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Voltammetric, potentiality and thermodynamic studies of some rhodanine sulfa drugs azo compounds in aqueous solutions

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ABSTRACT

The electrochemical behavior of some rhodanine sulfa drug azo compounds in Britton-Robinson universal buffers containing 40 % (v/v) ethanol was investigated at the mercury electrode using dc-polarography, cyclic voltammetry and controlled potential coulometry. The examined azo compounds were reduced in all *pH* in two diffusion-controlled irreversible steps, the first step corresponding to the cleavage of the N=N center via the consumption of four electrons whereas the second one is due to the saturation of the S=C of the rhodanine ring. The mechanistic path way of the electrode reaction of the studied compounds was elucidated and the kinetic parameters were calculated and discussed. The dissociation constants (pK_a) values of the examined azo compounds and the thermodynamic parameters were determined potentiometrically.

Key words: Rhodanine; sulfa drugs; polarography; coulometry; cyclic voltametry; potentiometry.

INTRODUCTION

Sulfa drugs containing azo group are of a great importance due to their usefulness as models for biological systems, *i.e*, antifungal, antibacterial, anticancer and antimalarial[1,2]. On the other hand, azo compounds based on rhodanine were synthesized as potential medicinal preparations[3]. Moreover, the azo compounds occupy a good position as analytical reagents[4,5]. Although voltammetric[6-10] and potentiomtric[11-14] studies of azo compounds were frequently carried out, little attention was paid to azo compounds formed by interaction of rhodanine and sulfa drugs as ligand[15].

The present study deals with dc-polarography, cyclic voltammetry, coulometrey and potentiometric investigations of some rhodanine azo sulfa drug compounds. It is aimed to throw light on the electrode reaction mechanism of reduction of these compounds at mercury electrode and also evaluation of their dissociation constants at different temperatures.

EXPERIMENTAL

Preparation of the solid compounds

The sulfa drug azo compounds (1-V) were prepared[15] by gradual addition of an aqueous cold solution of 0.01 mole of sodium nitrate to a concentrated hydrochloric acid solution of 0.01 mole of sulfadiazine (I), sulfadiamethoxine (II), sulfamethazine (III), sulfamerazine (IV) and sulfathiazole (V) with continuous stirring and kept

for about 20 min in ice bath. The formed diazonium salt chloride solutions were added gradually with vigorous stirring to a 0.01 mole cold solution of 3-phenyl-2-thioxo-4-thiazolidinone in 50 ml pyridine. After dilution, the obtained solid compounds were filtered off and washed with water. The crude materials were crystallized from ethanol and then dried in a vacuum desiccator over anhydrous calcium chloride. The prepared azo compounds were characterized by elemental analysis, melting point, IR and ^{1}H-NMR spectra. These compounds have the structural formulae listed in scheme 1.

Voltammetric measurements

DC-polarograms were recorded on an ink recording Sargent-Welch polarograph model 4001 The capillary possessed the following characteristics in 0.1 M KCl solution (open circuit). A saturated calomel electrode (SCE) was used as a reference electrode. A polarographic analyzer model 264A (PARC) from (EG&G) provided with the electrode assembly model 303 with a hanging mercury dropping electrode (HMDE) of a surface area 0.026 cm^2 as a working electrode, a platinum wire as a counter electrode and Ag/AgCl as a reference electrode was used for cyclic voltammetry measurements. X-Y recorder model 0091 (Houston Instrument Division from EG&G) was used for recording the voltammograms. A coulometer system model PARC-380 with a mercury pool cathode was used for determination of the total number of electrons involved in the overall reduction process.

Potentiometric measurements

The apparatus, conditions and methods of calculation were the same as in the previous work[11-17]. The following mixtures were prepared and titrated potentiometrically at 298k against 0.02M NaOH in 20% (v/v) ethanol–water mixture:

5ml 0.005M HCl + 5ml IM KCl + 15 ml ethanol.

