Determination of the Protonation Constants of Some 4-(Substituted benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones by the Potentiometric Method in Ethanol–Water Mixtures

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ABSTRACT

To gain more information about the effect of solvent on 4,5-dihydro-1*H*-1,2,4-triazol-5-ones, the stoichiometric protonation constants of thirteen triazoles in ethanol–water mixtures were determined at an ionic strength of 0.10 M NaCl and at 25.0 ± 0.1 °C under nitrogen atmosphere. A potentiometric method was used and the calculation was carried out using the PKAS computer program. The corresponding pK$_a$ values of these triazoles were determined in ethanol–water mixtures. Thus, the effects of solvent and molecular structure upon acidity were investigated. The logarithm of the protonation constants of the title 4,5-dihydro-1*H*-1,2,4-triazol-5-ones decreased linearly with increasing ethanol content, but the values determined with 80% ethanol did not follow this linear trend. The variation of these constants is discussed on the basis of specific solute–solvent interactions.

1. Introduction

Acidity measurements of organic compounds have a long history dating back to the end of the 19th century, when the first pK$_a$ was measured. Since then a vast body of data on acidities in various solvents has been collected.[1–4] The measurements have mostly been limited to polar solvents, however, with water being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents.

Several studies, involving the formation and investigation of biological activities of some 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, have been reported.[5–16] It is known that these derivatives have weak acidic properties.

The acidity of a compound in a given medium is influenced by both the electronic effects of the substituents and the solvent effects of the medium. Moreover, it is sometimes extremely difficult to assess how much each effect contributes to the acidity. Small differences in acidity between similar molecules are also extremely difficult to interpret and one must be very careful in deciding which structural effect has the main influence on acidity.

A number of studies have been reported on the protonation constants of these derivatives in different media,[17–20] however, very little information on the protonation constants of these derivatives in water and organic solvent-water mixtures has been published so far.[21–23]

This paper, therefore, deals with the determination of the stoichiometric protonation constants of these derivatives. Moreover this work reports an investigation aimed at gaining information about the effect of solvent composition on the protonation constants of these derivatives.
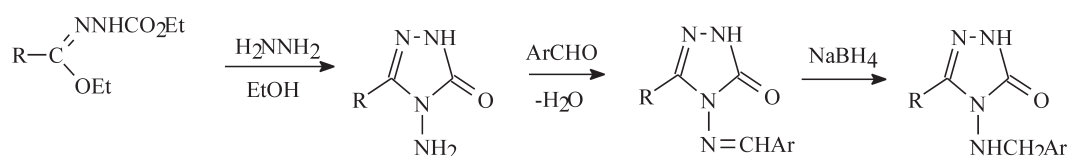
2. Experimental

In this study, thirteen new 3-alkyl(aryl)-4-(substituted benzylamino)-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-chloro-benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (5), 3-methyl-4-(p-fluoro-benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (6), 3-ethyl-4-(p-fluoro-benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (7), 3-benzyl-4-(p-fluoro-benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (8), 3-p-methylbenzyl-4-(p-fluorobenzyl amino)-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-bromobenzyl amino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (12) and 3-phenyl-4-(m-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (13)) were synthesized. All products were synthesized according to reported procedures.[24] The ethanol utilized was purified as described elsewhere.[25] Doubly distilled conductivity water was used as aqueous medium as well as for the preparation of ethanol–water mixtures. All other chemicals used in this investigation were reagent grade purity.

Hydrochloric acid solution (0.10 M) was prepared in water and standardized against sodium carbonate. The sodium hydroxide solutions (0.10 M) were prepared as 10%, 20%, 30%, 40%, 50%, 60%, 70% and 80% (v/v) aqueous ethanol solutions and stored in glass bottles protected against the atmosphere. The base solutions were standardized *via* a linear least-squares fit of Gran plots for end-point determination obtained from hydrochloric acid.[26,27]

All potentiometric measurements were performed in an 80 mL

Compounds 1–13

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

jacketed titration cell thermostated at 25.0 ± 0.1 °C and under nitrogen atmosphere. An Orion Model 720A pH ion meter, fitted with a combined pH electrode (Ingold) containing a filling solution of 0.10 M NaCl, was used for measuring the cell e.m.f. values. The potentiometric cell was calibrated before each experiment.[28,29] For all the solvent mixtures examined, reproducible values of autoprotolysis constants, K_{ap}, were calculated from several series of $[H^+]$ and $[OH^-]$ measurements with 0.10 M NaCl.[28,30]

