Potentiometric and Thermodynamic Studies of Azosulfonamide Drugs. X

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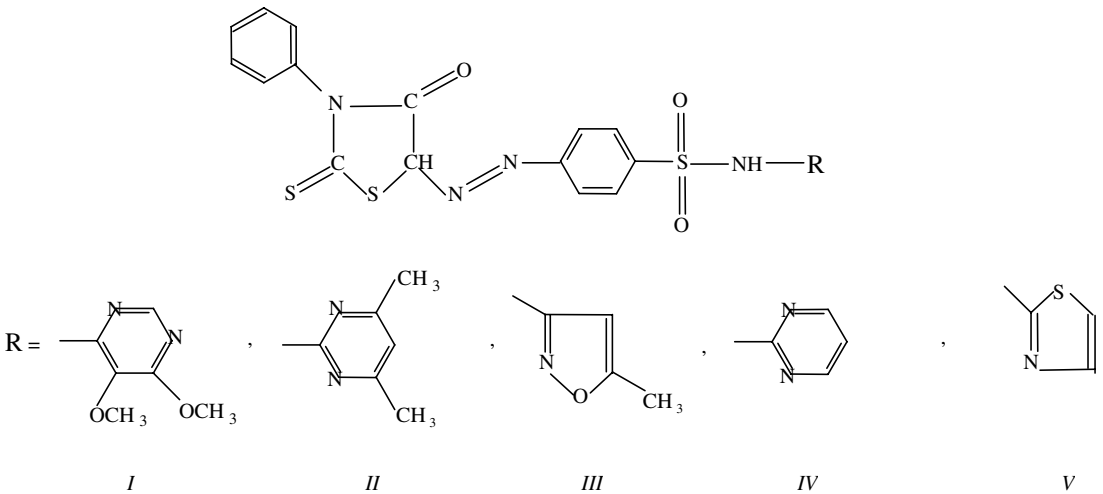
Dissociation constants of azosulfonamide derivatives of rhodanine have been determined potentiometrically in 0.1 M-KCl and 30 vol. % ethanol—water mixture. The data are discussed in terms of the electron nature of the substituents and of the change in temperature. The pK_1^H values have been found to increase with increasing electron-donating nature of the substituents. The evaluated thermodynamic parameters (ΔG, ΔH, and ΔS) indicated that the dissociation processes are not spontaneous, they are endothermic and entropically unfavourable.

Azo compounds based on rhodanine were synthesized as potential medicinal preparations [1]. Their qualitative reactions with some elements were also reported [2, 3]. Sulfonamides were the first effective chemotherapeutic agents employed for curing bacterial infections [4]. Although potentiometric studies of azo compounds are frequently carried out, little attention was paid to azo compounds formed by interaction of rhodanine and sulfonamide drugs as ligand.

In continuation of our earlier works [5—8], we report herein the dissociation constants of *N*-(5,6-dimethoxypyrimidin-4-yl) (*I*; sulfadimethoxine derivative), *N*-(4,6-dimethylpyrimidin-2-yl) (*II*; sulfamethazine derivative), *N*-(5-methylisoxazol-3-yl) (*III*; sulfamethoxazole derivative), *N*-(pyrimidin-2-yl) (*IV*; sulfadiazine derivative), and *N*-(thiazol-2-yl)-4-[(4-oxo-3-phenyl-2-thioxothiazolidin-5-yl)azo]benzenesulfonamides (*V*; sulfathiazole derivative) determined in 0.1 M-KCl and 30 vol. % ethanol—water mixture.

The influence of substituents on the proton affinity of the compounds was examined on the basis of inductive effects. The corresponding thermodynamic parameters are derived and discussed.

The average number of protons associated with the compounds *I*—*V* at different pH values, $\bar{n}_A$, was calculated from the titration curves of the acid in the absence and presence of compound. Thus, the formation curves ($\bar{n}_A$ *vs.* pH) for the proton—compound systems were constructed (Fig. 1). The $\bar{n}_A$ were found to range between 0 and 2 in the $\bar{n}_A$ scale. This means that the compounds have two dissociable protons (the enol of the sulfonamide group, pK_1^H and carbonyl oxygen in the rhodanine moiety, pK_2^H). It can be seen that for the same volume of NaOH added the com-



I *II* *III* *IV* *V*

pound titration curves showed a lower pH value than the titration curve of free acid. The displacement of a compound titration curve along the volume axis with respect to the free acid titration curve is an indication of proton dissociation. The dissociation constants were calculated using the method of *Irving* and *Rossotti* [9].

