

DETERMINATION OF PROTONATION CONSTANTS OF SOME 3-ALKYL(ARYL)-4-(*p*-t-BUTYL(BENZYL/BENZYLIDEN)AMINO)-4,5-DIHYDRO-1*H*-1,2,4-TRIAZOLE-5-ONE DERIVATIVES IN ETHANOL-WATER MIXTURES

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ABSTRACT. Stoichiometric protonation constants of some 3-alkyl(aryl)-4-(*p*-t-butyl(benzyl/benzyliden)amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one derivatives were determined potentiometrically in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M. The calculation of the stoichiometric protonation constants was carried out using a PKAS computer program. The effect of solvents composition on the stoichiometric protonation constants are discussed.

KEY WORDS: Ethanol-water mixtures, Stoichiometric protonation constants, Potentiometry

INTRODUCTION

There have been a number of systematic studies of the acidity in different media using different techniques [1-13], but unfortunately very few have dealt with triazoles. It is well known that two major factors influence the acidity of a molecule [14-17], namely, structural and solvent effects. In most molecules there are two or more structural effects and it is usually very difficult to assess how much each effect contributes to the acidity of a molecule. Moreover, it is sometimes extremely difficult to differentiate between structural and solvent effects.

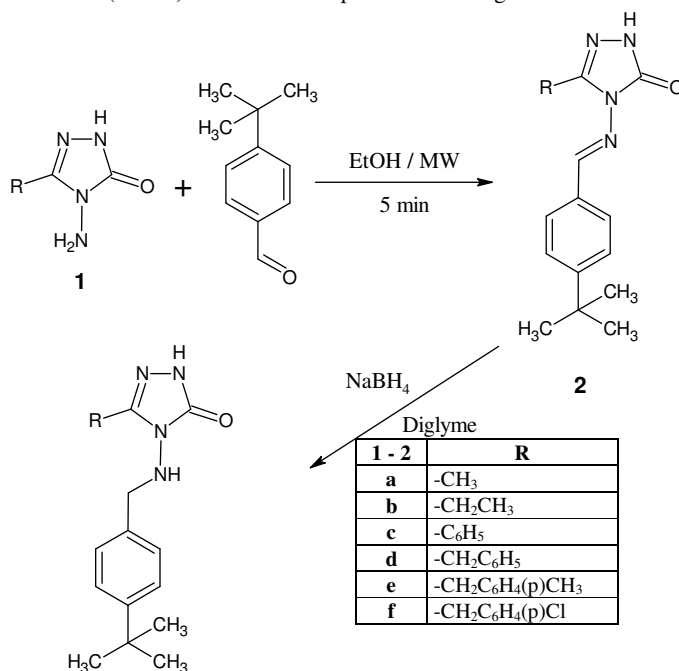
The considerable biological importance of triazoles has stimulated much work on these derivatives [18-22]. Some naturally occurring substances of pharmacological interest have been found to possess a triazole ring in their structure [23-25]. The exact role of these derivatives in the mode of action as antibiotic or antitumor drugs remains obscure [26]. In addition, these derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, antiinflammatory, antioxidant and anti-HIV properties [27-32].

An acceptable representation of the structure of triazoles must take into consideration its amphoteric nature; the mobility of the imino hydrogen atom; the great stability, aromatic character, and substitution pattern of the nucleus; and the physical evidence that suggests its considerably polar nature. Triazoles are readily soluble in polar solvents and only slightly soluble in nonpolar solvents, the solubility in the latter being increased by substitution on the nitrogen atom. In an attempt to obtain further information, we have determined potentiometrically the stoichiometric protonation constants of some 3-alkyl(aryl)-4-(*p*-t-butyl(benzyl/benzyliden)amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one derivatives in ethanol - water mixtures. Furthermore, the effect of solvents composition on these constants are discussed.

