Studies on the Electrochemical Behavior of Thiadiazole Derivatives. Electroreduction of 2-Benzoylamino-5-[cyanoaryl-hydrazonomethyl]-1,3,4-thiadiazoles

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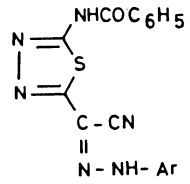
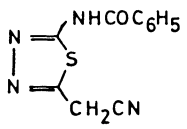
The electrochemical behavior of some 1,3,4-thiadiazole derivatives substituted at C_5 (carbon number five in thiadiazole ring) with a hydrazono group has been studied at a dropping mercury electrode (DME) in different pH values. Controlled potential electrolysis (CPE) in alkaline medium, cyclic voltammetry (CV), ultraviolet spectra (UV) and pK_a studies confirmed the proposed mechanism.

Literature scanning revealed that very little has been reported on the electroreduction of derivatives containing the thiadiazole ring structure. The results showed with no evidence or supports that the waves exhibited by these derivatives are due to the ring attack.[1-3] Furthermore, our laboratory investigated recently the electroreduction of a series of thiadiazole derivatives[4,5] substituted by an activated olefinic double bond where a Ziegler-Throp reaction[6] took place in which the hetero ring was unaffected. In a program aiming to study the electrochemical behavior of thiadiazole derivatives, it was found of interest to report the electroreduction of a series of 2-benzoylamino-5-[cyanoarylhydrazonomethyl]-1,3,4-thiadiazoles (**Ia—e**) together with a model compound namely 2-benzoylamino-5-cyanomethyl-1,3,4-thiadiazole (**II**) in order to increase data of such compounds to help in solving the conflicting results concerning the electroreactivity of this hetero ring which were proved to have pronounced medical and pharmaceutical activities.[7,8]



(I)

Ia Ar = C_6H_5
Ib Ar = p-Cl-C_6H_4
Ic Ar = p-OCH_3-C_6H_4
Id Ar = p-CH_3-C_6H_4
Ie Ar = m-NO_2-C_6H_4



(II)

Experimental

(1) Organic Syntheses. (a) 2-Benzoylamino-5-cyanomethyl-1,3,4-thiadiazole (II) was prepared according to literature[9] by refluxing a solution of 1-cyanoacetyl-4-benzoylthiosemicarbazide (1.0 g) in glacial acetic acid (30 ml) for five hours. The resulting solution was evaporated in vacuo and the remaining product was triturated with ethanol to give the solid product which was filtered off and recrystallized from acetic acid.

(b) 2-Benzoylamino-5-[cyanoarylhydrazonomethyl]-1,3,4-thiadiazoles (Ia—e) were prepared as follows: A solution of the appropriate aromatic diazonium salt (100 mmol) was added gradually to a cold solution of compound **II** (100 mmol) in ethanol (100 ml) and sodium acetate (13 g) with continuous stirring. The solid product thus formed was collected by filtration, washed with water, dried and finally crystallized from the appropriate solvent.

(2) Electrochemical Measurements. Polarograms were recorded with a Metrohm Polarecord E 506 with appropriate attachement E 505 using the Ag/10^{-2} M Ag^+ reference electrode and 10^{-4} M solutions in 50% by volume ethanolic Britton-Robinson buffers (1 M=1 mol dm^{-3}).[10] The capillary possessed the following characteristics in 0.1 M KNO_3 open circuit: t=3.9 s $drop^{-1}$, m=1.54 mg s^{-1} for h=52 cm. Cyclic voltammograms were recorded using a hanging drop mercury electrode (HDME) as working electrode with varying scan rates 50—800 mV s^{-1}. The pH-measurements were carried out with an Iskra Kranj pH-meter MA 5701.

