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Synthesis, Potentiometric Titrations and Antioxidant Activities of Some 4-Acylamino-4,5-dihydro-1H-1,2,4-triazol-5-one Derivatives

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Five novel 3-alkyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2**) were synthesized by the reactions of 3-alkyl-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones (**1**) with cinnamoyl chloride and characterized by elemental analyses and IR, ¹H NMR, ¹³C NMR and UV spectral data. The newly synthesized compounds **2** were titrated potentiometrically with tetrabutylammonium hydroxide in four non-aqueous solvents such as isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethylformamide and the half-neutralization potential values and the corresponding pK_a values were determined for all cases. In addition, these new compounds (except compound **2a**) and five recently reported 3-alkyl-4-isobutrylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones (**3**) were screened for their antioxidant activities.

Key Words: 4,5-Dihydro-1H-1,2,4-triazol-5-ones, Acylation, Acidity, Potentiometric titrations, pK_a, Antioxidant.

INTRODUCTION

Several articles on the acylation of some 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives have been published¹⁻⁷. In addition, 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, antiinflammatory, antioxidant, antitumor and anti-HIV properties^{3,8-12}.

On the other hand, it is known that 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one rings have weak acidic properties, so some 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives were titrated potention-

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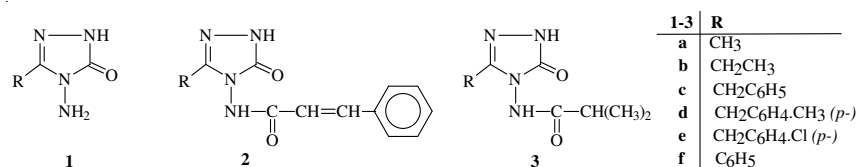
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metrically with tetrabutylammonium hydroxide (TBAH) in non-aqueous solvents and the pK_a values of the compounds were determined^{4,7,11-18}.

Furthermore, nowadays, antioxidants have become one of the major areas of scientific research. Antioxidants are extensively studied for their capacity to protect organisms and cells from damage that is induced by oxidative stress. Scientists in many different disciplines become more interested in new compounds, either synthesized or obtained from natural sources that could provide active components to prevent or reduce the impact of oxidative stress on cells¹⁹. Exogenous chemicals and endogenous metabolic processes in human body or in food system might produce highly reactive free radicals, especially oxygen derived radicals, which are capable of oxidizing biomolecules, resulting in cell death and tissue damage. Oxidative damages play a significantly pathological role in human diseases. For example, cancer, emphysema, cirrhosis, atherosclerosis and arthritis have all been correlated with oxidative damage. Also, excessive generation of ROS induced by various stimuli and which exceeds the antioxidant capacity of the organism leads to a variety of pathophysiological processes such as inflammation, diabetes, genotoxicity and cancer²⁰.

In present paper, antioxidant activity of five new 3-alkyl-4-cinnamoylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**), which were synthesized by the reactions of 3-alkyl-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with cinnamoyl chloride and five 3-alkyl-4-isobutyrylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3**), which were synthesized according to literature⁴ (**Scheme-I**) were determined. Moreover, the potentiometric titrations of the synthesized compounds **2** with tetrabutylammonium hydroxide (TBAH) in four non-aqueous solvents (isopropyl alcohol, *t*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide) are examined to determine the corresponding half-neutral-ization potentials (HNP) and the corresponding pK_a values. The data obtained from the potentiometric titrations was interpreted and the effect of the C-3 substituent in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring as well as solvent effects were studied^{4,7,11-18}.



Scheme-I

EXPERIMENTAL

Melting points were taken on a Electrothermal 9100 digital melting point apparatus and are uncorrected. IR spectra were registered on a Perkin-

Elmer 1600 FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide with TMS as internal standard on a Varian Mercury spectrometer at 200 and 50 MHz, respectively. UV absorption spectra were measured in 10 mm quartz cells between 200 and 400 nm using a Shimadzu UV-1201 spectrophotometer.

