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Acid Dissociation Constants of Some Mercaptobenzazoles in Aqueous-Organic Solvent Mixtures

Ahmed A. Ahmed Boraei* and Iman T. Ahmed

Department of Chemistry, Faculty of Science, Minia University, El-Minia 61519, Egypt

Maher Mohamed A. Hamed

Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt

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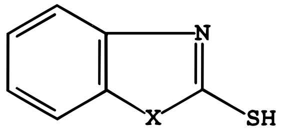
The acid dissociation constants of some 2-mercaptobenzazoles in aqueous-organic solvent mixtures are determined potentiometrically at (25 ± 0.1) °C and an ionic strength of $I = 0.02$ mol dm^{-3} (KNO_3). The organic solvents are methanol, ethanol, DMF, DMSO, and acetonitrile. The pK_a values are discussed in terms of the proportion and nature of the organic cosolvent. It was concluded that hydrogen bonding interactions of the conjugate base with the solvent and the solvent basicity in addition to the electrostatic effect contribute the major effects in the ionization process. Moreover, thermodynamic functions (ΔH, ΔG, and ΔS) of the ionization process in an aqueous medium containing 0.1 mole fraction of ethanol are also determined and discussed.

Introduction

Generally, sulfur and nitrogen containing compounds have widespread applications in the biological field (Agrawal and Sartorelli, 1978; Kulkarni and Kumar, 1984). Mercaptobenzazoles of diverse structures are known for their various biological activities such as antibacterial (Foye and Lo, 1972), antiviral (Thompson, 1947), antispasmodic (Zapadnyuk, 1962), and anti-inflammatory (Mohan *et al.*, 1985). The ionization constants of mercaptobenzazole compounds have been determined (Foye and Lo, 1972; Catalan *et al.*, 1988; Lomakina and Yakovskaya, 1969; Minkin *et al.*, 1972; Joshi *et al.*, 1973). However, the literature is lacking in studies concerning the medium effects on the pK_a values of such compounds. Therefore, the present article is devoted to the study of the medium effects on the pK_a values of 2-mercaptobenzothiazole (**I**), 2-mercaptobenzoxazole (**II**), and 2-mercaptobenzimidazole) in aqueous solutions containing varying mole fractions of organic solvents. The organic solvents used are methanol and ethanol (as amphiprotic solvents), *N*,*N*-dimethylformamide and dimethyl sulfoxide (as dipolar aprotic solvents), and acetonitrile (as a low basic aprotic solvent). The pK_a values are discussed in terms of the solvent characteristics. Further, the change of the thermodynamic functions (ΔH, ΔG, and ΔS), connected with the ionization process in an aqueous solution containing 0.1 mole fraction of ethanol, has been determined and discussed. The mercaptobenzazoles studied have the following structure:



X = S, O and NH for compounds **I**, **II** and **III,** respectively

Experimental Section

Material and Solutions. The mercaptobenzazoles used were Aldrich A. R. products. The purity of the compounds was ascertained by TLC using the method described previously (Foye and Lo, 1972). The purified compounds were dried at 120 °C for 12 h. The organic solvents utilized were of a high purity (spectrograde products) and were also distilled before use by standard methods (Vogel, 1986) and stored over molecular sieves (4 Å).

Stock solutions were prepared by dissolving an accurate mass of each benzazole compound in the appropriate volume of each solvent. CO_2-free NaOH solution (approximately 0.2 mol dm^{-3}) was prepared in doubly distilled water and standardized against a standard solution (0.1 mol dm^{-3}) of potassium hydrogen phthalate. A stock solution of nitric acid (approximately 0.1 mol dm^{-3}) was prepared and used after standardization. A 0.1 mol dm^{-3} stock solution of KNO_3 was used as a supporting electrolyte. Dilute solutions were prepared by an accurate volumetric dilution.

Procedure. The pK_a values of the compounds in the aqueous mixtures were determined by adopting the Irving−Rossotti pH-titration technique (Irving and Rossotti, 1953, 1954; Rossotti, 1978). pH-titrations were carried out with standard CO_2-free NaOH on a solution (50 cm^3) containing (a) HNO_3 [(4.0 to 5.0) × 10^{-3} mol dm^{-3}] + KNO_3 (0.02 mol dm^{-3}) and (b) solution a in the presence of 2 × 10^{-3} mol dm^{-3} of each benzazole compound and containing different mole fractions (0.1 to 0.3) of the organic solvent.