The following solutions were prepared in water and each of the solvent mixtures studied (total volume 50.0 mL) was titrated potentiometrically with CO_2-free standard 0.1 M sodium hydroxide dissolved in the following solvents: (i) 2.5×10^{-3} M HCl (for cell calibration); (ii) 2.0×10^{-3} M HCl + 2.5×10^{-3} M triazol compound. 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 these derivatives were calculated by analysing the titration data using a computer program developed by Motekaitis and Martell.[28,31]

3. Results and Discussion

The stoichiometric protonation constants, β, for these derivatives were determined in ethanol–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, 2 and 3 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 numerical $\log \beta$ values for these derivatives determined in ethanol–water mixtures decrease with increasing ethanol content in the solvent mixture, as shown in Tables 1, 2 and 3, for example.

It is observed that a nearly linear relationship exists between the protonation constants and the mole fraction of ethanol from 0.0717 to 0.4189 for all derivatives investigated. However, $\log \beta$ values at a mole fraction of ethanol of 0.4189 are slightly higher than those expected from the linear trend. The linear equations and the related correlation coefficients for all these derivatives are given in Tables 4, 5 and 6.

Many studies have shown that the equilibrium constant is linearly related to the fraction of organic solvent.[32–36] Our results obtained for these derivatives are in good agreement with them. The dissociation constants of charged acids in ethanol–water mixtures vary with solvent composition in a manner that is not completely understood. Bates and coworkers[37,38] and Chattopadhyay and Lahiri[39] have examined the effect of a change in solvent composition on the dissociation of BH^+ and the related Gibbs energies of transfer in mixed solvents.

In this paper it is suggested that electrostatic charging effects resulting from the change in dielectric constant with solvent effects and the solute–solvent interactions have greater significance in the interpretation of solvent effects. Thus, we can explain the results obtained for these derivatives by specific solvation effects. The deviations from linearity in 80% ethanol may result from the preferential solvation of solute by one of the components of the solvent mixture that could change the effective relative permittivity value in the cibotactic region.[40]

Furthermore, another factor why an increase in the $\log \beta$ values of all these derivatives is observed in ethanol-rich regions can be satisfactorily explained by differences in the solvent stabilization of the ionic species (H^+ and A^-), brought about by changing the percentage of ethanol.[38,41]

Using the protonation constants obtained in this work, the effects of the type of substituted groups on the acidity of these derivatives have been discussed. The most important factor that affects the acidity and therefore the protonation constant of a compound is the structural effect.

Table 1 Stoichiometric protonation constants of some 4-(chlorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones at 25.0 ± 0.1 °C for different ethanol–water mixtures (μ = 0.1 M NaCl, E: ethanol, W: water, x = the mole fraction of ethanol).

Number	Compound	%20 E–%80 W x = 0.0717 log β	%30 E–%70 W x = 0.1169 log β	%40 E–%60 W x = 0.1708 log β	%50 E–%50 W x = 0.2360 log β	%60 E–%40 W x = 0.3167 log β	%70 E–%30 W x = 0.4189 log β	%80 E–%20 W x = 0.5527 log β
(1)	3-ethyl-4-(p-chlorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	5.04 ± 0.03	4.98 ± 0.05	4.90 ± 0.03	4.80 ± 0.02	4.68 ± 0.01	4.53 ± 0.02	4.34 ± 0.02
(2)	3-benzyl-4-(m-chlorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	3.95 ± 0.02	3.85 ± 0.03	3.73 ± 0.02	3.59 ± 0.04	3.41 ± 0.03	3.19 ± 0.03	2.89 ± 0.02
(3)	3-benzyl-4-(p-chlorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.80 ± 0.02	4.68 ± 0.01	4.54 ± 0.02	4.38 ± 0.04	4.17 ± 0.03	3.91 ± 0.02	3.57 ± 0.02
(4)	3-p-chlorobenzyl-4-(p-chloro benzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	5.51 ± 0.02	5.40 ± 0.02	5.27 ± 0.03	5.11 ± 0.02	4.92 ± 0.02	4.67 ± 0.03	4.35 ± 0.02
(5)	3-p-methylbenzyl-4-(p-chloro benzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	3.87 ± 0.02	3.76 ± 0.02	3.64 ± 0.03	3.49 ± 0.02	3.30 ± 0.02	3.06 ± 0.03	2.75 ± 0.04

Table 2 Stoichiometric protonation constants of some 4-(fluorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones at 25.0 ± 0.1 °C for different ethanol–water mixtures (μ = 0.1 M NaCl, E: ethanol, W: water, x = the mole fraction of ethanol).

