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Research Article

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Determination of Acid Dissociation Constants of Some Di-[2-(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] Isophtalates

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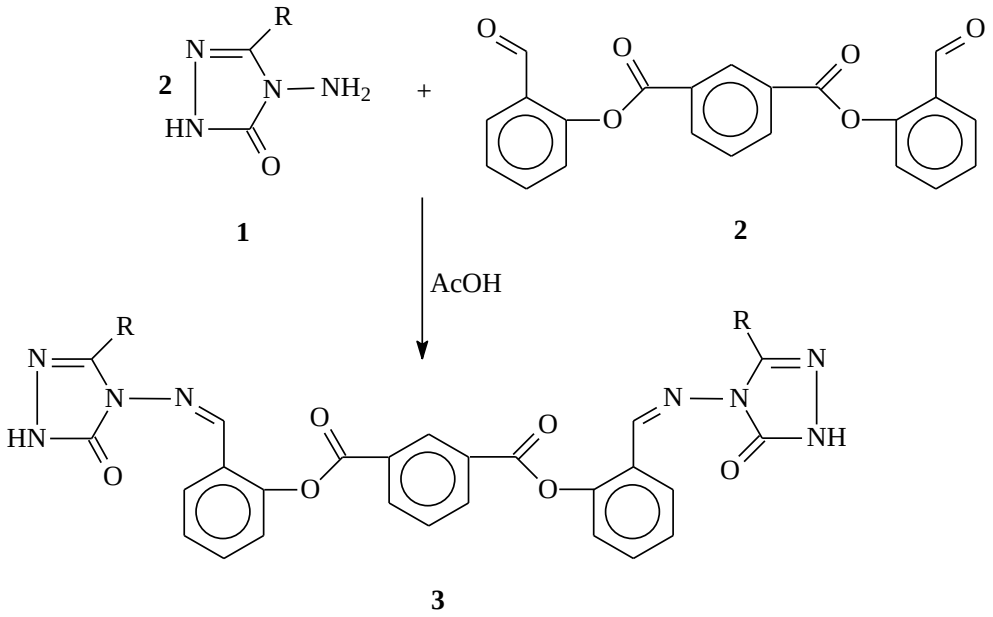
Abstract A series of di-[2-(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3**) were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetone and *N*,*N*-dimethylformamide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

Keywords 1,2,4-triazol-5-one, non-aqueous solvent, acidity, potentiometric titration, pK_a

Introduction

It is known that 4,5-dihydro-1*H*-1,2,4-triazol-5-one rings have weak acidic properties, so that some 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutylammonium hydroxide (TBAH) in non-aqueous solvents, and the pK_a values of the compounds were determined [1-12]. Determination of pK_a values of the active constituent of certain pharmaceutical preparations is important because the distribution, transport behavior, bonding to receptors, and contributions to the metabolic behavior of the active constituent molecules depend on the ionization constant [13-15].

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 pK_a values of some 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives in non-aqueous media using potentiometric measurements in determined. These di-[2-(3-alkyl/aryl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3**) were obtained from the reactions of 3-alkyl/aryl-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with di-(2-formylphenyl) isophtalate (**2**) according to literature (Scheme 1) [17].



a) R = CH_3, b) R = CH_2CH_3, c) R = $CH_2CH_2CH_3$, d) R = $CH_2C_6H_5$, e) R = $CH_2C_6H_4CH_3$ (*p*-), f) R = $CH_2C_6H_4Cl$ (*p*-), g) R = C_6H_5

Materials and Methods

Chemistry

In this study, seven different 4,5-dihydro-1*H*-1,2,4-triazole derivatives {di-[2-(3-methyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3a**), di-[2-(3-ethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3b**), di-[2-(3-*n*-propyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3c**), di-[2-(3-benzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3d**), di-[2-(3-*p*-methylbenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3e**), di-[2-(3-*p*-chlorobenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3f**), di-[2-(3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-azomethinephenyl] isophtalates (**3g**)} were titrated with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetone), using potentiometric method.