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 (Irving and Rossotti, 1953, 1954):

$$\bar{n}_H = \left(yC_L + \frac{(V_a - V_b)C_B}{V_o}\right)(C_L)^{-1} \qquad (1)$$

where y is the number of dissociable protons (y = 1 in our case), C_L is the concentration of a ligand, and V_o is the original volume (50 cm^3). V_a and V_b are the volumes of NaOH consumed to reach the same pH values in curves a and b, respectively. C_B is the concentration of NaOH. The

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Table 1. Mean pK_a Values for Mercaptobenzazoles I−III in Different Organic Solvent (1) + Water (2) at 25 °C and I = 0.02 mol dm^{-3} (KNO$_3$)

			pK_a values[c]		
solvent	$[x_{(1)}]$[a]	$[(\epsilon_r)m]$[b]	**I**	**II**	**III**
methanol	0.10	73.82	7.69 ± 0.03	7.09 ± 0.02	10.59 ± 0.03
	0.15	71.53	7.80 ± 0.02	7.20 ± 0.03	10.74 ± 0.05
	0.20	69.24	7.95 ± 0.02	7.45 ± 0.03	10.95 ± 0.03
	0.25	66.95	8.15 ± 0.03	7.80 ± 0.02	11.00 ± 0.03
	0.30	64.66	8.31 ± 0.04	8.01 ± 0.04	11.01 ± 0.04
ethanol	0.10	72.99	7.65 ± 0.02	7.16 ± 0.02	10.55 ± 0.02
	0.15	70.29	7.72 ± 0.04	7.25 ± 0.03	10.70 ± 0.03
	0.20	67.58	7.88 ± 0.03	7.38 ± 0.03	10.88 ± 0.05
	0.25	64.88	7.92 ± 0.04	7.60 ± 0.04	10.90 ± 0.03
	0.30	62.17	8.09 ± 0.06	7.89 ± 0.03	10.99 ± 0.02
DMSO	0.10	75.22	7.30 ± 0.04	7.00 ± 0.02	10.30 ± 0.02
	0.15	73.63	7.42 ± 0.02	7.10 ± 0.03	10.45 ± 0.05
	0.20	72.04	7.56 ± 0.03	7.26 ± 0.02	10.66 ± 0.03
	0.25	70.45	7.63 ± 0.04	7.50 ± 0.04	10.73 ± 0.03
	0.30	68.86	7.70 ± 0.02	7.80 ± 0.03	10.80 ± 0.04
DMF	0.10	74.23	7.07 ± 0.02	6.87 ± 0.02	10.22 ± 0.05
	0.15	72.15	7.28 ± 0.03	7.00 ± 0.03	10.30 ± 0.04
	0.20	70.06	7.46 ± 0.03	7.16 ± 0.02	10.35 ± 0.01
	0.25	67.98	7.52 ± 0.02	7.50 ± 0.04	10.47 ± 0.02
	0.30	65.89	7.75 ± 0.04	7.85 ± 0.03	10.65 ± 0.03
AN	0.10	74.16	8.83 ± 0.06	7.53 ± 0.03	*d*
	0.15	72.04	9.02 ± 0.05	7.90 ± 0.02	*d*
	0.20	69.92	9.30 ± 0.06	8.30 ± 0.04	*d*
	0.25	67.80	9.35 ± 0.04	8.35 ± 0.03	*d*
	0.30	65.68		8.43 ± 0.04	*d*

$[x_{(1)}]$ is the mole fraction of the organic solvent. [b] $\epsilon_{r(m)}$ is the relative permittivity of the medium. [c] I−**III** refer to 2-mercaptobenzothiazole, 2-mercaptobenzoxazole, and 2-mercaptobenzimidazole, respectively. [d] The compound is not soluble in acetonitrile (AN).

values were calculated from the following relationship (Rossotti, 1978):

$$\bar{n}_H = \beta[H^+]/1 + \beta[H^+] \tag{2}$$

Here β is the formation constant of the ligand.

All calculations were performed using a computer program based on unweighted linear least-squares fits.

pH-titrations were carried out using an Orion model 701A digital pH-meter (accurate to ±0.005 units). A Fisher Scientific Isotemp Refrigerated Circulator Model 9000 water thermostat accurate to ±0.1 deg was used.

To account for the differences in acidity, basicity, relative permittivity, 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 using the method described by Douhéret (1967), where the meter reading pH$_R$ obtained in a partially aqueous medium differs by an amount δ from the corrected reading pH*:

$$pH^* = pH_R - \delta \tag{3}$$

Values of δ for the various proportions of each organic solvent were determined as recommended by Douhéret (1967, 1968).

The pK_a values for mercaptobenzazoles were determined by applying two different methods: the average value and straight line methods. The mean pK_a values along with the error as obtained by applying the least-squares fits are given in Table 1. However, since the solubility of the compounds in water is very small, the acid dissociation constants in pure water could not be determined.

