e-ISSN: 2687-6698 **Research Article**

Turkish Journal of Analytical Chemistry
www.turkjac.org
2019
TurkJAC

Investigation of acidic properties of 2-ethoxy-6-(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoates

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Abstract

In this study, to determine the pK_a values of 2-ethoxy-6-(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoates (**1-9**) were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetone and *N*,*N*-dimethylformamide (DMF), and graphs were drawn for all cases. In addition, the effects of solvents and molecular structure upon acidity compounds **1-9** were also determined and discussed. The half-neutralization potential values and the corresponding pK_a values were determined by the half neutralization method.

Keywords: 1,2,4-triazole, Schiff base, acidic properties, HNP, potentiometric titrations, pK_a

1. Introduction

Biological activities of 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiviral, anti-inflammatory, antitumor, antioxidant, and anti-HIV properties are well known [1-13]. Several reports explaining the synthesis of some *N*-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have been published [8-13].

Although water is an extraordinarily versatile solvent in which to carry out acid-base titrations, there are occasions when a nonaqueous solvent may be necessary or preferred, such as when the reagent is not water-soluble, and the neutralization reactions are not sufficiently complete in water. The completeness of a neutralization reaction depends, in part, on the acid or base strength of the analyte. But Bronsted and Lowry have made it clear that the observed acidity or basicity depends on the solvent because it is participating in the ionization [14]. There are two major factors such as solvent and structural effects influencing the acidity or basicity of a molecule. An acid or base too weak to titrate in water sometimes can be titrated in a non-aqueous solvent, where its observed acidity is greater [15-17].

Acidity measurements of organic compounds have carried out end of the 19th century when the first pK_a was measured. Since then, a large of data on the acidities of many solvents have been reported [18-21]. The measurements have mostly been made for polar solvents. Generally, water as a polar solvent has been used in these studies. Also, data have been reported for alcohols and dipolar aprotic solvents [22]. It is known that 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one rings possess weak acidic properties so that some 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents. So, the pK_a values of the compounds were determined [9,10,17,22-29].

Determination of pK_a values of the active constituent of some pharmaceutical preparations is critical since the distribution, transport behavior, bonding to receptors, and contributions to the metabolic behavior of the active constituent molecules depend on the ionization constant [30-32].

The protonation constants of weak acidic compounds can be found by a number of different methods like potentiometric, chromatographic, electrophoretic methods [33]. In the present study, the pK_a values of some 1,2,4-triazole derivatives in non-aqueous media by using potentiometric measurements are found. These

Citation: H. Yüksek, F. Kardaş, S. Manap, G. Özdemir, Investigation of acidic properties of 2-ethoxy-6-(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoates, Turk J Anal Chem, 3(2), 2021, 39-44.
https://doi.org/10.51435/turkjac.940613

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Received: May 21, 2021
Accepted: November 11, 2021

4,5-dihydro-1H-1,2,4-triazol-5-one derivatives have been prepared according to the reported reference in the literature [34].

2. Experimental

2.1. Chemistry

2-Ethoxy-6-(3-substitue-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoates (**1-9)** used in this study were prepared from the reactions of the corresponding 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones with 2-benzoxy-3-ethoxy-benzaldehyde as described in the literature [34]. Nine different 4,5-dihydro-1*H*-1,2,4-triazole derivatives [2-Ethoxy-6-(3-methyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoate (**1**), 2-Ethoxy-6-(3-ethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoate (**2**), 2-Ethoxy-6-[3-(*n*-propyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine]-phenyl benzoate (**3**), 2-Ethoxy-6-(3-benzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoate (**4**), 2-Ethoxy-6-[3-(*p*-methylbenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine]-phenyl benzoate (**5**), 2-Ethoxy-6-[3-(*p*-methoxybenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine]-phenyl benzoate (**6**), 2-Ethoxy-6-[3-(*p*-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine]-phenyl benzoate **(7)**, 2-Ethoxy-6-[3-(*m*-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine]-phenyl benzoate (**8**) and 2-Ethoxy-6-(3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl-azomethine)-phenyl benzoate (**9**)] were titrated with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetone).

