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Acidic properties of some 1,2,4-triazole derivatives in non-aqueous media

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ABSTRACT

Some 1,2,4-triazole derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, N,N-dimethylformamide (DMF), tert-butyl alcohol and acetonitrile, and the half-neutralization potential values and the corresponding pKa values were determined for all cases.

Key words: 1,2,4-triazole derivatives, acidity, potentiometric titrations, pKa.

INTRODUCTION

Acidity measurements of organic compounds have a long history dating back to the end of the 19th century, when the first pKa was measured. Since then a vast body of data on acidities in various solvents has been collected [1–4]. The measurements have mostly been limited to polar solvents, however, with water being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents.

1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, anti-inflammatory, antioxidant, antitumor and anti-HIV properties [5-9].

In addition, it is known that 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one rings have weak acidic properties, so that some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents, and the p*K*a values of the compounds were determined [5,11-15]. We have previously described the synthesis and potentiometric titrations of some new 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives in different non-aqueous medium, where we determined the p*K*a values of these compounds for each non-aqueous solvent [11-15].

Protonation constant of weak acidic compounds can be determined by several different methods. The potentiometric, chromatographic, electrophoretic methods also have been used widely [16]. In this work, the pKa values of some 1,2,4-triazole derivatives in non-aqueous media using potentiometric measurements in determined. These 1,2,4-triazole derivatives were synthesized according to the reported reference [17,18].

MATERIALS AND METHODS

In this study, six different triazole derivatives [1,4-di-(5-p-tolil-1,2,4-triazol-3-il)-n-butan (**1**), di-3-n-propil-1,2,4-triazol-5-il-metan (**2**), 1,4-di-(3-p-chlorobenzil-1,2,4-triazol-5-il)-n-butan (**3**), di-3-n-propil-1,2,4-triazol-5-il (**4**), 1,4-di-(3-benzil-1,2,4-triazol-5-il)-n-butan (**5**), 1,4-di-(5-m-nitrofenil-1,2,4-triazol-3-il)-n-butan (**6**)] were titrated with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (isopropyl alcohol, *N*,*N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile), using potentiometric method.

Table 1 Studied 1,2,4-Triazole Derivatives

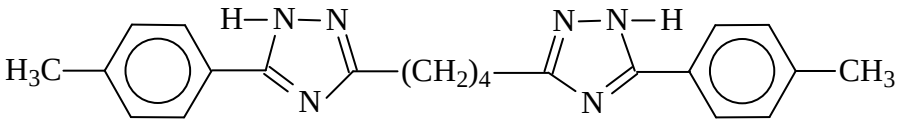
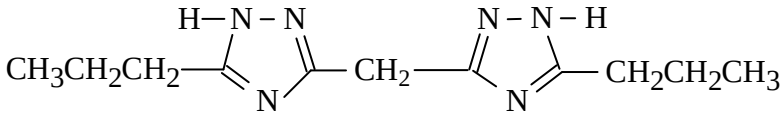
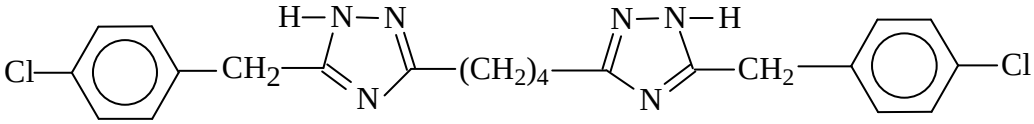
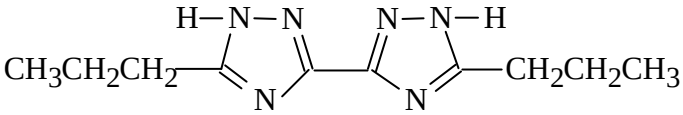
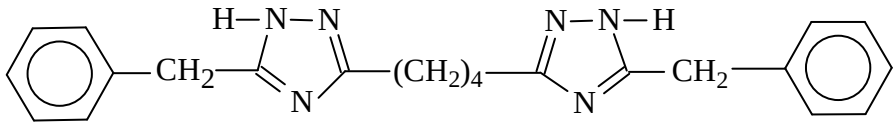
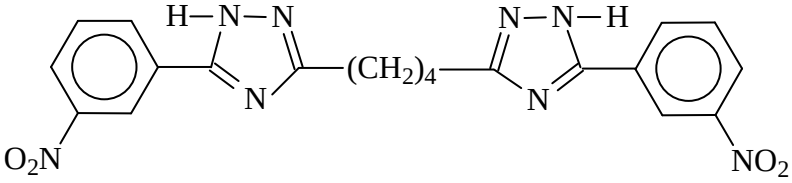
Compound	Triazole derivatives
1	
2	
3	
4	
5	
6	