The starting compounds **1a-f** were prepared according to the literature^{1,21}. In addition, the compounds **3** were synthesized according to literature⁴.

Preparation of 3-alkyl(aryl)-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones (2): 3-Alkyl(aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-one (**1**) (0.01 mol) was heated with 1.68 mL (0.01 mol) of cinnamoyl chloride in 40 mL of *n*-butyl acetate for 7 h and then allowed to cool. The crystals formed were filtered. The product was recrystallized from an appropriate solvent to give **2**.

3-Methyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-one (2a): Yield 75 % (1.84 g); m.p. 232-233 °C (EtOH). IR (KBr, ν_{max} , cm^{-1}): 3500, 3300 (NH), 1770, 1700 (C=O), 1630 (C=C), 1585 (C=N), 770 and 710 (monosubstituted aromatic ring). ^1H NMR (DMSO- d_6 , 200 MHz): δ 2.22 (s, 3H, CH_3), 6.86 (d, 1H, =CH, $J = 15.9$ Hz), 7.96 (d, 1H, =CH, $J = 15.9$ Hz), 7.50-7.77 (m, 5H, Ar-H), 11.39 (s, 1H, NH). ^{13}C NMR (DMSO- d_6 , 50 MHz): δ 10.77 (CH_3), 116.87, 143.28 (C=C), 128.33, 128.75 (2C), 129.24, 131.28, 134.17 (aromatic carbons), 146.73 (triazole C_3), 150.10 (triazole C_5), 165.09 (C=O). UV (ethanol) λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$): 293 (19090), 222 (10650) nm.

3-Benzyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-one (2c): Yield 879 % (2.78 g); m.p. 120-121 °C (EtOH). IR (KBr, ν_{max} , cm^{-1}): 3450, 3220 (NH), 1710, 1660 (C=O), 1635 (C=C), 1595 (C=N), 770 and 705 (monosubstituted aromatic ring). ^1H NMR (DMSO- d_6 , 200 MHz): δ 3.80 (s, 2H, CH_2), 6.79 (d, 1H, =CH, $J = 16.2$ Hz), 7.22-7.71 (m, 10H, Ar-H), 7.72 (d, 1H, =CH, $J = 15.9$ Hz), 11.10 (s, 1H, NH), 11.93 (s, 1H, NH). ^{13}C NMR (DMSO- d_6 , 50 MHz): δ 31.02 (CH_2), 117.83, 142.76 (C=C), 127.15, 128.33 (2C), 128.77 (2C), 129.04 (2C), 129.34 (2C), 130.66, 134.33, 135.18 (aromatic carbons), 147.40 (triazole C_3), 153.04 (triazole C_5), 165.19 (C=O). UV (ethanol) λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$): 277 (18680), 216 (17130) nm. Anal. calcd. (%) for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.0; H, 5.5; N, 17.1 %.

3-*p*-Methylbenzyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-one (2d): Yield 85 % (2.85 g); m.p. 244-45 °C (EtOH- H_2O , 1:2). IR (KBr, ν_{max} , cm^{-1}): 3450, 3200 (NH), 1730, 1680 (C=O), 1640 (C=C), 1600 (C=N), 805 (1,4-disubstituted aromatic ring), 770 and 715 (monosubstituted aromatic ring). ^1H NMR (DMSO- d_6 , 200 MHz): δ 2.28 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 6.77 (d, 1H, =CH, $J = 15.9$ Hz), 7.01-7.67 (m, 9H, Ar-H), 7.71 (d, 1H, =CH, $J = 14.3$ Hz), 11.04 (s, 1H, NH), 11.87 (s, 1H, NH). ^{13}C

NMR (DMSO-*d*₆, 50 MHz): δ 20.80 (CH₃), 30.50 (CH₂), 117.80, 142.80 (C=C), 128.25 (2C), 128.83 (3C), 129.27 (3C), 130.90, 132.10, 134.20, 136.10 (aromatic carbons), 147.40 (triazole C₃), 153.10 (triazole C₅), 165.20 (C=O). UV (ethanol) λ_{\max} (ϵ , L mol⁻¹ cm⁻¹): 269 (27990), 223 (24820) nm. Anal. calcd. (%) for C₁₉H₁₈N₄O₂: C, 68.3; H, 5.4; N, 16.7. Found: C, 68.5; H, 5.4; N, 16.6 %.