Potentiometric titrations

In this study, a Jenway 3040-model ion analyzer was used for potentiometric titrations. An Ingold pH electrode was preferred because of the advantage. For each compound that would be titrated, the 0.001 M solution was separately prepared in each non-aqueous solvent. The 0.05 M solution of TBAH in isopropyl alcohol, which is widely used in the titration of acids, was used as titrant. The mV values, that were obtained in pH-meter, were recorded. Finally, the HNP values were determined by drawing the mL (TBAH)-mV graphic.

Results & Discussion

In this study, potentiometric analysis of **3a-g** compounds in amphiprotic and dipolar aprotic solvents. Acid strengths determined using the half-neutralization method. The effects of the functional groups included in the compounds, the autoprotolysis constant of the solvent, the dielectric constant and the leveling-differentiation effect on the acidity strength were investigated.

The pH of weak acids can be calculated using the following equation: pH = pK_a + log[A-] / [HA] where pH = pK_a when [A-] is equal to [HA] at the half-neutralization points. Therefore, the pH values at the half-neutralization points were taken as pK_a. Taking into consideration the dielectric permittivity of the solvents, the acidity ranking might be expected to be as follows: *N*,*N*-dimethylformamide (ε=37); acetone (20,6); isopropyl alcohol (ε=19.4); *tert*-butyl alcohol (ε=12.0) [3].

In amphiprotic solvents, the data obtained for the compound **3d** showed that it was in agreement with the theoretical ranking for isopropyl alcohol and *tert*-butyl alcohol. However, the acidity strengths of the other compounds could not be compared with the theoretical ranking. Since compounds **3a**, **3b**, **3c**, **3e**, **3f** and **3g** in isopropyl alcohol, compounds **3a** and **3g** in *tert*-butyl alcohol, HNP values and corresponding pK_a values were not obtained, the acidity of the compounds between solvents could not be compared. The data obtained for the compound **3d** showed that it was in agreement with the theoretical ranking for isopropyl alcohol and *tert*-butyl alcohol.

The half-neutralization potential (HNP) values and the corresponding pK_a values of compounds **3a-g**, 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 pK_a values of compounds **3a-g** in isopropyl alcohol, *tert*-butyl alcohol, DMF and acetone at 25 °C

Compd. no	DMF		Acetone		*tert*-Butyl alcohol		Isopropyl alcohol	
	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a
3a	-490	15.76	-464	15,56	-	-	-	-
3b	-507	16.05	-760	-	-592	17.62	-	-
3c	-515	16.16	-719	-	-687	19.17	-	-
3d	-487	15.75	-	-	-609	17.71	-358	13.53
3e	-487	15.70	-752	-	-701	19.37	-	-
3f	-472	15.51	-745	-	-689	19.28	-	-
3g	-506	16.08	-762	-	-	-	-	-

In dipolar aprotic solvents, it was found that the acidic strengths of other compounds in acetone and DMF solvents, except compound **3a**, were in accordance with the theoretical order. Dipolar aprotic solvents give SH_2^+ ions but not S^- ions.

$$HA + S \rightleftharpoons S...HA \rightleftharpoons SH^+A^- \rightleftharpoons SH^+ + A^-$$

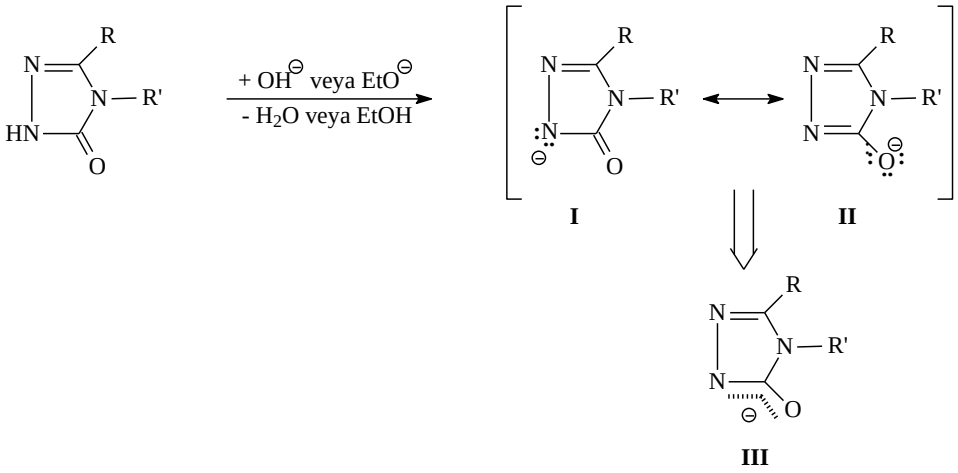
(a) (b) (c)

(HA: Acid (Molecular) and S: Solvent). When the equilibrium is examined, the equilibrium of (a) and (b) occur more in protophilic (DMF) solvents than in protophobic (acetone) solvents. The equilibrium of (c) is very low in protophilic solvents, but in trace amounts in protophobic solvents. The SH^+ in the protophobic solvent is the much stronger.

