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Bazı 3-Alkil(Aril)-4-ftalimido-4,5-dihidro-1H-1,2,4-triazol-5-on Bileşiklerinin Yarı-Nötralizasyon Metodu ile HNP ve pKa Değerlerinin Tayini

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Makalenin Alanı: Matematik

Makale Bilgileri

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Titrasyon

Öz

Bu çalışmada, asitlik üzerine çözücü ve moleküler yapının etkilerini incelemek için, beş 3-alkil(aril)-4-ftalimido-4,5-dihidro-1*H*-1,2,4-triazol-5-on (**3-7**) bileşiğinin dört farklı susuz çözücüde (izopropil alkol, asetonitril, tert-butil alkol ve N,N-dimetilformamid) tetrabutilamonyum hidroksitle (TBAH) potansiyometrik olarak titrasyonları yapılmış ve yarı nötralizasyon yöntemi ile HNP ve karşın olan pKa değerleri her durum için tayin edilmiştir.

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Abstract

In this study, the effects of solvents and molecular structure upon acidity, five 3-alkyl(aryl)-4-phthalimido-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3-7**) were potentiometrically titrated with tetrabutylammonium hydroxide (TBAH) in four different anhydrous solvents (isopropyl alcohol, acetonitrile, *tert*-butyl alcohol and *N,N*-dimethylformamide) and HNP and corresponding pK_a values were determined by half-neutralization method for all cases.

INTRODUCTION

Triazoles are heterocyclic compounds that contain three nitrogen atoms. It has been reported that 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have a wide spectrum of biological activities such as antioxidant (Koç et al., 2020; Yüksek et al., 2020), antimicrobial (Gursoy-Kol et al., 2020; Yüksek et al., 2020), antifungal (Kahveci et al., 2008), Gursoy-Kol et al., 2012), anti-inflammatory (Uzgoren-Baran et al., 2012), antiviral (Henen et al., 2012) and antitumor (Demirbaş et al., 2002).

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It is known that 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring show weak acidic properties due to the N-H group it carries, and many studies have been conducted on acidity studies of these compounds in recent years (Ocak, 2003; Gürbüz et al., 2021; Aktaş-Yokuş et al., 2017; Yüksek et al., 2017). In these studies, anhydrous solvents were used because of the low solubility of these heterocyclic compounds in water. The solutions of these compounds in anhydrous solvents were potentiometrically titrated with tetrabutylammonium hydroxide (TBAH). Potentiometric titrations are often used to titrate very weak acids and bases, sometimes even mixtures of acids and bases (Huber, 1967). As a result of the titrations, the pH and mV values corresponding to the titrant volume were read and a titration graph was drawn according to these values. There are turning points from the plotted graphs. The turning points are the points where the largest jump in mV versus the volume of titrant added (mL) occurs. From these values, half-neutralization points are determined. Since the pK_a values at the half-neutralization points are equal to the pH values, the pH values are taken as the pK_a values.

In order to determine the acidity of 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, the first two studies were carried out in 1991 on the potentiometric titration of their solutions in isopropyl alcohol with TBAH and the determination of their pK_a values (İkizler and Erdoğan, 1991; İkizler et al., 1991).