(3) Spectrophotometric Measurements. Spectrophotometric measurements were carried out on a PYE Unicam 1800 spectrophotometer supplemented with a program controller automatic linear recording unit. The spectra were recorded on 4×10^{-5} M of the studied compound in 50% ethanolic Britton-Robinson buffer solutions. The pK_a were determined using the graphical correlation between pH and absorbance with their appropriate equations.[11]

(4) Preparative Electrolysis and Identification of the Resulting Products. The mercury pool electrolysis was carried out on 250 mg of the unsbstituted derivative in 200 ml 0.2 M NaOH due to the high insolubility of the compounds in acid media (BR acid mixture, dil HCl up to 2 M, H_2SO_4 up to 3.6 M and acetate buffer). By controlling the potential at −1.60 V vs. SCE, the current fell from 60 to 0.5 mA in ca. 4.5 hours of electrolysis. After complete electrolysis, the reaction mixture (pH=12.5) was acidified with concd HCl till pH≈1 at which the resulting compound began to precipitate. The product was filtered off and washed several times with hot ethanol (due to its insolubility in most solvents) to give a faint yellow compound of

mp=175 °C (yield ca. 60%) and identified as 2-benzoylamino-5-(α-aminocarboxymethyl)-1,3,4-thiadiazole. Azo dye test on the mother liquor gave a positive scarlet red color. IR of the resulting product (KBr) ν/cm^{-1}; 3460, 3240, 3030 (NH); 2900, 2760, 2700, 2640 (CH); 1660 (amide CO) (Fig. 1). ^1H NMR in DMSO: δ=4.08 (br., 1H, NH); 4.38 (1H, CH); 7.50 (6H, 3H aromatic protons and 3H, NH); 8.02 (2H, ortho-aromatic protons). ^1H NMR with D_2O: δ=4.38 (1H, CH); 7.50 (3H, aromatic protons); 8.02 (2H, ortho-aromatic protons). UV (in DMF) λ_{max} at 270, 372 nm respectively. Calcd: C, 47.4; H, 3.6; S, 11.5; N, 20.1; O, 17.2%. Found: C, 47.1; H, 5.0; S, 12.3; N, 18.8; O, 16.5%. MS m/z=278, 256, 212, 206, 195, 181, 151, and 110.

Results and Discussion

The polarograms of 10^{-4}M of **Ia**, taken as a typical example for the studied series **Ia—e**, are illustrated in Fig. 2. From the effect of mercury-height variation on i_l, cyclic voltammetry and routine analyses, it is found that each compound exhibits a four-electron diffusion-controlled irreversible wave A. This wave splits into two wavelets A_1 and A_2 of approximate

