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A Polarographic, Voltammetric and Coulometric Study of Phenazopyridine Hydrochloride **

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ABSTRACT

The electrochemical properties of phenazopyridine hydrochloride (pyridium) were studied at different pH values in Britton-Robinson buffer solutions by differential pulse and direct current polarography, square wave and cyclic voltammetry, controlled potential coulometry techniques. Polarographic reduction of pyridium takes place in a single 4-electron transfer, giving a diffusion-controlled irreversible wave in the pH range 2.00-10.50. At high pH values (pH 11.00-12.00), reduction of the compound exhibits a single, 2-electron diffusion-controlled reversible wave. A possible mechanism has been suggested on the basis of the number of electrons involved in the reduction process.

KEY WORDS : Phenazopyridine Hydrochloride, Polarography, Voltammetry and Coulometry.

INTRODUCTION

Aromatic azo dyes are a commercially important class of compounds and have been the subject of many polarographic investigations (1-13).

Heterocyclic azo compounds, especially 2,6 - diamino - 3 - phenylazopyridinium chloride (pyridium) have been found to play an important role in pharmaceutical chemistry (14,15). However, the polarographic behaviour of heterocyclic azo compounds has received little attention (16) and no data is available about the electrochemical behaviour of pyridium. Only the polarographic and voltammetric study of a pyridium-copper complex has been given (17).

In this paper, the electrochemical behaviour of pyridium, which has the analgesic effect in urinary infections, has been studied in Britton-Robinson buffer solutions.

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EXPERIMENTAL

Chemicals and solutions

The drug was kindly supplied by Roche (Türkiye) and used without further purification. A stock solution (1×10^{-3} M) of pyridium was prepared by dissolving the pure substance in water. Britton-Robinson buffers (18) in the pH range 2.00-12.00 were prepared from analytical-reagent grade chemicals. All solutions were prepared daily. The water used in these experiments was triply distilled and deionized.

Apparatus

Polarography and voltammetry. A PAR 384B polarographic analyzer with PAR 303A static mercury drop electrode was used. The sample cell (PAR model 6062) was fitted with a saturated Ag/AgCl reference electrode and a platinum wire auxiliary electrode. Differential pulse and DC modes were used with dropping mercury electrode and square wave and cyclic modes were used with hanging mercury drop electrode. In the first three modes, the scan rate was 2 mVs^{-1} , drop time 1.0 s (DC), drop size small (DPP,SWV) and pulse amplitude was 20 mV. However, in cyclic mode, different scan rates were used.

DMP-40 Series Digital Plotter X-Y recorder for differential pulse, square wave and cyclic modes and IBM Proprietary (IIIXL) for DC mode were used.

A Crison MicropH 2000 was used to measure the pH of the buffer solutions in polarography and voltammetry experiments.

Controlled-potential electrolysis. A Coulometry system Model BAS-100B with Cell-2 was employed to determine the number of electrons involved in the reduction of pyridium. The working electrode was a mercury pool of approximately 19.6 cm^2 area which was stirred continuously during the controlled potential electrolysis. The auxiliary electrode was a platinum wire and the reference electrode was a saturated Ag/AgCl electrode. The pH values of the buffer solutions in controlled potential coulometry (CPC) were measured with a Orion research model 174A pH-meter. All the measurements were carried out at $20 \pm 1^\circ\text{C}$. Note that CPC experiments was carried out at Electrochemistry Research Laboratory of Science Faculty in Ankara University (Türkiye).

Procedures

10 ml buffer solution and 50 μl of stock solution of pyridium are mixed thoroughly in polarographic cell, deaerated by passing pure nitrogen gas for about 5 min and the polarograms and voltammograms recorded.

In the CPC, the progress of electrolysis was followed by recording the decrease in current with time. The current was integrated during the course of the experiment. When the electrolysis of pyridium is complete, the total charge value was used to calculate the number of electrons transferred per molecule by means of Faraday's Law.

RESULTS AND DISCUSSION

DC-Polarography

The polarograms of 1.5×10^{-5} M pyridium in Britton-Robinson buffer solutions at pH values between 2.00 and 12.00 were recorded. Pyridium exhibits a single wave over the whole pH range studied (Fig.1). This wave was found to be diffusion-controlled, as there is a linear dependence of its limiting current on the compound concentration.