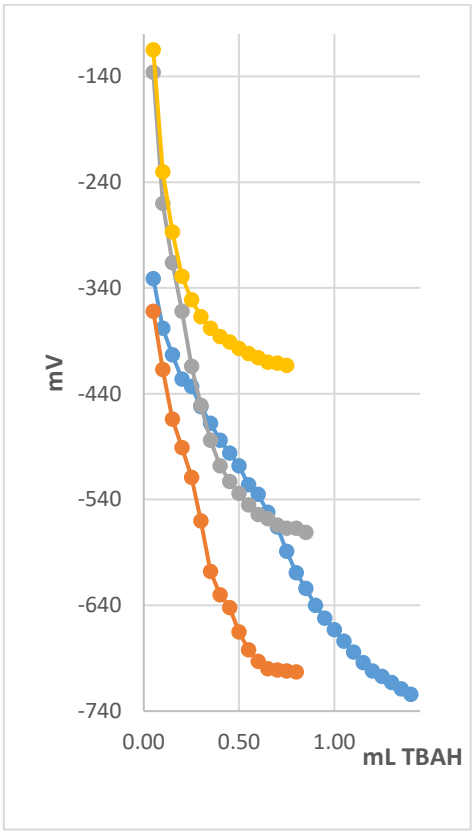
Considering the autoprotolysis constant, it was seen that the HNP values of the compounds **3** and the potential measured ranges of the solvents in *tert*-butyl alcohol (1200 mV), isopropyl alcohol (1000 mV), DMF (1300 mV), and acetone (1550 mV) medium are weakly acidic compounds **3d** and **3e** were leveled in DMF medium. It has been differentiated in other solvents.

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 [1-12,18]. Table **1** shows that the HNP values and corresponding p*K*a values obtained from the potentiometric titrations depends on the non-aqueous solvents used and the substituents at C-3, in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring.

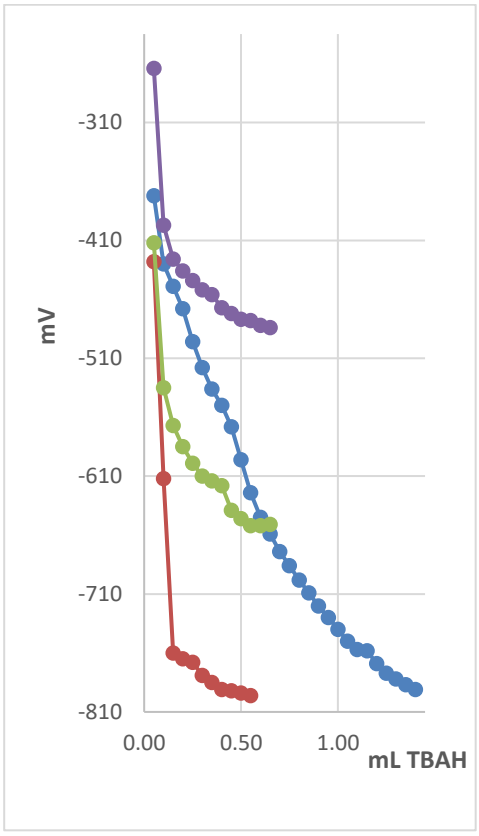
4,5-Dihydro-1*H*-1,2,4-triazol-5-one ring having N-H group has weak acidic properties. This situation may be attributed to resonance structures as seen below.