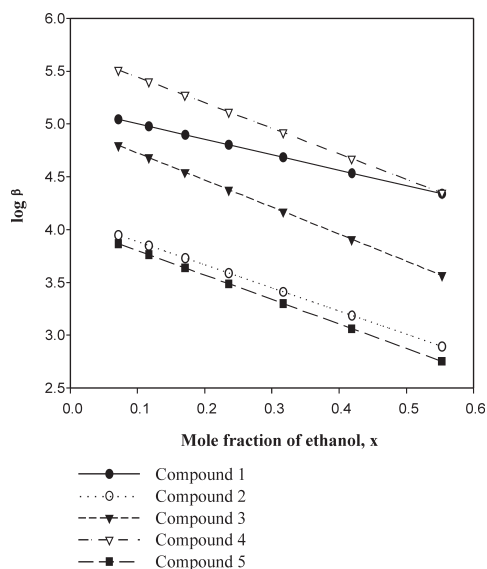| Number	Compound	%20 E–%80 W x = 0.0717 log β	%30 E–%70 W x = 0.1169 log β	%40 E–%60 W x = 0.1708 log β	%50 E–%50 W x = 0.2360 log β	%60 E–%40 W x = 0.3167 log β	%70 E–%30 W x = 0.4189 log β	%80 E–%20 W x = 0.5527 log β
(6)	3-methyl-4-(p-fluorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.78 ± 0.02	4.70 ± 0.03	4.59 ± 0.02	4.46 ± 0.03	4.30 ± 0.01	4.10 ± 0.03	3.84 ± 0.02
(7)	3-ethyl-4-(p-fluorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	3.99 ± 0.03	3.88 ± 0.02	3.73 ± 0.02	3.56 ± 0.02	3.35 ± 0.03	3.09 ± 0.04	2.74 ± 0.02
(8)	3-benzyl-4-(p-fluorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.05 ± 0.03	3.97 ± 0.02	3.89 ± 0.04	3.78 ± 0.03	3.65 ± 0.02	3.48 ± 0.02	3.27 ± 0.03
(9)	3-p-methylbenzyl-4-(p-fluorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.02 ± 0.03	3.93 ± 0.02	3.83 ± 0.03	3.71 ± 0.03	3.56 ± 0.02	3.37 ± 0.02	3.13 ± 0.03
(10)	3-p-chlorobenzyl-4-(p-fluorobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.99 ± 0.02	4.89 ± 0.04	4.78 ± 0.03	4.64 ± 0.03	4.46 ± 0.02	4.24 ± 0.02	3.95 ± 0.03

Figure 1 Variation in the protonation constants of compounds 1, 2, 3, 4 and 5.
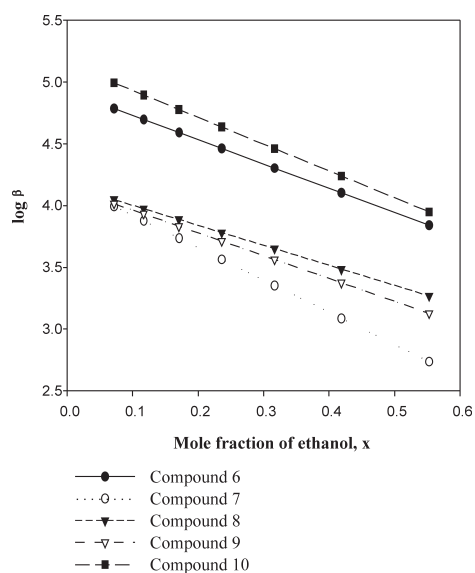

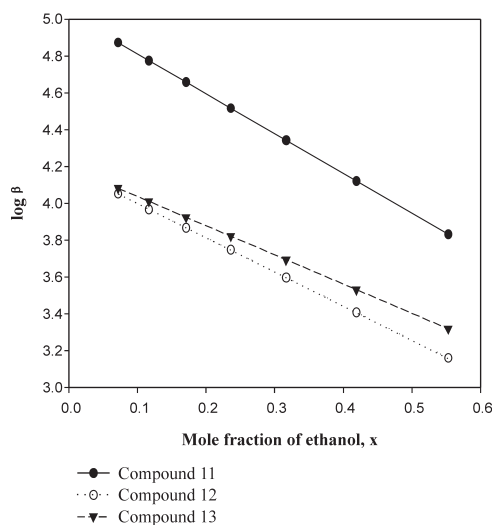**Figure 2** Variation in the protonation constants of compounds 6, 7, 8, 9 and 10.