5 ml 0.005 M HCl+ 5ml IM KCl + 10 ml ethanol + 5 ml 0.0001 M ligand for each mixture, the volume was made up to 50 ml with doubly distilled water before the titration. These titrations were repeated at 308 and 318 k. The temperature was maintained at ± 0.5k using an ultra thermostat (Neslab 2 RTE 220).

RESULTS AND DISCUSSION

Voltammetric studies

DC-polarography

The dc-polarograms of 2.5 x 10^{-4} of azo compounds I-V were measured in Briton-Robinson buffer solutions of pH 2-11 containing 40% (v/v) ethanol to insure the complete solubility of these compounds due to their difficult solubility in pure aqueous media. The polarograms of all compounds exhibited two reduction waves in all solutions. The second wave in strong acid solutions is ill-defined whereas in alkaline ones the limiting current (i_1) decreases gradually with increasing the pH. On the other hand, the limiting current of the first wave is considered to be pH- independent. Also, it is important to notice that the height of the first wave is almost twice that of the second one, denoting that the number of electrons involved in the reduction process for the first wave is double that for the second one (Fig. 1).

The half-wave potential ($E_{1/2}$) of the polarographic waves shift to more negative values on increasing the pH of the solution denoting that hydrogen ions are consumed in the reduction process and the proton uptake precedes the electron transfer[16]. The effect of mercury height (h) on the limiting current of the polarographic waves using the equation[17]: $i_1 = k\ h^x$ revealed that the reduction process is mainly controlled by diffusion with some adsorption contribution. The value of the exponent x amounts to 0.5-0.65, the value in general decreases with rise of pH. Analysis of the reduction waves using the fundamental equation of polarographic waves[18] showed that the electrode reaction proceeds irreversibly. The values of the transfer coefficient α and the number of electrons participating in the rate–determining step (n_a) were determined from the reciprocal slope of logarithmic analysis (S_1) given in Table -1. It was found that, the most probable α-values were obtained at $n_a = 2$, which denoted that the rate-determining step should involve one electron.

The $E_{1/2}$-pH plots for all azo compounds gave straight lines of slopes (S_2) given in Table -1. The number of protons (p) involved in the rate-determining step was determined from the slopes S_1 and S_2 according to the relation[18,19]: $p=S_2/S_1$.

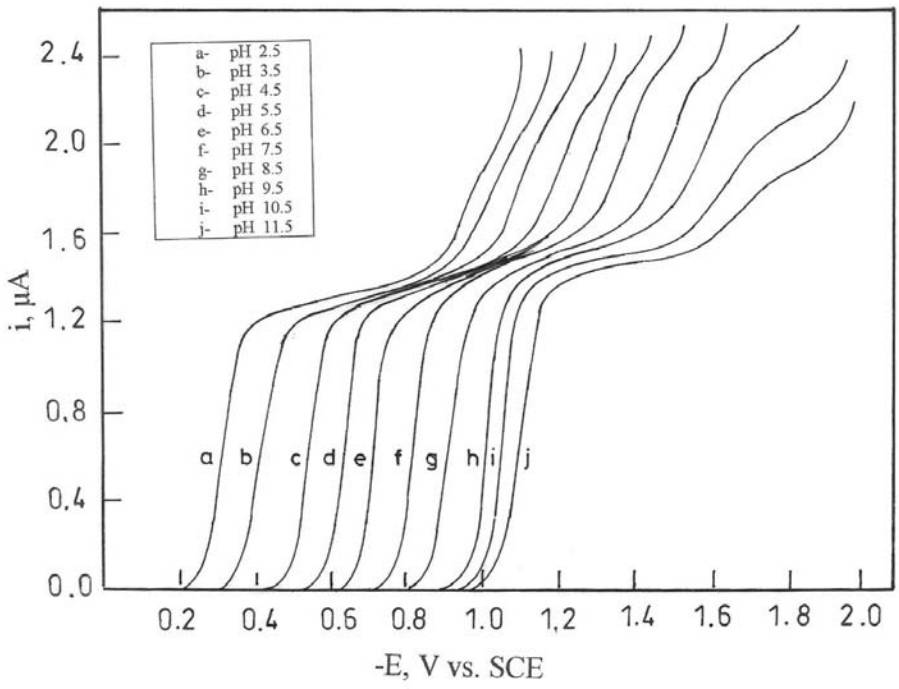


Fig. - 1: The polarograms of compounds exhibiting two reduction waves in solutions

