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POLAROGRAPHIC REDUCTION OF SOME POTENTIAL ANTIDIABETIC COMPOUNDS

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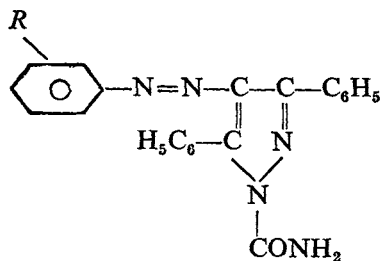
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Polarographic reduction of N¹-Carbamoyl-3,5-diphenyl-4-arylazopyrazoles takes place in a single 4-electron transfer, giving a diffusion controlled irreversible wave in buffers of pH range 2.0-11.0. The reduction in these compounds takes place at the -N=N- bond and a (H⁺, e, e, H⁺) type mechanism has been proposed for the reduction process. Effect of various cations, anions, ionic strength and solvent percentage on the reduction has been discussed. The effect of substituents and its correlation with the Hammett substituent constant (σ) have also been studied.

Keywords: Polarography; Potential Antidiabetic; Reduction; Arylazopyrazoles; Hammett Equation

INTRODUCTION

ARYLAZOPYRAZOLES have been found to play an important role in the field of medicinal chemistry as they possess interesting antineoplastic or antidiabetic activity (Malik *et al.*, 1970; and Garg & Sharma, 1970). Recently, studies on the polarographic behaviour of some of these compounds have been carried out in aqueous (Malik & Goyal, 1976) and non-aqueous (Malik *et al.*, 1978) medium. A review of the electrochemical properties of N¹-carbamoyl-3,5-diphenyl-4-arylazopyrazoles reveals that the polarographic behaviour of these compounds has attracted little attention in spite of their importance as antidiabetic compounds (Garg & Singh, 1970). Since physiological activity of a molecule is closely related to the properties at the solid-solution interface, it was considered worthwhile to study their electrochemical reduction at the DME. The objectives of the study are to gather sufficient information to elaborate the essential features of the electrode reaction *vis-a-vis* the effect of substituents on these pyrazoles (A),



where R represents various substituents.

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EXPERIMENTAL

Instrumentation

The polarographic curves were recorded using a 'Cambridge Pen-recording Polarograph'. The capillary used for the dropping mercury electrode had an out-flow velocity of 2.09mg/s at 60cm head of mercury and a natural drop time of 3.58 sec. Capillary characteristics were determined at zero potential in 0.1M solution of KCl. The reference electrode was a standard calomel electrode. The pH metric measurements were carried out on an Expanded Scale Elico pH meter with glass electrode which was previously standardised with buffers of known pH (potassium hydrogen phthalate buffer pH 4.0 and borax buffer pH 9.2).

MATERIALS AND METHODS

N¹-carbamoyl-3,5-diphenyl-4-arylazopyrazoles and its 2-Cl, 3-Cl, 4-Cl, 2-CH₃, 3-CH₃, 4-CH₃, 2-OCH₃, 3-OCH₃, 4-OCH₃, 2OC₂H₅, 4OC₂H₅, 2-Br, 4-Br, 4-I, 2,3-(CH₃)₂, 2,4-(CH₃)₂, 3,5-(CH₃)₂, 2,6-(CH₃)₂ derivatives were synthesised in the laboratory (Garg & Singh, 1970). All the compounds were recrystallised from ethanol and their purity was checked by T.L.C. Stock solutions (1 × 10⁻³M) of the compounds were prepared in dimethylformamide. The following buffers (Britton, 1956) were used for the pH ranges indicated (a) pH 1-2.1 H₂SO₄, (b) pH 2.0-8.10, citrate (c) pH 8.2-11.0 ammonia-ammonium chloride.

The polarographic measurements were carried out in 1.0 × 10⁻⁴M solutions of the compounds investigated. Solutions of the compound contained 20 per cent D.M.F. in that all solutions were prepared by pipetting 1ml of the stock solution into 6.5ml of the appropriate buffer, 1ml KCl, 1ml of D.M.F. (which was necessary to keep the compound in solution) and 0.5 ml gelatin (0.1%) immediately before placing the sample solution in the polarographic cell. The solution was then deaerated with a stream of nitrogen for a period of 2 minutes before recording the polarogram. To determine the number of electrons involved in the reduction, the waves for the 1 × 10⁻⁴M solution of 3,5-diphenyl-4-arylazopyrazole was compared with those for cadmium sulphate in citrate buffer of pH 6.2 by the method of DeVries and Kroon (1953) using a mercury pool cathode. The formula used was,

$$n_2 = n_1 \left(\frac{i_a \text{ Cad.}}{i_a \text{ Cad.}} \right) \left(\frac{i_a \text{ sub.}}{i_a \text{ sub.}} \right) \frac{V_1 C_1}{V_2 C_2}$$

where i_a Cad is the original diffusion current for cadmium, V_1 its volume, C_1 its concentration and i_a Cad is the change in the diffusion current produced by the electrolysis, i_a sub, i_a Sub V_2 and C_2 are the corresponding quantities for the solution of the substance and n_1 and n_2 are the number of electrons involved for cadmium ions and substance respectively. As the concentrations and volume of Cad. ions and substance were the same, the last factor in the equation is unity.

