reading to be stable, a spectrum was recorded, all relevant data were stored and new volume of titrant was added to restart the cycle. All data were calculated using the linearization method with Henderson - Hasselbach equation.

$$\log(A_\lambda - A_{\lambda HA} / A_{\lambda A} - A_\lambda) = pH - pK_a$$

In non-aqueous media for potentiometric titrations, an Orion 720A model *p*H-ionmeter equipped with a combined pH electrode (Ingold) and indicator elektrode were used. A magnetic stirrer, a semi micro burette and a 25 mL beaker were also used in titrations. Before potentiometric titrations, the pH meter was calibrated according to the instructions supplied by the manufactures of the pH meter. During the titrations, the titrant was added in increments of 0.05 mL after each stable reading and mV values were recorded. All compounds were titrated potentiometrically with tetrabutyl ammonium hydroxide in non-aqueous solvents such as isopropyl alcohol (ε=19.4), *t*-butyl alcohol (ε=12), N,N-dimethylformamide (ε=37) and acetonitrile (ε=36).

The necessary chemicals were supplied from Fluka and Merck. After purifications, isopropyl alcohol was used to prepare 0.05 N tetrabutylammonium hydroxide. For all potentiometric titrations, 0.05 N tetrabutylammonium hydroxide in isopropyl alcohol, which was prepared from 0.1 N tetrabutylammonium hydroxide by dilution, was used. The mV values, which were read from pH meter, were plotted versus tetrabutylammonium hydroxide volumes (mL) added and thus potentiometric titration curves were formed for all the cases. From these curves, the half-neutralization potential values were measured and the corresponding pKa values were calculated. The mV values read in each titration were drawn against TBAH volumes (mL) were added and potentiometric titration curves were formed for all the cases. From the titration curves, the HNP values were measured and the corresponding pKa values were calculated. The half-neutralization potential (HNP) values and the corresponding pKa values of all triazole derivatives, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide. All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. The half-neutralization potentials and the corresponding pKa values for all compounds, obtained from the potentiometric titrations with 0.05 M tetrabutylammonium hydroxide in isopropyl alcohol, *t*-butyl alcohol, N,N-dimethyl formamide and acetonitrile.

Results and discussions

The potentiometric titrations of different 12 triazole derivatives in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures were carried out and their pKa values were found between 11.90±0.09 - 13.80±0.06 in ethanol %50 – water %50, 12.08±0.08 - 13.85±0.07 in dioxan %50 – water %50, 11.77±0.08 - 13.66±0.07 in dioxan %50 – water %50 mixtures. In this study, 12 different triazole derivatives were titrated potentiometrically in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. The mV values, which were read from *p*H meter, were plotted versus sodium hydroxide volumes (mL) added and thus potentiometric titration curves were formed for all the cases (fig. 3). From these curves, potential values were measured and the corresponding pKa values were calculated using a PKAS computer program at 25°C with an ionic strength of 0.10 M. All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. The corresponding pKa values for all compounds, obtained from the potentiometric titrations with sodium hydroxide in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water are given in table 1.

Table 1 shows that the corresponding pKa values obtained from potentiometric titrations depend on the solvents used and molecular structure of the compounds. As seen in Table 1, the acidic arrangement for ethanol %50 – water %50; 2>4>3>7>11>1>8>10>9>12>6>5, for dioxan %50 – water %50; 2>3>4>11>7>1>8>9>12>6>10>5, for methanol %50 – water %50; 2>4>7>3>1>11>8>10>9>6>12>5.

Compound **2** shows the strongest acidic properties but compound **5** shows the weakest acidic properties in all mixtures. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. As it is well known, the acidity of a compound depends on some factors. The two most important factors are the solvent effect and molecular structure.