The value of (p) as determined for the azo compounds I-V was found to be one (Table -1).

Cyclic voltammetry

The cyclic voltammetry of azo compounds I-V was measured in buffer solutions of different pH containing 40% (v/v) ethanol. Three pH media were chosen for this study. The voltammograms were recorded at different sweep rates (20-500mV/s). As shown in Fig. -2, the voltammograms for all compounds consist of three cathodic peaks but no anodic peaks were observed in the reverse direction, denoting the irreversibility of the reduction process. The peak potential (E_P) shifts to more negative values on increasing the pH of the solution, revealing that the reduction process required higher energy in alkaline solutions due to the decreased hydrogen ion activity at higher pH.

On plotting the peak potential (i_p) as a function of the square root of sweep rate ($v^{½}$) linear relations were obtained passing through the origin indicated that the electrode reaction is mainly governed by diffusion[20]. The values of the transfer coefficient (α) were determined using Galus equation[21], which relates the values of E_P and αn_a. The plots of E_p versus 1nv (logarithm of sweep rate) were straight lines of slopes (S_3). From these slopes, α-values were calculated and given in Table -2. It was found that the most probable values of a were obtained at n_a = 1. This means that the rate-determining step of the electrode reaction should involve one electron. The same results were obtained from dc-polarography.

Determination of the total number of electrons in the electrode reaction

The total number of electrons (n) involved in the electrode reaction was determined using I1kovic equation and controlled potential

Table - 1: DC-polarographic data of rhodanine sulfa azo compounds (I-V) in aqueous buffer solutions of different pH values, at 25 °C.

Comp.	pH	i_l , (uA)	$E_{1/2}$ (mV)	S_1 (mV	S_2 (mV	αn_a	$\Delta \log i_l / \Delta \log h$	p
I	2.5	1.23a	0.30	82	88	0.72	0.65	1.07
		0.48b	0.86	79	45	0.75	0.53	0.60
	9.5	1.48a	1.03	87	88	0.68	0.49	1.01
		0.48b	1.55	78	45	0.76	0.52	0.58
II	2.5	1.14a	0.38	79	56	0.75	0.69	0.71
		0.40b	0.38	90	51	0.66	0.53	0.57
	9.5	1.26a	0.78	105	56	0.56	0.51	0.53
		0.40b	1.28	79	51	0.75	0.62	0.65
III	2.5	0.72a	0.24	80	75	0.74	0.61	0.94
		0.48b	0.83	78	34	0.76	0.65	0.44
	9.5	0.64a	0.83	78	75	0.76	0.49	0.96
		0.32b	1.28	79	34	0.75	0.52	0.43
IV	2.5	0.80a	0.32	95	85	0.62	0.58	0.89
		0.40b	1.00	78	40	0.76	0.56	0.51
	9.5	0.82a	0.90	81	85	0.73	0.53	1.05
		0.48b	1.32	78	40	0.76	0.56	0.51
V	2.5	1.26a	0.18	90	62	0.66	0.62	0.69
		0.56b	0.91	80	68	0.73	0.65	0.85
	9.5	1.28a	0.79	85	62	0.69	0.58	0.73
		0.64b	1.38	78	68	0.76	0.60	0.87

a- first wave b-second wave.

electrolysis technique.