2.2. Potentiometric Titrations

For potentiometric titrations, an Orion 720A model pH ion meter equipped with a combined pH electrode (Ingold) and indicator electrode were employed. A 25 mL beaker, a magnetic stirrer, and a semi-micro burette were used in titrations. The pH meter was calibrated according to the instructions supplied by the manufacturers of the device before potentiometric titrations. In titrations, the titrant was added in increments of 0.05 mL then each stable reading and mV value were documented.

The used chemicals were supplied from Fluka and Merck. Purificated isopropyl alcohol was used to prepare a 0.05 N tetrabutylammonium hydroxide. 0.05 N tetrabutylammonium hydroxide in isopropyl alcohol was employed in potentiometric titrations. This solution was prepared from 0.1 N tetrabutylammonium hydroxide (TBAH) by dilution. The 0.05 M solution of TBAH in isopropyl alcohol as the titrant was used in the titration of acids. The half-neutralization potentials and the corresponding pK_a values of the compounds were determined from the potentiometric titrations with 0.05 M tetrabutylammonium hydroxide in isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide, and acetone. The mV values that were determined with the pH-meter.

The half neutralization potential (HNP) values and the found pK_a values of the compounds are given in Table **1**. The half-neutralization potential (HNP) values were calculated by drawing the mV-mL (TBAH) graphic. From the titration curves, the HNP values were found and the corresponding pK_a values were calculated [28,35].

3. Results and discussion

In this study, compounds **1-9** were titrated potentiometrically with TBAH in four non-aqueous solvents such as isopropyl alcohol (ε=17.9), *tert*-butyl alcohol (ε=12), acetone (ε=20.7) and *N*,*N*-dimethylformamide (ε=36.7). The mV values found in each titration were plotted against added 0.05 M TBAH volumes (mL) and potentiometric titration curves were obtained for all the experiments. From the titration curves, the HNP values were determined, and the corresponding pK_a values were founded.

The pH of weak acids can be calculated using Equation 1.

$$pH = pKa + log[A^-] / [HA] \qquad (1)$$

At the half-neutralization points, pH = pK_a when [A^-] is equal to [HA]. Therefore, the pH values at the half-neutralization points were stated as pK_a.

The half-neutralization potential (HNP) values and the corresponding pK_a values of compounds **1-9**, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetone, and DMF, are given in Table **1**.

As seen in Table **1**, for compounds **2** and **9** in *tert*-butyl alcohol, compound **5** in isopropyl alcohol and compound **8** in acetone, the HNP values and the corresponding pK_a values have not been obtained.

According to dielectric constant, the acidic arrangement can be expected as follows; *N*,*N*-dimethylformamide (ε=37) > acetone (ε=20.6) > isopropyl alcohol (ε=19.4) > *tert*-butyl alcohol (ε=12) [23-28,35]. However, as seen in Table **1**, the acidic arrangement for compounds **5** and **6** is: isopropyl alcohol > DMF > acetone > *tert*-butyl alcohol, for compound **1**, it is: acetone > DMF > *tert*-butyl alcohol, for compound **2**, it

is: isopropyl alcohol > acetone > DMF, for compound **3**, it is: DMF > isopropyl alcohol > *tert*-butyl alcohol > acetone, for compound **4**, it is: *tert*-butyl alcohol > DMF > isopropyl alcohol > acetone, for compound **7**, it is: acetone > isopropyl alcohol > *tert*-butyl alcohol > DMF, for compound **8**, it is: isopropyl alcohol > DMF > *tert*-butyl alcohol, and for compound **9**, it is: DMF > isopropyl alcohol > acetone.