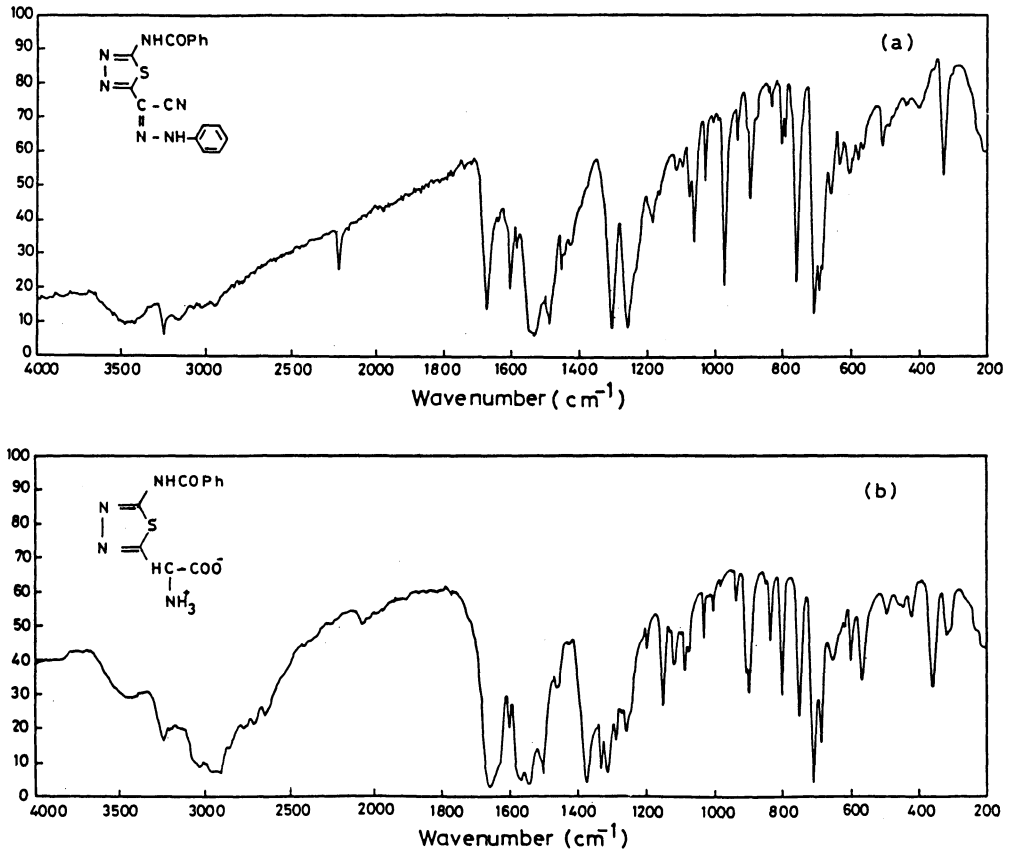


Fig. 1. (a) IR spectrum of starting compound **Ia** in KBr. (b) IR spectrum of product, obtained from CPE, in KBr.

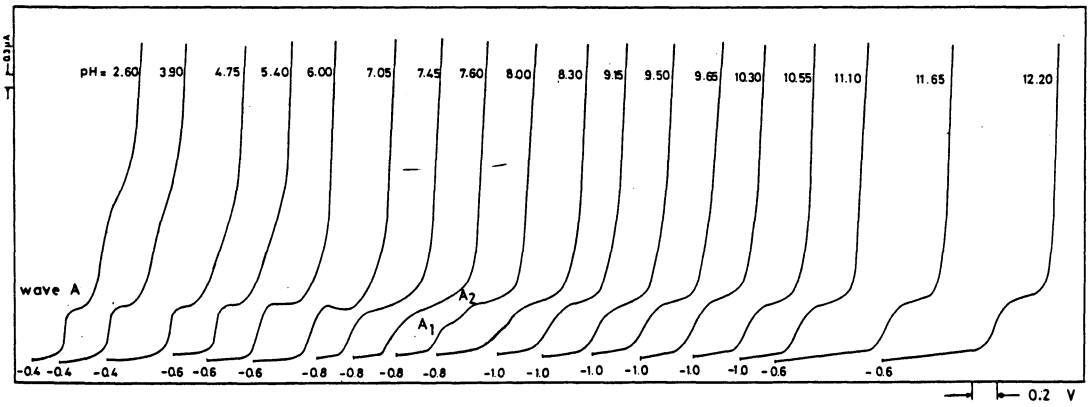


Fig. 2. Schematic representation of the polarograms of 10^{-4} M of compound **Ia** in 50% (v/v) ethanolic Britton-Robinson buffers.

Table 1. Linear Representation of $E_{1/2}$-pH Dependence for Wave A and Spectrophotometric Acid Dissociation Constants of 2-Benzoylamino-5-[cyanoaryl-hydrazonomethyl]-1,3,4-thiadiazole (**Ia—e**)

Compound	$E_{1/2}$-pH equation[a]	$E_{1/2}$-pH equation[b]	pK_{a1}	pK_{a2}
Ia	$E_{1/2}$=−0.51−0.076 pH	$E_{1/2}$=−1.08−0.031 pH	6.06	10.9
Ib	$E_{1/2}$=−0.53−0.071 pH	$E_{1/2}$=−0.87−0.050 pH	6.17	10.2
Ic	$E_{1/2}$=−0.52−0.077 pH	$E_{1/2}$=−1.20−0.024 pH	6.07	11.4
Id	$E_{1/2}$=−0.52−0.077 pH	$E_{1/2}$=−1.20−0.023 pH	6.17	11.2
Ie	$E_{1/2}$=−0.47−0.076 pH $E_{1/2}$=−0.01−0.063 pH[c]	$E_{1/2}$=−1.02−0.035 pH	6.02	9.03

a) Equation valid in the pH range 2—7.5. b) Equation valid at pH >9. c) Equation of the NO_2 group in the whole pH range.