i- Using the I1kovic equation[22]: $i_d = 607\ D^{½}\ m^{2/3}\ t^{1/6}\ C$

In this equation, the diffusion coefficient (D_o) values were calculated using Stock-Eintein equation[23]: $D_o = 3.22 \times 10^{-5} / (V_m) = 3.22 \times 10^{-5} / (M/d)^{1/3}$ in which V_m and M are molar volume and molecular weight of the depolarizer, d is the density of the solid compound. The densities of the azo compounds I-V were determined using the simple density bottle methods and the values obtained were corrected for medium effect. The values of (n) determined by I1kovic equation were found to be 4 and 2 electrons for the first and second waves, respectively (Table -3).

ii. Using controlled potential electrolysis (cpe) technique

The total number of electrons was determined using cpe technique using a mercury pool cathode. The accumulated charge (Q) was taken from the digital coulometer at a potential corresponding to the limiting current of the polarographicwave. Applying the equation:

$$Q = nFw / M$$

where w is the weight of the sample in grams and M its molecular weight, the values of (n) for the azo compounds I-V was found to be four and two electrons for the first and second waves, respectively as indicated before from IIkovic equation. Thin layer chromatography (TLC) was applied on the completely electrolyzed solution for azo compounds I and II (as example) to characterize the products of the reduction process. The completely electrolyzed solution was firstly concentrated and the buffer ingredients were removed by extracting the slurry with ether. On comparing the TLC extract in petroleum ether-ethy1 acetate mixture with the authentic sulfadiazine and

Table - 2: Cyclic voltammetric data of rhodanine azo compounds I-V in aqueous buffer solutions of different pH

Compound	pH	Ep	dEp/dlnv	α_{na}
		0.62a	0.020	0.64
	2.5	0.75b	0.030	0.43
		1.25c	0.024	0.53
I		0.84a	0.031	0.41
	9.5	1.16b	0.035	0.37
		1.74c	0.030	0.43
		0.38a	0.045	0.28
	2.5	0.56b	0.030	0.43
		1.09c	0.032	0.40
II		0.73a	0.026	0.49
	9.5	0.84b	0.033	0.39
		1.40c	0.030	0.42
		0.51a	0.040	0.32
	2.5	0.90c	0.041	0.31
III		0.87a	0.045	0.28
	9.5	1.54b	0.045	0.28
		1.85c	0.400	0.32
		0.18a	0.018	0.71
	2.5	0.44b	0.028	0.47
		1.02c	0.030	0.43
IV		0.63a	0.025	0.51
	9.5	0.85b	0.021	0.61
		1.38c	0.016	0.80
		0.38a	0.020	0.64
	2.5	0.54b	0.025	0.51
		1.08c	0.040	0.32
V		0.66a	0.017	0.75
	9.5	0.90b	0.075	0.17
		1.44c	0.017	0.75

a- first peak b- second peak c- third peak

sulfamethzine samples, it was found that the first is one of the main electrolysis products of azo compound I, while the latter is one of the main electrolysis products of azo compound II.

Mechanism of the electrode reaction

The data obtained from dc-polarography and cyclic voltammetry of azo compounds I-V revealed that the rate-determining step of the electrode reaction involved one proton and two electrons for both waves A and B. Also, the protonation of the depolarizer molecule should precede the electron transfer proper[19]. On the other hand, cpe indicated that 4 electrons are involved in the first wave which represents the reduction of the more easily reducible azo group via cleavage of the double bond (N=N) to the amine stage whereas the second wave represent the saturation of the

Table - 3: Kinetic parameters and total number of electrons (n) calculated from dc- polarography