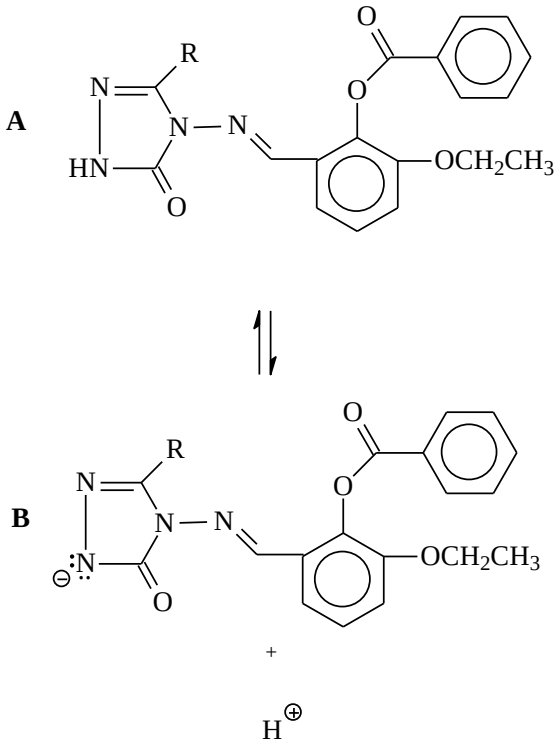
Table 1. The HNP and the corresponding pK_a values of compounds 1-9 in isopropyl alcohol, tert-butyl alcohol, DMF and acetone at 25 °C

Compound No	DMF		Acetone		tert-Butyl alcohol		Isopropyl alcohol	
	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a
1	-342	15.15	-316	14.12	-378	14.12	-	-
2	-361	15.66	-325	14.37	-365	15.05	-276	12.48
3	-172	11.08	-416	16.93	-340	14.32	-321	14.69
4	-372	15.88	-411	16.66	-193	8.14	-409	16.90
5	-267	13.35	-	-	-357	11.82	-211	11.93
6	-304	14.35	-446	17.30	-503	18.84	-	-
7	-324	14.85	-154	11.20	-229	12.10	-	-
8	-364	15.54	-	-	-409	16.22	-327	14.57
9	-267	13.22	-568	19.67	-	-	-393	16.07

In isopropyl alcohol, compounds **2**, **5**, **6**, and **8**, in acetone compounds **1** and **7**, in DMF compounds **3** and **9**, in *tert*-butyl alcohol, compound **4** show the strongest acidic properties. On the other hand, in *tert*-butyl alcohol, compounds **1**, **5**, **6**, and **8**, **in** acetone, compounds **3**, **4**, and **9**, **in** DMF, compounds **2** and **7**, show the weakest acidic properties. This situation may be attributed to the hydrogen bonding between the negative ions (**B**) formed and the solvent molecules in the amphiprotic neutral solvents [23,35-39] (Scheme **1**).

In addition, acidity is determined in each solvent and is observed in the following order: **7** > **5** > **6** > **2** > **3** > **8** > **9** > **4** in isopropyl alcohol, **4** > **7** > **3** > **5** > **1** > **8** > **6** **in** *tert*-butyl alcohol, **3** > **5** = **9** > **6** > **7** > **1** > **2** > **8** > **4** in DMF and **7** > **1** > **2** > **5** > **4** > **3** > **6** > **9** in acetone. According to these results, compound **7** in isopropyl alcohol and acetone, compound **4** in *tert*-butyl alcohol and compound **3** in DMF showed the strongest acidic properties; compound **4** in isopropyl alcohol and DMF, **6** in *tert*-butyl alcohol and compound **9** in acetone showed the weakest acidic properties [35].

The acidity of a compound alters according to some factors. The two most significant factors are solvent effects and molecular structure of the compound [9,10,12,15-17,22-27,36-40]. Table **1** shows that the HNP values and the corresponding pK_a values determined by the potentiometric titrations alter depending on the non-aqueous solvents in which the titration took place. Also, it is seen from Table **1** that the molecular structure of the compounds affects the HNP values as well as the corresponding pK_a values. Namely, the HNP values and corresponding pK_a values are related to the substituents linked to C-3 in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring for the same solvent [40].