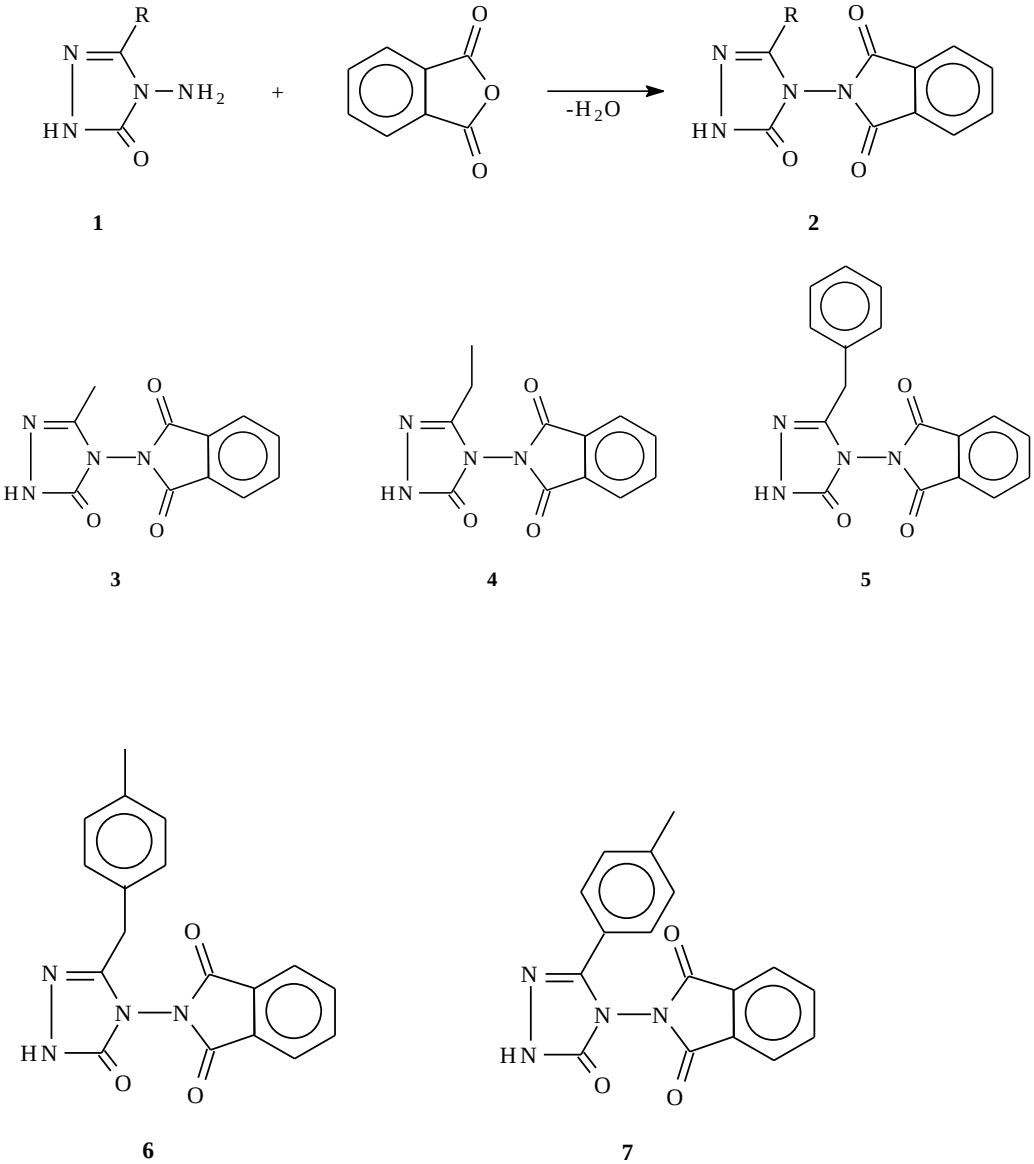
In many studies, especially after 2002, titration graphs were drawn by potentiometrically titration of the newly synthesized 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives in different non-aqueous solvents with TBAH. Then, titration graphs were drawn and pK_a values were determined by half-neutralization method (HNP) and molecular structure on acidity were investigated (Bahçeci et all., 2002; İslamoğlu et al., 2011; Yüksek and Gürsoy-Kol, 2008; Aktaş-Yokuş et al., 2020).

Knowing the pK_a values of the active ingredient of pharmaceutical preparations is important because the distribution of active ingredient molecules, transport behavior, binding to receptors and their contribution to metabolic behavior depend on the ionization constant (Demirbaş et al., 1998; Putun et al., 1995; Frey et al., 1971).

MATERIALS and METHODS

Chemical Compounds

In the study, firstly five N,N'-linked biheterocyclic 3-alkyl(aryl)-4-phthalimido-4,5-dihydro-1H-1,2,4-triazol-5-ones (3-7)) required for work were synthesized according to the literature (Ikizler and Yuksek 1996; Ikizler and Un 1979; Ikizler and Yuksek 1993) (Schema 1).



