

ELECTROCHEMICAL BEHAVIOUR OF SOME PYRIMIDINE DERIVATIVES: POLAROGRAPHIC REDUCTION OF 1,3-DIMETHYL-2,4,6(1H, 3H, 5H) PYRIMIDINTRIONE AND ITS SUBSTITUTED 5-PHENYL AZO

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السلوك الكهروكيميائي لبعض مشتقات البيريميديينات :

الأختزال البولاروجرافي لـ ١, ٣ - ثنائي ميثيل - ٢, ٤, ٦
(1H, 3H, 5H) بيريميدين ثلاثي الكيتون و ٥ - فينيل آزو

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درس الأختزال البولاروجرافي لـ ١, ٣ - ثنائي ميثيل حمض البريتيوريك (I) وكذلك ١, ٣ ثنائي ميثيل - ٥ - فينيل آزو حمض البريتيوريك في محاليل منظمة ذات رقم هيدروجين ٢ - ١١ ، ٤٠٪ (حجم/حجم) كحولية (II) وأوضح الأختزال البولاروجرافي لـ (I) وجود موجه إختزالية لمجموعة كيتون واحدة . وبالنسبة لـ (II) سجلت النتائج موجتين إختزاليين الأولى (الأكثر إيجابية) لمجموعة الأزو والثانية (الأكثر سالبة) لمجموعة كيتون واحدة . وقد أقترح نسق الأختزال الكهربي لكلا المركبين . كما درس تأثير المجموعات الأستبدالية على كل من جهود نصف الموجه وقيم ثابت التآين الحمضي pK_a لتبيان مدى إنطباق علاقات الحرارة الخطية على المركبات موضع الدراسة .

Key Words: Pyrimidine derivatives, Polarographic reduction, Electrochemistry.

ABSTRACT

The polarographic behaviour and spectrophotometric pK_a of 1,3-dimethyl barbituric acid and 5-phenylazo substituted products were investigated in buffer solution of pH ~ 2-11. The results revealed an azo form of the substituted products, a mechanism for the electroreduction pathway was suggested. Half wave potentials showed fair correlation with σ constants while pK_a showed practically no dependence on substitutes.

INTRODUCTION

The chemistry of pyrimidines occupied unlimited attraction of researchers. Barbituric acid and barbiturates, as a class of these compounds, found a great share of this importance. This because of its wide medicinal applications, in particular its hypnotic action. The literature includes countless papers, reports and reviews. Representative of these articles may be mentioned here are those dealing with its hypnotic action[1,2] enzyme stimulation and inhibition[3,4] its anticonvulsant potency[5-7] and imitation of anesthesia[8,9]. Relevant reviews were also published[10-12]. The use of these compounds as chelating agents for metal ions have been also reported[13,14]. The electroreduction of these compounds received, relatively little attention. Some articles dealing with its polarographic reduction could be traced in literature[15,16].

Bearing such importance, the present work aimed to throw more light on the polarographic reduction of 1,3-dimethyl barbituric acid (I) and its 5-phenyl azo coupled product (II)_{a-f} in buffer solution covering the pH range ~2-12 to demonstrate the actual mechanistic reduction pathway taking place at the DME, also to test the fidelity of LFER to the series under consideration through $E_{1/2-\sigma}$ and $pK_a-\sigma$ correlations.

EXPERIMENTAL

1,3-dimethylbarbituric acid (I) was Aldrich product recrystallized twice from water before use, m. p. 125 ± 1 °C.

Organic Synthesis

5-Arylazo-1,3-dimethyl barbituric acid derivatives barbituric (II)_{a-f} were prepared according to the following procedure:

Aniline or the corresponding aromatic amine (200m mol) was dissolved in 15 ml concentrated hydrochloric acid and 15 ml of water, cooled to 0 °C and then treated with a cold solution of 1.5 g sodium nitrite in 10 ml water. The diazotized amine was then added gradually to an ice cold solution of 20 m mol of 1,3-dimethyl barbituric acid in alcohol, containing sodium acetate (pH ~ 7-9 after coupling) where the corresponding coupling product separates. The reaction mixture was left overnight in refrigerator, filtered, recrystallized from ethanol. Microelemental analysis which agreed well with the theoretical values; also TLC proved fair purity credit.