3-*p*-Chlorobenzyl-4-cinnamoylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one (2e): Yield 60 % (2.13 g); m.p. 186-87 °C (EtOH-H₂O, 1:2). (KBr, ν_{\max} , cm⁻¹): 3470, 3200 (NH), 1710, 1685 (C=O), 1630 (C=C), 1595 (C=N), 815 (1,4-disubstituted aromatic ring), 765 and 720 (mono-substituted aromatic ring). ¹H NMR (DMSO-*d*₆, 200 MHz): δ 3.78 (s, 2H, CH₂), 6.73 (d, 1H, =CH, *J* = 15.9 Hz), 7.24-7.67 (m, 9H, Ar-H), 7.76 (d, 1H, =CH, *J* = 15.9 Hz), 11.01 (s, 1H, NH), 11.86 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆, 50 MHz): δ 30.20 (CH₂), 117.90, 142.80 (C=C), 128.25 (2C), 128.60 (2C), 129.26 (2C), 130.70 (2C), 130.87 (2C), 131.90, 134.10 (aromatic carbons), 147.10 (triazole C₃), 153.00 (triazole C₅), 165.30 (C=O). UV (ethanol) λ_{\max} (ϵ , L mol⁻¹ cm⁻¹): 278 (25710), 220 (14220) nm.

3-Phenyl-4-cinnamoylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one (2f): Yield 59 % (1.82 g); m.p. 186-87 °C (EtOH-H₂O, 1:2). IR (KBr, ν_{\max} , cm⁻¹): 3450, 3200 (NH), 1740, 1705 (C=O), 1630 (C=C), 1585 (C=N), 770 and 715 (monosubstituted aromatic ring). ¹H NMR (DMSO-*d*₆, 200 MHz): δ 6.77 (d, 1H, =CH, *J* = 15.9 Hz), 7.36-7.71 (m, 11H, Ar-H + =CH), 11.34 (s, 1H, NH), 12.28 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆, 50 MHz): δ 117.80, 142.90 (C=C), 126.86 (2C), 128.33 (2C), 129.09 (2C), 129.24 (2C), 130.64 (2C), 131.60, 134.20 (aromatic carbons), 147.40 (triazole C₃), 153.04 (triazole C₅), 165.19 (C=O). UV (ethanol) λ_{\max} (ϵ , L mol⁻¹ cm⁻¹): 270 (28340), 220 (23820) nm.

Antioxidant activity: Butylated hydroxyl toluene (BHT) was purchased from E. Merck. Ferrous chloride, α -tocopherol, 1,1-diphenyl-2-picrylhydrazyl (DPPH^{*}), 3-(2-pyridyl)-5,6-bis(phenyl-sulfonic acid)-1,2,4-triazine (ferrozine), butylated hydroxyanisole (BHA) and trichloroacetic acid (TCA) were purchased from Sigma (Sigma-Aldrich GmbH, Sternheim, Germany).

Reducing power: The reducing power of the synthesized compounds was determined according to the method of Oyaizu²². Different concentrations of the samples (50-250 μ g/mL) in 1 mL of DMSO were mixed phosphate buffer (2.5 mL, 0.2 M, pH = 6.6) and potassium ferricyanide (2.5 mL, 1 %). The mixture was incubated at 50 °C for 20 min after incubation period; a portion of trichloroacetic acid (2.5 mL, 10 %) was added to the mixture, which was then centrifuged for 10 min at 1000 \times g. The upper layer of solution (2.5 mL) was mixed with distilled water (2.5 mL) and FeCl₃ (0.5 mL, 0.1 %), and the absorbance was measured at 700 nm in a spectrophotometer. Higher absorbance of the reaction mixture indicated greater reducing power.