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EXPERIMENTAL

In this study, 12 new 3-alkyl(aryl)-4-(*p*-*t*-butyl(benzyl/benzyliden)amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one: (1) 3-methyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (2) 3-ethyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (3) 3-phenyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (4) 3-benzyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (5) 3-(*p*-methylbenzyl)-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (6) 3-(*p*-chlorobenzyl)-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (7) 3-methyl-4-(*p*-*t*-butylbenzyl amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (8) 3-ethyl-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (9) 3-phenyl-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (10) 3-benzyl-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (11) 3-(*p*-methylbenzyl)-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one, (12) 3-(*p*-chlorobenzyl)-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) were synthesized. All products are synthesized according to the reported procedures [33]. Stock solutions of them were prepared in double-distilled conductivity water. Purified ethanol was used for preparation of ethanol-water mixtures. All other chemicals used in this study were reagent grade purity. Stock solutions of strong acid and strong base were prepared by using analytical reagent-grade hydrochloric acid and sodium hydroxide, respectively. Acid solutions prepared in water were standardized by titration against primary standard sodium carbonate (Merck). Solutions of standard bases containing 0.10 M NaCl were prepared as 50% (v/v) aqueous ethanol-water was potentiometrically standardized against hydrochloric acid solutions by use of Gran's plot techniques, allowing determination of dissolved carbonate impurity [34]. Primary standard sodium chloride (Merck) was used to keep the ionic strength constant.



Scheme 1. Synthesis of some 3-alkyl(aryl)-4-(*p*-*t*-butyl(benzyl/benzyliden)amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one derivatives.

All potentiometric measurements were performed in an 80 mL jacketed titration cell thermostated at 25.0 ± 0.1 °C and under nitrogen atmosphere. An Orion 720 A Model pH ionmeter, fitted with a combined pH electrode (Ingold) containing a filling solution of 0.01 M NaCl, was used for measuring the cell emf values. The potentiometric cell was calibrated before each experiment so that the hydrogen ion concentration rather than the activity was measured [35-36]. For all the solvent mixtures examined, reproducible values of autoprotolysis constants K_w were calculated from several series of $[H]^+$ and $[OH]^-$ measurements at 0.10 M NaCl [37-39].

The following solutions prepared in water and each of the solvent mixtures studied (total volume = 50 mL) were titrated potentiometrically with CO_2 -free standard 0.1 M NaOH dissolved in the corresponding solvents: (a) 2.5×10^{-3} M HCl (for cell calibration); (b) $(2.5 \times 10^{-3} - 7.5 \times 10^{-3})$ M HCl + 1.5×10^{-3} M triazoles. During each titration the ionic strength was maintained at 0.1 M NaCl and a potential reading was taken after a suitable time (normally 2-3 min) for equilibration. The protonation constants of the triazoles were calculated by analyzing the titration data using the PKAS computer program developed by Motekaitis and Martell [35-40].

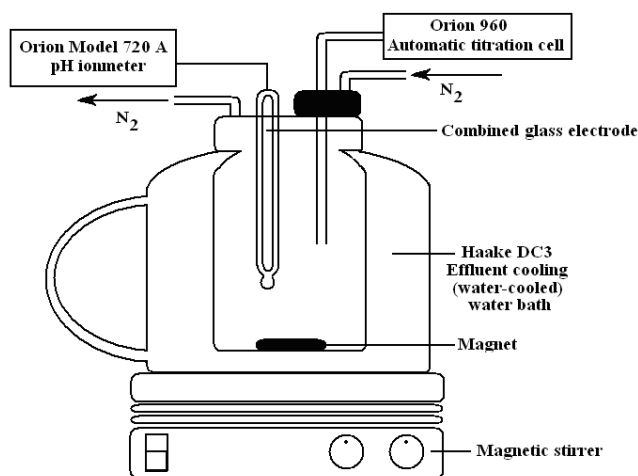


Figure 1. Potentiometric titration cell.

RESULTS AND DISCUSSION

The potentiometric titrations of different 12 triazole derivatives in 50% (v/v) ethanol-water mixtures were carried out and their pK_a values were found between 8.180 ± 0.024 - 10.582 ± 0.022 . In this study, six compounds (1-6) which are derivatives of 3-alkyl(aryl)-4-(*p*-*t*-butylbenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one and six compounds (7-12) which are derivatives of 3-alkyl(aryl)-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one were titrated potentiometrically in 50% (v/v) ethanol-water mixtures. The mV values, which were read from pH meter, were plotted versus sodium hydroxide volumes (mL) added and thus potentiometric titration curves were formed for all the cases (Figure 2-5). From these curves, potential values were measured and the corresponding pK_a values were calculated using a PKAS computer program at 25 °C with an ionic strength of 0.10 M (Figure 6, 7). All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. The corresponding pK_a values for all compounds, obtained from the potentiometric titrations with sodium hydroxide in 50% (v/v) ethanol-water are given in Table 1.