Table 2 Half-Neutralization Potentials (HNP) and the Corresponding pKa Values of All Compounds in Isopropyl Alcohol, *tert*-Butyl Alcohol, *N,N*-Dimethyl formamide and Acetonitrile

Compound No.	Isopropyl alcohol		*N,N*-Dimethyl formamide		*tert*-Butyl alcohol		Acetonitrile	
	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)
1	13.31 ± 0.19	-372.5 ± 10.3	15.22 ± 0.13	-517.5 ± 8.70	14.40 ± 0.08	-438.2 ± 5.90	15.61 ± 0.26	-511.0 ± 12.5
2	12.78 ± 0.10	-342.5 ± 6.70	14.48 ± 0.14	-443.6 ± 6.10	13.69 ± 0.11	-396.4 ± 8.30	14.15 ± 0.18	-423.3 ± 9.80
3	12.47 ± 0.13	-322.6 ± 7.60	15.61 ± 0.17	-498.1 ± 11.8	14.85 ± 0.12	-463.1 ± 7.60	15.00 ± 0.26	-472.2 ± 12.1
4	12.25 ± 0.07	-310.8 ± 4.50	14.40 ± 0.15	-438.0 ± 8.60	13.59 ± 0.09	-388.5 ± 5.40	15.48 ± 0.16	-325.5 ± 9.20
5	15.30 ± 0.14	-419.3 ± 7.80	14.76 ± 0.19	-476.0 ± 12.4	14.41 ± 0.07	-383.3 ± 4.40	15.15 ± 0.12	-411.3 ± 8.60
6	12.90 ± 0.16	-290.9 ± 11.7	13.62 ± 0.12	-400.6 ± 8.20	13.20 ± 0.15	-317.2 ± 9.70	15.59 ± 0.12	-325.7 ± 8.90

Potentiometric titrations, an Orion 720A model pH-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.

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.