Polarographic investigations

Apparatus

Polarographic curves were recorded with an E 506 pen type recorder polarograph (Metrohm-Switzerland). The capillary possessed the following characteristics in H₂O open circuit: $t = 4.8 \text{ s drop}^{-1}$, $m = 1.46 \text{ mg s}^{-1}$ for $h = 40 \text{ cm}$.

Solution

Here 10^{-3} M stock solution were prepared by dissolving an accurately weighed quantity of material in the appropriate volume of absolute ethanol. Due to the limited solubility of the *m*-NO₂ & *p*-NO₂ substituents, the stock solution was prepared using the least possible amount of DMF (5%). Britton-Robinson modified universal buffers^[17] was used as supporting electrolyte.

Measurements

All experiments were carried out at $25 \pm 2 \text{ }^\circ\text{C}$, the halfwave potentials were measured graphically and expressed Vs. SCE with an accuracy of $\pm 0.005 \text{ V}$.

Procedure

Here 12 ml of buffer solution and 7 ml of ethanol were introduced in the polarographic cell. The mixture was then deaerated with H₂ gas for 12 min. Then 1 ml of 10^{-3} depolarizer was introduced into the cell so that the final concentration was $5 \times 10^{-5} \text{ M}$ in 20 ml 40% (V/V) ethanolic buffer.

Controlled potential electrolysis and determination of the number of electrons

Mercury pool electrolysis was carried out on (I_a) (200 mg) in 10^{-2} M HCl (200 ml) and II_a taken as a representative example for the studied series (100 mg) in 50% (V/V) ethanol/ 10^{-2} M HCl (200 ml). The electrolysis cell was a 250 ml conical flask with a working area of $\sim 50 \text{ cm}^2$ in which the gas inlet, reference and auxiliary electrodes were fixed. The potential was controlled by a tutorial T6 transistorized potentiostat at -1.2 V (in case of I) and -0.4 V (in case of II_a, wave (a). vs. SCE (i.e. on the limiting current plateau of the respective polarographic waves of I and II_a). Progress of electrolysis was followed by recording the decrease in current with time and the number of electrons was computed from *i*-*t* curves following the procedure outlined by Lingane^[18] and found to be 2e in case of (I) and 4e in case of II_a. After disconnecting the electrolysis cell, 1 ml of the resulting solution (in case of II_a) was withdrawn and the presence of aniline in this solution was revealed by a standard spot

test^[19]. No trials was made to separate solid product from electrolysis product.

Spectrophotometric measurements and determination of the apparent dissociation constant

These were carried out using a PYE Unicam 1800 spectrophotometer supplemented with a Unicam SP 1805 programme controller automatic recording unit. The runs in the visible and UV range were carried out for $5 \times 10^{-5} \text{ M I}$ and II_{a-f}, 40% alcoholic Britton-Robinson buffer solutions at a roughly increasing 0.5 pH unit. The pH of the solution was measured and the spectrophotometric run was recorded within a few minutes. The pK_a was calculated using the equation^[20].

$$\text{pH} = \text{pK}_a + \log \left[\frac{(A - A_{\text{min}})}{(A_{\text{max}} - A)} \right]$$

where A_{min} is the absorbance of the undissociated acid, A the absorbance of the organic reagent at a given pH value and A_{max} the absorbance of the completely dissociated acid at pH medium. The intersection of the straight line of pH vs. $\log \left[\frac{(A - A_{\text{min}})}{(A_{\text{max}} - A)} \right]$ with the pH axis at $\log \left[\frac{(A - A_{\text{min}})}{(A_{\text{max}} - A)} \right] = 0$ gave the pK_a directly. The obtained pK_a values for I and II_{a-f} are collected in Table 1.