The phenolic —OH group is known to be weakly acidic, indicating a stronger bonding between the proton and the oxygen donor. This means that the dissociation constant of —OH group of rhodanine moiety (pK_2^H) should be higher than that of the sulfonamide group (pK_1^H) [10].

Three types of tautomerism can be suggested for the compounds *I*—*V*.

An inspection of the results in Table 1 reveals that the pK_1^H values of the compounds are influenced by the inductive effect of the substituents. The electron-donating —OCH_3 and —CH_3 groups enhance the electron density by their high positive inductive effect, whereby stronger O—H bond in the sulfonamide group is formed [11].

The dissociation constants of the compounds have been evaluated at 298 K, 308 K, and 318 K and are given in Table 1. The slope of the plot (pK^H *vs.* $1/T$) was utilized to evaluate the enthalpy change ΔH for the dissociation process. From the Gibbs energy change ΔG and enthalpy change ΔH values one can deduce the entropy changes (ΔS) using the relationships

$$\Delta G = 2.303\, RT\ pK \qquad (1)$$

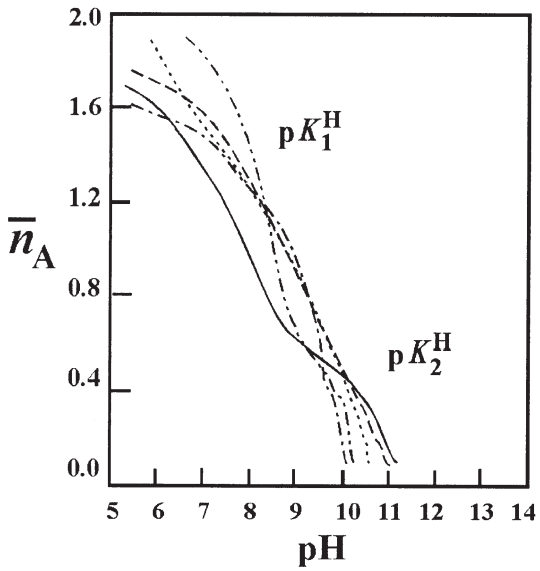


Fig. 1. Dissociation constants of the compounds *I* (– · ·–), *II* (– – –), *III* (· · ·), *IV* (– · –), and *V* (——) in 30 vol. % ethanol—water mixture at 298 K.

$$\Delta S = (\Delta H - \Delta G)/T \qquad (2)$$

All thermodynamic parameters for the dissociation process of the compounds are recorded in Table 1. From these results the following conclusions can be drawn:

The pK^H values decrease with increasing temper-

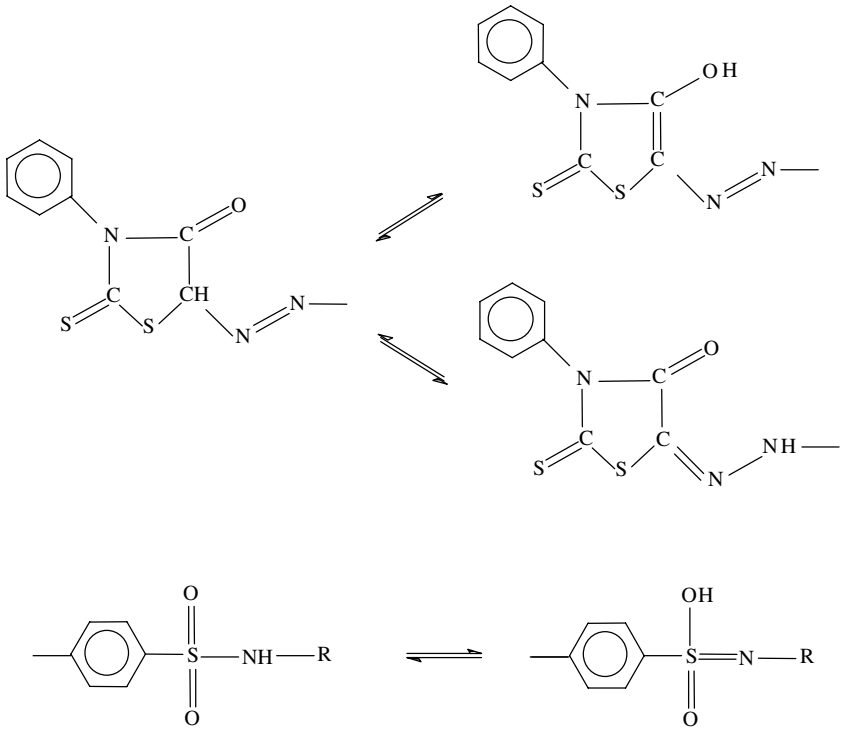


Table 1. Thermodynamic Functions for the Dissociation of Azosulfonamide Derivatives of Rhodanine in 30 vol. % Ethanol—Water Mixture and 0.1 M-KCl