Scheme 1

The potentiometric titration curves of compounds **1-9** solutions titrated with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide, and acetone are given in Figure **1-9**. The mV values were plotted versus the added TBAH volumes (mL), and thus potentiometric titration curves were obtained for all the experiments. From these curves, the HNP values were determined and the corresponding pK_a values were calculated.

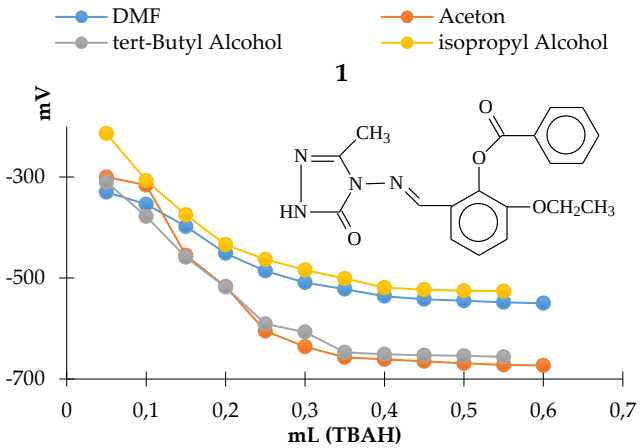


Figure 1. Potentiometric titration curves of 0.001 M solutions of compound **1** titrated with 0.05 M TBAH

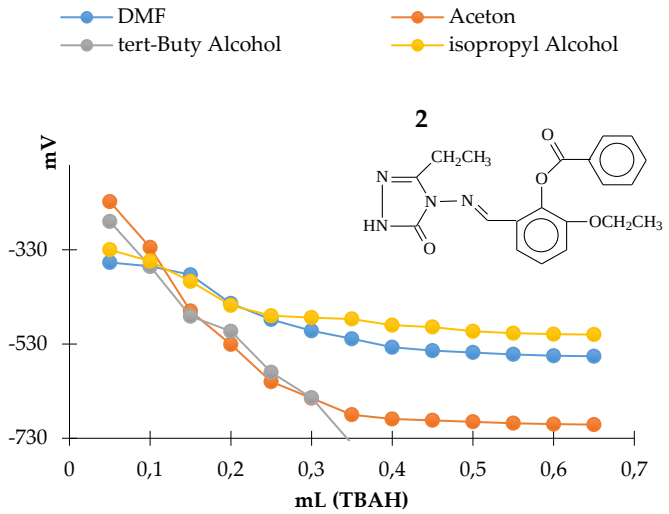


Figure 2. Potentiometric titration curves of 0.001 M solutions of compound **2** titrated with 0.05 M TBAH

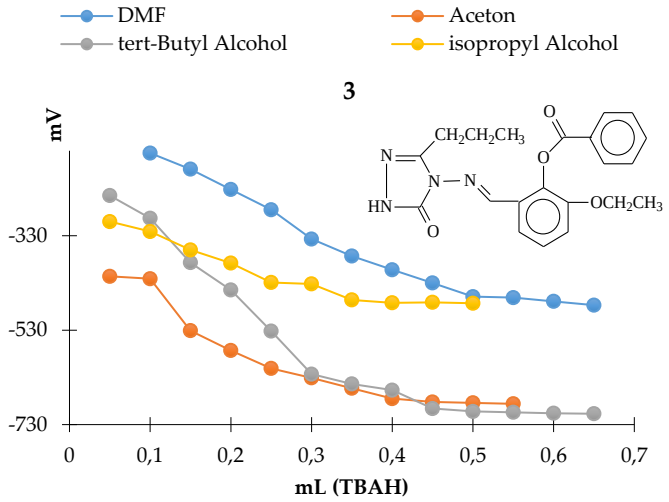


Figure 3. Potentiometric titration curves of 0.001 M solutions of compound **3** titrated with 0.05 M TBAH