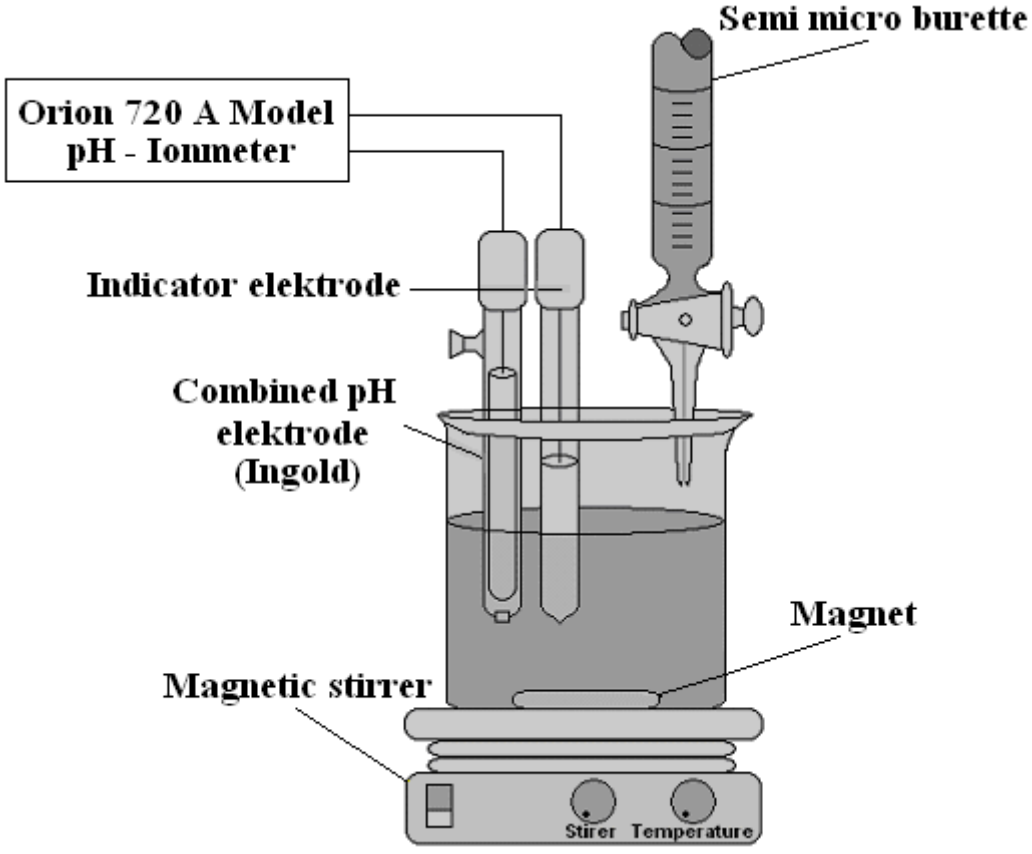


Figure 1 Potentiometric titration cell

RESULTS AND DISCUSSION

In this study, six 1,2,4-triazole derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents such as isopropyl alcohol (ε = 19.4), *tert*-butyl alcohol (ε = 12), *N*,*N*-dimethylformamide (ε = 37) and acetonitrile (ε = 36). 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 (Figure 2-6), 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, *tert*-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, *tert*-butyl alcohol, *N*,*N*-dimethyl formamide and acetonitrile, are given in Table-2. 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. Table-1 shows that the half-neutralization potentials values and the corresponding pKa values obtained from potentiometric titrations depend on the non-aqueous solvents used.