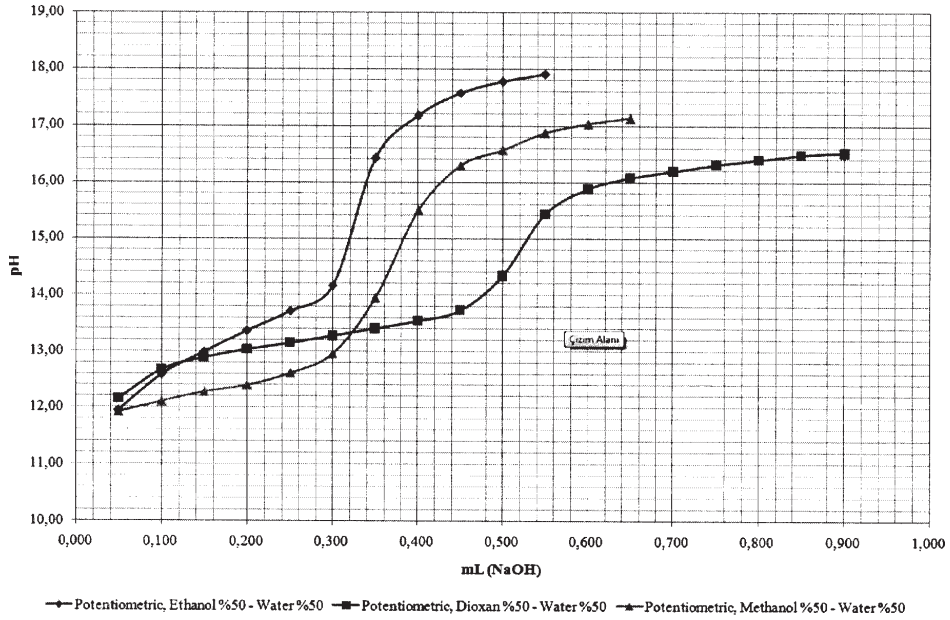

Fig. 3. *p*H – mL (NaOH) potentiometric titration curve of compound **9** titrated in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures at 25°C with an ionic strength of 0.10 M

Table 1
STOICHIOMETRIC PROTONATION CONSTANTS OF STUDIED 12 TRIAZOLE DERIVATIVES AT 25°C IN ETHANOL %50 – WATER %50, DIOXAN %50 – WATER %50 AND METHANOL %50 – WATER %50 MIXTURES (M= 0.1 M NACL)

Compound No	Studied Media		
	Ethanol %50 – Water %50 (Potentiometric, pKa)	Dioxan %50 – Water %50 (Potentiometric, pKa)	Methanol %50 – Water %50 (Potentiometric, pKa)
1	12.90 ± 0.05	13.07 ± 0.03	12.66 ± 0.08
2	11.90 ± 0.07	12.08 ± 0.08	11.77 ± 0.05
3	12.49 ± 0.03	12.51 ± 0.06	12.40 ± 0.06
4	12.33 ± 0.06	12.53 ± 0.04	12.25 ± 0.04
5	13.78 ± 0.04	13.85 ± 0.07	13.66 ± 0.07
6	13.18 ± 0.07	13.26 ± 0.05	13.04 ± 0.03
7	12.57 ± 0.05	12.83 ± 0.06	12.38 ± 0.05
8	12.95 ± 0.04	13.05 ± 0.08	12.89 ± 0.06
9	13.08 ± 0.06	13.22 ± 0.04	12.94 ± 0.04
10	13.07 ± 0.05	13.29 ± 0.05	12.90 ± 0.05
11	12.79 ± 0.08	12.80 ± 0.06	12.71 ± 0.07
12	13.16 ± 0.04	13.25 ± 0.03	13.05 ± 0.06