Table 1. Stoichiometric protonation constants of some 3-alkyl(aryl)-4-(*p*-*t*-butyl(benzyl/benzyliden)-amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one derivatives at 25 °C in 50% (v/v) ethanol-water mixtures ($\mu = 0.1$ M NaCl).

Compound	pK _a	Compound	pK _a
2a	9.001 ± 0.018	3a	9.993 ± 0.011
2b	8.180 ± 0.024	3b	10.297 ± 0.021
2c	8.737 ± 0.013	3c	9.421 ± 0.016
2d	10.132 ± 0.009	3d	10.582 ± 0.022
2e	9.259 ± 0.015	3e	9.861 ± 0.020
2f	8.608 ± 0.022	3f	9.921 ± 0.014

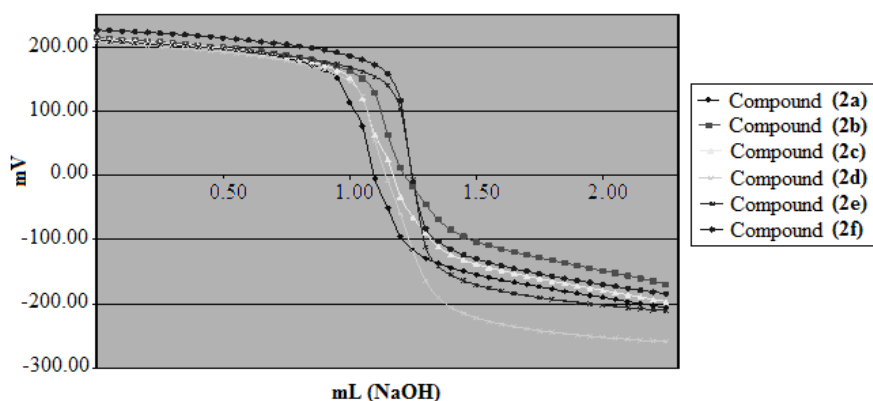


Figure 2. mV – mL (NaOH) potentiometric titration curves of compounds **2a**, **2b**, **2c**, **2d**, **2e** and **2f** (3-alkyl(aryl)-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M.

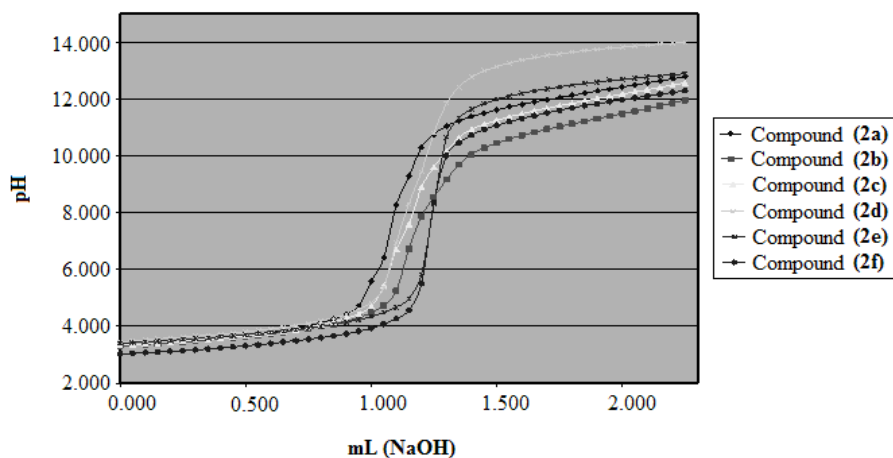


Figure 3. pH – mL (NaOH) potentiometric titration curves of compounds **2a**, **2b**, **2c**, **2d**, **2e** and **2f** (3-alkyl(aryl)-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M.

