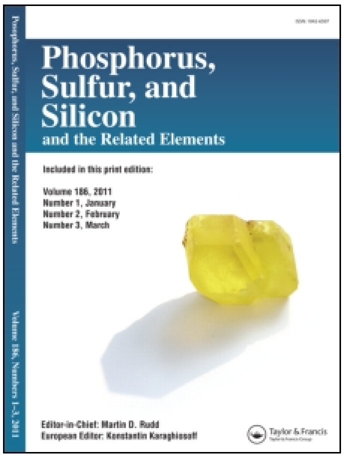

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THE ACID IONIZATION CONSTANTS OF SOME THIAZOLIDINE COMPOUNDS: MEDIUM EFFECTS AND THERMODYNAMIC STUDIES

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THE ACID IONIZATION CONSTANTS OF SOME THIAZOLIDINE COMPOUNDS: MEDIUM EFFECTS AND THERMODYNAMIC STUDIES

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The pK_a values of some thiazolidine compounds in various aqueous-organic solvent mixtures were determined pH-metrically at 25 °C and at an ionic strength of $I = 0.02$ mol dm^{-3} (KNO_3). The organic solvents used are methanol or ethanol (as amphiprotic solvent), DMF or DMSO (as dipolar aprotic solvent), and acetonitrile (as a low basic aprotic solvent). The pK_a values obtained are discussed in terms of solvent characteristics. The pK_a values of investigated compounds are increased on increasing the mole fraction of the amphiprotic or low basic aprotic organic solvent, whereas they are decreased in the presence of a dipolar aprotic solvent. Hydrogen bonding interactions and the medium basicity, in addition to the electrostatic effect, are the main factors influencing the ionization process in aqueous-amphiprotic or a low basic aprotic solvent mixture. The high stabilization of the conjugate base by dispersion forces and of the proton by its interaction with solvent as well as the solvent basicity play a vital role in determining the ionization equilibria of the investigated compounds in aqueous mixture of dipolar aproptic solvents. The effect of molecular structures of the compounds on pK_a values is also discussed. Thermodynamic functions (ΔH, $\Delta G°$, and $\Delta S°$) of the ionization processes of all compounds in aqueous media are determined and discussed.

Keywords: Thiazolidines; Thermodynamic Studies; Ionization Constants

INTRODUCTION

Thiazolidine compounds of diverse structures are considered important compounds in many biological activities such as antibacterial[1], anti-inflammatory[2], antifungal[3], and antiviral[4]. Such compounds have

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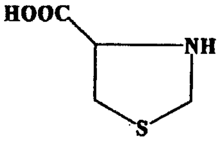
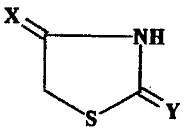
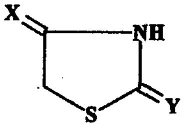
* Correspondence Author.

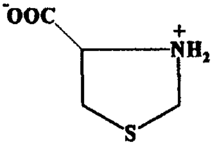
been found to be active against some viruses and certain types of tumors[5,6], and are used also as anticancer as well as hypoglycemic agents[7,8]. Although the ionization constants of thiazolidine compounds have been determined[9–11], scanning the literature revealed that no data has been reported concerning the medium effects on the ionization constants of such compounds. Therefore, in continuing our studies concerning medium effect on the ionization processes of heterocyclic compounds[12,13] the medium effect on the acid ionization constants of some thiazolidine compounds was studied. For this purpose, the pK_a values of thiazolidine-4-carboxylic acid (**I**), 2,4-thiazolidinedione (**II**), and 2-thioxo-4-thiazolidineone, rhodanine (**III**) have been determined in aqueous solutions containing varying mole fractions (0.1–0.35) of organic solvent.







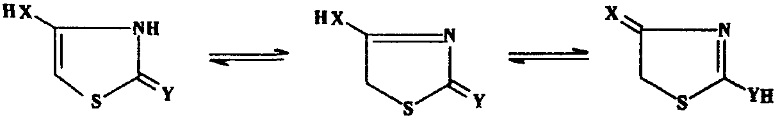
Where X =Y =O, for compound **II**, and X =O, Y = S, for compound **III**. It is worth mentioning that a previous studies using IR, and ^{13}C-NMR spectra confirmed the presence of compound **I** in a zwitter-ion form[14].