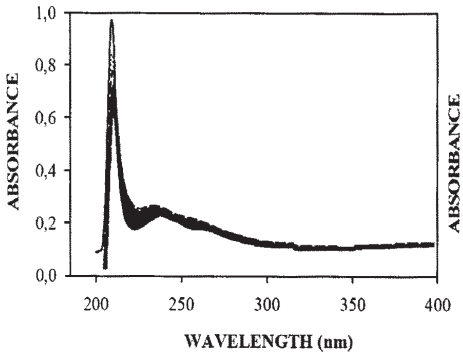

Fig. 4. Plot of experimental absorbance values of compound 9 wavelength as a function of *p*H in ethanol %50 – water %50 mixtures

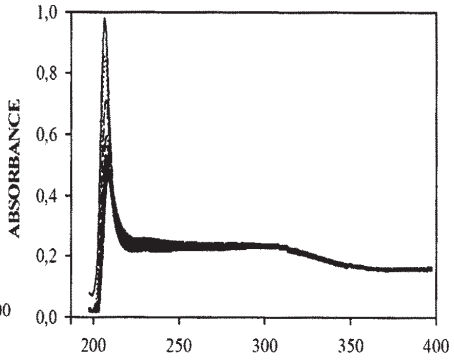

Fig. 5. Plot of experimental absorbance values of compound 9 wavelength as a function of *p*H in dioxan %50 – water %50 mixtures

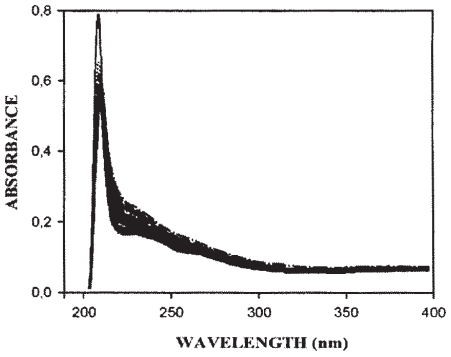

Fig. 6. Plot of experimental absorbance values of compound 9 wavelength as a function of *p*H in methanol %50 – water %50 mixtures

In spectrophotometric method, the electronic absorption spectra of these triazole derivatives in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures at various *p*H values 200 – 400 nm intervals were recorded. The calibration of the electrode system was done potentiometrically by Gran's method. Data were calculated using the linearization method with Henderson-Hasselbach equation. The obtained results are in good accordance with potentiometric values. Spectra of all triazole derivatives at different *p*H values in studied media are shown in figures 4-6.

All data were calculated using the linearization method with Henderson-Hasselbach equation. And plot of $\log(A_{\lambda} - A_{\lambda HA} / A_{\lambda^-} - A_{\lambda})$ values of all triazole derivatives as a function of *p*H in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. Plot of calculated $(A_{\lambda HA} / A_{\lambda^-} - A_{\lambda})$ all triazole derivatives as a function of *p*H in studied media are shown in figure 7. All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. The corresponding pKa values for all compounds, obtained from the spectrophotometric methods using the linearization method with Henderson-Hasselbach equation in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures are given in table 2.

Table 1 shows that the corresponding pKa values obtained from spectrophotometric titrations depend on the solvents used and molecular structure of the compounds. The spectrophotometric titrations of different 12 triazole derivatives in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures were carried out and their pKa values were found between 11.83±0.06 - 13.70±0.05 in ethanol %50 – water %50, 11.96±0.07 - 13.85±0.06 in dioxan %50 – water %50, 11.70±0.07 - 13.55±0.03 in dioxan %50 – water %50 mixtures. As seen in table 1, the acidic arrangement for ethanol %50 – water %50; 2>4>7>3>1>11>8>10>9>6> 12>5, for dioxan %50 – water %50; 2>4>3>7>11>1>8>10>9>6> 12>5, for methanol %50 – water %50; 2>4>3>7> 11>8>1>9>10>12>6>5. Compound **2** shows the strongest acidic properties but compound **5** shows the weakest acidic properties in all mixtures. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures. As it is well known, the acidity of a compound depends on some factors. The two most important factors are the solvent effect and molecular structure.