At different pH values, the plots of E vs. $\log [i/(i_d-i)]$ were straight lines with different slopes ($58.1/\alpha n \text{ mV}$) as shown in Table 1 (where E = potential, i = current , and i_d = diffusion controlled limiting current). The transfer coefficients of electrons (α) were calculated from the slopes. The α values are less than unity confirming the irreversible nature of the waves at $\text{pH} \leq 10.50$.

The half-wave potential of the polarographic waves exhibits a cathodic shift on increasing the pH of electrolysis medium, revealing that H^+ ions are consumed in the reduction process and the protonation proceeds with the electron uptake (19). The number of protons (p) participating in the rate determining step was computed from the slopes of $E_{1/2}$ vs. pH as well as the slopes of E vs. $\log [i/(i_d-i)]$ according to the relation (20):

$$\frac{dE_{1/2}}{dpH} = \frac{0.0581}{\alpha n} \quad (20^\circ\text{C})$$

The values of p were found to be almost unity and the most probable values of the number of electrons (n) involved in the rate-determining step, may be two or four. However, the α values are close to unity confirming the reversible nature of the waves in the pH range 11.00-12.00. The results are given in Table 1.

The decrease in $E_{1/2}$ with the increase of pH can be expressed by the following equations:

$$\begin{aligned} E_{1/2} &= -0.235 - 0.054 \text{ pH} & r &= -0.999 & (\text{pH } 2.00 - 4.00) \\ E_{1/2} &= -0.115 - 0.084 \text{ pH} & r &= -0.999 & (\text{pH } 4.50 - 7.00) \\ E_{1/2} &= -0.420 - 0.043 \text{ pH} & r &= -0.994 & (\text{pH } 7.50 - 12.00) \end{aligned}$$

These equations correspond to the breaks observed in the $E_{1/2}$ - pH plot (Fig. 2) at approximately pH 4.00 and 7.40, respectively.

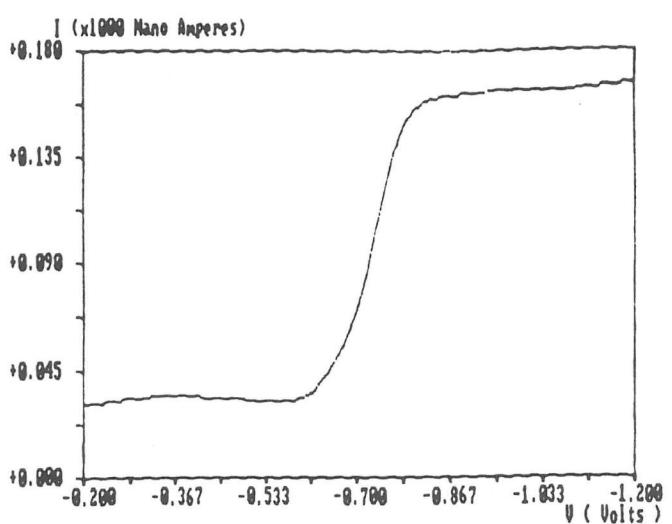
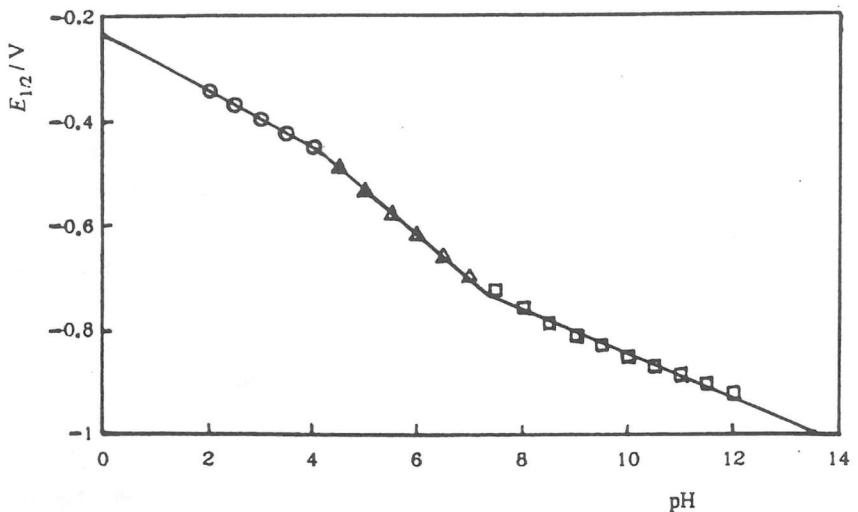
Fig. 1. DC polarogram of 1.5×10^{-5} M pyridium in Britton - Robinson buffer at pH 7.50Fig. 2. $E_{1/2}$ - pH plot for pyridium. Lines are drawn for least squares fit.