RESULTS AND DISCUSSION

Polarographic behaviour of (I)

Contrary to barbituric acid which showed no reduction polarographic waves, the polarograms of 1,3-dimethyl barbituric acid showed well defined 2 electron E_{1/2}-pH dependent reduction wave in the pH range ~2-5. At pH > 5 the wave height starts to decrease in the form of a dissociation curve with pK_a 6.2 as to be compared with the spectrophotometric pK_a = 4.50. The E_{1/2}-pH and *i*_l-pH plots for the wave are shown in Fig. 1 and the respective equation of E_{1/2} = f(pH) also other polarographic calculations are given in Table 1. The high irreversibility of the wave is well reflected from the transition coefficient value where $\alpha n = 0.31$ (cf. Table 1). The pronounced spectrophotometric acidity of I^{*} (pK_a = 4.5) could be attributed to stabilization of its anion by delocalization of the negative charge. Spreading to the third ketonic groups is least likely, probably due to the lone pair of electrons on the N atom. The polarograms of this compound sustains

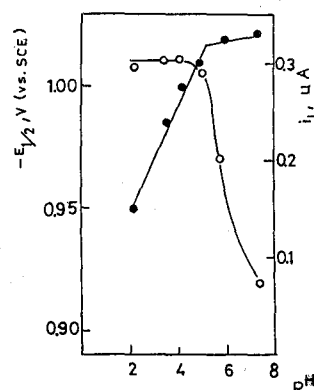


Fig. 1. Dependence of E_{1/2}(●) and *i*_l(O) on pH for $5 \times 10^{-5} \text{ M}$ in 40% V/V ethanolic buffers of I.

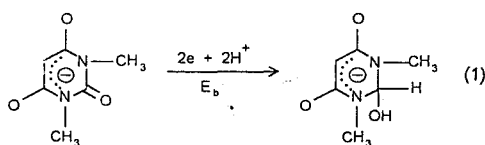
Table 1
Polarographic data and potentiometric pK_a of I and 5-phenylazo-1,3-dimethyl barbituric acid.

Compound	$E_{1/2} = f(\text{pH})$	$\frac{2.3RT^a}{\alpha n}$	αn^b	pH^c	Spectrophotometric pK_a
I	$E_{1/2} = -0.904 - 0.025 \text{ pH}$	0.19	0.31	3.5	4.50
IIa	$E^a_{1/2} = -0.180 - 0.066 \text{ pH}$ $E^b_{1/2} = -0.940 - 0.044 \text{ pH}$	0.064	0.90	3.2	8.40
IIb	$E^a_{1/2} = -0.190 - 0.066 \text{ pH}$ $E^b_{1/2} = -0.950 - 0.048 \text{ pH}$	0.080	0.737	3.2	9.35
IIc	$E^a_{1/2} = -0.225 - 0.064 \text{ pH}$ $E^b_{1/2} = -0.970 - 0.043 \text{ pH}$	0.070	0.843	3.15	8.85
IId	$E^a_{1/2} = -0.144 - 0.058 \text{ pH}$ $E^b_{1/2} = -0.090 - 0.044 \text{ pH}$	0.062	0.952	4.20	7.52
IIe	$E^a_{1/2} = -0.015 - 0.055 \text{ pH}$ $E^c_{1/2} = -0.185 - 0.066 \text{ pH}$	0.070	0.84	3.15	8.51
IIf	$E^a_{1/2} = -0.070 - 0.045 \text{ pH}$ $E^c_{1/2} = -0.255 - 0.060 \text{ pH}$	0.062	1.95	3.15	8.75

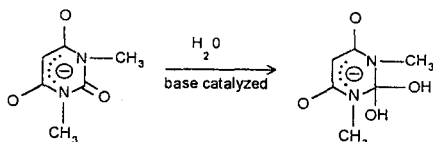
- a) Slope of logarithmic analysis.
b) Transition coefficient.
c) Individual pH value at which logarithmic analysis was carried out.

this view, since only one two-electron wave have been registered in acid and fairly neutral medium assigned to reduction of the C=O group to the corresponding enol. At higher pH's the rate of protonation decreases hence deactivation of the carbonyl group probably through enolization. Scheme 1 is thought to demonstrate these arguments.