Compounds **I** and **II** exhibit a type of tautomerism that makes it possible from a structural standpoint, to classify them as true thiazoles **IV**, as thiazolidines **V**, and perhaps also as thiazolines **VI**[10].

The organic solvents used are methanol and ethanol (as amphiprotic solvents), *N,N*-dimethylformamide and dimethylsulfoxide (as dipolar aprotic solvents), and acetonitrile (as a low basic aprotic solvent). The acid ionization constants are discussed in terms of solvent characteristics. Effect of the molecular structures of the compounds on their pK_a values is also dis-

(IV) (V)



a b c

(VI)

cussed. Further, the change of thermodynamic functions associated with the ionization processes of the subjected compounds in pure aqueous medium has been determined and discussed.

EXPERIMENTAL SECTION

Materials and Solutions

The investigated thiazolidine compounds were A. R. products. These compounds were recrystallized by the methods described previously[9,15,16] and their purity was ascertained using a TLC method. The purified compounds were desiccated over P_4O_{10} at room temperature. The organic solvents used were of a high purity (spectrograde products) and were also distilled before use by standard methods[17], and stored over molecular sieves (4 or 3Å).

Stock solution (5×10^{-2} mol dm^{-3}) of each thiazolidine was prepared by dissolving an accurate amount in the appropriate volume of doubly distilled water Carbonate-free KOH solution (~ 0.2 mol dm^{-3}) was prepared by dissolving the appropriate mass in CO_2-free, doubly distilled water and standardized before use with a standard solution (0.1 mol dm^{-3}) of potassium hydrogen phthalate. A stock solution of nitric acid (~0.1 mol dm^{-3})

was prepared and used after standardization. An ionic strength (0.02 mol dm^{-3}) was maintained by using a solution of KNO_3 as a supporting electrolyte. Dilute solutions were prepared by accurate volumetric dilutions of the stock solution.

Procedure

The following two solutions were prepared (total volume 50 cm^3) and titrated individually against carbonate-free KOH solution:

a. HNO_3 [(2.0 – 5.0) × 10^{-3} mol dm^{-3})];
b. solution (a) in the presence of 2.0 × 10^{-3}mol dm^{-3} of each thiazolidine and containing different mole fractions (0.1–0.35) of the organic solvent used. A solution of (0.10 mol dm^{-3}) KNO_3 was used to maintain a constant ionic strength at 0.02 mol dm^{-3} for the two solutions.

From the titration curves corresponding to solutions (a) and (b), the average number of protons associated per one mole of a ligand ($\bar{n}_H$) at several pH values was calculated using the following equation[18]:

$$\bar{n}_H = \{y\,C_L + \frac{(V_a - V_b)C_B}{V_0}\}(C_L)^{-1} \qquad (1)$$

where y is the number of dissociable protons (y = 1, where the titration curve corresponding to solution (b) show only one inflection indicating the release of only one proton, and $\bar{n}_H$ did not exceed unity), C_L is the concentration of a ligand, and V_0 is the original volume (50 cm^3). $V_a$and V_b are the volumes of KOH consumed to reach the same pH values in curves (a) and (b), respectively. C_B is the concentration of KOH. The pK_a values were calculated from the following relationship[19]:

$$\bar{n}_H = \beta[H^+](1 + \beta[H^+])^{-1} \qquad (2)$$

Here β is the formation constant of the ligand. All calculations were performed using a computer program based on unweighted linear least-squares fits.

The pH-measurements were carried out using an Orion model 701A digital pH-meter (accurate to ±0.005 pH units) with a glass calomel electrode. A water thermostat Fischer Scientific Isotemp Refrigerated Circulator Model 9000 accurate to ±0.1 °C was used to attain the desired temperature.

TABLE I The Mean pK_a Values for Thiazolidine Compounds I-III in Different Organic Solvent -Water Mixtures at 25 °C and I = 0.02 mol dm^{-3} KNO_3