Compound	pH	D^o $Cm^{2/s}$	n	$K_{f,h}$, cm/s	ΔG*, k J
	2.5	$4.8x10^{-6}$	4.00	$2.00x10^{-8}$	79.08a
I			1.92	$5.60x10^{-12}$	98.40b
	9.5	$5.0x10^{-6}$	3.84	$1.90x10^{-22}$	111.12a
			2.00	$7.30x10^{-27}$	170.19b
II	2.5	$3.8x10^{-6}$	4.00	$1.17x10^{-10}$	96.84a
			2.01	$4.20x10^{-15}$	112.52b
	9.5	$4.2x10^{-6}$	4.02	$4.41x10^{-20}$	108.00a
			2.00	$5.08x10^{-25}$	170.81b
	2.5	$2.1x10^{-6}$	3.96	$1.00x10^{-9}$	81.46a
III			2.00	$1.00x10^{-16}$	121.91b
	9.5	$2.4x10^{-6}$	4.00	$7.14x10^{-20}$	140.10a
			1.98	$4.70x10^{-20}$	174.60b
	2.5	$5.1x10^{-6}$	4.00	$5.00x10^{-9}$	77.04a
			1.96	$3.06x10^{-14}$	107.39b
VI	9.5	$5.0x10^{-6}$	3.92	$3.41x10^{-20}$	141.95a
			2.00	$3.00x10^{-27}$	174.21b
	2.5	$3.4x10^{-6}$	3.98	$3.10x10^{-8}$	81.22a
			2.00	$4.95x10^{-17}$	123.75b
V	9.5	$3.6x10^{-6}$	4.00	$5.96x10^{-18}$	115.21a
			1.98	$2.99x10^{-31}$	220.07b

a- first wave b-second wave

C=S in the heterocyclic ring. In the light of the explanation of Zuman[16], the sequence of the electrode reaction would be H+, e, e, H^+ according to the steps in scheme 1.