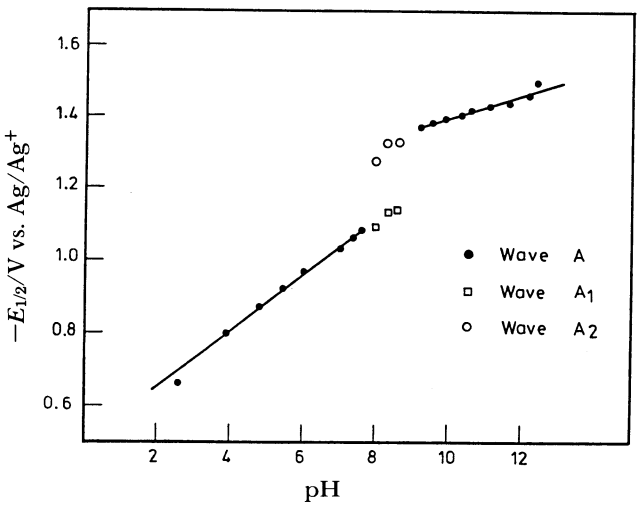


Fig. 3a. $E_{1/2}$-pH plots of the polarographic waves of 10^{-4} M compound **Ia** in 50% (v/v) ethanolic Britton-Robinson buffers.

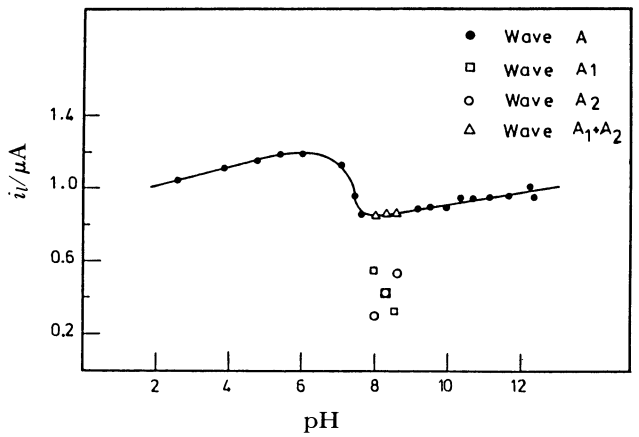


Fig. 3b. i_l-pH plots of the polarographic waves of 10^{-4} M compound **Ia** in 50% (v/v) ethanolic Britton-Robinson buffers.

equal heights in the narrow pH range 7.8—9.0, then A_1 and A_2 merge again to give A. The variation of $E_{1/2}$ and i_l with pH is given in Figs. 3a and 3b respectively. The shift of $E_{1/2}$ towards more negative potential with increase of pH for compounds **Ia—e** is compiled in Table 1.

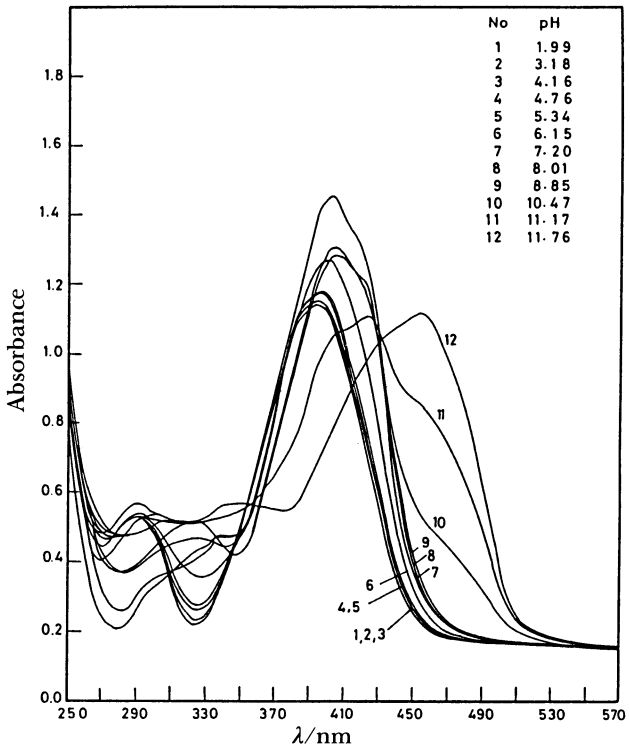


Fig. 4. Electronic absorption spectra of 4×10^{-5} M compound **Ia** in 50% (v/v) ethanolic Britton-Robinson buffers.