Mole fraction of organic solvent	*Dielectric constant of the medium $(D)_m$*	*$(1/D)_m\ 10^2$*	*pK_a values*[a]		
			I	*II*	*III*
0.00	78.40	1.28	6.36±0.03	6.24±0.02	6.87±0.04
			6.10[b)]		6.90[c)]
		Methanol			
0.10	73.82	1.36	6.85±0.03	6.68±0.02	7.02±0.03
0.15	71.53	1.40	7.00±0.02	6.71±0.03	7.28±0.05
0.20	69.24	1.44	7.22±0.02	6.92±0.03	7.42±0.03
0.25	66.95	1.49	7.40±0.03	7.08±0.02	7.61±0.03
0.30	64.66	1.55	7.63±0.04	7.32±0.04	7.78±0.04
0.35	62.37	1.60	7.68±0.03	7.40±0.04	7.86±0.05
		Ethanol			
0.10	72.99	1.37	7.12±0.02	6.80±0.02	7.20±0.02
0.15	70.29	1.42	7.34±0.04	6.98±0.03	7.47±0.03
0.20	67.58	1.48	7.52±0.03	7.14±0.03	7.66±0.05
0.25	64.88	1.54	7.69±0.04	7.36±0.04	7.84±0.03
0.30	62.17	1.61	7.81±0.06	7.63±0.03	8.10±0.02
0.35	59.47	1.68	7.85±0.04	7.69±0.03	8.18±0.03
		DMSO			
0.10	75.22	1.33	6.29±0.04	6.14±0.02	6.45±0.02
0.15	73.63	1.36	6.07±0.02	5.97±0.03	6.20±0.05
0.20	72.04	1.39	5.80±0.03	5.75±0.02	5.92±0.03
0.25	70.45	1.42	5.50±0.04	5.48±0.04	5.80±0.03
0.30	68.86	1.45	5.29±0.02	5.22±0.03	5.68±0.04
0.35	67.27	1.49	5.23±0.03	5.15±0.02	5.53±0.03
		DMF			
0.10	74.23	1.35	6.17±0.02	6.10±0.02	6.38±0.05
0.15	72.15	1.39	6.00±0.03	5.88±0.03	6.08±0.04
0.20	70.06	1.43	5.78±0.03	5.62±0.02	5.78±0.01
0.25	67.98	1.47	5.42±0.02	5.32±0.04	5.53±0.02
0.30	65.89	1.52	5.15±0.04	5.11±0.03	5.38±0.03
0.35	63.81	1.57	5.11±0.02	5.03±0.04	5.32±0.02

Mole fraction of organic solvent	*Dielectric constant of the medium $(D)_m$*	$(1/D)_m\ 10^2$	*pK_a values^a*		
			I	*II*	*III*
		Acetonitrile			
0.10	74.16	1.35	7.28±0.06	6.88±0.03	7.28±0.04
0.15	72.04	1.39	7.44±0.05	7.18±0.02	7.56±0.03
0.20	69.92	1.43	7.62±0.06	7.33±0.04	7.75±0.04
0.25	67.80	1.47	7.90±0.04	7.58±0.03	7.98±0.02
0.30	65.68	1.52	8.23±0.03	7.85±0.04	8.24±0.05
0.35	63.56	1.57	8.30±0.04	7.94±0.03	8.30±0.04

a) I-III refer to thiazolidine-4-carboxylic acid, 2,4-thiazolidinedione, and rhodanine, respectively.

b) Determined at 30 °C and I = 0.1 mol dm^{-3} (KNO_3)[9]; and c) determined in 50% (v/v) ethanol-water medium at 25 °C and I = 0.1 mol dm^{-3}($NaCLO_4$)[11].

To account for the differences in acidity, basicity, dielectric constant, and ion activities for an aqueous mixture relative to pure water, where the pH-meter is standardized using aqueous buffers, the pH values in the former medium were corrected according to the method described by Douhéret[20]. The meter reading pH_Robtained in a partially aqueous medium differs by an amount δ from the corrected reading pH^*:

$$pH^* = pH_R - \delta \qquad (3)$$

Values of δ for the various proportions of each organic solvent were determined as recommended by Douhéret[20].

RESULTS AND DISCUSSION

The pK_a values for the thiazolidines **I-III** in different media were determined by using two different methods *viz*, average value and straight line methods. The mean pK_avalues at 25 °C, along with the error obtained by applying the least-squares fits, are listed in Table I. The data in this Table clearly reveal that both the nature and the proportion of the organic solvent have a profound influence on the acid ionization constant values of the compounds.

Generally, the acid ionization constant for each compound decreases as the mole fraction of the amphiprotic solvent (methanol or ethanol) or the low basic aprotic solvent (acetonitrile) in the medium is increased. Increasing the mole fraction of the dipolar aprotic solvent (DMF or DMSO) leads to an increase in the acid ionization constant values.