The temperature coefficient was calculated by Nejedly's (1922) method.

RESULTS AND DISCUSSION

All compounds studied are reduced in one to two electron diffusion controlled wave in the pH range 2.0-11.0, corresponding to the reduction of azo group, the limiting

current of which was pH independent. Some of the typical polarograms are shown in Fig. 1. The dependence of the heights of the waves on the square root of mercury pressure shows that waves are diffusion controlled. The low value of temperature coefficient (1.10–1.6% K^{-1}) further verified the diffusion controlled nature of the waves.

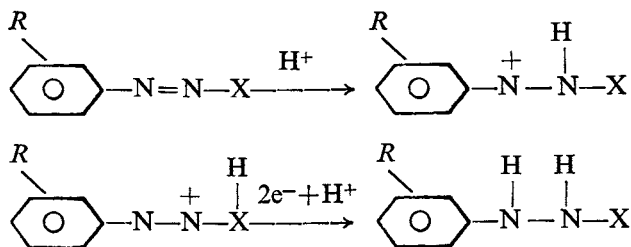
The half-wave potentials are dependent on pH and shift towards more negative potential with increase in pH . From this behaviour, it is apparent that protonation takes place before first electron uptake. Similar dependence of $E_{1/2}$ on pH has also been found by other workers in the case of azo compounds (Alyward *et al.*, 1967, Sadler & Bard 1968; and Issa *et al.*, 1973). The plots of $E_{1/2}$ vs. pH are linear with slopes in the range 0.50–0.57V/ pH . The shift in $E_{1/2}$ towards more negative potential with increasing concentration of the depolariser and logarithmic analysis of the polarograms confirmed the irreversible nature of the electrode process (Meites, 1967). The values of n_a (product of transfer coefficient and number of electrons involved per molecule of the reactant in the rate determining step of the electrode process) and of P (number of protons involved per molecule of the reactant in the rate determining step) are calculated using equation (Meites, 1967; and Janik & Elving, 1969).

$$P = \frac{\frac{dE_{1/2}}{dpH} \times \alpha n_a}{0.05915}$$

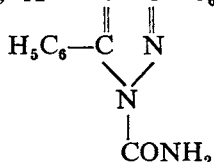
$$\alpha n_a = \frac{0.0517}{E_{3/4} - E_{1/4}}$$

The values of P are summarised in Table I.

As the number of electrons involved in the reduction are two and the number of proton involved in the rate determining step is one, a mechanism can be proposed for the reduction of these compounds which is analogous for the reduction of azobenzene and related azo compounds (Malik *et al.*, 1974; and Castor & Saylor, 1953).



where, $\text{X} = \text{---C---C---C}_6\text{H}_5$



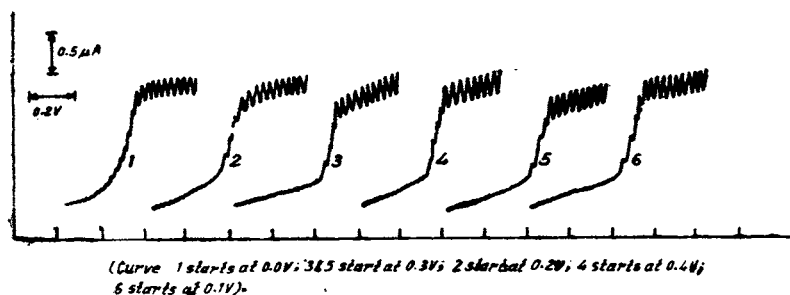


FIG. 1. Some typical polarograms of N^1 -carbamoyl-3,5-diphenyl-4-arylazopyrazoles at various pH ($C = 1.0 \times 10^{-4}M$). (1) $R = 2-CH_3$ at pH 4.0; (2) $R = 2-Cl$ at pH 6.2; (3) $R = 4-CH_3$ at pH 6.2; (4) $R = 3-OCH_3$ at pH 7.8; (5) $R = 4-Br$ at pH 7.8; (6) $R = H$ at pH 4.0.