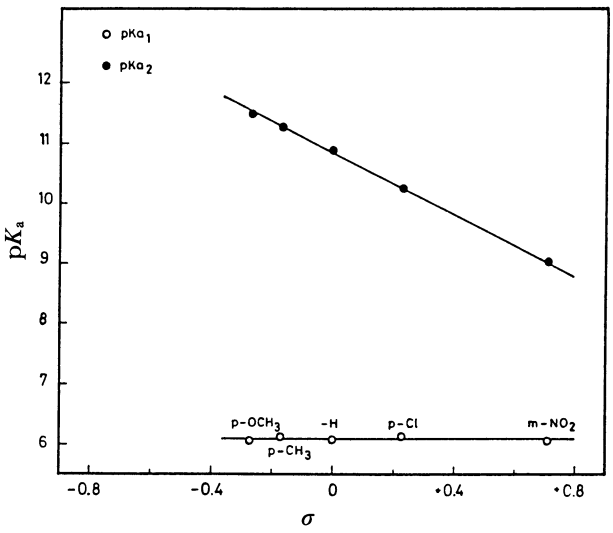
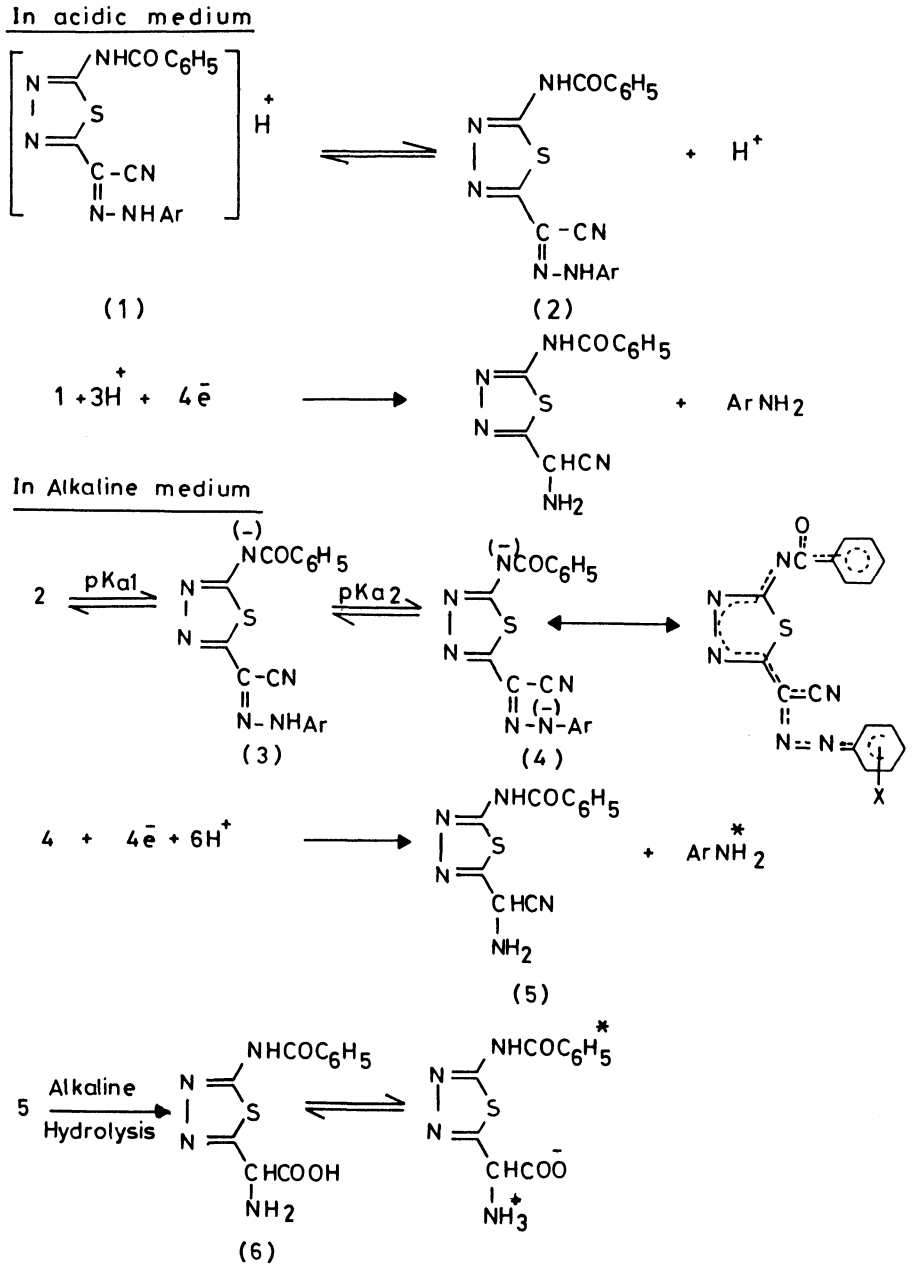