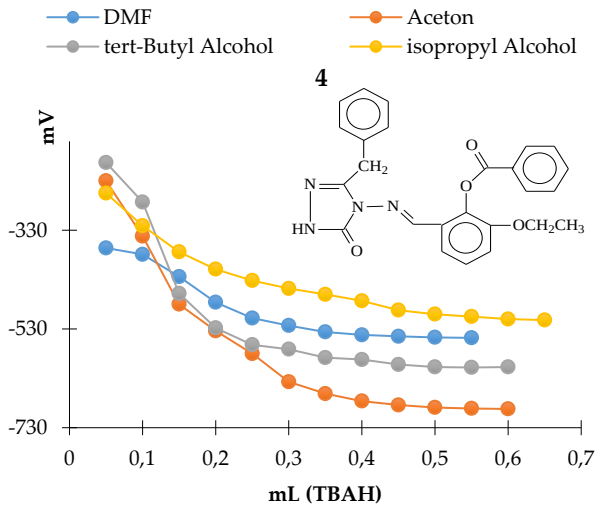


Figure 4. Potentiometric titration curves of 0.001 M solutions of compound **4** titrated with 0.05 M TBAH

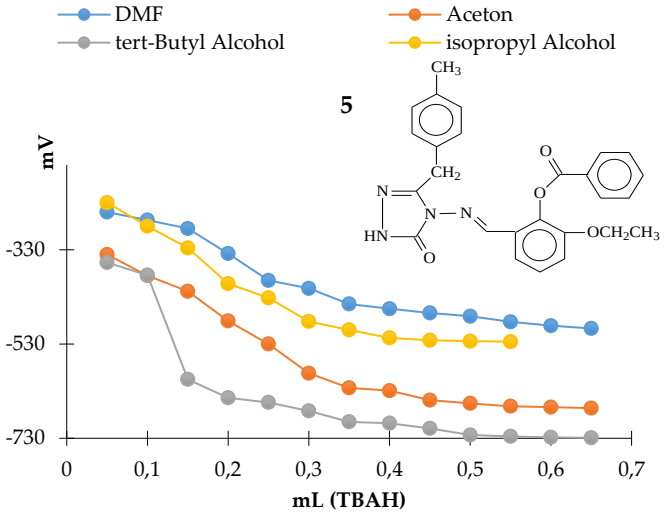


Figure 5. Potentiometric titration curves of 0.001 M solutions of compound **5** titrated with 0.05 M TBAH

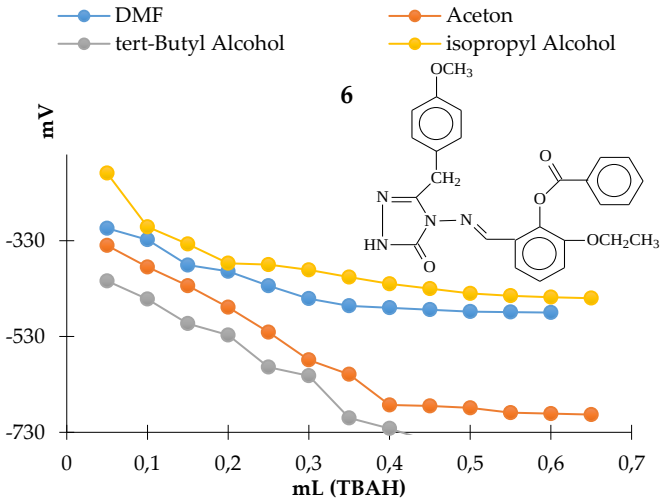


Figure 6. Potentiometric titration curves of 0.001 M solutions of compound **6** titrated with 0.05 M TBAH