Table 1. DC polarographic data obtained for pyridium in Britton-Robinson buffer solutions.

pH	$-E_{1/2}, \text{V}$	58.1	$dE_{1/2}$	p	α	
		, mV αn	, mV/pH dpH		$n=4.0$	$n=2.0$
2.00	0.343	73.9	54.0	0.73	0.20	0.39
2.50	0.370	72.9	54.0	0.74	0.20	0.40
3.00	0.396	70.1	54.0	0.77	0.21	0.41
3.50	0.424	65.0	54.0	0.83	0.23	0.45
4.00	0.451	68.3	54.0	0.79	0.21	0.42
4.50	0.489	70.9	83.7	1.18	0.20	0.41
5.00	0.534	65.9	83.7	1.27	0.22	0.44
5.50	0.578	63.9	83.7	1.31	0.23	0.45
6.00	0.620	69.1	83.7	1.21	0.21	0.42
6.50	0.660	66.9	83.7	1.25	0.22	0.43
7.00	0.698	70.9	83.7	1.18	0.21	0.41
7.50	0.726	71.0	42.6	0.60	0.21	0.41
8.00	0.758	61.7	42.6	0.69	0.24	0.47
8.50	0.788	60.0	42.6	0.71	0.24	0.48
9.00	0.812	54.6	42.6	0.78	0.27	0.53
9.50	0.831	54.6	42.6	0.78	0.27	0.53
10.00	0.852	54.6	42.6	0.78	0.27	0.53
10.50	0.870	52.6	42.6	0.81	0.28	0.55
11.00	0.889	40.9	42.6	1.04	0.36	0.71
11.50	0.906	36.7	42.6	1.16	0.40	0.79
12.00	0.924	34.9	42.6	1.22	0.42	0.83

Differential Pulse Polarography (DPP)

Pyridium displays only one polarographic signal in the pH-range studied. This polarographic response is very well resolved (Fig. 3.). As shown in Fig. 3, this peak corresponds to the reduction of the azo group in the pyridium molecule. The peak potential (E_p) strongly depends on pH, showing a cathodic shifting with increasing the pH. The E_p - pH plot (Fig.4) shows two breaks approximately at pH 4.00 and pH 6.85, respectively. It was shown that, at different pH values, different electroactive species coexist in solution. However 2,6-diamino-3-phenylazopyridine is a base. Thus, pyridium is an ionic compound, the cation being the conjugate acid of the base. pH 4.00 corresponds to dissociation of proton (pK_a) in the amino group ($-\text{NH}_3^+$) or $>\text{NH}^+$ where N is the ring nitrogen (Scheme 1). The second pH value (6.85) shows that different electroactive species probably coexist in solution owing to amino-imine tautomeric equilibria (Scheme 2). The slope of the corresponding linear portions were: 59.6 mV/pH (2.00 < pH < 4.00); 85.2 mV/pH (4.50 < pH < 6.50) and 46.5 mV/pH (7.00 < pH < 12.00).

Due to the linear relation obtained between the peak current and pyridium concentration we can use the polarographic method in order to quantify the drug. The peak current-concentration relations are described by the following equations, obtained by the least-squares linear regression method:

$$i_p = 6.168 \times 10^6 C + 0.304$$

(Correlation coefficient = 0.999, concentration range
 5.0×10^{-6} - 45.0×10^{-6} M, pH 4.00 and 20°C),

$$i_p = 9.295 \times 10^6 C + 1.072$$

(Correlation coefficient = 0.999, concentration range
 5.0×10^{-6} - 45.0×10^{-6} M, pH 7.00 and 20°C) and

$$i_p = 7.464 \times 10^6 C + 1.568$$

(Correlation coefficient = 0.999, concentration range
 5.0×10^{-6} - 45.0×10^{-6} M, pH 10.00 and 20°C)

where i_p is the peak current, in nA, and C is the molar concentration of pyridium.

