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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2011, Vol. 27, No. (4):
Pg. 1451-1456

Determination of the pKa of Some Triazole Derivatives by the Potentiometric Method in Dioxan-Water Mixtures

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(Received: November 10, 2011; Accepted: November 24, 2011)

ABSTRACT

Stoichiometric protonation constants of some 3-alkyl(aryl)-4-(substituted benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones derivatives were determined potentiometrically in 50% (v/v) dioxan-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 : Potentiometric titration, protonation constants, solvent effect, triazoles.

INTRODUCTION

There have been a number of systematic studies of the basicity and acididity in different media using different techniques,[1-13] but unfortunately few have dealt with triazoles. It is well known that two major factors influence the basicity or 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 difficult to assess how much each effect contributes to the basicity or 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, anti- inflammatory, antioxidant and anti-HIV properties.[27-32]

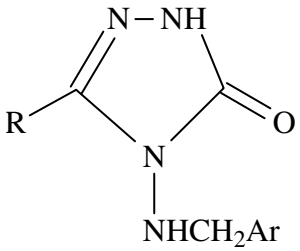
In this paper, we tried to investigate structural and solvent effects of several substituents on the basicity or acidity. Some 3-alkyl(aryl)-4 -(substitutedbenzylamino)-4,5- dihydro -1*H*-1,2,4-triazol - 5 - ones derivatives were titrated potentiometrically in 50% (v/v) dioxan-water mixtures at 25°C 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.

EXPERIMENTAL

In this study, thirteen new 3-alkyl(aryl)-4-(substitutedbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones [3-ethyl - 4 - (*p* - chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (1), 3-benzyl-4-(*m* -chlorobenzylamino) -4,5-dihydro-1*H*-1,2,4-triazol-5-one (2), 3-benzyl-4-(*p* - chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (3), 3-*p* -chlorobenzyl-4-(*p*-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (4), 3-*p*-methylbenzyl - 4 -(*p* - chlorobenzyl amino)-4,5-dihydro-1*H*-1,2,4-triazol-5 -one (5), 3-methyl-4-(*p*-fluorobenzy lamino)-4,5 - dihydro -1*H*-1,2,4-triazol-5-one (6), 3-ethyl-4-(*p*-fluorobenzyl amino)- 4,5 - dihydro -1*H*-1,2,4-triazol-5-one (7), 3-benzyl-4-(*p*-fluorobenzyl amino)- 4,5 - dihydro -1*H*-1,2,4-triazol-5-one (8), 3-*p*-methyl benzyl - 4-(*p* - fluorobenzylamino) - 4,5 - dihydro-1*H*-1,2,4-triazol-5-one (9), 3-*p*-chloro benzyl-4 - (*p* - fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol -5-one (10), 3-methyl-4-(*m*-bromobenzylamino)-4,5 - dihydro-1*H*-1,2,4-triazol -5-one (11), 3-ethyl-4-(*m*-bromo benzyl amino)-4,5-dihydro-1*H*-1,2,4-triazol - 5-one (12) and 3-phenyl-4-(*m*-bromobenzyl amino) -4,5-dihydro-1*H*-1,2,4-triazol-5-one (13)] were synthesized. All products were synthesized according to reported procedures.[33] Studied 3-alkyl(aryl)-4-(substitutedbenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones derivatives is given scheme 1.

Compound	R	Ar
1	Ethyl	4-Chlorophenyl
2	Benzyl	3-Chlorophenyl
3	Benzyl	4-Chlorophenyl
4	p-Chlorobenzyl	4-Chlorophenyl
5	p-Methylbenzyl	4-Chlorophenyl
6	Methyl	4-Fluorophenyl
7	Ethyl	4-Fluorophenyl
8	Benzyl	4-Fluorophenyl
9	p-Methylbenzyl	4-Fluorophenyl
10	p-Chlorobenzyl	4-Fluorophenyl
11	Methyl	3-Bromophenyl
12	Ethyl	3-Bromophenyl
13	Phenyl	3-Bromophenyl



Scheme 1

Stock solutions of them were prepared in double-distilled conductivity water. Purified dioxan was used for preparation of 50% (v/v) dioxan-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 dioxan-water was potentiometrically standardized against hydrochloric acid solutions by use of Gran's plot techniques, allowing determination of dissolved carbonate impurity.[33] Primary Standard sodium chloride

(Merck) was used to keep the ionic strength constant.