Effect of the amphiprotic and low basic aprotic solvents

The acid-base equilibrium of the ionization step can be represented, in general, by the following equation:

$$BH \rightleftharpoons B^- + H^+ \qquad (4)$$

The acid ionization constant in a pure aqueous medium (K_{a1}) is related to that in a partially aqueous medium (K_{a2}) by the relation[21]:

$$K_{a1} = K_{a2}\ \gamma_{B^-}\ \gamma_{H^+}/\gamma_{HB} \qquad (5)$$

where γ is the activity coefficient of the subscripted species in a partially aqueous medium relative to that in pure water. It is known that the electrostatic effect resulting from the change in the dielectric constant of the medium operates on the activity coefficient of any charged species[21]. Thus, the activity coefficient of both the H^+ and conjugate base B^- is expected to increase with increasing the proportion of the organic solvent in the medium. Consequently, according to equation 5, increasing the mole fraction of the organic solvent should decrease the acid ionization constant (i.e., pK_a is high). This is consistent with the results given in Table I for water-alcohol (methanol or ethanol) and water-acetonitrile mixtures. Since methanol and acetonitrile have similar dielectric constants (32.6 and 36.0, respectively, at 25 °C), the electrostatic effects in aqueous solutions containing the same mole fraction of these two solvents should be virtually identical (i.e., pK_a values for a compound in such solutions should be the same). However, the data obtained indicate that the ionization process of each compound is more pronounced in presence of methanol than in presence of acetonitrile. Moreover, in the light of the relation given by Charlot and Tremillon[22] which relate the variation of pK_a values with the dielectric constant of the medium $(D)_m$, the plots of pK_a values against $1/(D)_m$ are not linear (Figure 1), where the $(D)_m$ is obtained from the relation:

$$(D)_m = (D)_w\chi_{(w)} + (D)_s\chi_{(s)} \qquad (6)$$

Here D and χ are the dielectric constant and mole fraction, and the subscripts w and s refer to water and solvent, respectively.

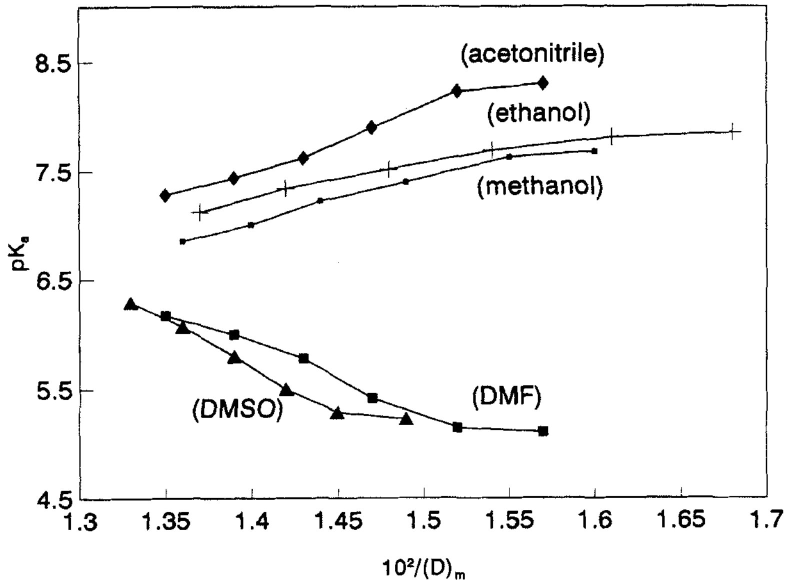


FIGURE 1 Plot of pK_a against $1/(D)_m$ of thiazolidine –4-carboxylic acid (I) in water-organic solvent mixtures at 25 °C and an ionic strength $I = 0.02$ mol dm^{-3} (KNO_3)

This indicates that other solvent effects, in addition to the electrostatic effect, strongly influence the acid ionization process of all compounds in the aqueous mixture of methanol, ethanol, or acetonitrile. It is recognized that solvent effects, such as hydrogen bonding and solvent basicity are considered to be important factors affecting the ionization process of weak acids[21]. Thus, based on the principle that water has a high tendency to donate hydrogen bonds compared with the solvents employed, the observed increase in the pK_a values of the compounds upon increasing the mole fraction of methanol, ethanol, or acetonitrile in aqueous mixtures can also be ascribed, in addition to the electrostatic effect, to the possible hydrogen bonding interaction established between the conjugate base B^- and the organic solvent molecules. Therefore, it is expected that the conjugate base B^- will be less stabilized by hydrogen bonding interaction as the mole fractions of the above-mentioned organic solvents in the medium are increased (i.e., γ_{B^-} increases). Accordingly, the pK_a values will increase as the mole fraction is increased as implied by equation 5.