Schema 1. *N,N*'-Linked biheterocyclic compounds whose acidity was studied

Chemicals

Anhydrous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide were used to determine the pK_a constants of compounds **3-7**. Required solvents were obtained from Merck

Prepared Solutions

In the titration of compounds 3-7, which are weak acids, 0.05 N solution prepared by diluting from a standard 0.1 N solution of TBAH in isopropyl alcohol was used as titrant. 10^{-3} M 100 mL solutions of the compounds **3-7** were prepared in isopropyl alcohol, *tert*-butyl alcohol, *N,N*-dimethylformamide and acetonitrile.

Devices

A Jenway 3040 Model Ion Analyzer was used in the study. The Ion Analyzer used has an sensibility of ±0.001 with an accuracy of ±0.005 in pH measurements, an sensibility of ±0.1 in mV measurements and an accuracy of ±0.2. As the electrode, ingold combined pH electrode was preferred. A 50 µL micropipette was used for the titrations.

Half-Neutralization Method

As a result of the titrations, the pH and mV values corresponding to the titrant volume were read and a titration graph was drawn according to these values. The turning points were found by using the first and second derivative graphs.

Weak acid and its salt form a buffer solution. In a buffer solution, the pH of weak acids can be calculated using the following equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

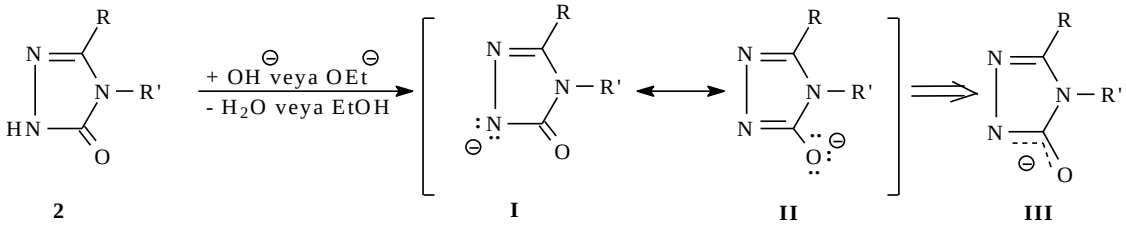
Where pH = pK_a when [A-] is equal to [HA] at the half-neutralization points (Skoog and Leary. 1992; Gündüz and Gündüz 2002; Ocak 2003).

As a result, the pH values of weak acids at the half-neutralization points can be taken as pK_a.

RESULTS and DISCUSSION

In the study, half-neutralization values and corresponding acidity constants of five *N,N'*-linked biheterocyclic compounds, which are 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, were determined. The assays were carried out at 25˚C in anhydrous environment using potentiometric titration. Since the solubility of 4,5-dihydro-1*H*-1,2,4-triazol-5-one compounds in aqueous media is very low, non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide are preferred. As titrant, a solution of tetrabutylammonium hydroxide (TBAH), which is widely used in these determinations, in isopropyl alcohol was used (Bahçeci et all., 2002; İslamoğlu et all., 2011; Yüksek and Gürsoy-Kol, 2008; Aktaş-Yokuş et all., 2020).

The reason why the 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring has weak acidity can be explained as follows (Alkan et al., 2007):



2 I II III

The resonance hybrid of I and II resonance structures is III, showing that the negative charge is delocalized to include electronegative nitrogen and oxygen atoms.

The half-neutralization potentials of compounds **3-7** in four different non-aqueous solvents and their corresponding pK_a values are given in Table **1.**

Table 1. The HNP and the corresponding pK_a values of compounds **3-7** in isopropyl alcohol, *tert*-butyl alcohol, DMF and acetonitrile at 25 °C

Compd. no	DMF		Acetonitrile		*tert*-Butyl alcohol		Isopropyl alcohol	
	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a
3	-497	15,70	-619	18,04	-606	17,81	-	-
4	-392	13,67	-486	15,31	-578	16,98	-76	7,62
5	-447	14,74	-409	13,98	-415	13,97	-351	12,73
6	-475	15,18	-471	15,08	-	-	-336	15,52
7	-550	16,94	-318	12,29	-392	13,41	-295	11,80

When Table **1** is examined, it is seen that the typical S-shaped titration curves of the compounds **3-7** are obtained in each solvent, and the HNP and the corresponding pK_a values are obtained. However, since S-shaped titration curves could not be obtained for compound **3** in isopropyl alcohol and compound **6** in tert-butyl alcohol, acidity values could not be determined. Therefore, a comparison could not be made.