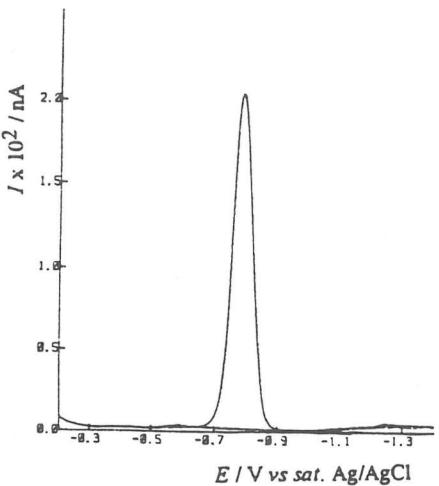


Fig. 3. DPP polarogram of 2.8×10^{-5} M pyridium in Britton - Robinson buffer at pH 9.00

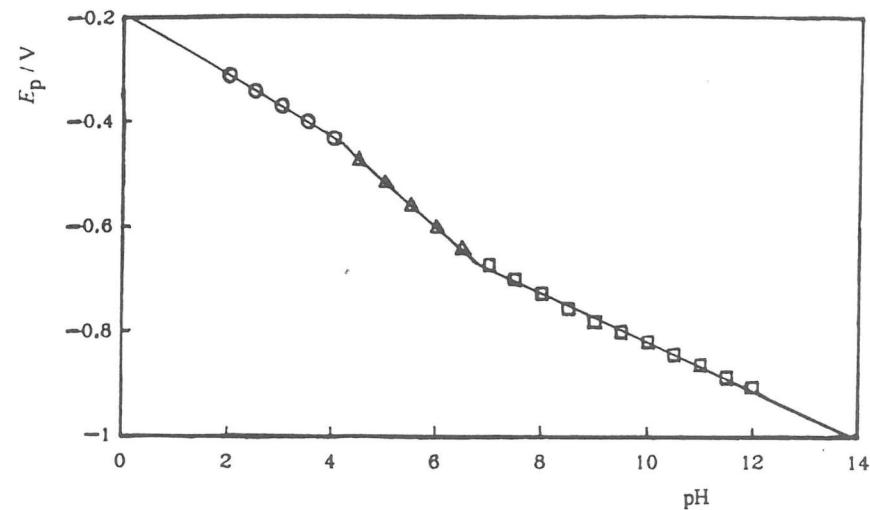
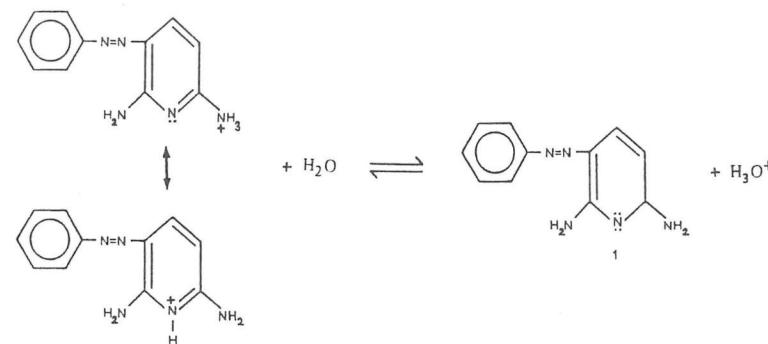
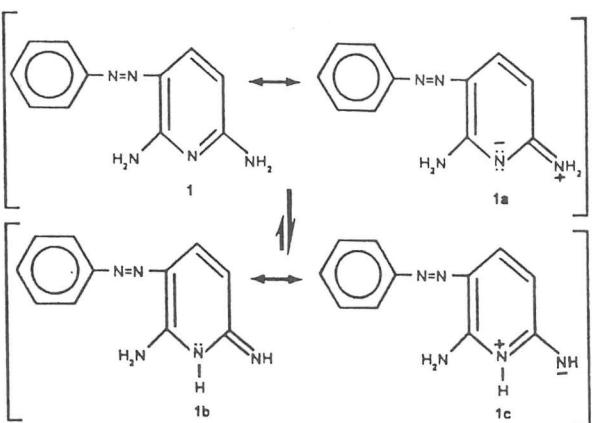


Fig. 4. E_p - pH plot for pyridium. Lines are drawn for least squares fit.