The data cited in Table I indicate that the variation of pK_a values in solutions containing the same mole fraction of alcohol or acetonitrile appears to be in the order, methanol < ethanol < acetonitrile. This is presumably due to the decrease in the tendency of the solvent to develop a hydrogen bond to the conjugate base on going from methanol to acetonitrile. This was deduced from the fact that the tendency of alcohol to associate with solutes through hydrogen bonding decreases with an increase in the molecular weight of alcohol[23]. Furthermore, acetonitrile is characterized by a lower tendency to develop hydrogen bonds to a solute than alcohols[24].

On the other hand, the amphiprotic solvent (methanol or ethanol) and acetonitrile are characterized by low basicity compared to water[21]. Therefore, the proton becomes less stabilized in presence of these solvents in the aqueous medium. Thus, increasing the mole fractions of such solvents in the aqueous mixture would lead to an increase in the activity coefficient of H^+ ion, i.e., a high pK_a value. Accordingly, one can suggest that changing the basicity of the medium by increasing the mole fraction of methanol, ethanol, or acetonitrile is an additional factor affecting the ionization process of the investigated compounds in aqueous mixtures of these organic solvents.

Effect of dipolar aprotic solvents (DME and DMSO)

The results reported in Table I reveal that the values of the acid ionization constants of the compounds increase on increasing the mole fraction of the dipolar aprotic solvents DMF and DMSO. This behavior can be mainly ascribed to the high stabilization of the conjugate base B^- of each compound by the dispersion forces which are established between the delocalised oscillator dipole of the conjugate base and the localized oscillator dipole of the solvent. The high stabilization of the conjugate base by dispersion forces in partially aqueous media is due to the fact that the effective density of the dispersion centers of DMF or DMSO is higher than that of water[12]. Furthermore, the high stabilization of proton by its interaction with organic solvent and water molecules in an aqueous mixture (ion-solvent interaction) compared with water molecules alone in pure water can be considered, in part, responsible for the decrease in pK_a values as the organic solvent content in the medium is increased. On the other hand, the observed high acidity of each compound in aqueous mixtures of DMF and

DMSO could be also attributed to the high basic character of these solvents. This is expected to lead to the construction of a stronger hydrogen bond between the unionized solute (BH) and solvent molecules by which the ionization is enhanced.

Therefore, one can conclude that the hydrogen bonding interaction and the change in the basicity of the medium, in addition to the electrostatic effect resulting from the change in the dielectric constant of the medium, seem to be the major effects in determining the ionization equilibria of the compounds in aqueous mixtures of methanol, ethanol, or acetonitrile. On the other hand, the high stabilization of the conjugate base B^- by the dispersion forces and of the proton by its interaction with solvent as well as the basicity of the solvent are the main factors responsible for the increase in the ionization constants of the compounds in water-organic solvent mixtures of DMSO or DMF.

Effect of Molecular Structure on pK_a Values

The results cited in Table I clearly indicate that the acidity of compound **III** in pure aqueous medium, as well as in presence of the same mole fraction of an organic solvent, is lower than that of compound **II.** This can be interpreted in terms of the following considerations[10]. The intermolecular hydrogen bond, which is expected to develop from solvent to the imino-hydrogen, is weakened upon replacement of a carbonyl group (compound **II**) by the less electronegative thiocarbonyl group (compound **III**). This will result in a low tendency of ionization by compound **III** compared with compound **II** (i. e., high pK_a). Moreover, the sulfur $p\pi$-orbitals are of energy closer to those of carbon and nitrogen than that of oxygen. This implies a greater interaction between π-electrons of the sulfur atom and those of all other ring atoms of compound **III,** which will result in a high electron density on the heterocyclic nitrogen atom. Accordingly, this will lead to a difficult deprotonation of this nitrogen atom affording a high pK_a value for compound **III.** Furthermore, it was reported that the net stabilization of the conjugate base B^-, *via* resonance, is lowered on going from compound **II** to compound **III**[10] (i.e., γ_{B^-} increases). Consequently, and according to equation 5, the pK_a value of compound **III** is increased. Generally, the aforementioned considerations can be substantiated by the high ionization energy (20.67 kJ mol^{-1}) of compound **III** (see the following section) compared with that of compound **II**(15.06 kJ mol^{-1}).

