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Non-Aqueous medium titrations of some 3-alkyl(aryl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones

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Abstract

A series of 3-alkyl(aryl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1-9**) were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetonitrile, and *N*,*N*-dimethylformamide (DMF), and graphs were drawn for all cases. The half-neutralization potential values and the corresponding pK_a values were determined by the half neutralization method. Thus, the effects of solvents and molecular structure upon acidity were discussed.

Keywords: 1,2,4-triazol-5-one, Schiff base, acidity, potentiometric titrations, pK_a

1. Introduction

Several reports, involving the synthesis of some N-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives (Schiff bases), have been published up to date [1-9]. 1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are investigated to show a broad spectrum of biological activities such as antimicrobial, antifungal, antihypertensive, hypoglycemic, analgesic, antiparasitic, antiviral, anti-inflammatory, hypocholesteremic, antitumor, antioxidant, and anti-HIV properties [3,5-16].

Weak acidic properties of 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one rings have been well known. In this study, some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatived compounds were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents, and their pK_a values were determined [1-7,9,12,17-22]. We have previously reported the synthesis and potentiometric titrations of some new 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives in different non-aqueous mediums and determined the pK_a values of the compounds for each non-aqueous solvent [1-7,9,12,17-22]. Determination of p*K*a values of the active constituent of pharmaceutical preparations is valuable. Because distribution, transport behavior, bonding to receptors, and contributions to the metabolic behavior of the active constituents in the preparations depend on the ionization constant of the corresponding molecule [23-25].

The protonation constant of weak acidic compounds can be calculated by different methods. The potentiometric, chromatographic, and electrophoretic methods have been employed widely for this aim [26]. In the present work, the p*K*a values of some 1,2,4-triazole derivatives in non-aqueous media have been determined by using potentiometric titrations. These 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have been synthesized according to the reference in the literature [8].

2. Experimental

2.1. Preparation of compounds

The compounds **1-9** 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 3-(2-metylbenzoxy)-4-methoxybenzaldehyde as described in the literature [8].

In this study, nine different 4,5-dihydro-1*H*-1,2,4-triazole derivatives [3-methyl-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**1**), 3-ethyl-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-

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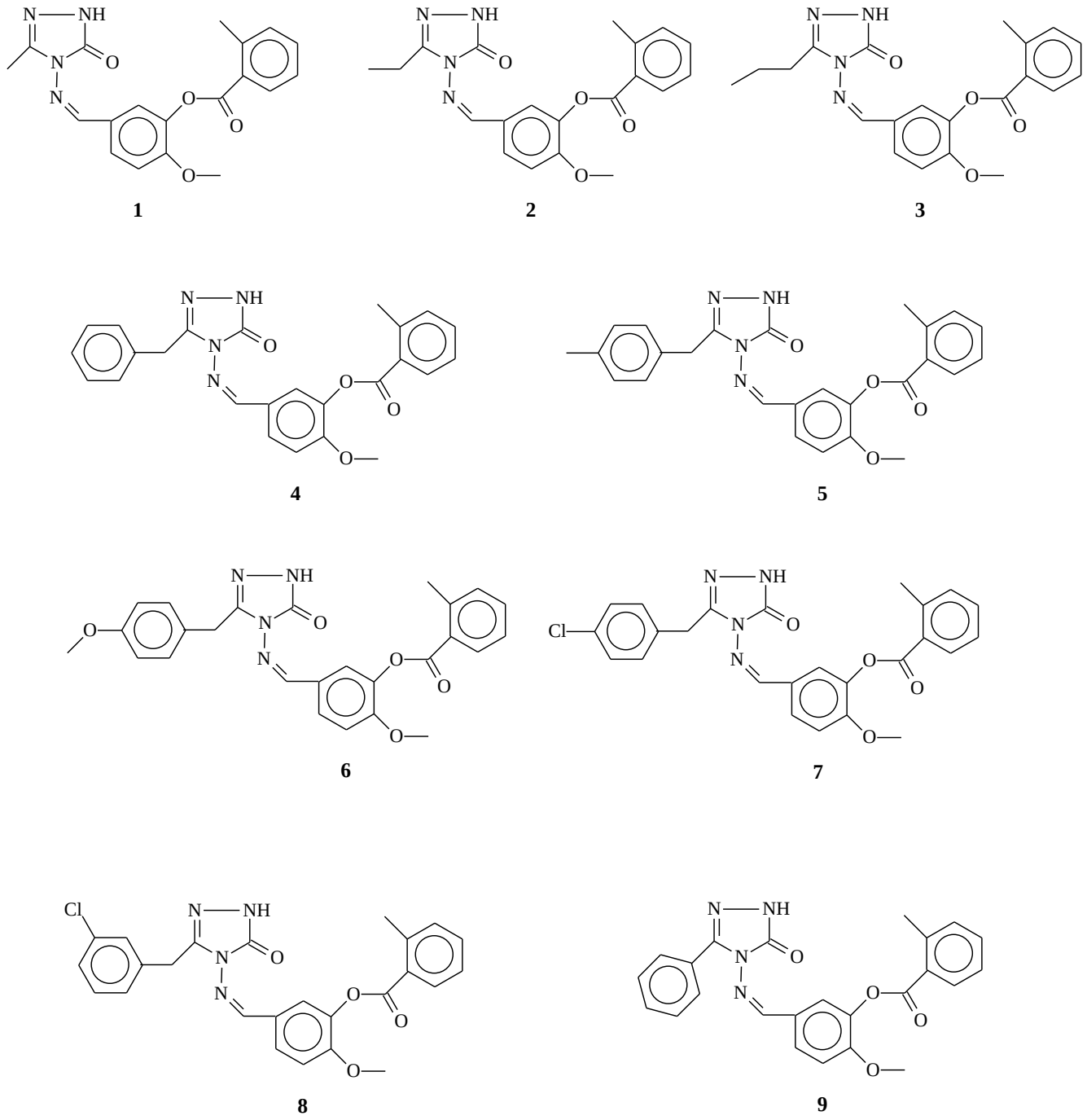