Scheme 1



Scheme 2

Cyclic Voltammetry (CV)

The cyclic voltammograms of 5×10^{-6} M pyridium were recorded in Britton-Robinson (pH 2.00-12.00) buffer solutions. The voltammograms of the compound show one single cathodic peak in the pH range 2.00 - 8.00 and two cathodic peaks in the pH range 8.00-12.00 (Fig.5 and Fig.6). The first peak in CV voltammograms has not been observed in DPP and DC techniques. Since the scan in CV is 200 times faster than in DC, shorter lived species may be detected by CV and not by DC. Therefore the first peak and the less negative peaks, at left hand side of Fig. 6 and Fig. 7a, probably are attributed to the reduction and oxidation of the shorter lived electroactive species. The second peak corresponds to the reduction of azo (-N=N-) group which is irreversible at pH values lower than 11.00. For $\text{pH} \geq 11.00$, the anodic peak is seen (Fig.6). However, it appears that the electrochemical system is reversible; the separation between anodic (E_{pa}) and cathodic (E_{pc}) peak potentials is near 32 mV for a scan rate of 666.6 mVs^{-1} at pH 12.00 (Fig.7), a value close to the correct value (29 mV) for a reversible two electron transfer. Further it has been observed that the peak separation does not show a considerable change at other scan rates.

On the other hand, the absence of any peaks in the reverse scan (in the anodic direction) and the shift of the cathodic peak potential (E_{pc}) to more negative values on increasing the scan rate (V) confirm the irreversibility of the reduction process in the pH range 2.00-10.50.

The irreversible nature of the electrode process for this compound (pH 2.00 - 10.50) differs from reversibility observed under comparable conditions for azobenzene (21). This may be due to the bulky group present at the end of -N=N- linkage (3).

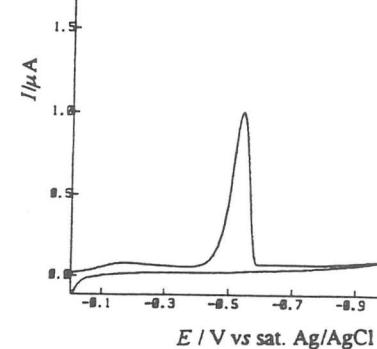


Fig. 5. CV voltammogram of 5×10^{-6} M pyridium in Britton-Robinson buffer at pH 5.00, scan rate: 400 mVs^{-1}

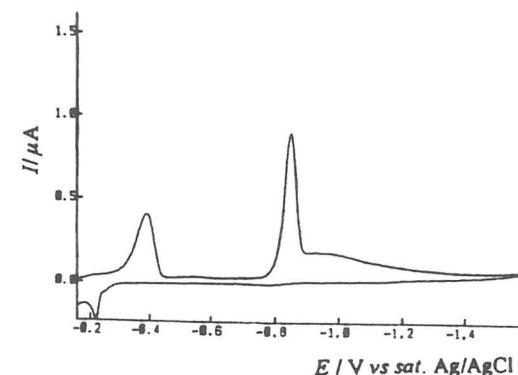


Fig. 6. CV voltammogram of 5×10^{-6} M pyridium in Britton-Robinson buffer at pH 10.00, scan rate: 400 mVs^{-1}

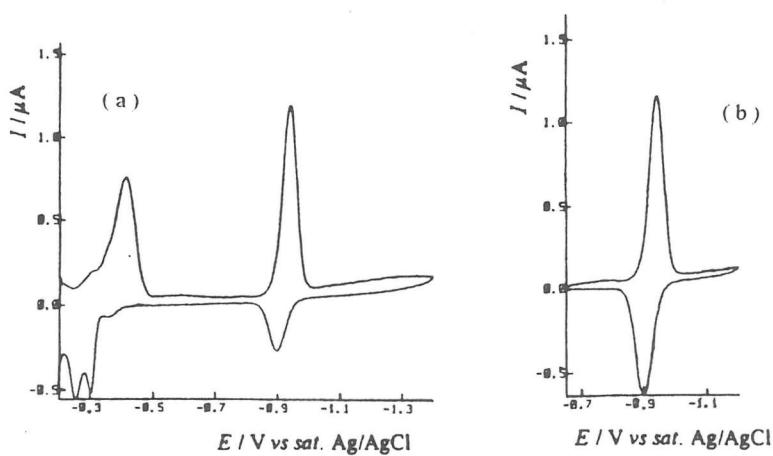


Fig. 7. a) CV voltammogram of $5 \times 10^{-6} \text{ M}$ pyridium in Britton-Robinson buffer at pH 12.00, scan rate: 666.6 mVs^{-1}
b) CV voltammogram is belong to the only azo group of $5 \times 10^{-6} \text{ M}$ pyridium in Britton-Robinson buffer at pH 12.00, scan rate: 666.6 mVs^{-1}