According to the results obtained, the order of the compounds in the solvents is as follows, taking into account the HNP values:

3: DMF > *tert*-butyl alcohol > acetonitrile

4: isopropyl alcohol > DMF > acetonitrile > *tert*- butyl alcohol

5: isopropyl alcohol > acetonitrile > *tert*- butyl alcohol > DMF

6: isopropyl alcohol > acetonitrile > DMF

7: isopropyl alcohol > acetonitrile > *tert*- butyl alcohol > DMF

Compound **3** showed the highest acidity in DMF, while the other compounds had the highest acidity in isopropyl alcohol. In addition, compound **3** showed the lowest acidity in acetonitrile, while compound **2** in *tert*-butyl alcohol, and compounds **5-7** in DMF.

When all the compounds were taken into consideration, it was found that the compound **2** showed the highest acidity in isopropyl alcohol, while the compound **3** showed the lowest acidity in acetonitrile.

Considering the acidity order of the R functional groups, it was seen that the acidity order of the compounds for each solvent was as follows:

DMF	**:** 4 > 5 > 6 > 3 > 7
Acetonitrile	**:** 7 > 5 > 6 > 4 > 3
tert-Butyl alcohol	**:** 7 > 5 > 4 > 3
Isopropyl alcohol	**:** 4 > 7 > 6 > 5

As can be understood from the ranking, it was observed that the groups linked to C-3 did not have a significant effect on acidity since they were far away. It is thought that factors such as London gravitational forces and solubility are also effective on this ranking in acidity strength, as can be seen from the literature.

Titration graphs of compounds **3-7** in DMF, acetonitrile, isopropyl alcohol and *tert*-butyl alcohol at 25 °C are given in Figure **1-5**.

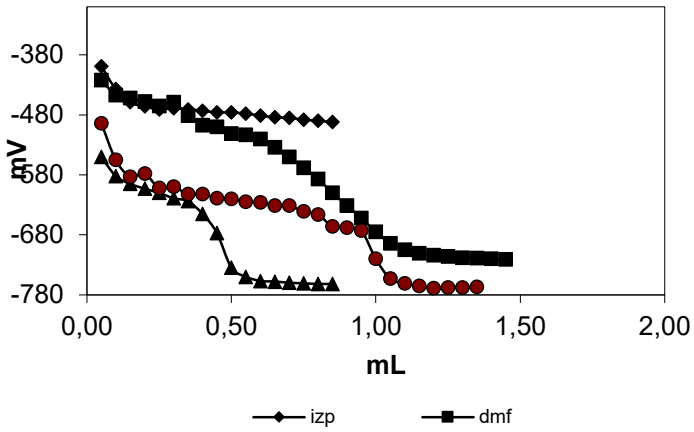


Figure 1. Potentiometric titration curves of 0.001 M solutions of compound **3** in 10^{-3} M solutions of DMF, acetonitrile, isopropyl alcohol, and tert-butyl alcohol with 0.05 N TBAH

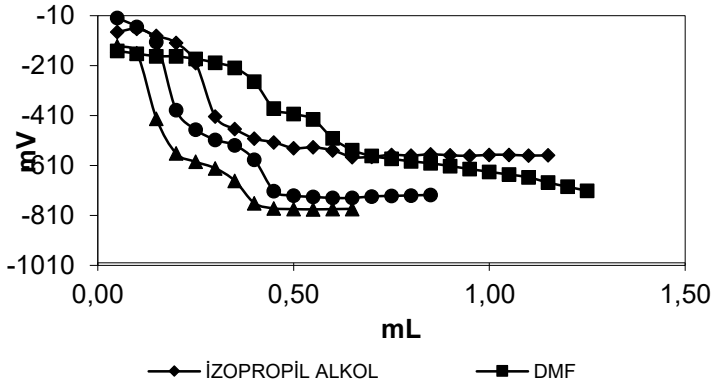


Figure 2. Potentiometric titration curves of 0.001 M solutions of compound **4** in 10^{-3} M solutions of DMF, acetonitrile, isopropyl alcohol, and tert-butyl alcohol with 0.05 N TBAH