TABLE I

Polarographic characteristics of some N^1 -carbamoyl-3,5-diphenyl-4-arylazopyrazoles at pH 7.8 in 1M KCl, Conc. = $1.0 \times 10^{-4}M$

No.	R	$-E_{1/2}$ V	$\Delta E_{1/2}$	$i_d(\mu A)$	$\frac{dE_{1/2}}{dpH}, \frac{V}{pH}$	αn	P	σ
1.	H	0.77	0.00	1.05	0.054	0.63	1.12	0.00
2.	2- CH_3	0.74	0.03	1.00	0.050	0.67	1.02	-0.17
3.	3- CH_3	0.78	0.01	1.00	0.054	0.69	1.12	-0.07
4.	4- CH_3	0.80	0.03	1.10	0.057	0.63	1.12	-0.17
5.	2-Cl	0.70	0.07	1.00	0.057	0.63	1.10	+0.20
6.	3-Cl	0.73	0.04	1.05	0.054	0.67	1.10	+0.37
7.	4-Cl	0.75	0.02	1.05	0.054	0.67	1.10	+0.23
8.	2- OCH_3	0.77	0.00	1.10	0.054	0.69	1.02	-0.39
9.	3- OCH_3	0.79	0.02	1.10	0.052	0.63	1.07	-0.11
10.	4- OCH_3	0.81	0.04	1.05	0.057	0.62	1.02	-0.27
11.	2- OC_2H_5	0.78	0.01	1.05	0.054	0.62	1.07	-0.35
12.	4- OC_2H_5	0.80	0.03	1.10	0.054	0.67	1.07	-0.23
13.	2-Br	0.72	0.05	1.10	0.054	0.67	1.05	+0.21
14.	4-Br	0.75	0.02	1.05	0.052	0.63	1.07	+0.23
15.	4-I	0.74	0.03	1.05	0.054	0.67	1.02	+0.27
16.	2,3- $(CH_3)_2$	0.78	0.01	1.10	0.057	0.62	1.05	-0.24
17.	2,4- $(CH_3)_2$	0.72	0.05	1.05	0.057	0.63	1.05	-0.34
18.	3,5- $(CH_3)_2$	0.77	0.00	1.00	0.054	0.63	1.05	-0.14
19.	2,6- $(CH_3)_2$	0.76	0.03	1.05	0.054	0.63	1.07	-0.34

The irreversibility of the processes studied at low pH values differs from reversibility observed under comparable conditions for azobenzene (Nygard, 1966), even though other characteristics of these waves are similar. The difference in the behaviour at low pH may be due to bulky groups present at the end of $-N=N-$ linkage in those pyrazoles.

Structural Effects

The effect of substituents on shift of $E_{1/2}$ can be treated quantitatively only when the slopes of the plots of $E_{1/2}$ vs. pH and degree of irreversibility (α) remain constant in the entire reaction series (Zuman, 1967). Since in the series studied (I-XIX) the values of αn and $dE_{1/2}/dpH$ are practically constant (Table I) it was considered worthwhile to correlate the $E_{1/2}$ of these compounds with Hammett substituent constants to express the effect of substituent quantitatively. The values of Hammett substituent constant ($\sigma_0 - X$) were taken from literature (Jaffe, 1953). Fig. 2 shows linear plot of $E_{1/2}$ vs. σ in citrate buffer of pH 7.8. The values of *m*- and *p*-derivatives fitted in a straight line from which the value of specific reaction

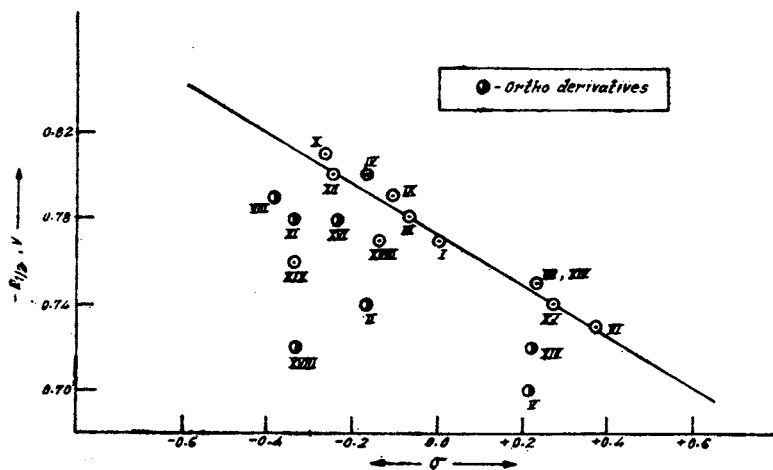


FIG. 2. Plot of $-E_{1/2}$ vs. σ for N^1 -carbamoyl-3,5-diphenyl-4-arylazopyrazoles in citrate buffer at pH 7.8, $C = 1.0 \times 10^{-4}M$.