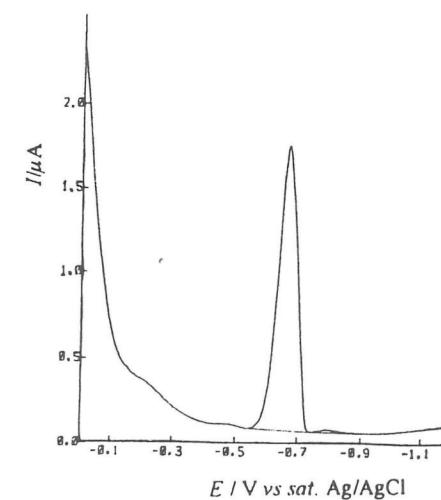


Fig. 8. SWV voltammogram of $5 \times 10^{-6} \text{ M}$ pyridium in Britton-Robinson buffer at pH 6.00

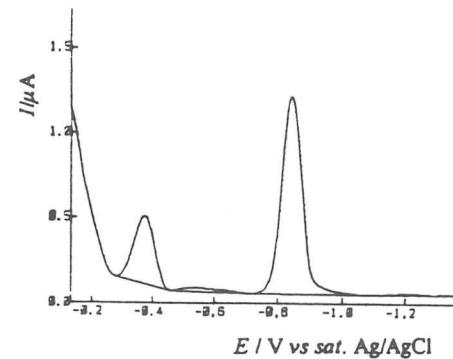


Fig. 9. SWV voltammogram of $5 \times 10^{-6} \text{ M}$ pyridium in Britton-Robinson buffer at pH 9.00

Square Wave Voltammetry (SWV)

In the voltammograms of pyridium only one peak was obtained in the pH range 2.00-8.00 (Fig.8). Although, the compound exhibits two reduction peaks in the pH range 8.00-12.00 (Fig.9). For the first peak, it seems more reasonable to consider that, at different pH values, different electroactive species coexist in solution, as suggested previously by cyclic voltammetry. The potential of this peak was found to be pH-independent. However, the second peak is attributed to the reduction of azo group. The second peak potential shifts toward more negative values as the pH increases. This behaviour confirms that protons are involved in the reduction process.

Controlled Potential Coulometry (CPC)

CPC was carried out at different values of pH with 7.4×10^{-5} M pyridium in Britton-Robinson buffer solutions. It was found that faradaic n-values are close to 4 in the pH range 2.00-10.50 and to 2 at high pH values (pH 11.00-12.00). Below pH 10.50, this behaviour can be explained by the four-electron two step reduction model. The first step is a two-electron reduction yielding the hydrazo form. The hydrazo form then undergoes irreversible reductive-cleavage to give the corresponding aromatic amines. Eventually the second step also involves a two-electron reduction.

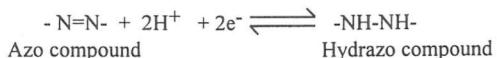
Mechanism Proposed for the Electroreduction of Pyridium :

In the pH range 2.00-10.50, the hydrazo compound formed in the first step of the reduction of the -N=N- centre of pyridium is capable of being reduced further to the corresponding amine, involving a total of four electrons, as was calculated by coulometry. In acid medium possibly the hydrazo compound is somewhat protonated and this weakens the N-N bond. At high pH values (pH 11.00-12.00) the reduction of the azo centre takes places via two electrons giving the hydrazo compound also. In strong alkaline medium, there is not enough H^+ to protonate the hydrazo group and the N-N bond will not be weakened.

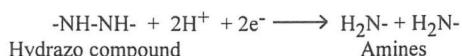
However, the polarographic reduction of some monoazo compounds (21-25) involves the four and two electrons in acid and alkaline media, respectively.

In the pH range 2.00-10.50, the reduction process can be represented as follows:

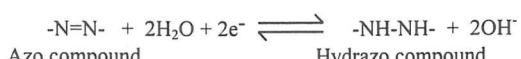
First step:



Second step:



The reduction process in the pH range 11.00-12.00 can be expressed as



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