Results and Discussion

The mean pK_a values at 25 °C of the benzazoles (Table 1) indicate that the acid ionization constant values depend largely on both the nature and the proportion of the organic solvent. Generally, increasing the mole fraction of the organic solvent leads to a decrease in the acid ionization constants.

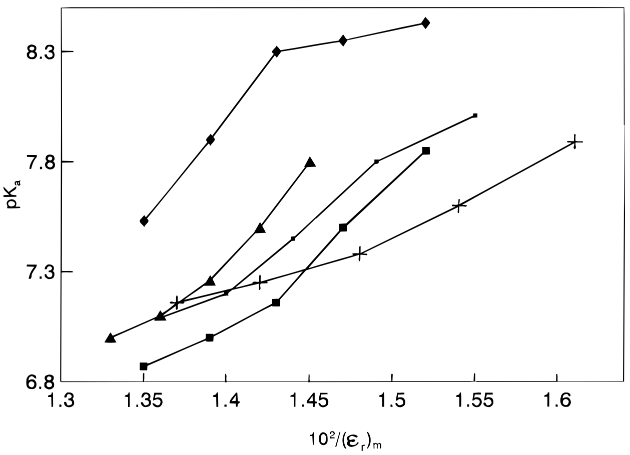

Figure 1. Plot of pK_a against $1/\epsilon_{r(m)}$ of 2-mercaptobenzoxazole in water + organic solvent at 25 °C: (•) methanol; (+) ethanol; (▲) DMSO; (■) DMF; (♦) acetonitrile.

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

$$BH \rightleftharpoons B^- + H^+ \tag{4}$$

According to Coetzee and Ritchie (1969) the acid dissociation constant in water (K_{a1}) is related to that in a partially aqueous medium (K_{a2}) by the relation

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

where γ is the activity coefficient of the respective species in an aqueous mixture medium relative to that in pure water. It is known that the electrostatic effect resulting from the change in the relative permittivity of the medium only affects the activity coefficient of the charged species (Coetzee and Ritchie, 1969). Thus, one can expect that increasing the amount of the organic solvent in the medium will increase the activity coefficient of both H$^+$ and conjugate base B$^-$. Consequently, according to eq 5, the acid dissociation constants of the compounds should decrease on increasing the mole fraction of the organic solvent (i.e., high pK_a value). This is consistent with the results reported in Table 1. Since DMF and acetonitrile have similar relative permittivities (ϵ_r = 36.7 and 36.0 *l*, respectively at 25 °C), the electrostatic effects in aqueous solutions containing the same mole fraction of these solvents should be similar (i.e., pK_a for each compound in such solutions should be the same). However, the pK_a values in solutions containing the same mole fraction of these solvents are markedly different (see Table 1). This indicates that the decrease in the acid ionization constants, though governed by the electrostatic effect, is strongly influenced by other solvent effects. This conclusion is further substantiated by the nonlinear plots of pK_a values against the reciprocal of the relative permittivity of the medium $(\epsilon_r)_m$ (Figure 1), according to the relation given by Charlot and Tremillon (1969), where $(\epsilon_r)_m$ is obtained from the relation

$$(\epsilon_r)_m = (\epsilon_r)_{(w)}x_{(w)} + (\epsilon_r)_{(s)}x_{(s)} \tag{6}$$

where ϵ_r and x are the relative permittivity and mole

Table 2. Thermodynamic Functions of the Ionization Process of Mercaptobenzazoles I–III in an Aqueous Medium Containing 0.10 Mole Fraction of Ethanol at $I = 0.02$ mol dm^{-3} (KNO$_3$)

	pK_a values at t/°C				ΔH/kJ	ΔG^b/kJ	ΔS/J
compd^a	15	25	35	45	mol^{-1}	mol^{-1}	mol^{-1} K^{-1}
I	7.86	7.65	7.56	7.46	22.49	43.64	−70.97
II	7.46	7.16	6.95	6.46	56.19	40.85	51.48
III	10.86	10.55	10.46	10.37	27.32	60.19	−110.30

[a] **I**–**III** refer to 2-mercaptobenzothiazole, 2-mercaptobenzoxazole and 2-mercaptobenzimidazole, respectively. [b] ΔG values calculated at 25 °C.

fraction and the subscripts w and s refer to water and organic solvent, respectively.