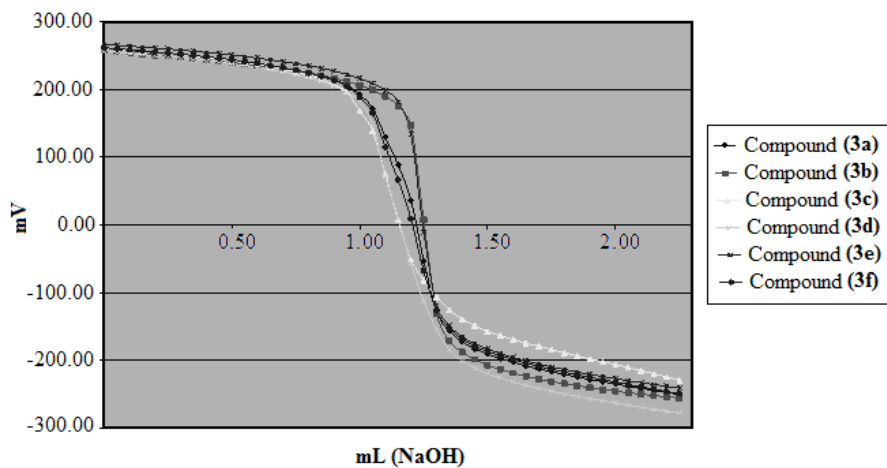


Figure 4. mV – mL (NaOH) potentiometric titration curves of compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3f** (3-alkyl(aryl)-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M.

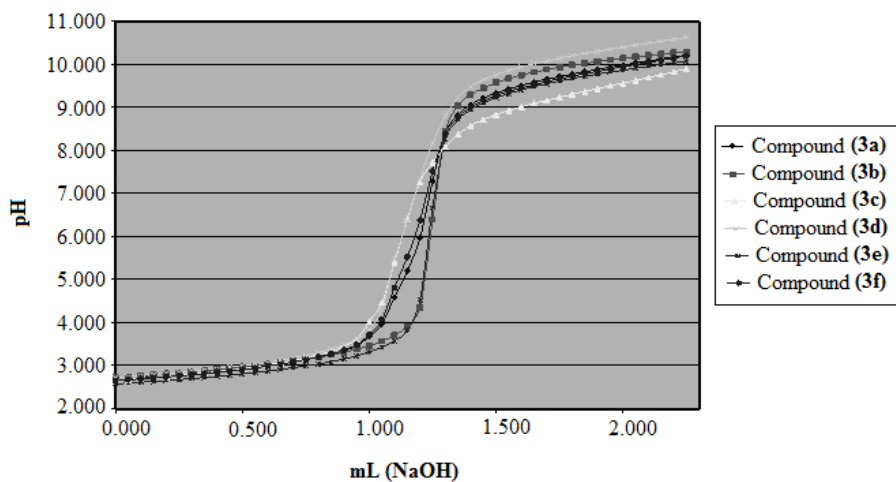


Figure 5. pH – mL (NaOH) potentiometric titration curves of compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3f** (3-alkyl(aryl)-4-(*p*-*t*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M.