constant (p) was determined and found to be 0.15. The deviation in the case of ortho derivatives, viz., 2-Cl, 2-CH₃, 2-OCH₃, 2-OC₂H₅, 2,3-(CH₃)₂, 2,4-(CH₃)₂, and 2,6-(CH₃)₂ can be accounted for on the basis of steric hindrance to coplanarity. The corrected values of $E_{1/2}$ for ortho derivatives were obtained from the relationship (Zuman, 1967),

$$(E_{1/2})_{\text{corr.}} = E_{1/2} - [\delta_{\pi,R}(E_s)_{o-x}]$$

where steric reaction constant ($\delta_{\pi,R}$) is

$$\delta_{\pi,R} = (\Delta E_{1/2}, -\rho_{\pi,R}\sigma_{o-x})(E_s)_{o-x}$$

The plot of corrected $E_{1/2}$ vs. σ gave straight line from which the specific reaction constant was found to be $-0.14V$, as against $0.15V$ for *m*- and *p*-derivatives. This value is in good agreement with the existing values for similar systems. The positive value of the specific reaction constant (ρ) indicate a nucleophilic mechanism (Zuman, 1960) of the electrode process, i.e., electron uptake as the potential determining step.

The magnitude of the polarographic ortho shift (Δ_0) is expressed by the equation (Zuman, 1967),

$$\Delta_0 = (E_{1/2})_{0-R} - (E_{1/2})_{p-R}$$

was determined for various groups of substituents, viz., methyl, chloro, methoxy and ethoxy at different pH (Table II). The positive value for all these groups indicates that ortho derivatives are reduced at more positive potential than their para analogues. The positive polarographic ortho shift in the case of these substituents has been reported by other workers (Zuman, 1967) also.

TABLE II

Values of polarographic ortho shift (Δ_0) in volts for *N*¹-carbamoyl-3,5-diphenyl-4-arylazopyrazoles

S. No.	R	pH			
		4.0	6.2	7.8	10.2
1.	Methyl	0.060	0.055	0.060	0.600
2.	Chloro	0.050	0.060	0.050	0.055
3.	Methoxy	0.035	0.040	0.040	0.035
4.	Ethoxy	0.020	0.020	0.020	0.025

It was also possible to handle our experimental data from the point of view of the additivity of substituent (Pfister & Bonastre, 1966) effect, for which the data precise to 0.01V, the shift caused by individual substituent, can be considered as additive. It is observed that in the present series 3,5-dimethyl derivative shows reasonable additivity of shifts due to 3 and 5 substituted derivatives, where 2,4-(CH₃)₂, 2,6-(CH₃)₂ and 2,3-(CH₃)₂ derivatives did not show such an additivity.

Effect of Ionic Strength

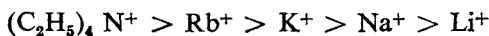
The effect of the double layer structure on the $E_{1/2}$ of a process preceded by the protonation is given by the equation (Mairanovskij, 1962).

$$\Delta E_{1/2} = \Delta \psi_1 \left(\frac{\alpha n_a - z}{\alpha n_a} - \frac{\partial E_{1/2} F}{\partial pH 2.3 RT} \right) \quad \dots(1)$$

where ψ_1 is the variation in the double layer potential, α in the transfer coefficient, n is the number of electrons transferred, z is the charge of the particle being discharged. Undoubtedly, a marked effect of change in ionic strength on $E_{1/2}$ should be observed in case where the depolarizer is in the ionic form, no such effect should be observed when it is in the non-ionic form, i.e., when $z = 0$. Since the second term in the bracket of equation(1) is nearly -1 and $z = 0$, $E_{1/2}$ will be almost independent of ψ_1 or of ionic strength. It is actually found that at constant pH, $E_{1/2}$ for the reduction of *N*¹-carbamoyl-3,5-diphenyl-4-arylazopyrazoles is almost independent of ψ_1 .