Other solvent effects such as hydrogen bonding and solvent basicity as well as dispersion forces and proton–solvent interactions exert a profound influence on the ionization process (Coetzee and Ritchie, 1969). Thus, the increase in the pK_a values of the compounds on increasing the mole fraction of the organic solvent can be ascribed, in addition to the electrostatic effect, to the hydrogen bonding interaction between the organic solvent and the conjugate base B$^-$. Since water has a high tendency to donate hydrogen bonds compared with other solvents (Franks and Ives, 1966), the conjugate base B$^-$ is expected to be less stabilized by hydrogen bonding interaction as the mole fraction of the organic solvent in the medium is increased, γ_{B^-} increases). Accordingly, the pK_a values increase as the mole fraction of the organic solvent is increased, as eq 5 implies. The observed high pK_a values of the compounds in water+acetonitrile relative to those in water+alcohol (methanol or ethanol), where both have the same mole fraction, are consistent with the fact that acetonitrile has a lower tendency to develop hydrogen bonds to B$^-$ than alcohols (Deno and Wisotsky, 1963). This behavior emphasizes that the difference in stabilization of the conjugate base B$^-$ of the compounds by a donor hydrogen bond from the solvent plays a vital role in the ionization process. However, the results in Table 1 indicate that the ionization of the compounds is more pronounced in the presence of the poorer hydrogen bond donor solvents DMF and DMSO than in the presence of other solvents. This behavior can be ascribed to the high basic character of DMF and DMSO comparing to the other solvents (Coetzee and Ritchie, 1969). This is expected to lead to the construction of a stronger hydrogen bond acceptor from the unionized solute (BH) and, consequently, promotes the ionization process (i.e., low pK_a).

If the dispersion forces and proton–solvent interactions have important effects on the ionization process of the compounds, one should expect that by increasing the mole fraction of the organic solvent both B$^-$ and H$^+$ will be highly stabilized (i.e., γ_{B^-} and γ_{H^+} decrease). Thus, in light of eq 5, the pK_a values will decrease on increasing the mole fraction of the organic solvent. This is not the case, as is evident from the results given in Table 1. Therefore, one can conclude that the dispersion forces and proton–solvent interaction effects do not have an effective contribution in the ionization process of the compounds.

Thermodynamic Functions of the Ionization Process. The acid dissociation constants in an aqueous medium containing 0.1 mole fraction of ethanol at a constant ionic strength $I = 0.02$ mol dm^{-3} (KNO$_3$) within the temperature range 15 to 45 °C have been determined. The pK_a values are given in Table 2. According to the van't Hoff relationship, from a plot of log K_a *vs* $1/T$ (Figure 2) the values of the enthalpy change (ΔH) are determined. The free energy change (ΔG) and the entropy change (ΔS) are calculated from $\Delta G = -RT \ln K_a$ and $\Delta G = \Delta H - T\Delta S$, respectively. The results in Table 2 indicate that the acid dissociation constants increase as the temperature is increased. This is consistent with the endothermic nature of the ionization process. The values of pK_a and therefore of ΔG of compounds **I**–**III** increase in the order **III** > **I** > **II**. This behavior is in accordance with the increase in the donating power of the heteroatom. The positive value in the entropy change ΔS for compound **II** indicates the solvent molecules are less ordered upon dissociation, which points to a greater association (Mui *et al.*, 1974; Masoud *et al.*, 1983). This is consistent with the high value of ΔH for this compound, indicating the dissociation of this compound requires a great amount of energy relative to the other compounds.

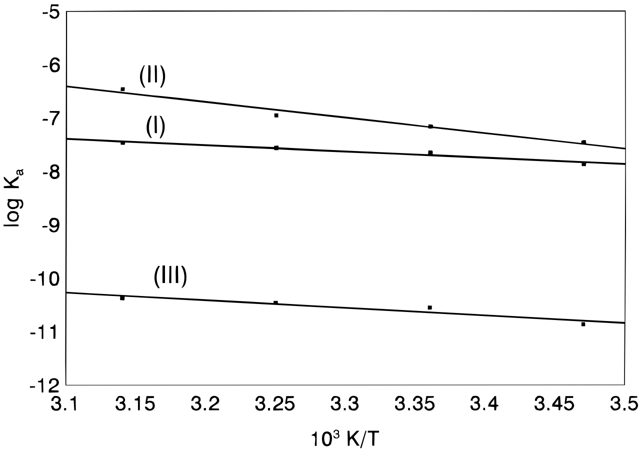

Figure 2. Plot of log K_a against $1/T$ for 2-mercaptobenzothiazole (**I**), 2-mercaptobenzoxazole (**II**), and 2-mercaptobenzimidazole (**III**) in ethanol (1) + water (2) at $x_1 = 0.1$.

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