$\text{pH} < pK_a$



$\text{pH} > pK_a$



Scheme (1)

Polarographic behaviour of II_{a-f}

The polarograms of $5 \times 10^{-5} \text{ M}$ 40 % ethanolic buffers of these compounds displayed well defined 4 electron diffusion controlled irreversible wave a, except for the *m*-NO₂ & *p*-NO₂ substituents where additional waves for the nitro group have been registered. At more negative potentials a less defined two electron wave (b) appeared in

the polarograms. While wave (a) remained well defined over the whole pH range of study (pH ~ 2-12), wave (b) practically disappears at pH > 5. For wave (a), while the half-wave potential is pH-dependent shifting to more negative values with increase of pH ($dE_{1/2} = 0.66$) (cf. Table 1), the limiting current is practically pH-independent. The fact that this wave predominates over the whole pH range of study indicates that these molecules are highly basic in nature. The shifts in $E_{1/2}$ with pH, also i_l -pH relation of II_a taken as a representative example of compounds (II_{a-d}) are graphically shown in Fig.2.

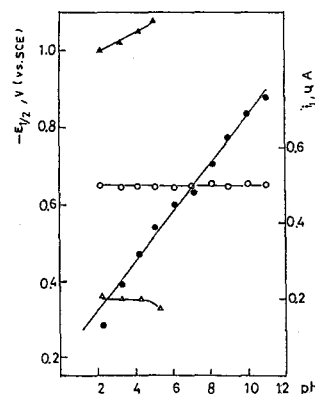
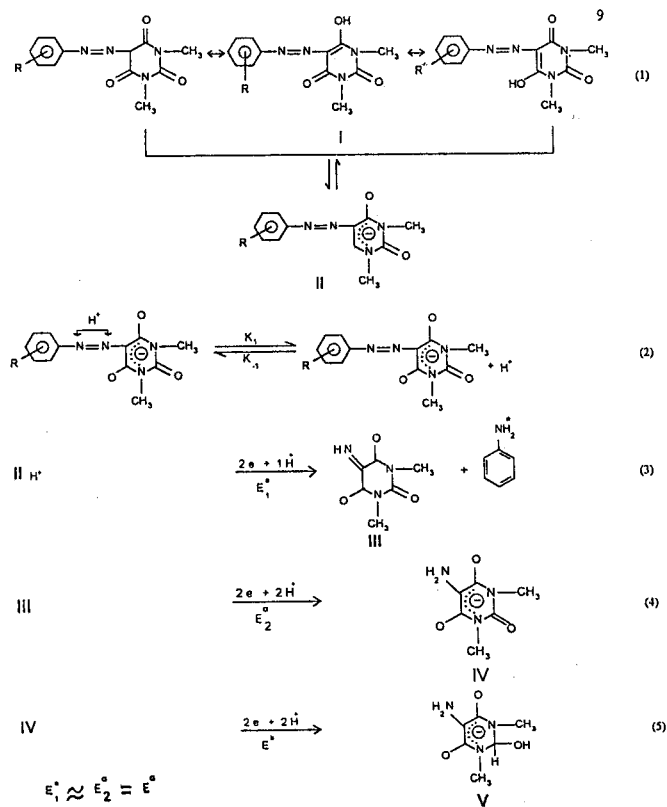


Fig. 2. Dependence of $E_{1/2}$ (●, ▲) and i_l (O, Δ) on pH for $5 \times 10^{-5} \text{ M}$ in 40% ethanolic buffers of II_a: (●, O) wave (a); (▲, Δ) wave (b).

Linear equation of $E_{1/2} = f(\text{pH})$ and other polarographic data were compiled in Table 1. The more positive 4-electron wave (a) is assigned to reduction of the -N=N-C moiety while the more negative 2-electron wave (b) assigned to reduction of the carbonyl group to the corresponding hydroxy group since azo group are known to

be reduced at significantly more positive potentials than the carbonyl group. Moreover, proof of aniline in the sample after controlled potential electrolysis (CPE) at the limiting current of wave (a) support such an assignment. Scheme 2 provides an interpretation of these results.