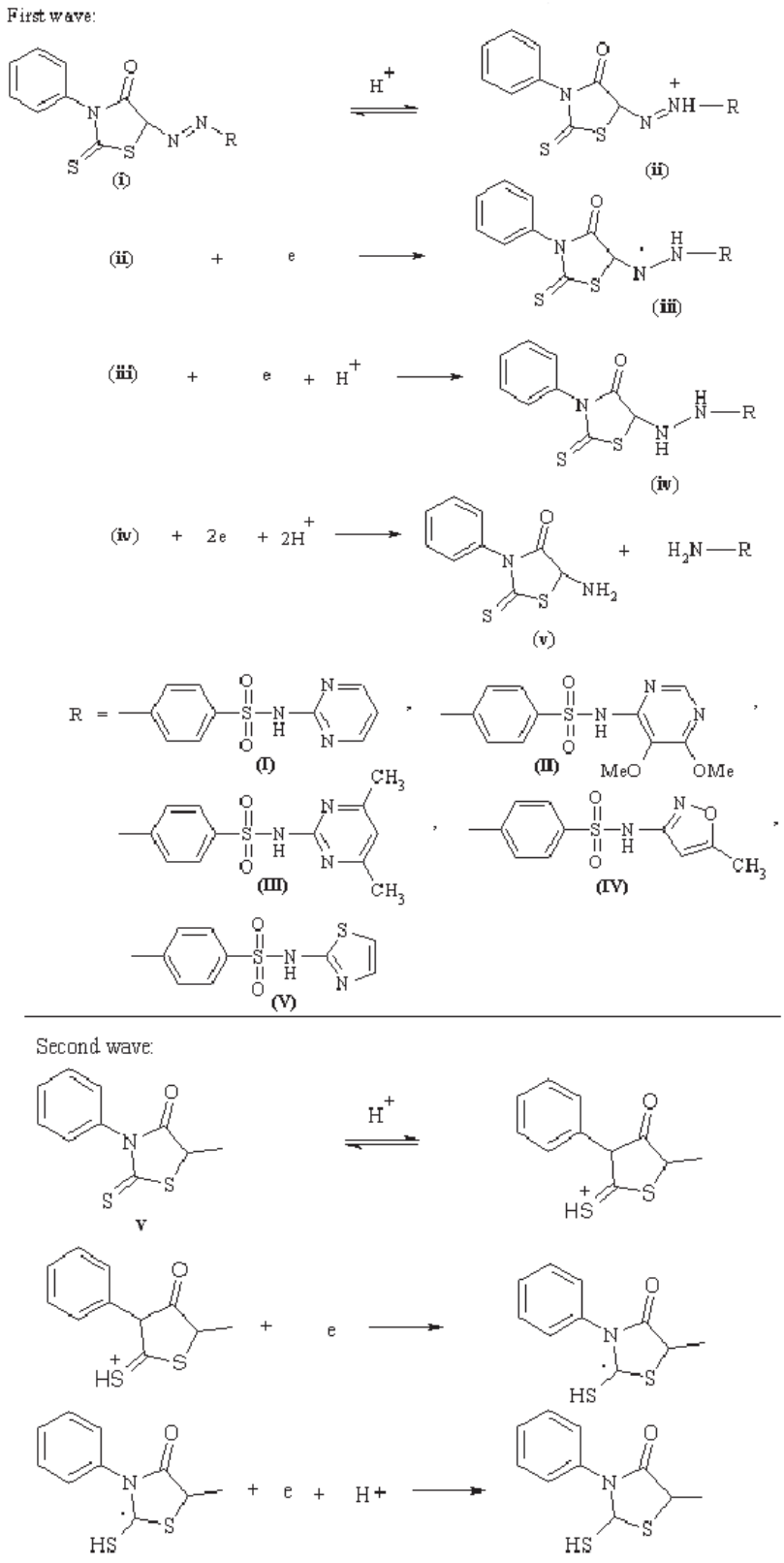
Kinetic parameters

The values of the heterogeneous rate constant ($k^o_{f,h}$) of the electrode reaction were determined from dc polarography based on the equation of Koutecky equation[24]. The results are given in Table (3), which indicated that the electrode reaction is irreversible, and that the reaction tends to be more difficult or irreversible with rise of pH of the medium. Also, the values of the activation energy (ΔH*) determined using Heyrovesky[25] were found to increase on increasing the pH (Table 3). This can be explained on the basis that the pre-protonation reaction slow down with rise of pH since the reaction will depend on the H^+ ion activity in the medium. At low pH, the H^+ ions activity is higher hence leads to a decrease of the activation energy. At higher pH the proton transfer to the depolarizer molecule would involve a break of a water molecule which requires a higher energy than a simple proton transfer process.

Potentiometric studies

Proton – ligand dissociation constants:

From the titration curves (pH vs. ml of Na OH) of rhodanine sulfa drugs I-V, it can be seen that for the same volume of NaOH added the ligand titration curve had a lower pH value than the acid titration curve. The displacement of a ligand titration curve along the volume axis with respect to the acid titration curve is and indication of proton dissociation.



Scheme 1

Table - 4: Thermodynamic functions of the dissociation of ligands I-V in 30% (v/v) ethanol – water mixture in presence of 0.1M KCl, at different temperatures.

Compd.	Temp. (k)	Dissociation constant		Free energy change(kJ mol^{-1})		Enthalpy change(kJ mol^{-1})		Entropy change (J. mol^{-1})	
		pK_1^H	pK_2^H	$\Delta G_1^\bullet$	$\Delta G_2^\bullet$	$\Delta H_1^\bullet$	$\Delta H_2^\bullet$	$\Delta S_1^\bullet$	$\Delta S_2^\bullet$
	298	7.9	9.75	45.08	55.63	19.15	19.15	87.01	122.42
I	308	7.8	9.65	46.00	56.91			87.18	122.60
	318	7.7	9.54	46.88	58.09			87.20	122.45
	298	7.4	9.98	42.22	56.94	19.15	25.85	77.42	104.33
II	308	7.3	9.85	43.05	58.09			77.60	104.68
	318	7.2	9.71	43.83	59.12			77.61	104.62
	298	7.15	9.95	40.80	56.77	23.93	24.89	56.61	106.98
III	308	7.02	9.81	41.40	57.85			56.72	107.01
	318	6.90	9.67	42.01	58.88			56.86	106.89
	298	6.85	9.65	39.08	55.06	26.81	25.85	41.17	98.02
IV	308	6.71	9.51	39.57	56.08			41.43	98.15
	318	6.56	9.37	39.94	57.05			41.29	98.11
	298	6.50	9.80	37.09	55.92	25.85	26.81	37.72	97.68
V	308	6.35	9.65	37.45	56.91			37.66	97.73
	318	6.21	9.51	37.81	57.09			37.61	97.72