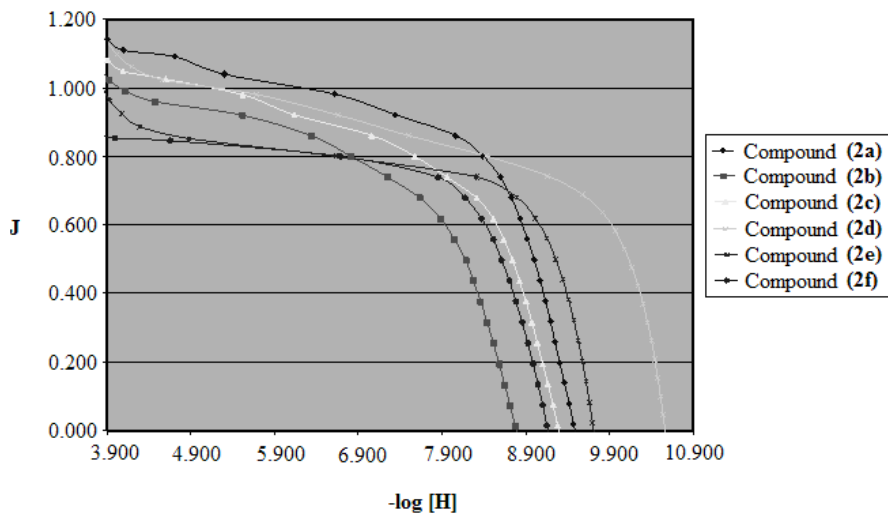


Figure 6. $J - \log [H]^+$ (using PKAS computer program calculated these values of J and $-\log [H]^+$) curves of compounds **2a**, **2b**, **2c**, **2d**, **2e** and **2f** (3-alkyl(aryl)-4-(*p*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M.

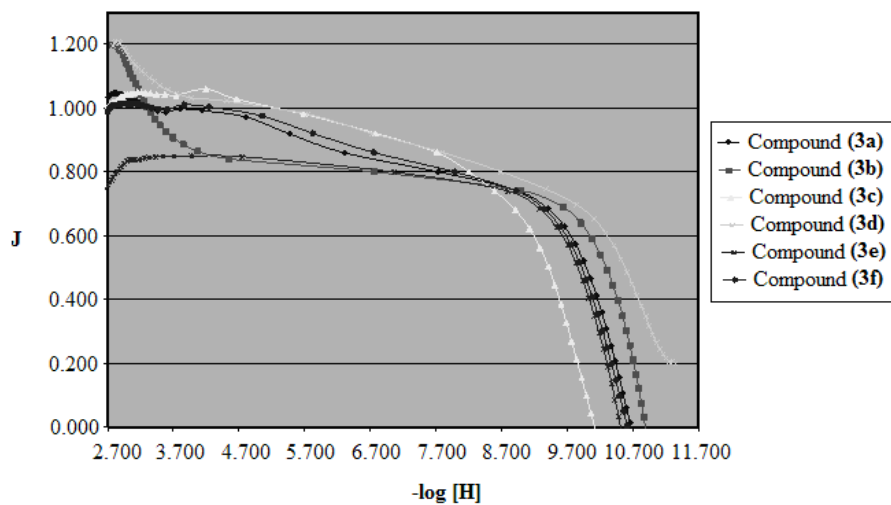


Figure 7. $J - \log [H]^+$ (using PKAS computer program calculated these values of J and $-\log [H]^+$) curves of compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3f** (3-alkyl(aryl)-4-(*p*-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated in 50% (v/v) ethanol-water mixtures at 25 °C with an ionic strength of 0.10 M.

This study is also concerned with the effect of solvent composition on the stoichiometric protonation constants. The literature data indicate that the equilibrium constants are directly related to the solvent composition [41-43]. The data we obtained in our study also verify this.

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 [44-49]. Table 1 shows that the corresponding pK_a values obtained from potentiometric titrations depend on the solvents used and molecular structure of the compounds. As seen in Table 1, the acidic arrangement for compounds **2a**, **2b**, **2c**, **2d**, **2e** and **2f** (3-alkyl(aryl)-4-(*p*-t-butylbenzyliden amino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) is: **2b** > **2f** > **2c** > **2a** > **2e** > **2d**, for compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3f** (3-alkyl(aryl)-4-(*p*-t-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) is: **3c** > **3e** > **3f** > **3a** > **3b** > **3d**. The acidic arrangement for all the compounds is **2b** > **2f** > **2c** > **2a** > **2e** > **3c** > **3e** > **3f** > **3a** > **2d** > **3b** > **3d**. Compound **2b** shows the strongest acidic properties but compound **2d** shows the weakest acidic properties within **2a**, **2b**, **2c**, **2d**, **2e** and **2f** (3-alkyl(aryl)-4-(*p*-t-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) in 50% (v/v) ethanol-water. Compound **3c** shows the strongest acidic properties but compound **3d** shows the weakest acidic properties within **3a**, **3b**, **3c**, **3d**, **3e** and **3f** (3-alkyl(aryl)-4-(*p*-t-butylbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) in 50% (v/v) ethanol-water. For all compounds; compound **2b** shows the strongest acidic properties and compound **3d** shows the weakest acidic properties. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in 50% (v/v) ethanol-water mixtures. 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.

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