Fig. 5. pK_a-σ plots for compounds **Ia—e**.

Table 2. Polarographic Characteristics of 2-Benzoylamino-5-[cyanoarylhydrazonomethyl]-1,3,4-thiadiazole (**Ia—e**)

Compound No.	pH	$-E_{1/2}$/V vs. Ag/AgCl	$i_d/\mu A$	$RT/\alpha nF$	n	$D\times10^{-6}$/ $cm^2 s^{-1}$
Ia	4.75	0.88	1.16	0.058	4	5.9895
	10.30	1.14	0.96	0.090	4	4.1022
Ib	4.75	0.88	0.95	0.050	4	4.0172
	10.30	1.37	0.89	0.079	4	3.5258
Ic	3.90	0.81	1.14	0.042	4	5.7847
	10.40	1.44	0.99	0.110	4	4.3626
Id	4.75	0.895	0.96	0.05	4	4.1022
	11.65	1.45	0.82	0.075	4	2.9930
Ie	4.75	0.835	0.99	0.070	4	4.3626
	11.65	1.41	0.93	0.060	4	3.8498

t=3.9 s. m=1.54 mg s^{-1}. c=0.1 mM(for D)=10^{-4} M for $E_{1/2}$ and i_l.



* Isolated and identified products

Scheme 1.