Figure 3 Variation in the protonation constants of compounds 11, 12 and 13.

Table 3 Stoichiometric protonation constants of some 4-(bromobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones at 25.0 ± 0.1 °C for different ethanol–water mixtures ($\mu = 0.1$ M NaCl, E: ethanol, W: water, x = mole fraction of ethanol).

Number	Compound	%20 E–%80 W x = 0.0717 $\log \beta$	%30 E–%70 W x = 0.1169 $\log \beta$	%40 E–%60 W x = 0.1708 $\log \beta$	%50 E–%50 W x = 0.2360 $\log \beta$	%60 E–%40 W x = 0.3167 $\log \beta$	%70 E–%30 W x = 0.4189 $\log \beta$	%80 E–%20 W x=0.5527 $\log \beta$
(11)	3-methyl-4-(m-bromobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.87 ± 0.03	4.77 ± 0.02	4.66 ± 0.02	4.52 ± 0.03	4.34 ± 0.02	4.12 ± 0.02	3.83 ± 0.03
(12)	3-ethyl-4-(m-bromobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.05 ± 0.02	3.97 ± 0.03	3.87 ± 0.02	3.75 ± 0.02	3.60 ± 0.04	3.41 ± 0.02	3.16 ± 0.02
(13)	3-phenyl-4-(m-bromobenzylamino)-4,5-dihydro-1H-1,2,4-triazol-5-one	4.08 ± 0.03	4.01 ± 0.04	3.92 ± 0.03	3.82 ± 0.03	3.69 ± 0.03	3.53 ± 0.02	3.32 ± 0.03

Table 4 Linear relationships between the protonation constants of some 4-(chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and the mole fractions of ethanol (x) (from 0.0717 to 0.4189).

Compound	Equation	Correlation coefficient, *r*
(1) 3-ethyl-4-(p-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -1.463$ (x) + 5.147	–0.995
(2) 3-benzyl-4-(m-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.187$ (x) + 4.104	–0.989
(3) 3-benzyl-4-(p-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.562$ (x) + 4.982	–0.986
(4) 3-p-chlorobenzyl-4-(p-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.415$ (x) + 5.684	–0.992
(5) 3-p-methylbenzyl-4-(p-chlorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.318$ (x) + 4.034	–0.997

Table 5 Linear relationships between the protonation constants of some 4-(fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and the mole fractions of ethanol (x) (from 0.0717 to 0.4189).

Compound	Equation	Correlation coefficient, *r*
(6) 3-methyl-4-(p-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -1.966$ (x) + 4.926	–0.988
(7) 3-ethyl-4-(p-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.617$ (x) + 4.182	–0.982
(8) 3-benzyl-4-(p-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -1.621$ (x) + 4.164	–0.991
(9) 3-p-methylbenzyl-4-(p-fluorobenzyl amino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -1.845$ (x) + 4.147	–0.996
(10) 3-p-chlorobenzyl-4-(p-fluorobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.172$ (x) + 5.149	–0.995

Table 6 Linear relationships between the protonation constants of some 4-(bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and the mole fractions of ethanol (x) (from 0.0717 to 0.4189).

Compound	Equation	Correlation coefficient, *r*
(11) 3-methyl-4-(m-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -2.163$ (x) + 5.028	–0.987
(12) 3-ethyl-4-(m-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -1.853$ (x) + 4.185	–0.994
(13) 3-phenyl-4-(m-bromobenzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one	$\log \beta = -1.586$ (x) + 4.196	–0.997

4. Conclusion

The acidity of these derivatives is a result of various factors such as (i) the solvent effect; solvation power, the tendency of forming hydrogen bonds, selective solvation, relative permittivity and the composition of the solution in the first solvation layer in the case of mixed solvents and (ii) structural effect, electronic effect, steric effect and the formation of hydrogen bonding.

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