All compounds were titrated potentiometrically according to half neutralization method with tetrabutyl

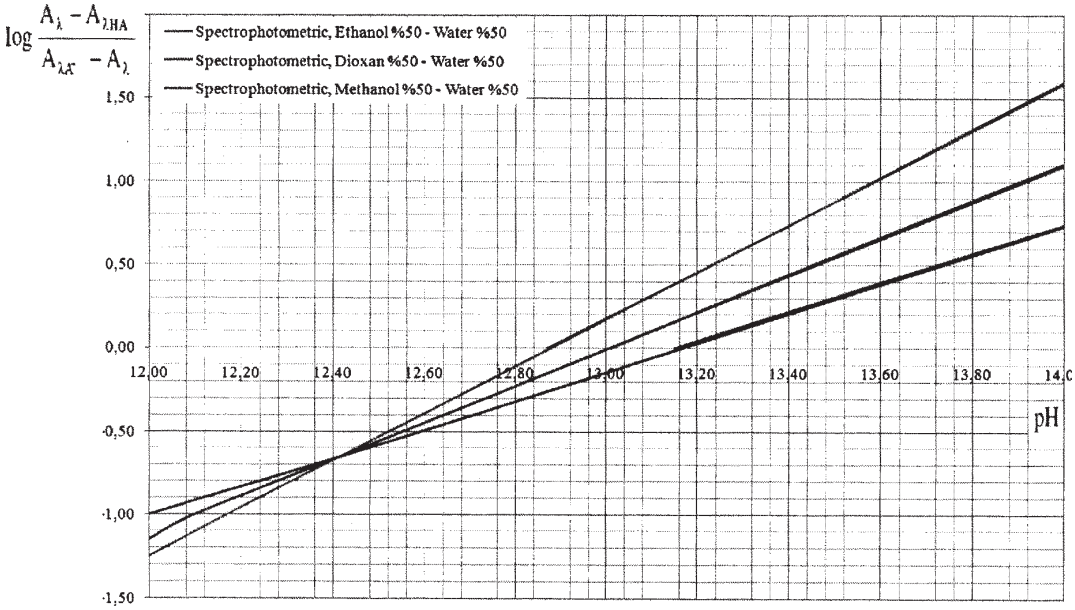

Fig. 7. Plot of calculated $\log(A_\lambda - A_{\lambda,HA} / A_{\lambda,-} - A_\lambda)$ of compound 9 as a function of pH in studied ethanol %50 – water %50, dioxan %50 – water %50 and methanol %50 – water %50 mixtures

Table 2

STOICHIOMETRIC PROTONATION CONSTANTS OF COMPOUND 9 AT 25°C IN STUDIED ETHANOL %50 – WATER %50, DIOXAN %50 – WATER %50 AND METHANOL %50 – WATER %50 MIXTURES (M = 0.1 M NaCl)

Compound No	Studied Media		
	Ethanol %50 – Water %50 (Spectrophotometric, pKa)	Dioxan %50 – Water %50 (Spectrophotometric, pKa)	Methanol %50 – Water %50 (Spectrophotometric, pKa)
1	12.78 ± 0.04	12.97 ± 0.03	12.73 ± 0.05
2	11.83 ± 0.06	11.96 ± 0.07	11.70 ± 0.07
3	12.48 ± 0.08	12.56 ± 0.05	12.29 ± 0.04
4	12.26 ± 0.03	12.40 ± 0.04	12.13 ± 0.06
5	13.70 ± 0.05	13.85 ± 0.06	13.55 ± 0.03
6	13.10 ± 0.04	13.24 ± 0.08	12.97 ± 0.05
7	12.45 ± 0.07	12.64 ± 0.05	12.36 ± 0.08
8	12.84 ± 0.06	13.02 ± 0.06	12.70 ± 0.07
9	13.01 ± 0.04	13.15 ± 0.04	12.87 ± 0.05
10	12.98 ± 0.05	13.14 ± 0.07	12.89 ± 0.06
11	12.80 ± 0.08	12.86 ± 0.03	12.58 ± 0.04
12	13.13 ± 0.06	13.26 ± 0.06	12.94 ± 0.06