* Identified product

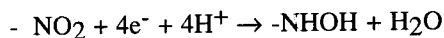
Scheme (2)

As the value of $dE_{1/2}/dpH = 0.066$ (cf. Table 1) it is not unreasonable to assume preprotonation of the molecule followed by its reduction in the sequence described by equations (2) & (3). In the aforesaid scheme an azo and not hydrazone structure have been proposed since if a hydrazone structure [-NH-N=] is thought to prevail it will not let tautomeric forms in step (1) and charge delocalization, hence deactivation of two carbonyl groups be possible as disclosed from the polarogram of the compounds. Further evidence for discrimination between tautomeric azo/hydrazone structure could be ascertained in light of the behaviour of the nitro derivative. The importance of the nitro derivative lies in the fact that literature survey of azo compounds containing a nitro substituent in any location of the molecule reveals that the N=N function is always reduced before the nitro group[21-24] while in hydrazones the opposite has been found[25-27]. At this point it seemed mandatory to run and inspect the polarograms of the nitro substituent.

In addition to wave (a) and (b) in the polarograms of (II)_{a-d} compounds II_e and II_f displayed additional waves corresponding to reduction of their nitro group. (II)_e (*m*-NO₂) showed an additional 4 electron irreversible diffusion controlled wave (c) lying between waves (a) and (b). The behaviour of the addition; wave can be described by the linear equation (1):

$$E^c_{1/2} = -0.185 - 0.066 \text{ pH} \dots\dots\dots(1)$$

Since the behaviour of this wave is comparable to that known for *m*-nitro group[28] it is not unreasonable to attribute this extra wave to the reduction of the *m*-nitro group to hydroxylamine:



On the otherhand the polarograms of *p*-NO₂ substituent (II_f) displayed six electron additional wave (c) which at pH < 5 splits into two successive waves (C₁, 4 electron and C₂, 2 electron). In the intermediate pH range (5 < pH < 8) the two electron wave disappear. Fig. 3 illustrates graphically E_{1/2}-pH and i₁-pH relations for all the waves.

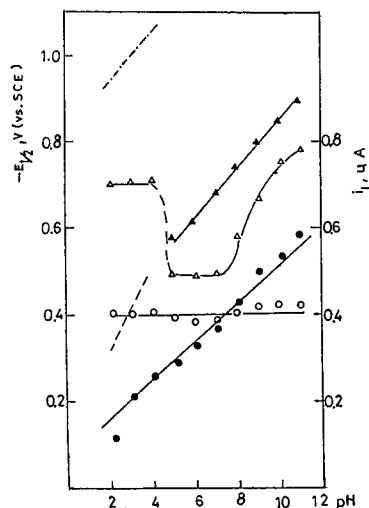
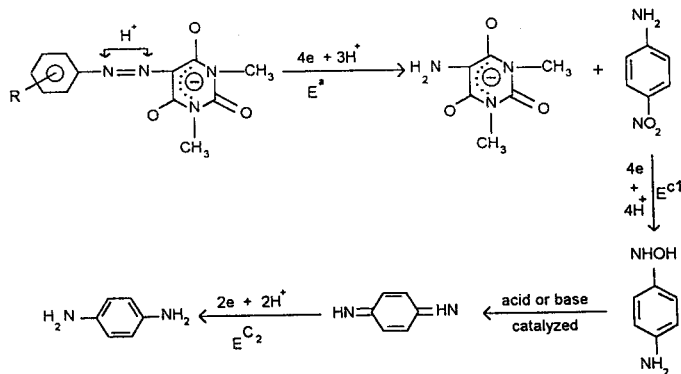


Fig. 3. Dependence of E_{1/2}(●, ▲, ---, -.-) and i₁(○, ○, △) on pH for 5 × 10⁻⁵M in 40% V/V ethanolic buffers of II_f: (P-NO₂): (●, ○) wave a; (▲, △) wave c; (---, -.-) waves c₁, c₂.

This behaviour have been reported previously for reduction of *p*-nitro group[29-31] through dehydration of hydroxylamine (formed along the 4 electron wave) to the corresponding quinonoid structure Nc1ccc(N)cc1. Presumably, this dehydration is sufficiently rapid and is only acid and base catalyzed since in the nearly neutral pH range the two-electron reduction wave of the quinonoid form disappeared. This findings could be illustrated by Scheme 3.