Compound	T/K	Logarithm of dissociation constant*		Gibbs energy change		Enthalpy change		Entropy change	
		pK_1^H	pK_2^H	ΔG_1	ΔG_2	ΔH_1	ΔH_2	$-\Delta S_1$	$-\Delta S_2$
				kJ mol^{-1}	kJ mol^{-1}	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}	J mol^{-1} K^{-1}
I	298	7.90 (0.09)	9.75 (0.08)	45.08	55.63			87.01	122.42
	308	7.80 (0.08)	9.65 (0.08)	46.00	56.91	19.15	19.15	87.18	122.60
	318	7.70 (0.10)	9.54 (0.10)	46.88	58.09			87.20	122.45
II	298	7.40 (0.11)	9.98 (0.10)	42.22	56.94			77.42	104.33
	308	7.30 (0.10)	9.85 (0.11)	43.05	58.09	19.15	25.85	77.60	104.68
	318	7.20 (0.09)	9.71 (0.10)	43.83	59.12			77.61	104.62
III	298	7.15 (0.08)	9.95 (0.09)	40.80	56.77			56.61	106.98
	308	7.02 (0.09)	9.81 (0.08)	41.40	57.85	23.93	24.89	56.72	107.01
	318	6.90 (0.09)	9.67 (0.08)	42.01	58.88			56.86	106.89
IV	298	6.85 (0.09)	9.65 (0.10)	39.08	55.06			41.17	98.02
	308	6.71 (0.10)	9.51 (0.11)	39.57	56.08	26.81	25.85	41.43	98.15
	318	6.56 (0.10)	9.37 (0.10)	39.94	57.05			41.29	98.11
V	298	6.50 (0.11)	9.80 (0.08)	37.09	55.92			37.72	97.68
	308	6.35 (0.08)	9.65 (0.09)	37.45	56.91	25.85	26.81	37.66	97.73
	318	6.21 (0.09)	9.51 (0.11)	37.81	57.90			37.61	97.77

*Standard deviations are given in parentheses.

ature, *i.e.* the acidity of the compounds increases, independently of the nature of the substituent [12].

A positive value of ΔH indicates that dissociation is accompanied by absorption of heat and the process is endothermic.

A large positive value of ΔG indicates that the dissociation is not spontaneous [13].

A negative value of ΔS is obtained due to the increased order as a result of solvation processes [14]. Further, the order increases as the electron-donating nature of the substituent increases.

EXPERIMENTAL

Compounds *I*—*V* were prepared [3] by gradual addition of an aqueous solution of 0.01 mol of sodium nitrite to a concentrated hydrochloric acid solution of 0.01 mol of *I*—*V*, respectively, with stirring and keeping the mixture in an ice bath for about 20 min. The formed diazonium chloride solutions were added gradually with vigorous stirring to a cold solution of 0.01 mol of 3-phenyl-2-thioxothiazolidin-4-one [6] in 50 cm^3 of pyridine. After dilution, the compounds *I*—*V* formed were filtered off and washed with water. The crude materials were recrystallized from ethanol and then dried in a vacuum desiccator over anhydrous calcium chloride. The purity was checked by elemental analyses, IR and ^{1}H NMR spectra [7, 8]. 0.01M solutions of the compounds were prepared in ethanol (Analar). Solutions of 0.005 M-HCl and 1 M-KCl were prepared in doubly distilled water. A carbonate-free sodium hydroxide solution in a 30 vol. % ethanol—water mixture was used as titrant and standardized against oxalic acid (Analar).

Apparatus, general conditions, and methods of calculation were the same as in the previous works [5—8, 15]. The following mixtures were prepared and titrated potentiometrically at 298 K against standard 0.02 M-NaOH in 30 vol. % ethanol—water mixture:

i) 5 cm^3 0.005 M-HCl + 5 cm^3 1 M-KCl + 15 cm^3 ethanol;

ii) 5 cm^3 0.005 M-HCl + 5 cm^3 1 M-KCl + 10 cm^3 ethanol + 5 cm^3 0.01 M solution of the respective compound.

Each mixture was made up to 50 cm^3 with doubly distilled water before titration. The titrations were performed at 308 K and 318 K. A constant temperature was maintained to ± 0.05 K by using an ultrathermostat (Neslab 2 RTE 220). The pH-meter readings in 30 vol. % ethanol—water mixtures were corrected using the *van Uitert* and *Hass* relation [16].

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