Free radical scavenging activity: Free radical scavenging activity of compounds was measured by DPPH[•] using the method of Blois²³. Briefly, a 0.1 mM solution of DPPH[•] in ethanol was prepared and this solution (1 mL) was added to sample solutions in DMSO (3 mL) at different concentrations (50-250 µg/mL). The mixture was shaken vigorously and allowed to stand at room temperature for 0.5 h. Then the absorbance was measured at 517 nm in a spectrophotometer. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The DPPH[•] concentration (mM) in the reaction medium was calculated from the following calibration curve, determined by linear regression (R: 0.997):

$$\text{Absorbance} = 0.0003 \times \text{DPPH}^{\bullet} - 0.0174$$

The capability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH}^{\bullet} \text{ scavenging effect (\%)} = (A_0 - A_1/A_0) \times 100$$

where A_0 is the absorbance of the control reaction and A_1 is the absorbance in the presence of the samples or standards.

Metal chelating activity: The chelating ferrous ions by the synthesized compounds and standards were estimated by the method of Dinis *et al.*²⁴. Briefly, compounds (50-250 µg/mL) were added to a solution of 2 mM FeCl₂ (0.05 mL). The reaction was initiated by the addition of 5 mM ferrozine (0.2 mL) and the mixture was shaken vigorously and left standing at room temperature for 10 min after the mixture had reached equilibrium, the absorbance of the solution was then measured spectrophotometrically at 562 nm in a spectrophotometer. All test and analyses were run in triplicate and averaged. The percentage of inhibition of ferrozine-Fe²⁺ complex formation was given by the formula:

$$\% \text{ Inhibition} = (A_0 - A_1/A_0) \times 100$$

where A_0 is the absorbance of the control and A_1 is the absorbance in the presence of the samples or standards. The control did not contain compound or standard

HNP and pK_a value determination: 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 AND DISCUSSION

In this study, the structures of five new 3-alkyl-4-cinnamoylamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) were identified using elemental analysis and IR, ¹H NMR, ¹³C NMR and UV spectral data. In addition, the compounds **2** (except compound **2a**) and **3** were screened for their *in vitro* antioxidant activity. Several methods are used to determine antioxidant activities.

Total reductive capability using the potassium ferricyanide reduction method: The reductive capabilities of compounds are assessed by the extent of conversion of the Fe³⁺/ ferricyanide complex to the Fe²⁺/ferrous form. The reducing powers of the compounds were observed at different concentrations and results were compared with BHA, BHT and α-tocopherol. The reducing capacity of a compound may serve as a significant indicator for its potential antioxidant activity²⁵. The antioxidant activity of putative antioxidant has been attributed to various mechanisms, among which are prevention chain initiation, binding of transition metal ion catalyst, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging²⁶. In this study, all the amounts of the compounds showed lower absorbance than blank. Hence, no activities were observed to reduce metal ions complexes to their lower oxidation state or to take part in any electron transfer reaction. In other words, compounds did not show the ability of electron donor to scavenge free radicals.

DPPH[•] radical scavenging activity: The model of scavenging the staple DPPH radical is a widely used method to evaluate antioxidant activities in a relatively short time compared with other methods. The effect of antioxidants on DPPH radical scavenging was thought to be due to their hydrogen donating ability²⁷. DPPH is a stable free radical and accepts an electron or hydrogen radical to become a stable diamagnetic molecule²⁸. The reduction capability of DPPH radicals was determined by decrease in its absorbance at 517 nm induced by antioxidants. The absorption maximum of a stable DPPH radical in ethanol was at 517 nm. The decrease in absorbance of DPPH radical was caused by antioxidants, because of reaction between antioxidant molecules and radical, progresses, which result in the scavenging of the radical by hydrogen donation. It is visually noticeable as a discolouration from purple to yellow. Hence, DPPH is usually used as a substrate to evaluate antioxidative activity of antioxidants²⁹. BHA and α-tocopherol were used as a reference to antioxidant compounds. All the compounds tested with this method showed lower absorbance than absorbance of the control reaction and higher absorbance of the standard antioxidant reactions. These results indicate that the newly synthesized compounds showed mild activities as a radical scavenger, indicating that it has moderate activities as hydrogen donors (Fig. 1).