Figure 1. Studied 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives
1: 3-Methyl-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
2: 3-Ethyl-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
3: 3-(*n*-Propyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
4: 3-Benzyl-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
5: 3-(*p*-Methylbenzyl)-4-[3-(2-metylbenzoxy)-4-methoxy-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
6: 3-(*p*-Methoxybenzyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
7: 3-(*p*-Chlorobenzyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
8: 3-(*m*-Chlorobenzyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylidene-amino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one
9: 3-Phenyl-4-[3-(2-metylbenzoxy)-4-methoxy-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one

triazol-5-one (**2**), 3-(*n*-propyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**3**), 3-benzyl-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**4**), 3-(*p*-methylbenzyl)-4-[3-(2-metylbenzoxy)-4-methoxy-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**5**), 3-(*p*-methoxybenzyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**6**), 3-(*p*-chlorobenzyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**7**), 3-(*m*-chlorobenzyl)-4-[3-(2-metylbenzoxy)-4-methoxybenzylidene-amino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**8**), 3-phenyl-4-[3-(2-

metylbenzoxy)-4-methoxy-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**9**)] (Fig. 1) were titrated with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (*tert*-butyl alcohol, isopropyl alcohol, acetone, and *N*,*N*-dimethylformamide).

2.2. Potentiometric titrations

A Jenway 3040-model ion analyzer was used in potentiometric titration experiments. An Ingold pH electrode was employed in these experiments. The 0.001 M solution was separately prepared in each non-aqueous solvent for titration of each compound. The 0.05 M solution of TBAH in isopropyl alcohol because of widely its usage was employed as titrant. The mV values were recorded in the pH meter. Finally, the HNP values were found by drawing the mL (TBAH)-mV graphic.

3. Results and discussion

In this study, compounds **1-9** were titrated potentiometrically with TBAH in four non-aqueous solvents such as isopropyl (ε=19.4), *tert*-butyl alcohol (ε=12), acetone (ε=20.6) and *N*,*N*-dimethylformamide (ε=37) [3,6]. The mV values read in each titration were plotted against 0.05 M TBAH volumes (mL) added, and potentiometric titration curves were obtained for all the cases. From the titration curves, the HNP values were measured, and the corresponding p*K*a values were calculated.

The pH of weak acids can be found by using the Equation 1.

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

In Equation 1, pH equals p*K*a when [A$^-$] equals [HA], which is the half-neutralization point. Therefore, the *p*H values at the half-neutralization points were determined as p*K*a.