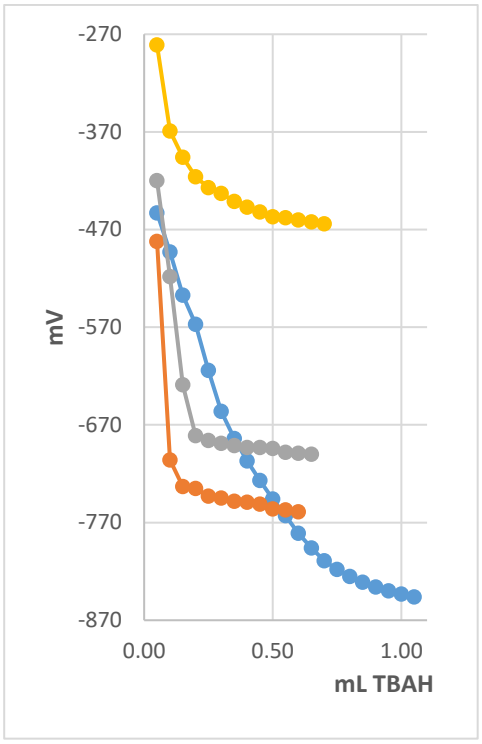
The potentiometric titration curves for 0.001 M compouds **3a-g** solutions titrated with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, *N*,*N*-dimethylformamide and acetone are given in Figure **1**.