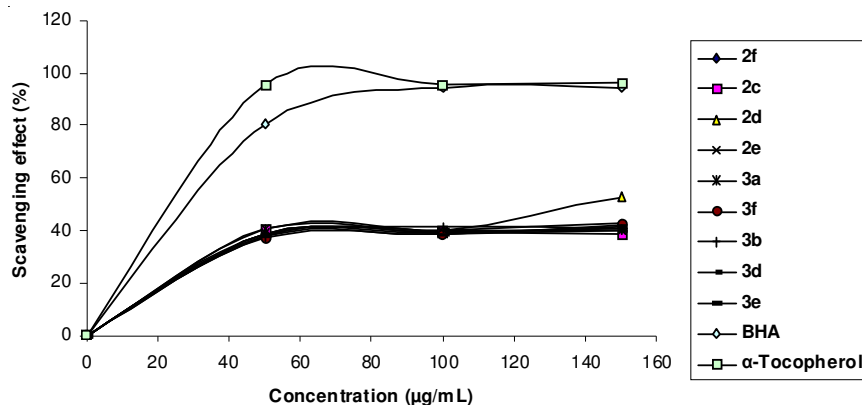


Fig. 1. Scavenging effect of compounds, BHA and α -tocopherol at different concentrations (50-100-150 $\mu\text{g/mL}$)

Ferrous ions chelating activity: The chelating effect of ferrous ions by the compounds and standards was determined according to the method of Dinis²⁴. Ferrozine can quantitatively form complexes with Fe^{2+} . In the presence of chelating agents, the complex formation is disrupted with the result that the red colour of the complex is decreased. Measurement of colour reduction therefore allows estimation of the chelating activity of the coexisting chelator³⁰. Transition metals have pivotal role in the generation oxygen free radicals in living organism. The ferric iron (Fe^{3+}) is the relatively biologically inactive form of iron. However, it can be reduced to the active Fe^{2+} , depending on condition, particularly pH³¹ and oxidized back through Fenton type reactions with the production of hydroxyl radical or Haber-Weiss reactions with superoxide anions. The production of these radicals may lead to lipid peroxidation, protein modification and DNA damage. Chelating agents may not activate metal ions and potentially inhibit the metal-dependent processes³². Also, the production of highly active ROS such as $\text{O}_2^{\bullet-}$, H_2O_2 and OH^{\bullet} , are also catalyzed by free iron through Haber-Weiss reactions:



Among the transition metals is known as the most important lipid oxidation pro-oxidant due to its high reactivity. The ferrous state of iron accelerates lipid oxidation by breaking down the hydrogen and lipid peroxides to reactive free radicals via the Fenton reactions:



Also Fe^{3+} ion produces radicals from peroxides, although the rate is tenfold less than of Fe^{2+} ion, which is the most powerful pro-oxidant among various sort of metal ions³³.

Ferrous ion chelating activities of the compounds, BHT and α -tocopherol are shown in Fig. 2. In this study, metal chelating capacity was significant since it reduced the concentrations of the catalyzing transition metal. It was reported that chelating agents that form σ -bonds with a metal are effective as secondary antioxidants because they reduce the redox potential thereby stabilizing the oxidized form of metal ion³⁴. The data obtained from Fig. 2 reveal that the compounds demonstrate a marked capacity for iron binding, except for **2f**, suggesting that their action as peroxidation protector may be related to its iron binding capacity. On the other hand, free iron is known to have low solubility and a chelated iron complex has greater solubility in solution, which can be contributed solely from the ligand. Furthermore, the compound-Fe may also be active, since it can participate in iron-catalyzed reactions.