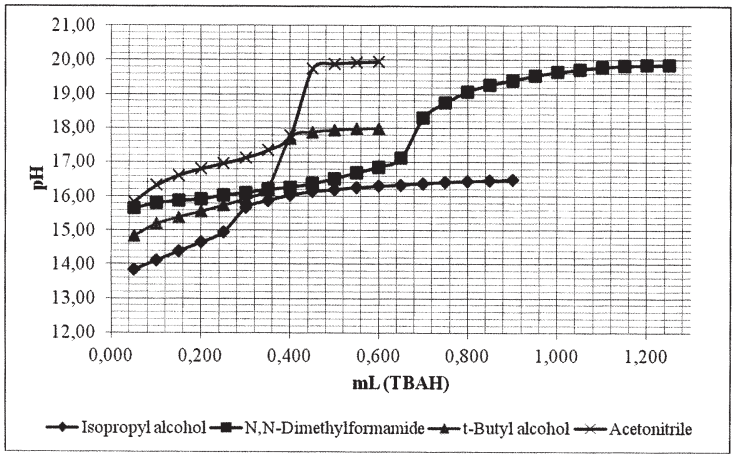

Fig. 8.*p*H – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **9** titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25°C

ammonium hydroxide (TBAH) in non-aqueous solvents such as isopropyl alcohol (ε=19.4), *t*-butyl alcohol (ε=12), N,N-dimethylformamide (ε=37) and acetonitrile (ε=36). The half neutralization potential values and the corresponding *p*Ka values were determined for all cases. pKa values were found between 12.82±0.05 - 18.32±0.05. The mV values, which were read from pH meter, were plotted *versus* tetrabutyl ammonium hydroxide volumes (mL) added and thus potentiometric titration curves were formed for all the cases. From these curves, the half-neutralization potential values were measured and the corresponding pKa values were calculated. The mV values read in each titration were drawn against TBAH volumes (mL) added and potentiometric titration curves were formed for all the cases. From the titration curves (fig. 8-12), the HNP values were measured and the corresponding pKa values were calculated. The half-neutralization potential (HNP) values and the corresponding pKa values of all triazole derivatives, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, N,N-

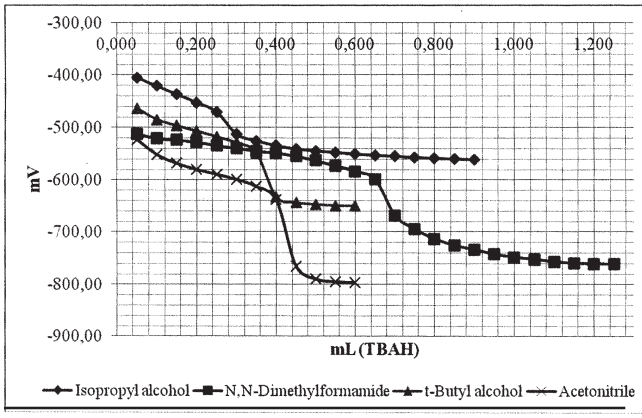

Fig. 9. mV – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **9** titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25°C

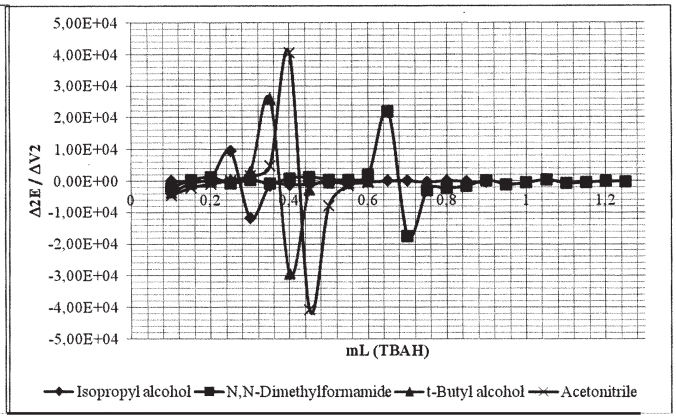

Fig. 11.$\Delta E / \Delta V^2$ – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **9** titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25°C

