

Electrochemical Behaviour of some Benzothiazolyhydrazonebarbituric Acids and Effect of Substituents on Redox-Mechanism

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Polarographic and cyclic voltammetric behaviour of twelve titled compounds have been studied in the pH range 2.0–11.2 at dropping mercury electrode, pyrolytic graphite electrode and platinum electrode. The effect of substituents, covering wide range of Hammett substituents constant values, has been evaluated quantitatively.

BARBITURIC acid derivatives, commonly known as barbiturates, have long been used as central nervous system depressants. In an effort to synthesise barbiturates that had no depressant action on the sensory cortex, a large number of hydrazone derivatives of 1,3-dimethylbarbituric acid have been synthesised¹ as potential hypnotics. It has been proved^{2,3} in many cases of purines that electrochemical oxidation studies provide an unique and valuable insight into chemical aspects of the redox mechanism of biological processes. The polarographic behaviour of some of the hydrazonebarbituric acid has been studied^{4,5} in Britton–Robinson buffers. However, the studies are restricted to the dropping mercury electrode and no information is available on their behaviour at solid electrodes.

This paper describes the results on the polarographic and voltammetric behaviour of 5-(2'-benzothiazolyhydrazone)-1,3-dimethylbarbituric acids in phosphate buffers. More elaborate studies are carried out at pH 7.0 to get an idea about the polarographic and voltammetric behaviour at pH close to physiological pH. A wide range of substituents have been selected to get a quantitative relation of effect of substituents on the ease of redox behaviour at varieties of electrodes. It was interesting to observe that potentials for reduction of these compounds are 200–300 mV more negative at solid electrodes in comparison to dropping mercury electrode.

Experimental

All the compounds were synthesised in the laboratory by the reported methods^{1,6}. Their purity was ascertained by repeated recrystallisation and elemental analysis. Equipment used for electrochemical studies has been described elsewhere⁷. The platinum and pyrolytic graphite electrodes used in these studies were fabricated in the laboratory by the reported method⁸. The area

of PGE and platinum electrodes were 2.0 and 2.5 mm², respectively. All potentials are referred to the SCE.

The 2 mM stock solution of all the compounds was prepared in *N,N'*-dimethylformamide (A.R.; H₂O ~0.1%). Investigations were carried out in phosphate buffers⁹ of different pH with constant ionic strength of 0.5 M. The solutions for recording polarograms and voltammograms were prepared by mixing the stock solution (1 ml) with dimethylformamide (2.0 ml) and buffer (7.0 ml) in a stream of purified nitrogen gas for 8–10 min and the curves were then recorded. Controlled-potential electrolysis was carried out in a three-compartment cell using mercury pool, platinum or pyrolytic graphite as working electrode, SCE as reference electrode and cylindrical platinum gauge as counter electrode in a buffer of the desired pH.

The identification of products was carried out by electrolysis of the compound (~6–8 mg) in a buffer of the desired pH. The progress of electrolysis was monitored by recording a cyclic voltammogram at different intervals of time. Electrolysis was stopped when the reduction peak completely disappeared, and the electrolysed solution was removed from the cell and lyophilised. The dried material was dissolved in 30% DMF (2–3 ml) and passed through a glass column (50 × 1.5 cm dia) packed with Sephadex G-10 (Pharmacia). The eluant used was 30% DMF, and different fractions (5 ml each) were collected. The absorbance at 210 nm was plotted against volume and three peaks were observed. The first peak between 50–75 ml was found to contain phosphate and hence was rejected. The other two peaks, 80–110 and 140–170 ml were collected separately, freeze-dried and analysed by tlc and mass spectra.

Results and Discussion

Polarographic behaviour: All the compounds (1–12) exhibited a well defined, pH-dependent, 4e

reduction wave in the entire pH range of 2.0–11.2. The nature of the limiting current was found to be diffusion-controlled as evidenced by linear i_d vs \sqrt{h} and i_d vs concentration plots. The low values of temperature coefficient (below 1.1% K⁻¹) further indicated the diffusion-controlled nature of the waves. The half-wave potentials were dependent on pH and shifted towards more negative potential with the increase in pH. The polarographic characteristics and linear $E_{1/2}$ vs pH relations of these compounds are presented in Table 1. The values of αn determined by usual methods¹⁰ were found practically constant in the range 1.10–1.20, indicating thereby the same mechanism of reduction in these compounds.