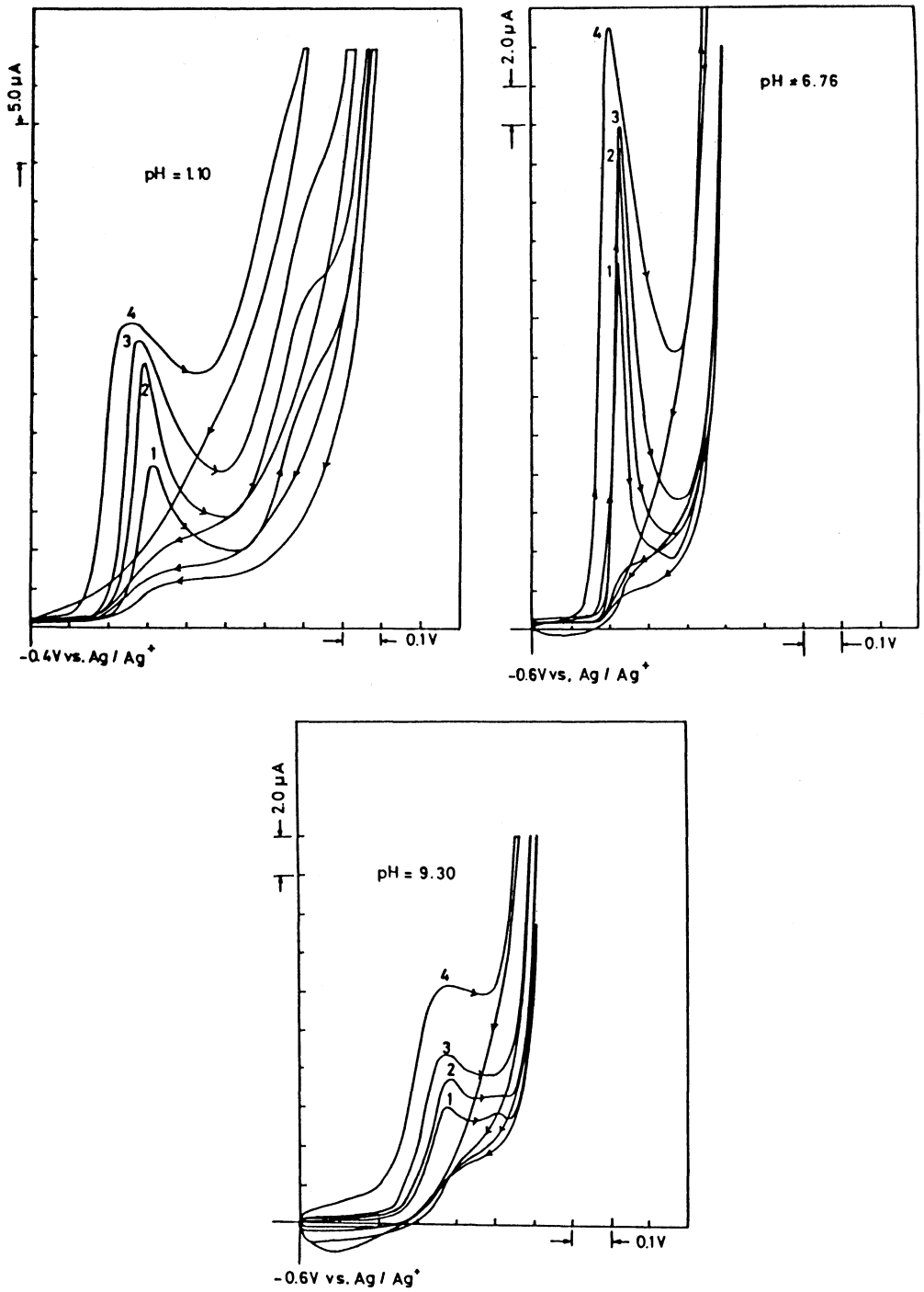


Fig. 6. Cyclic voltammograms of **Ia** at different pH values. 1; 50, 2; 100, 3; 200, 4; 500 mV s^{-1}.

The i_l-pH plot shows a moderate increase of i_l up to pH ca. 6 after which a weak dissociation curve appears in the pH range 6—8.5 followed again by a slight increase of i_l with increasing pH. In exception, compound **Ie** has revealed another four-electron wave. The less negative one was considered to correspond to the reduction of the NO_2 group into NHOH function. This assignment is based on the similar behavior of this wave with that reported for aromatic nitro compounds.[12]

Absorption Spectra of Compounds Ia—e and II. In solution of pH values 1.99—6.15 the absorption spectra of 4×10^{-5} M compound **Ia** are characterized by a strong band with λ_{max} at 396 and a weak one with λ_{max} at 290 nm. These are due to the absorption of the nonionized form liable to exist at low pH values. With increasing pH from 6.15 to 7.00 a red shift occurs giving rise to a band with λ_{max} at 404 nm and a shoulder at ca. 320 nm. As pH is further increased up to pH 8.85, the shoulder at 320 nm appears as a weak

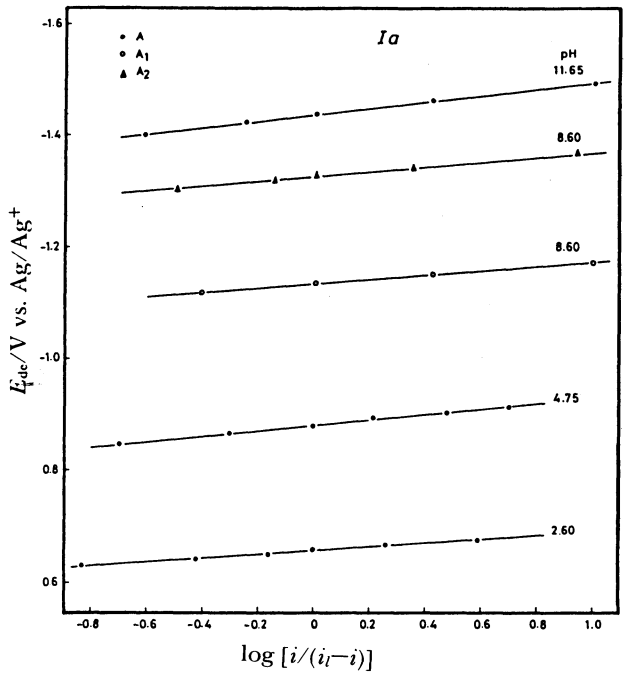


Fig. 7. Some representative logarithmic analysis plots for **Ia** at different pH values.