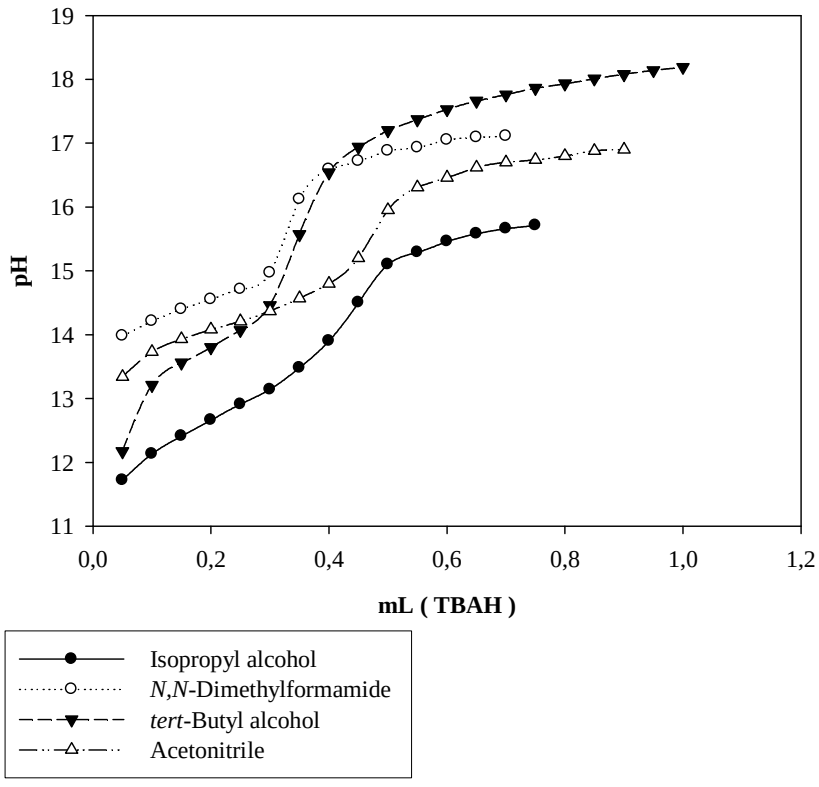


Figure 2 pH – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound 2 (Di-3-n-propil-1,2,4-triazol-5-il-metan) titrated with 0.05 M TBAH in isopropyl alcohol, *N*,*N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

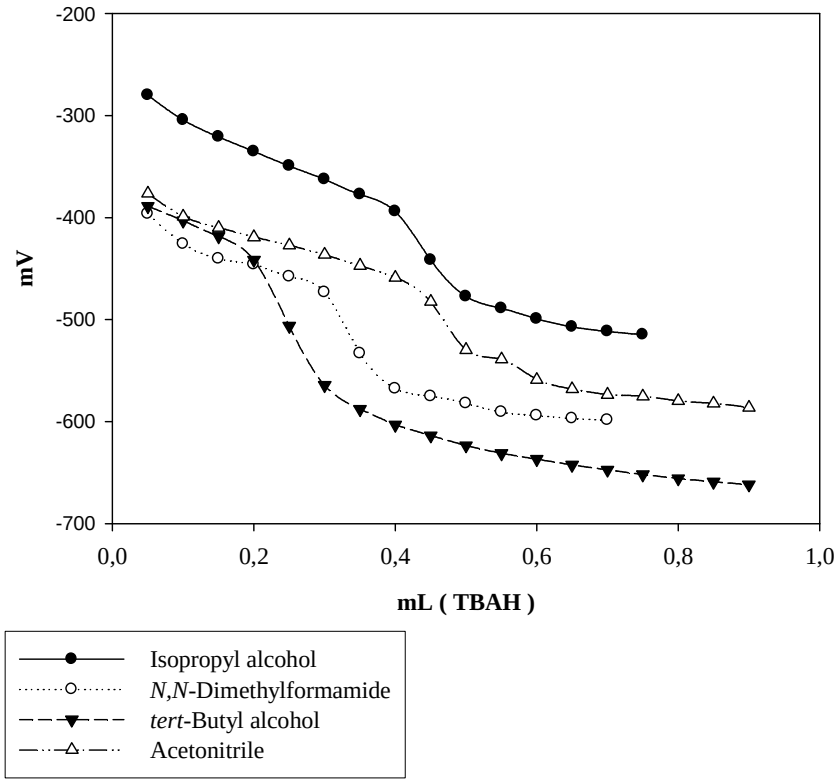


Figure 3 mV – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound 2 (Di-3-n-propil-1,2,4-triazol-5-il-metan) titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