According to the dielectric permittivity of the solvents, the acidity ranking might be expected to be as follows: *N*,*N*-dimethylformamide (ε=37) > acetone (ε=20.6) > isopropyl alcohol (ε=19.4) > *tert*-butyl alcohol (ε=12) [3,6]. However, as seen in Table 1, the acidic arrangement for compounds **3** and **6** is: isopropyl alcohol > acetone > *tert*-butyl alcohol > *N*,*N*-dimethylformamide, for compounds **4** and **9**, it is: isopropyl alcohol > *tert*-butyl alcohol > acetone > *N*,*N*-dimethylformamide, for compounds **5** and **8**, it is: *N*,*N*-dimethylformamide > acetone, for compound **1**, it is: *tert*-butyl alcohol > isopropyl alcohol > *N*,*N*-dimethylformamide > acetone, and for compound, **2** it is: acetone > isopropyl alcohol > *N*,*N*-dimethylformamide, while the order for compound **7** is: *tert*-butyl alcohol > acetone > *N*,*N*-dimethylformamide.

As seen in Table 1, in isopropyl alcohol, compounds **3, 4**, and **6**, in *tert*-butyl alcohol **1**, **7** and **9**, in DMF, compounds **5** and **8**, in acetone, compound **2** show the strongest acidic properties, while compounds **2-4**, **6**, **7** and **9** show the weakest acidic properties in *N*,*N*-dimethylformamide (acetone for compounds **1**, **5** and **8**). This situation can be result from the hydrogen bonding between the negative ions formed and the solvent molecules in the amphiprotic neutral solvents [1-7,9,12,17-22].

The half-neutralization potential (HNP) values and the corresponding p*K*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 presented in Table 1.

Table 1. The HNP and the corresponding p*K*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)	p*K*a	HNP (mV)	p*K*a	HNP (mV)	p*K*a	HNP (mV)	p*K*a
1	-334	14.32	-478	17.12	-185	10.71	-230	13.16
2	-315	14.36	-226	11.69	-	-	-277	13.48
3	-289	13.37	-215	11.55	-246	11.83	-152	10.34
4	-180	12.53	-159	11.21	-222	11.00	-106	9.16
5	-326	14.62	-418	16.53	-	-	-	-
6	-428	16.96	-195	11.56	-267	12.97	-148	10.08
7	-370	14.18	-218	12.18	-85	7.24	-	-
8	-279	13.20	-324	13.54	-	-	-	-
9	-336	14.99	-243	11.57	-209	10.12	-248	11.14

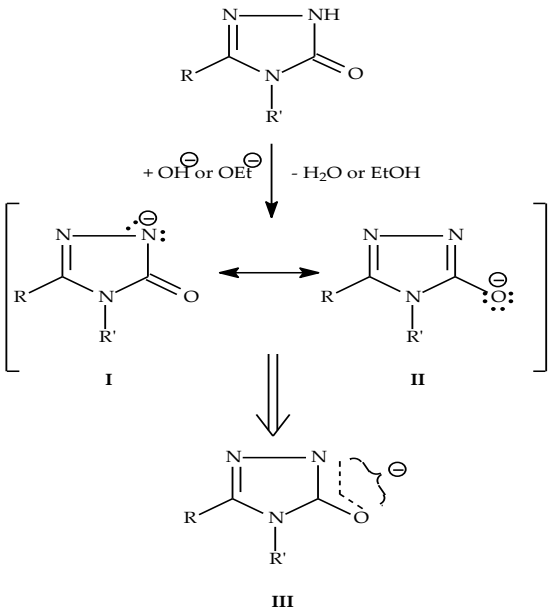

Figure 2. Resonance structures

As seen in Table 1, for compound **2** in *tert*-butyl alcohol, compound **5** in *tert*-butyl alcohol and isopropyl alcohol, compound **7** in isopropyl alcohol, compound **8** in acetone, *tert*-butyl alcohol, and isopropyl alcohol, compound **3e** in *tert*-butyl alcohol and isopropyl alcohol, the HNP values and the corresponding p*K*a values have not been obtained.