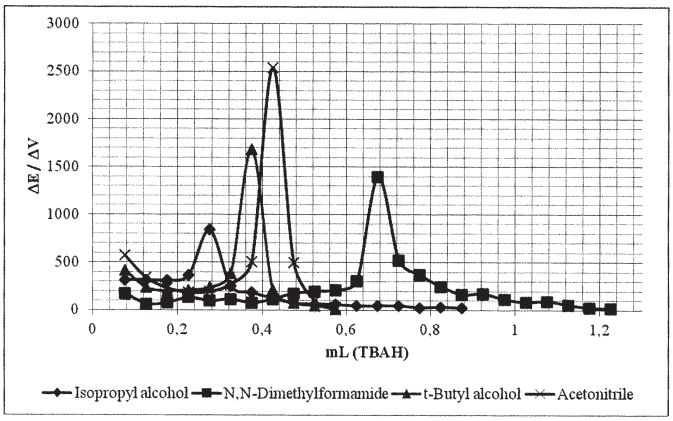

Fig. 10. $\Delta E / \Delta V$ – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **9** titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25°C

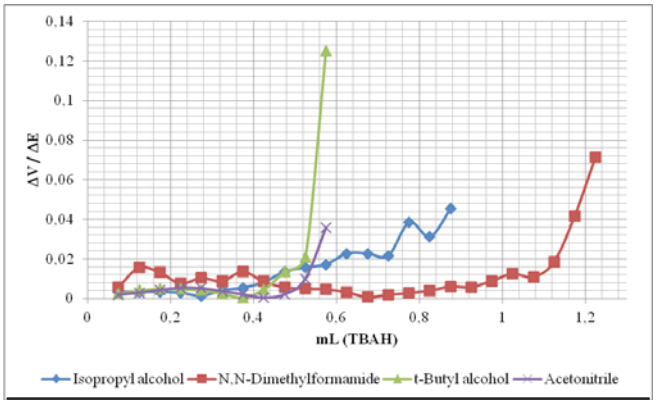

Fig. 12.$\Delta V / \Delta E$ – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **9** titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25°C

Table 3

HALF-NEUTRALIZATION POTENTIALS (HNP) AND THE CORRESPONDING pKa VALUES OF ALL COMPOUNDS IN ISOPROPYL ALCOHOL,T-BUTYL ALCOHOL, *N,N*-DIMETHYL FORMAMIDE AND ACETONITRILE