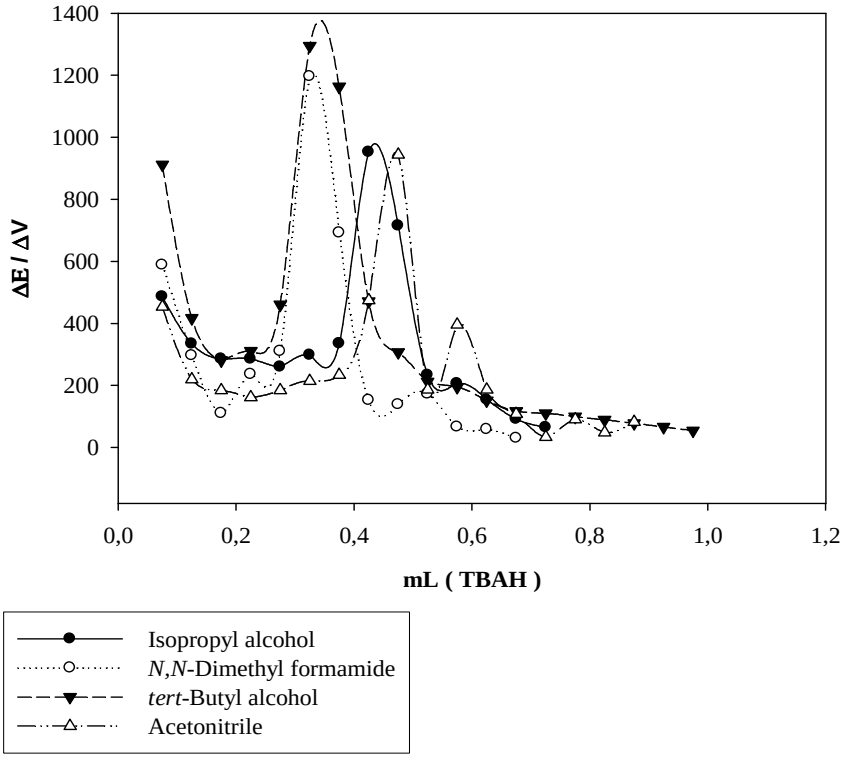


Figure 4 ΔE/ΔV – mL (TBAH) potentiometric titration curves of 0.001 M solutions compound 2 (Di-3-n-propil-1,2,4-triazol-5-il-metan) titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

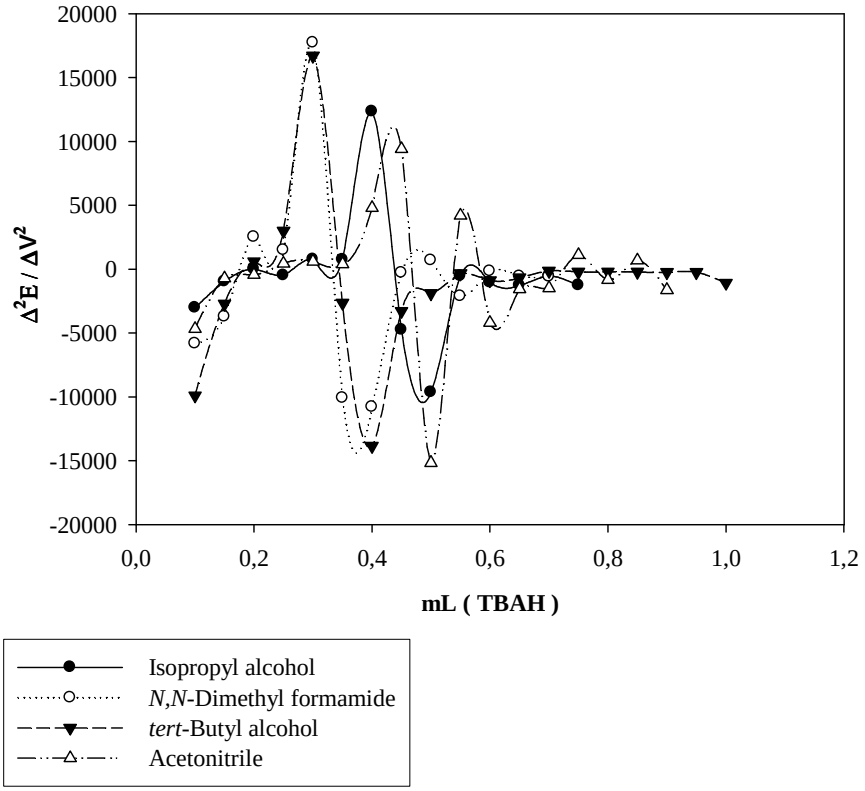


Figure 5 $\Delta^2E/\Delta V^2$ – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound 2 (Di-3-n-propil-1,2,4-triazol-5-il-metan) titrated with 0.05 M TBAH in isopropyl alcohol, *N*,*N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