Thermodynamic Functions of the Ionization Process

The acid ionization constants of the thiazolidines in aqueous medium at $I = 0.02$ mol dm^{-3} KNO_3 within the temperature range 5–45 °C have been determined. The values of the enthalpy change (ΔH) were determined graphically, according to the van't Hoff relationship, by plotting log K_a at different temperatures *vs* 1/T (Figure 2) and equating the gradient with $-\Delta H/19.15$. The standard free energy change $(\Delta G°)$ and entropy change $(\Delta S°)$ associated with the ionization process were calculated using the equations: $\Delta G° = -RT \ln K_a$ and $\Delta S° = (\Delta H - \Delta G°)/T$, respectively. The pK_a values, along with the thermodynamic functions, are reported in Table II. The results in this Table indicate that the pK_a values decrease as the temperature is increased. This behavior is consistent with the endothermic nature of the ionization process. The $pK_a$and the $\Delta G°$ values of the compounds **I-III** increase in the order **III>I>II.** This behavior is in agreement with the lower tendency of ionization of compound **III** compared with compound **II** or **I** as discussed. The negative sign of $\Delta S°$ values for all compounds is taken as a criterion for the presence of intermolecular hydrogen bond formation in aqueous media[25]. This indicates that the hydrogen bonds developed involving **I-III** with solvent are the main effect determining the ionization equilibria in aqueous media. However, the smaller negative value observed for the entropy change for **III** indicates less ordering of water molecules upon ionization which point to a reduced ionization[25,26]. This is consistent with the high ΔH value for this compound, indicating the ionization of this compound requires a relatively great amount of energy compared with the other compounds **I** and **II.**

TABLE II The Thermodynamic Functions Associated with the Ionization Process of Thiazolidine Compounds I-III in Pure Aqueous Medium at $I = 0.02$ mol dm^{-3} (KNO_3)

*Compound*a)	pK_a *values at °C*					ΔH/kJ mole^{-1}	ΔGb)/kJ mole^{-1}	ΔSb)/J mole^{-1} K^{-1}
	5	*15*	*25*	*35*	*45*			
I	6.57	6.48	6.36	6.29	6.20	15.82	36.28	-68.66
II	6.42	6.35	6.24	6.16	6.07	15.06	35.61	-68.95
III	7.12	6.98	6.87	6.76	6.62	20.67	39.20	-62.21

a)I-III refer to thiazolidine-4-carboxylic acid, 2,4-thiazolidinedione, and rhodanine, respectively.

b) Values calculated at 25 °C.

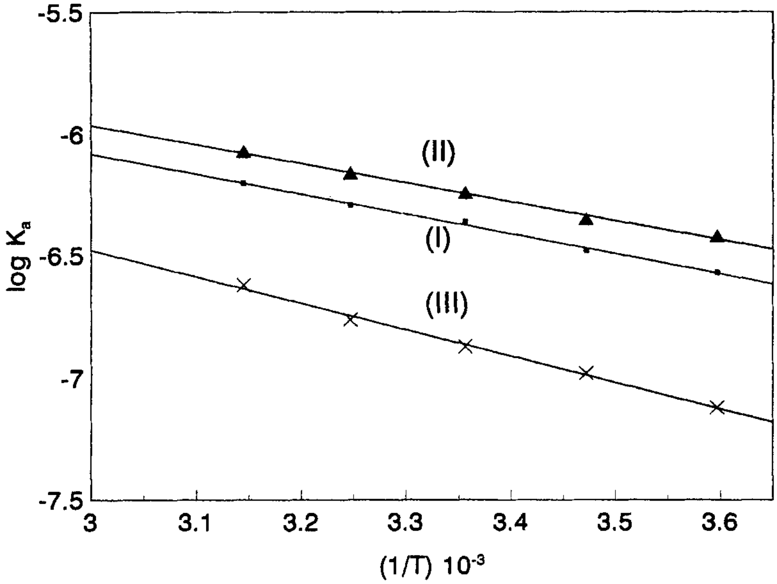


FIGURE 2 Plot of log K_a against 1/T for the compounds **I-III** in pure aqueous media

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