Effect of Cations and Anions

For evaluating the effect of the size of the cation of the supporting electrolyte on the nature and shape of the wave, polarograms of compounds (I-XIX) were polarographed in chlorides of lithium, sodium and rubidium and tetraethylammonium iodide. In these cases, the usual one well-defined wave was obtained. However, $E_{1/2}$ shifted towards more negative potential with increase in size of the cation without influencing the wave height. A further check was made by recording the polarograms with supporting electrolyte, having a common cation and different anions. No change in $E_{1/2}$ and i_d is observed, which goes to show that only the cation influences the electrical double layer at the cathode. It is interesting to observe that the nature of cation also influences the value of specific reaction constant (ρ). With increase in size of the cation the value of specific reaction constant increases. This is in agreement to the well-known fact that reduction of $-N=N-$ groups depends on the components of the supporting electrolyte in addition to the nature of the substituent present. Fig. 3 depicts that the value of the specific reaction constant (ρ) is a linear function of the $(E_{1/2})_H$ (half-wave potential of the parent unsubstituted compound in the same supporting electrolyte). It is also clear from the figure that the effect of the cations on the reduction is similar to that of crystallographic ionic radii.



Incidentally, this order is almost the reverse of the order of ions of the Hofmeister series for hydrophillic colloidal solutions.

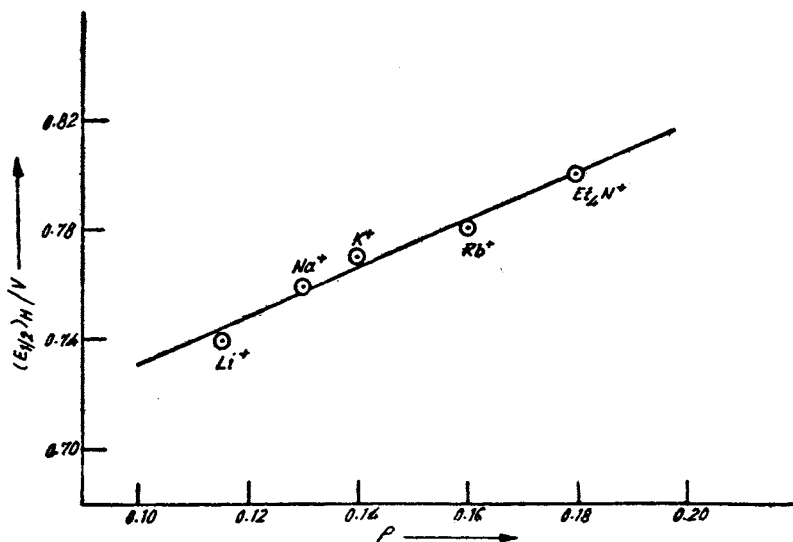


FIG. 3. Plot of $(E_{1/2})_H$ vs. ρ for N^1 -carbamoyl-3,5-diphenyl-4-arylazopyrazoles at $\text{pH} = 7.8$ for various cations.

Effect of Solvent Composition

Firstly, the polarograms of arylazopyrazoles were recorded in the minimum amount of D.M.F. (20%) necessary for dissolving the compound. The D.M.F. percentage was then progressively increased from 20 per cent to 70 per cent to see the effect of solvent composition on the electrode process. It was observed that $E_{1/2}$ shifted to more negative potential with increasing concentration of D.M.F. in the solvent mixture. In electrode processes accompanied by preprotonation, the shift in $E_{1/2}$ can be due to a rise of pH of solution and an increase in the dissociation constant of the protonated species. Both these factors sharply lower the rate of preprotonation and consequently lead to the shift in $E_{1/2}$ towards more negative potential. Schwabe (1957) supposed the shift of the $E_{1/2}$ be caused by inhibition of the electrode process by the solvent molecules adsorbed on the electrode. There is yet another factor which exerts a great influence in such cases and it is the viscosity of the solvent. With increasing concentration of D.M.F. in the solvent mixture, there is a gradual increase in viscosity upto a certain concentration (60% D.M.F.) after which it decreases. This optimum concentration points towards complete association of the solvent.

A survey of the data (Table III) on the variation of $E_{1/2}$ with solvent composition would reveal that potential reaches its peak value at about 60 per cent D.M.F. and after that remains independent of the concentration of the organic solvent. The i_d values, as expected, however goes on decreasing and at very high percentage of methanol in the solvent mixture, very ill defined waves are obtained.

TABLE III

Effect of D.M.F. concentration on N^1 -carbamoyl-3,5-diphenyl-4-arylazopyrazoles at pH 7.8 in 1M KCl

S. No.	% D.M.F.	$-E_{1/2}/V$	$i_d/\mu A$
1.	20	0.77	1.05
2.	30	0.79	0.98
3.	40	0.80	0.95
4.	50	0.82	0.93
5.	60	0.825	0.90
6.	70	0.825	0.82
7.	80	—	—

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