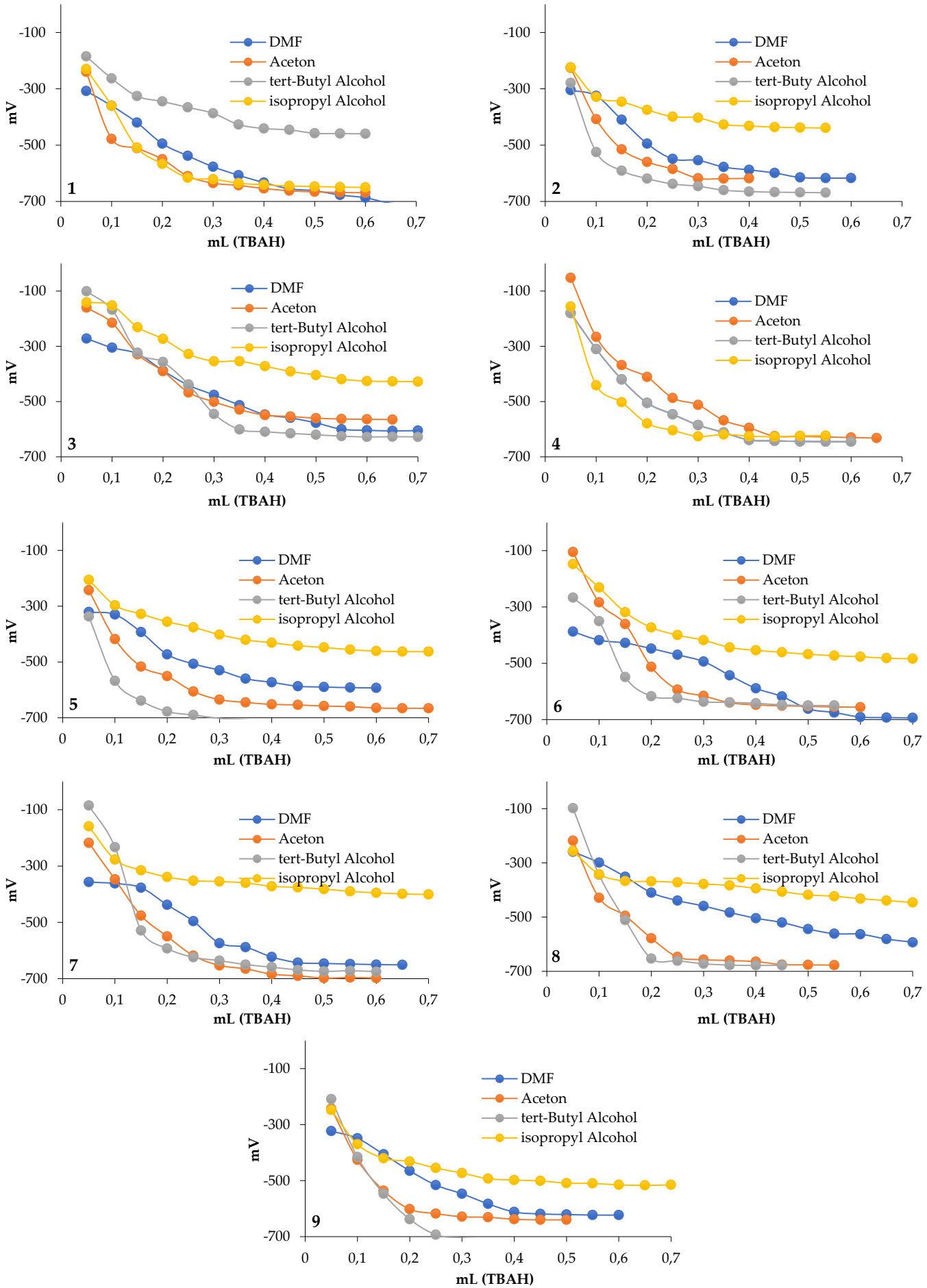

Figure 3. Potentiometric titration curves of 0.001 M solutions of compounds **1-9** titrated with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetone, and *N*,*N*-dimethylformamide at 25°C

Acidic properties of a compound depend on some structural and environmental factors. The two most important factors from these are the solvent effect and molecular structure of the compound [1-7,9,12,17-22,27]. Table 1 shows that the HNP values and corresponding p*K*a values determined from the potentiometric titration experiments depend on the non-aqueous solvents used and the substituents at C-3, in the 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring. This situation may be attributed to resonance structures as seen in Fig. 2.

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