All potentiometric measurements were performed in an 80 mL jacketed titration cell thermostated at 25.0±0.1°C and under nitrogen atmosphere.

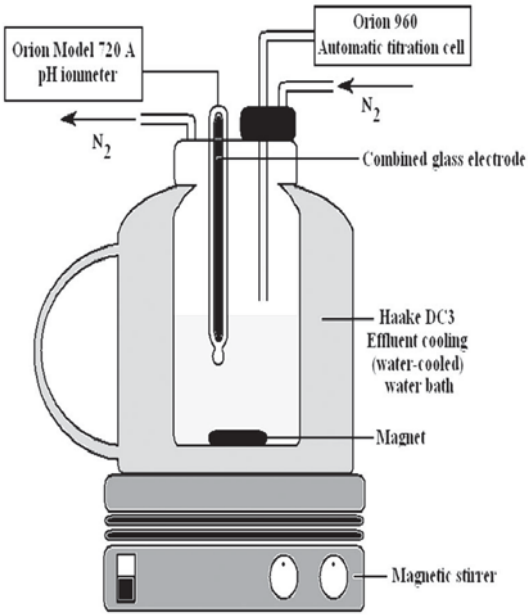


Fig. 1:

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. Potentiometric titration cell is given figure 1.

The potentiometric cell was calibrated before each experiment so that the hydrogen ion concentration rather than the activity was measured.[34-36] For all the solvent mixtures examined, reproducible values of autoprotolysis constants Kw were calculated from several series of $[H^+]$ and $[OH^-]$ measurements at 0.10 M NaCl.[37-38] 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) $2.5x10^{-3}$ M HCl (for cell calibration); (b) ($2.5x10^{-3}$ - $7.5x10^{-3}$ M) HCl + $1.5x10^{-3}$ 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.[34,39]

RESULTS AND DISCUSSION

The protonation constants, pKa, for these derivatives were determined in 50% (v/v) dioxan-water mixtures at 25.0±0.1°C. All the values presented are the average of at least five measurements and the standard deviations of each are listed. These values are the equilibrium constants of the $A^- + H^+ \rightleftharpoons AH$ reaction, where A^- and AH are the derivatives and their protonated species, respectively. The protonation constants given in tables 1 are considered in more detail in order to gain more information about the effect of solvent composition and specific effects of substituents on the acidity of these derivatives in solvent 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 2-3, pH – mL (NaOH) and mV – mL (NaOH) potentiometric titration curves of compound 3-ethyl-4-(*p*-chloro benzylamino) - 4,5 - dihydro-1*H* -1,2,4-triazol-5-one **(1)** titrated in 50% (v/v) dioxan-water mixtures at 25 °C with an ionic strength of 0.10 M). From these curves, potential values were measured and the corresponding pKa values were calculated using a PKAS computer program at 25°C with an ionic strength of 0.10 M (figure 4, J – -log $[H]^+$ (using PKAS computer program calculated these values of J and –log $[H]^+$) curves of compounds 3-ethyl-4-(*p* - chlorobenzylamino) -4,5-di hydro-1*H*-1,2,4-triazol-5-one **(1)** titrated in 50% (v/v) dioxan-water mixtures at 25°C with an ionic strength of 0.10 M). 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.