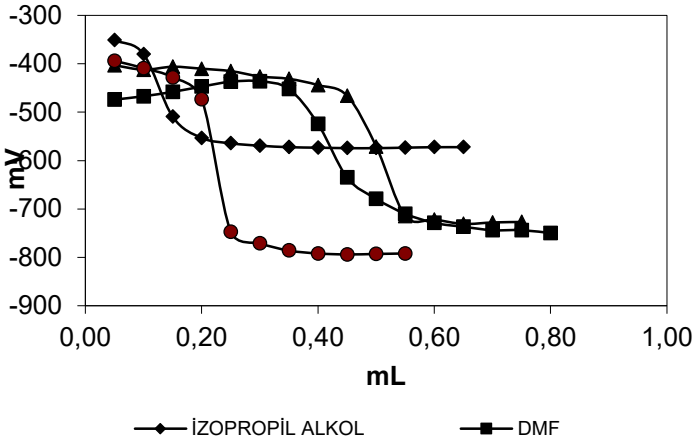


Figure 3. Potentiometric titration curves of 0.001 M solutions of compound **5** in 10-3 M solutions of DMF, acetonitrile, isopropyl alcohol, and tert-butyl alcohol with 0.05 N TBAH

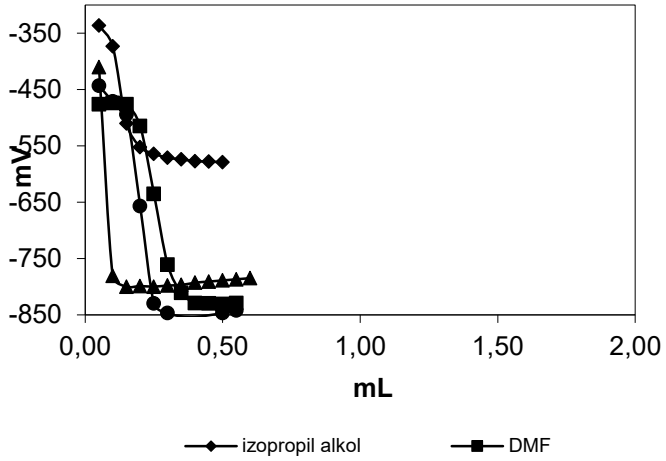


Figure 4. Potentiometric titration curves of 0.001 M solutions of compound **6** in 10^{-3} M solutions of DMF, acetonitrile, isopropyl alcohol, and tert-butyl alcohol with 0.05 N TBAH

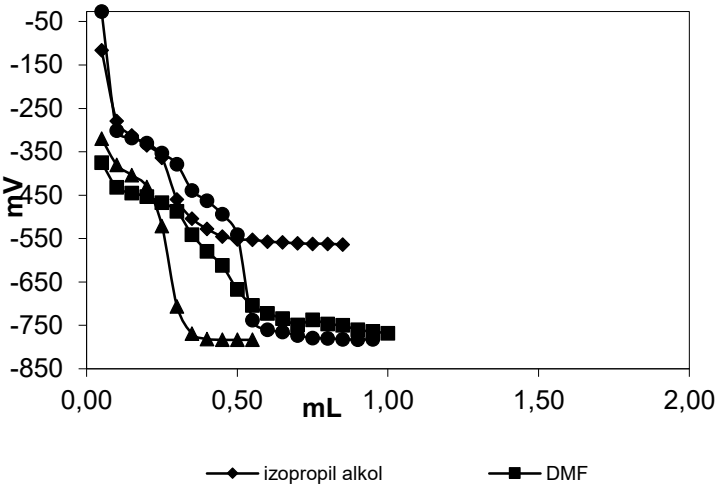


Figure 5. Potentiometric titration curves of 0.001 M solutions of compound **7** in 10^{-3} M solutions of DMF, acetonitrile, isopropyl alcohol, and tert-butyl alcohol with 0.05 N TBAH

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