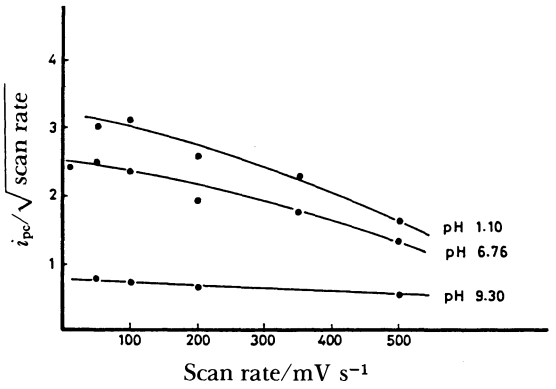


Fig. 8. Plots of the ratio of cathodic peak currents to the square roots of the scan rate as a function of the scan rate.

band at λ_{max}=322 nm. The shift of pH to the alkaline side is then accompanied by a red shift of the strong band as shown in Fig. 4. The absorption spectra are characterized by the presence of two isosbestic points at 304 and 346 nm in the pH range 1.99—8.85. The apparent ionization constant was calculated and the mean pK_a for each member is compiled in Table 1. The absorption spectra of model compound **II** showed one band at 270 nm in the pH range 1.99—6.15. At pH 6.15—11.76 the band is red-shifted acquiring λ_{max} at 310 nm. One isobestic point at 288 nm is observed throughout the whole pH range. Since all compounds **Ia—e** have practically constant pK_{a1} values ranging from 6.02 to 6.17 (cf. Table 1), it is clear that there is no dependence of ionization on the substituent effects. Hence, the ionizable center can be considered far from the aryl group, and this is confirmed by the fact that model compound **II** gave the same pK_a value (6.38). Therefore we can attribute the first pK_a to the ionization of the amide NH group (cf. Scheme 1). On the other hand, compounds **Ia—e** have another pK_{a2} depending mainly on the substituent effects as it is clear from the pK_a-σ correlation. Thus we can consider the pK_{a2} is due to hydrazono NH (cf. Scheme 1 and Fig. 5).

Mechanism of the Electrode Process. The behavior of wave A is in good agreement with the reported behavior of compounds containing the hydrazono linkage[13,14] and different from those containing the azo moiety.[15,16] This interpretation is confirmed by the fact that the wave corresponding to the reduction of the nitro moiety in compound **Ie** appeared before wave A.[17] Since the $E_{1/2}$ values of compounds **Ia—e** were pH-dependent and i_l-pH independent, it was concluded that both acidic and basic forms reach the electrode surface and are electroactive yielding the same product. Cyclic voltammograms at different pH values indicated that the processes are irreversible in nature (cf. Fig. 6) as confirmed by logarithmic analyses (cf. Table 2 and Fig. 7). It was shown that the relation between i_{pc} and $\sqrt{\nu}$ (where i_{pc} is the cathodic peak currents and ν is the scan rates) can be useful in deciding to which case in the Nicholson and Shain[18] classification a given process belongs. As is clear from Fig. 8 a CE mechanism takes place in acidic and neutral media which was confirmed by calculating $dE_{1/2}/d\,pH$ indicating that the protons are involved on the electrode reaction while it is an EC mechanism in alkaline medium. Based on the obtained results, one may propose Scheme 1 for the interpretation of these results. It is important to mention that it was difficult to carry out CPE in acidic medium due to the limited solubility of compounds **Ia—e**. Also, dianion **4** is stabilized through the spreading of the negative charge on the molecule. Finally we obtained compound **6** and not **5** due to the alkaline hydrolysis of the cyano group.[19]

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