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Table 1: Stoichiometric protonation constants of some 3-alkyl(aryl)-4-(substitutedbenzylamino) - 4,5 - dihydro -1*H*-1,2,4-triazol-5-ones derivatives at 25°C in 50% (v/v) dioxan-water mixtures (μ = 0.1 M NaCl)

No	Compound	pKa
(1)	3-ethyl-4-(*p*-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	5.96±0.03
(2)	3-benzyl-4-(*m*-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.54±0.02
(3)	3-benzyl-4-(*p*-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	5.47±0.03
(4)	3-*p*-chlorobenzyl-4-(*p*-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	6.28±0.05
(5)	3-*p*-methylbenzyl-4-(*p*-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.76±0.03
(6)	3-methyl-4-(*p*-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	5.54±0.02
(7)	3-ethyl-4-(*p*-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.44±0.04
(8)	3-benzyl-4-(*p*-fluorobenzylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.72±0.02
(9)	3-*p*-methylbenzyl-4-(*p*-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.60±0.03
(10)	3-*p*-chlorobenzyl-4-(*p*-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	5.36±0.03
(11)	3-methyl-4-(*m*-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	5.48±0.04
(12)	3-ethyl-4-(*m*-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.65±0.02
(13)	3-phenyl-4-(*m*-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	4.76±0.02

molecular structure. In this study was worked different three triazole derivatives series. This series are 3-alkyl (aryl) -4-(substitutedchlorobenzyl amino)-4,5-dihydro-1*H*-1,2,4-triazol -5-one, 3-alkyl(aryl)-4-(substitutedfluoro benzylamino)-4,5-dihydro-1*H* - 1,2,4-tri azol-5-one and 3-alkyl(aryl)-4-(substitutedbromobenzylamino) -4,5-di hydro - 1*H* - 1,2,4 - triazol - 5 - one derivatives. Table 1 shows that the corresponding pKa 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 3-alkyl(aryl)-4-(substituted chlorobenzylamino)-4,5-dihydro -1*H* -1, 2,4-triazol-5-one derivatives are 2 > 5 > 3 > 1 > 4, for compounds 3-alkyl (aryl) - 4 - (substitutedfluorobenzyl amino)-4,5-dihydro-1*H* - 1,2,4-triazol-5-one derivatives are 7 > 9 > 8 > 10 > 6 and for compounds 3-alkyl(aryl)-4-(substitutedbromobenzylamino) -4,5-di hydro - 1*H* - 1,2,4 - triazol - 5 - one derivatives are 12 > 13 > 11. Compound 2 shows the strongest acidic properties but compound 4 shows the weakest acidic

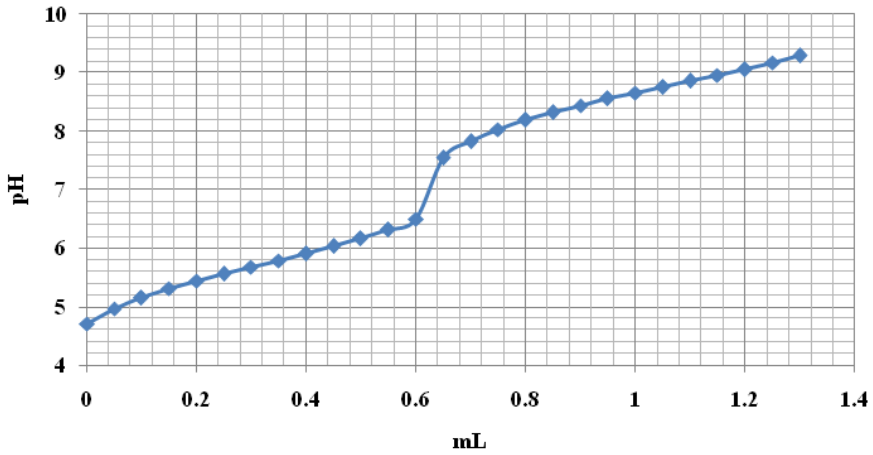

Fig. 2:

properties within 3-alkyl(aryl)-4-(substituted chlorobenzylamino)-4,5-dihydro -1*H* -1, 2,4-triazol-5-one derivatives. Compound 7 shows the strongest acidic properties but compound 6 shows the weakest acidic properties within 3-alkyl(aryl)-4-(substitutedfluoro benzylamino) - 4,5 -dihydro -1*H* -1,2,4-triazol-5-one derivatives and compound 12 shows the strongest acidic properties but compound 11 shows the weakest acidic properties within 3-alkyl(aryl)-4-(substituted bromobenzylamino)-4,5-dihydro - 1*H* -1,2,4-triazol-5-one derivatives. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in 50% (v/v) dioxan-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.