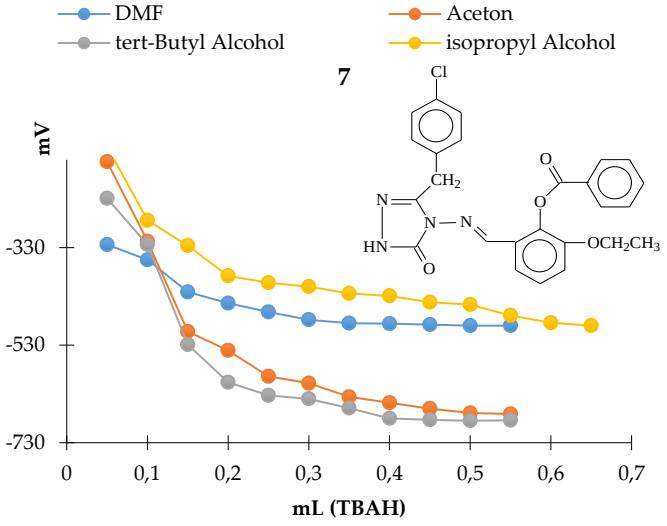


Figure 7. Potentiometric titration curves of 0.001 M solutions of compound 7 titrated with 0.05 M TBAH

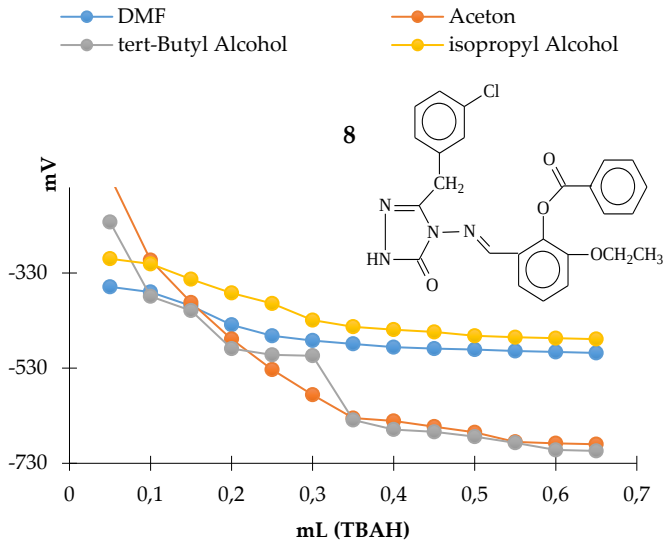


Figure 8. Potentiometric titration curves of 0.001 M solutions of compound **8** titrated with 0.05 M TBAH

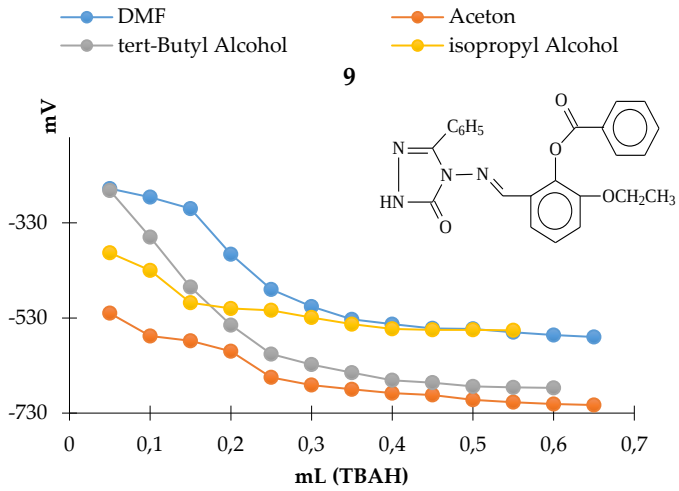


Figure 9. Potentiometric titration curves of 0.001 M solutions of compound **9** titrated with 0.05 M TBAH

Acknowledgements

This work was supported by the Scientific Research Projects Coordination Unit of Kafkas University (Project Number: 2011-FEF-31).

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