At pH > 8 : E^{c1} ≈ E^{c2} = E^c

Scheme (3)

The results obtained with the p -NO₂ derivative substantiate an azo and not hydrazo structure, since if the later is assumed its reduction wave (a) should follow but not prior to the six electron wave c definitely assigned for reduction of the nitro group which is not the case.

Structure-energy relationship

Further insight into the mechanism was tried through correlation of $E_{1/2}$ -Hammett's σ values at different pH. The constant value of the transition coefficient (αn), a prerequisite for quantitative study of the effects of substituent[32], was first ascertained. The value was found to be practically constant at individual pH values.

The most reliable $E_{1/2}$ values at selected pH have been correlated with different σ constants[33]. Statistical treatment of the data was carried using Jaffe calculations[34] (Table 2).

Table 2

Results of the statistical treatment of the $E_{1/2}$ - σ data for 5-phenylazo-1,3-barbituric acid derivatives II_{a-f} (wave a) at selected pH values.

pH	ρ^a	r^b	s.d ^c	n ^d
5	0.254	0.993	±0.008	6
8	0.307	0.992	±0.011	6
10	0.344	0.990	±0.013	6

- a reaction constant
 b correlation coefficient
 c standard derivation
 d number of points

Representative $E_{1/2}$ σ plots are illustrated in Fig. 4.

As is clear the plots have reasonable linearity with ρ values ranging between 0.255 and 0.344. That r and s are well correlated with σ constant is an indication that substituents can affect the reaction center mainly by their inductive effects. The fact that the points for p -NO₂ and m -NO₂ derivatives lies on the $E_{1/2}$ - σ plots is another confirmation that the compound is in the azo and not in the hydrazone form. If this is not the case one would expect reduction waves (c) of the NO₂ derivative to be prior that of the functional group, hence Hammett's σ_{NHOH} or σ_{NH_2} should fits the correlation, which is not the case.

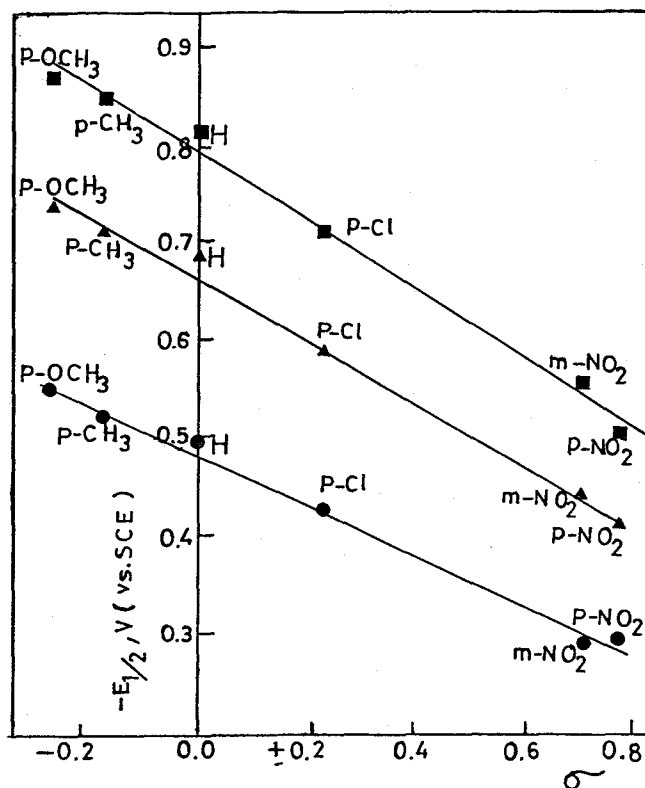


Fig. 4. $E_{1/2}$ - σ Relation for 5-phenyl azo 1, 3 -dimethyl barbituric acid at different pH: (●) pH 5; (▲) pH 8, (■) pH 10.

However, trials to correlate spectrophotometric pK_a values to different σ sets (σ , σ^o , σ^+) showed a weak dependence of the ionization on substituent effect.

This is to be anticipated since the negative charge, of the ionizing center is delocalized on the heterocyclic CO and N moiety of the molecule; also the substituent in the benzene ring is located far from this center.

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