In conclusion, the data here reported could be of the possible interest because of their activities of hydrogen donating and metal chelating could prevent redox cycling.

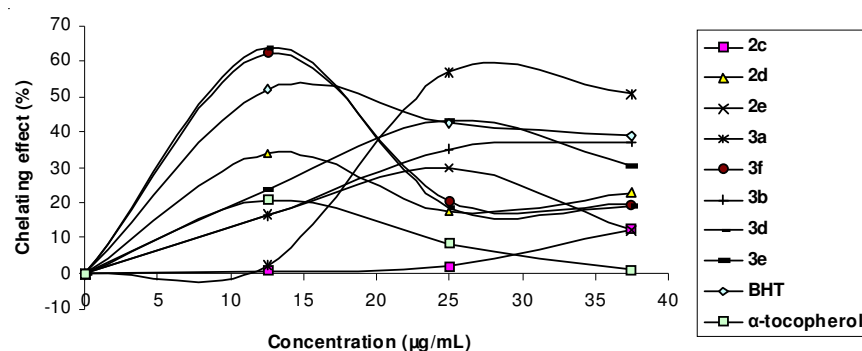


Fig. 2. Metal chelating effect of different amount of the compounds, BHT and α -tocopherol on ferrous ions

On the other hand, newly synthesized **2** type compounds were titrated potentiometrically with TBAH in four non-aqueous solvents such as isopropyl alcohol, *t*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide. The mV values read in each titration were drawn against TBAH volumes (mL) added and potentiometric titration curves were formed for all the cases. From the titration curves, the HNP values were measured and the corresponding pK_a values were calculated.

The half-neutralization potential (HNP) values and the corresponding pK_a values of compounds **2**, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide, are presented in Table-1.

TABLE-1
 HALF-NEUTRALIZATION POTENTIAL (HNP) VALUES AND THE
 CORRESPONDING pK_a VALUES OF COMPOUNDS **2** IN ISOPROPYL
 ALCOHOL, *tert*-BUTYL ALCOHOL, ACETONITRILE AND DMF

Compd.	Isopropyl alcohol		<i>tert</i> -Butyl alcohol		Acetonitrile		N,N-Dimethylformamide	
	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a	HNP (mV)	pK_a
2a	-349	12.68	-470	14.78	-437	14.48	-574	16.56
2c	-388	13.51	-445	14.32	-549	16.90	-440	14.33
2d	-384	13.20	-487	14.98	-459	14.53	-463	14.80
2e	-435	14.36	-480	15.12	-500	15.50	-438	14.38
2f	-401	13.76	-480	15.01	-460	14.78	-456	14.70

The pH of the weak acids are given by the following equation:

$$pH = pK_a + \log[A^-]/[HA]$$

$pH = pK_a$ occurs when $[A^-]$ is equal to $[HA]$ at the half-neutralization point. Therefore, the pH values can be regarded as pK_a at the half-neutralization points.

When the dielectric permittivity of solvents is taken into consideration, the acidic arrangement can be expected as follows: N,N-dimethylformamide ($\epsilon = 36.7$) > acetonitrile ($\epsilon = 36$) > isopropyl alcohol ($\epsilon = 19.4$) > *t*-butyl alcohol ($\epsilon = 12$). The pK_a values of compounds **2** in these solvents are given Fig. 3. In isopropyl alcohol, all these compounds show the strongest acidic properties.

The degree to which a pure solvent ionizes was represented by its autoprotolysis constant, K_{HS} .