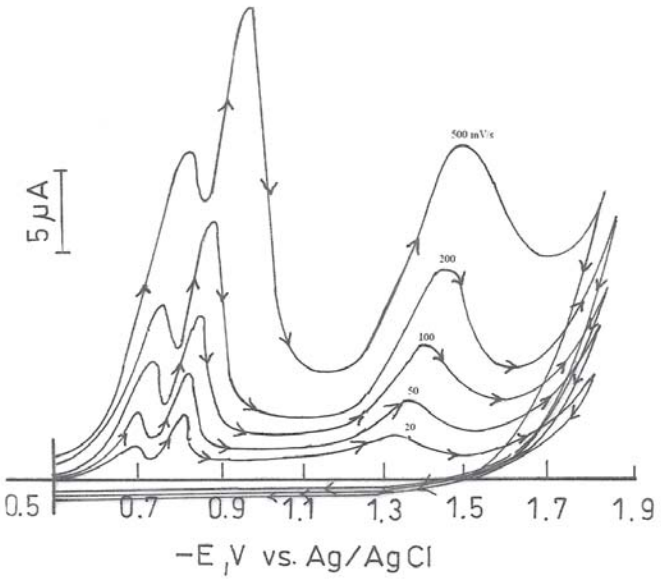


Fig. - 2: The voltammograms of compounds with three cathode peaks

Proton-ligand dissociation constants of these azo compounds, were determined potentiometrically using the method of Iriving and Rossotti[26]. The average number of proton associated with these ligands at different pH values, $\bar{n}_A$, was calculated from the titration curves of acid in absence and in presence of the legands I-V thus, the formation curves ($\bar{n}_A$ vs. pH) for the proton-ligand systems were calculated and found to extend between 0 and 2 in the scale. This means that all azo compounds I-V have two dissociable protons, the enolized proton of the hydroxyl group of rhodanine moiety (pk_2^H) and the sulfonamide proton (pk_1^H). The enolized OH group is known to be weakly acidic, indicating a stronger bonding between the proton and the oxygen donor. This means that the proton stability constant of the OH group in the rhodanine moiety (pK^H_2) should higher than the sulfonamide proton group (pk_1^H). The proton-legand stability constants of azo compounds I-V are listed in Table -4.

Effect of temperature

The dissociation constants pk_1^H and pk_2^H were evaluated also at 308 and 318 k and the data are given in Table - 4. The slopes of the plots $pk_1^H$and pk_2^H vs. 1/T were utilized to evaluate the enthalpy change (ΔH) for the dissociation process. From the free energy change (ΔG) and (ΔH) values, one can deduce the entropy change (ΔS) using the well known relationships:

$$\Delta G = 2.303\ RT\ pk = -\ 2.303\ RT \log K$$
$$\Delta S = (\Delta H - \Delta G)/T$$

All thermodynamic parameters of the dissociation process of azo compounds I-V are listed in Table - 4. Inspection of these results reveals that:

1. Values of pk_1^H and pk_2^H decrease with increasing temperature; *i.e,* the acidity of the legends increases[27].
2. Positive values of ΔH indicate that the dissociation process is accompanied by absorption of heat and the process is endothermic.
3. Positive values of ΔG indicate that the dissociation process is not spontaneous.
4. Negative values of ΔS are due to increased order as a result of solvation processes[28].

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