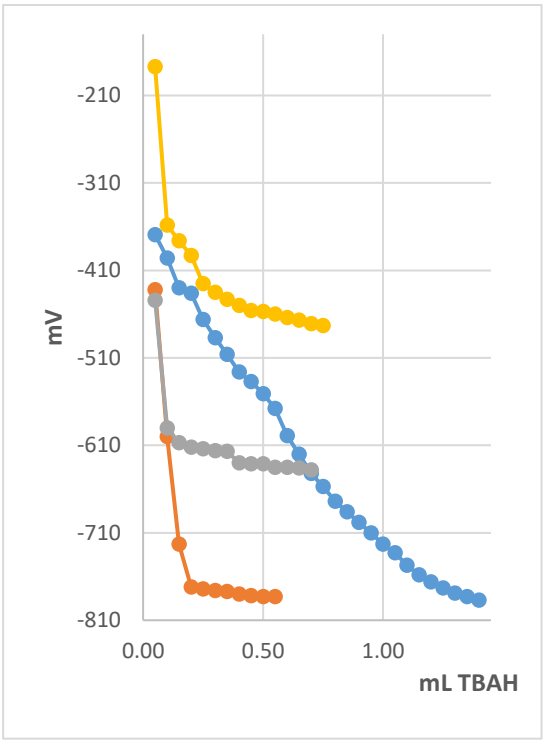
3a



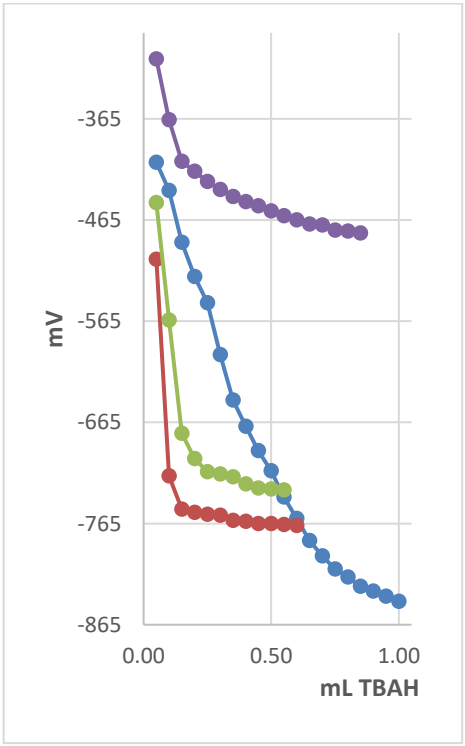
3b


-270
-370
-470
-570
-670
-770
-870
mV
0.00
0.50
1.00
mL TBAH

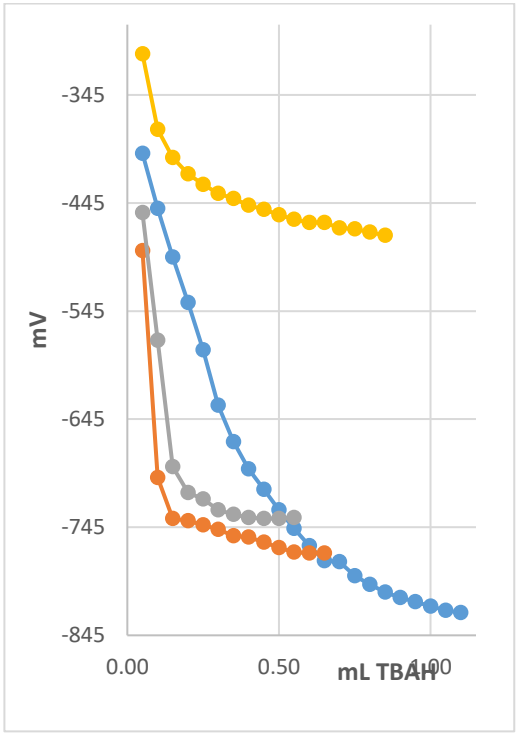
3c


-210
-310
-410
-510
-610
-710
-810
mV
0.00
0.50
1.00
mL TBAH

3d


-365
-465
-565
-665
-765
-865
mV
0.00
0.50
1.00
mL TBAH

3e


-345
-445
-545
-645
-745
-845
mV
0.00
0.50
mL TBAH

3f

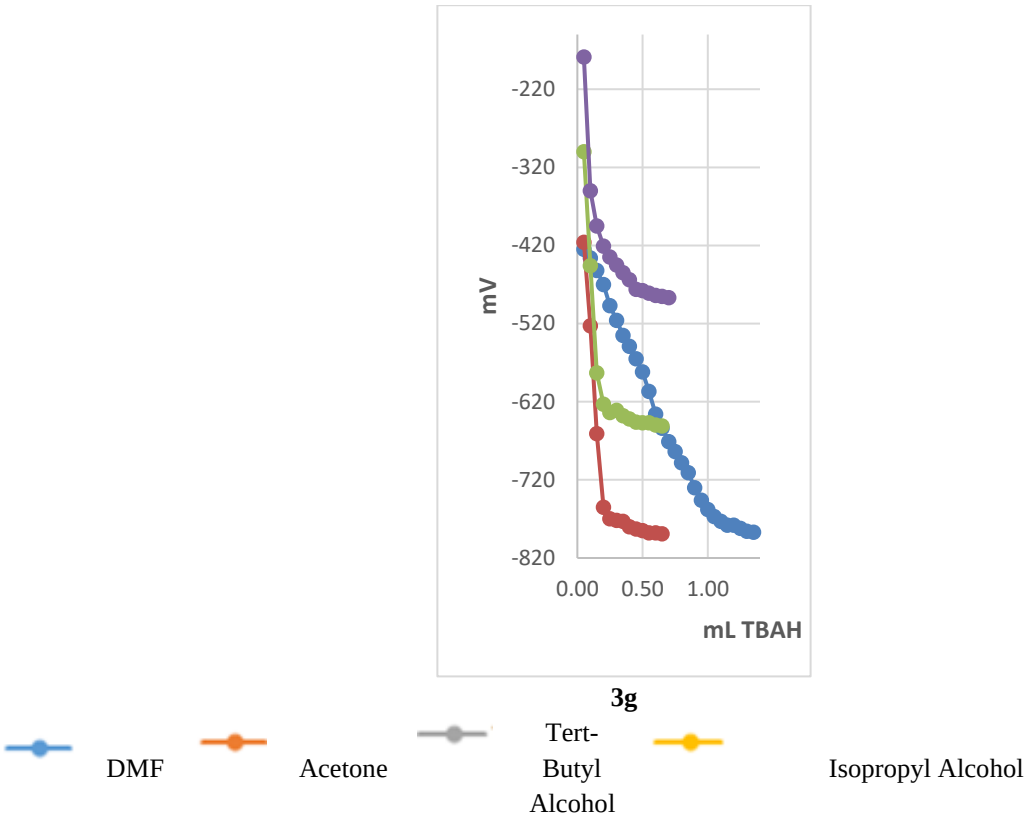


*Figure 1: Potentiometric titration curves of 0.001 M solutions of compound **3a-g** titrated with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, acetone and N,N-dimethylformamide at 25°C.*

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