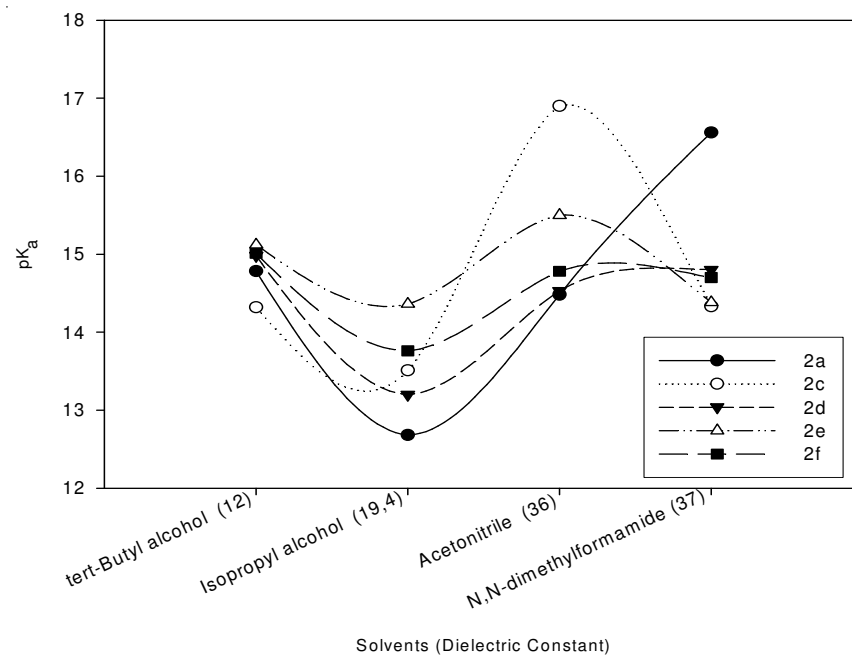
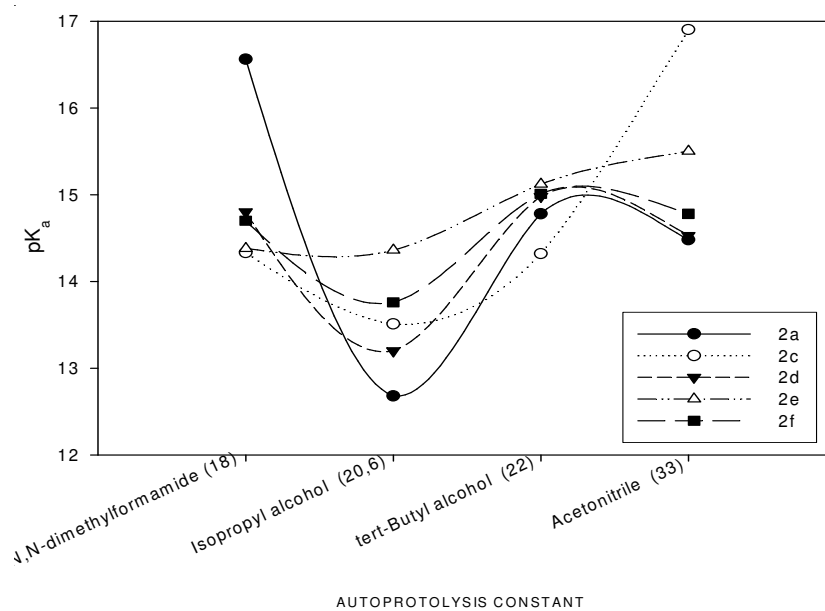


For the above reaction the constant is defined by

$$K_{HS} = [H_2S^+][S^-]$$

Autoprotolysis is an acid-base reaction between identical solvent molecules in which some act as an acid and others as a base. Consequently, the extent of an autoprotolysis reaction depends both on the intrinsic acidity and the intrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction³⁵. The exchange of the pK_a values with autoprotolysis constant are given in Fig. 4.

As it is well known, the acidity of a compound depends on several factors. The two most important factors are the solvent effect and molecular structure^{7-11,14-16}. Table-1 shows that the HNP values and the corresponding pK_a values obtained from potentiometric titrations depend on the type of non-aqueous solvents used and molecular structure of the compound tested.

Fig. 3. Exchange of the pK_a values with dielectric constantFig. 4. Exchange of the pK_a values with autoprotolysis constant

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