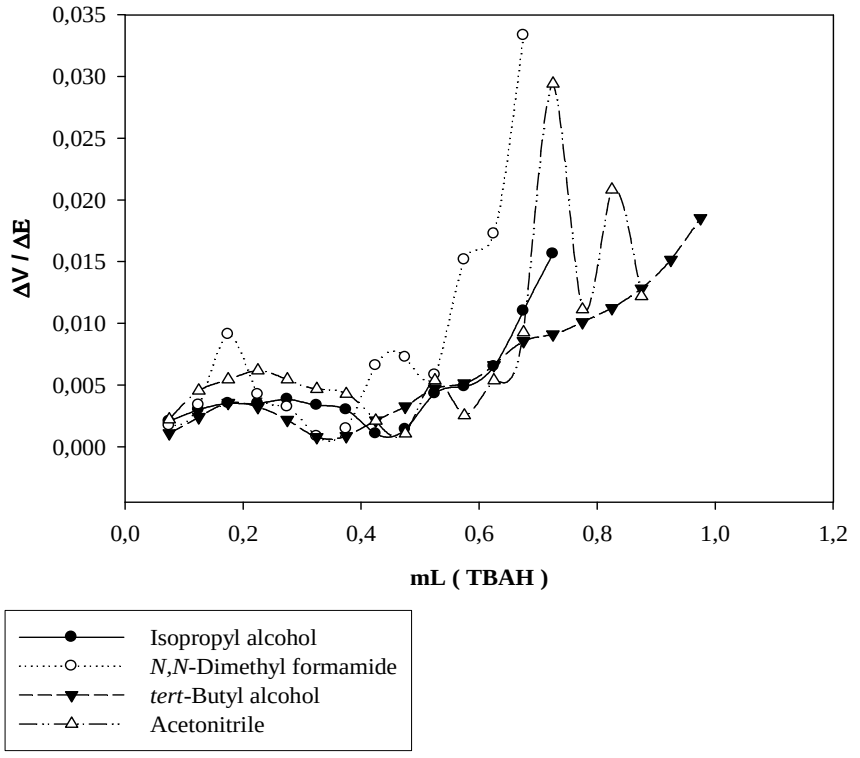


Figure 6 ΔV/ΔE – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound 2 (Di-3-n-propil-1,2,4-triazol-5-il-metan) titrated with 0.05 M TBAH in isopropyl alcohol, *N*,*N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

As seen in Table, the acidic order for compounds **1**, **4** and **6** is: isopropyl alcohol > *tert*-butyl alcohol > *N*,*N*-dimethyl formamide > acetonitrile, for compounds **2** and **3** is: isopropyl alcohol > *tert*-butyl alcohol > acetonitrile > *N*,*N*-dimethyl formamide, for compound 5 is: *tert*-butyl alcohol > *N*,*N*-dimethyl formamide > acetonitrile > isopropyl alcohol. In isopropyl alcohol, compounds **1**, **2**, **3**, **4** and **6** show the strongest acidic properties, in *tert*-butyl alcohol, compound **5** shows the strongest acidic properties. In acetonitrile, compounds **1**, **4** and **6**, in *N*,*N*-dimethyl formamide, compounds **2** and **3** and in isopropyl alcohol, compound **5** show the weakest acidic properties. 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 is which some act as an acid and others as a base.

CONCLUSION

The extent of an autoprotolysis reaction depends both on the intrinsic acidity and the instrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. The acidity of a compound depends on mainly two factors, *i.e.* solvent effect and molecular structure. Half-neutralization potential (HNP) values and corresponding pKa values obtained from the potentiometric titrations rely on the non-aqueous solvents used and the substituents at C-3, in triazole ring.

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