Compound No	Isopropyl alcohol		*t*-Butyl alcohol		N,N-Dimethyl formamide		Acetonitrile	
	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)
1	14.00 ± 0.04	-413.7 ± 2.7	15.09 ± 0.06	-477.6 ± 4.0	16.12 ± 0.08	-539.5 ± 5.0	16.34 ± 0.04	-552.1 ± 2.0
2	12.82 ± 0.05	-344.1 ± 3.1	14.17 ± 0.08	-424.1 ± 4.7	15.63 ± 0.04	-510.6 ± 2.4	15.00 ± 0.05	-473.2 ± 3.1
3	13.52 ± 0.04	-385.0 ± 2.4	14.59 ± 0.11	-448.4 ± 6.6	16.15 ± 0.01	-540.2 ± 0.6	16.17 ± 0.08	-542.4 ± 4.8
4	13.33 ± 0.04	-374.5 ± 2.3	14.46 ± 0,05	-440.7 ± 3.6	15.86 ± 0.08	-524.3 ± 4.5	15.66 ± 0.01	-512.5 ± 0.7
5	16.03 ± 0.07	-533.4 ± 4.2	16.04 ± 0.06	-534.7 ± 3.8	17.03 ± 0.04	-593.0 ± 2.5	18.32 ± 0.05	-667.9 ± 3.4
6	14.33 ± 0.05	-433.2 ± 3.1	16.39 ± 0.02	-552.0 ± 3.4	16.36 ± 0.09	-553.4 ± 4.8	16.78 ± 0.04	-577.8 ± 2.8
7	13.61 ± 0.02	-390.9 ± 1.2	15.02 ± 0.01	-473.9 ± 0.2	15.21 ± 0.03	-485.8 ± 2.1	15.46 ± 0.03	-500.2 ± 1.9
8	14.06 ± 0.01	-417.4 ± 0.6	15.30 ± 0.08	-491.1 ± 4.7	16.05 ± 0.09	-535.1 ± 5.1	16.46 ± 0.06	-559.6 ± 3.3
9	14.21 ± 0.05	-425.2 ± 3.9	15.44 ± 0.04	-499.1 ± 2.7	16.13 ± 0.09	-539.8 ± 5.3	16.82 ± 0.06	-580.9 ± 3.7
10	14.21 ± 0.06	-425.9 ± 3.8	16.04 ± 0.09	-534.5 ± 4.8	16.26 ± 0.07	-548.0 ± 4.1	16.52 ± 0.09	-564.6 ± 3.4
11	13.87 ± 0.03	-406.3 ± 1.5	15.58 ± 0.04	-507.1 ± 2.7	15.40 ± 0.06	-497.3 ± 3.1	16.19 ± 0.04	-540.5 ± 5.3
12	14.30 ± 0.05	-431.7 ± 2.9	15.94 ± 0.04	-528.2 ± 2.6	15.91 ± 0.08	-526.7 ± 5.6	16.51 ± 0.04	-562.2 ± 2.1

dimethyl formamide, *t*-butyl alcohol and acetonitrile, are given in table 3.

All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. Table 3. shows that the half-neutralization potentials values and the corresponding *p*Ka values obtained from potentiometric titrations depend on the non-aqueous solvents used. As seen in table 1, the acidic order for compounds **1**, **3**, **5**, **7**, **8**, **9** and **10** is: isopropyl alcohol > *t*-butyl alcohol > N,N-dimethyl formamide > acetonitrile, for compounds **6**, **11** and **12** is: isopropyl alcohol > N,N-dimethyl formamide > *t*-butyl alcohol > acetonitrile, for compounds **2** and **4** is: isopropyl alcohol > *t*-butyl alcohol > acetonitrile > N,N-dimethyl formamide. In isopropyl alcohol in all compounds show the strongest acidic properties, in acetonitrile, **1**, **3**, **5**, **6**, **7**, **8**, **9**, **10**, **11** and **12**

compounds show the weakest acidic properties, in N,N-dimethyl formamide, **2** and **4** compounds show the weakest acidic properties. Results are analyzed in each solvent group, compound **2** show the strongest acidic properties but compound **5** show weakest acidic properties in isopropyl alcohol, compound **2** shows the strongest acidic properties but compounds **6** show weakest acidic properties in *t*-butyl alcohol, compound **7** show the strongest acidic properties but compounds **5** shows weakest acidic properties in N,N-dimethyl formamide, compounds **2** shows the strongest acidic properties but compound **5** shows weakest acidic properties in acetonitrile. As seen in table 1 as a result, compound **2** shows weakest acidic properties in isopropyl alcohol but compound **5** shows weakest acidic properties in acetonitrile.

Conclusions

It is well known that the acidity of a compound depends on several factors. The two most important factors are the solvent effect and molecular structure.This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in the amphiprotic neutral solvents. Autoprotolysis is an acid-base reaction between identical solvent molecules in which some act as an acid and others as a base.

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