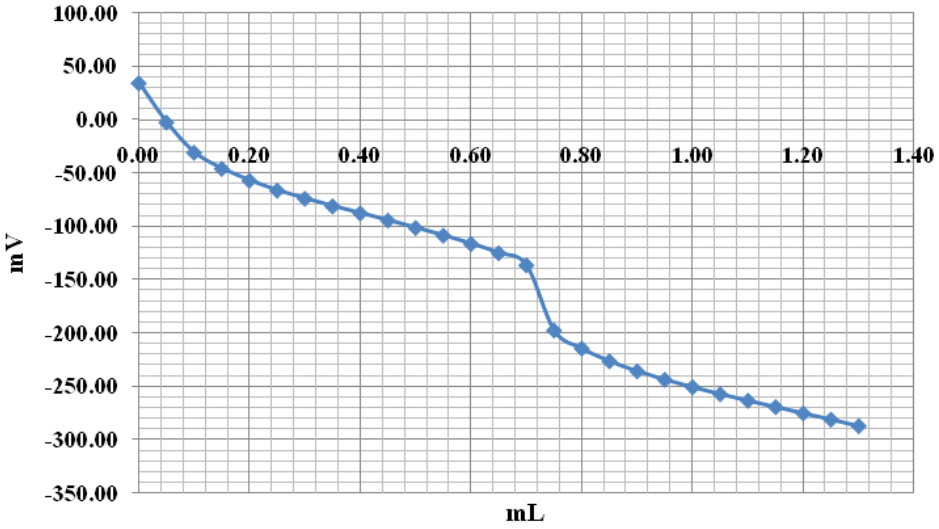

Fig. 3:

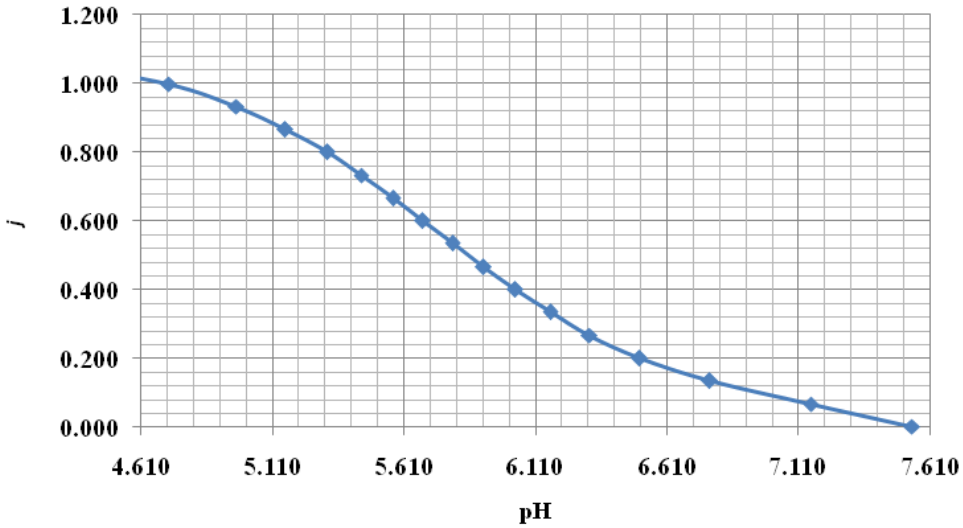

Fig. 4:

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