TABLE 1—POLAROGRAPHIC CHARACTERISTICS OF SUBSTITUTED-BARBITURIC ACIDS AT pH 7.0

Compd. no.	R	$-E_{1/2}$ V	i_d μA	αn	a^* V/pH	b^*
1	H	0.70	0.95	1.16	0.045	0.88
2	4'-OH ₂	0.64	0.97	1.10	0.048	0.80
3	5'-CH ₃	0.62	1.00	1.18	0.046	0.82
4	6'-CH ₃	0.70	0.95	1.21	0.048	0.86
5	4'-OCH ₃	0.70	0.97	1.16	0.045	0.88
6	5'-OCH ₃	0.71	1.00	1.16	0.050	0.86
7	6'-OCH ₃	0.72	1.10	1.11	0.048	0.89
8	4'-Cl	0.60	0.97	1.10	0.040	0.81
9	5'-Cl	0.55	0.95	1.18	0.039	0.80
10	6'-Cl	0.58	0.90	1.16	0.042	0.82
11	6'-Br	0.55	1.00	1.16	0.040	0.87
12	6'-F	0.58	0.95	1.20	0.041	0.29

* From the relation, $-E_{1/2} = (a \text{ pH} + b) V$.

Voltammetric behaviour : Linear sweep voltammetry of the compounds (1–12) exhibited a well defined peak (lc) at sweep rate of 5 mV s⁻¹ at platinum and pyrolytic graphite electrode. The peak potential of this peak was dependent on pH and shifted towards more negative potential with increase in pH. The plots of E_p vs pH were linear. It was interesting to observe that the peaks at platinum electrode were broad in comparison to pyrolytic graphite electrode. This difference in behaviour may be due to strong adsorption property of pyrolytic graphite. However, the peak potentials at platinum were about 50 mV more positive in comparison to PGE. The peak current (i_p) for this peak was found to increase linearly with concentration of depolariser in the range 0.1–1.0 mM. Thus these compounds can safely be estimated in this concentration range.

Cyclic sweep voltammetry of these compounds at a sweep rate 150 mV s⁻¹ showed a well defined reduction peak (lc). The typical cyclic voltammograms observed are shown in Fig. 1. In the reverse sweep, one oxidation peak was also observed at positive potentials. The voltammetric characteristics are presented in Table 2. To check whether oxidation peak is related to reduction peak lc, cyclic voltammograms were also recorded by initiating the sweep in positive direction. It was noticed that oxidation peak (11a) appeared at the

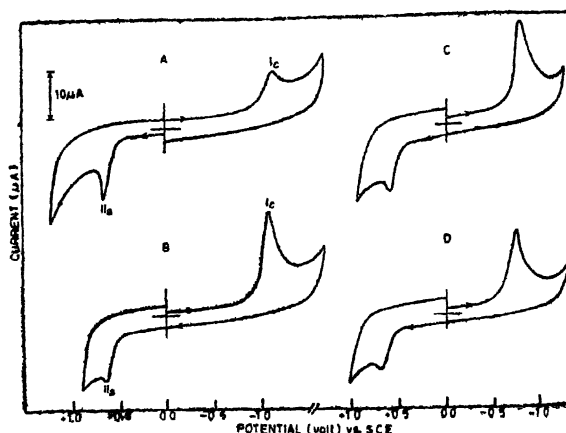


Fig. 1. Typical cyclic voltammograms of 0.2 mM barbiturates at PGE. Scan rate 150 mV s⁻¹: (A) and (B) compound 1 at pH 6.0, (C) 3 at pH 5.4, and (D) 6 at pH 3.8.

TABLE 2—VOLTAMMETRIC CHARACTERISTICS OF SUBSTITUTED-BARBITURIC ACIDS AT pH 7.0 AT PGE

Compd. no.	R	$(-E_p)_{Ic}$ V	$(E_p)_{IIa}$ V	E_p vs pH relation (V) Peak 1c
1	H	1.00	0.525	$(-E_p) = 0.070 \text{ pH} + 0.50$
2	4'-OH ₂	1.10	0.475	$= 0.070 \text{ pH} + 0.62$
3	5'-CH ₃	0.875	0.525	$= 0.080 \text{ pH} + 0.81$
4	6'-CH ₃	1.00	0.475	$= 0.075 \text{ pH} + 0.48$
5	4'-OCH ₃	0.95	0.500	$= 0.068 \text{ pH} + 0.41$
6	5'-OCH ₃	0.95	0.475	$= 0.068 \text{ pH} + 0.40$
7	6'-OCH ₃	1.10	0.450	$= 0.080 \text{ pH} + 0.54$
8	4'-Cl	0.90	0.475	$= 0.068 \text{ pH} + 0.43$
9	5'-Cl	0.83	0.475	$= 0.068 \text{ pH} + 0.35$
10	6'-Cl	0.87	0.450	$= 0.065 \text{ pH} + 0.43$
11	6'-Br	0.82	0.500	$= 0.070 \text{ pH} + 0.83$
12	6'-F	0.90	0.475	$= 0.072 \text{ pH} + 0.89$

same potential. A comparison of peak potentials for both the peaks by initiating the sweeps in both the directions is presented in Table 3. Thus it was

TABLE 3—EFFECT OF SWEEP DIRECTION ON PEAK POTENTIAL OF SUBSTITUTED-BARBITURIC ACID (1) AT DIFFERENT pH

pH	Scan initiation			
	Positive		Negative	
	$(E_p)_{Ic}$ V	$-(E_p)_{IIa}$ V	$(E_p)_{Ic}$ V	$-(E_p)_{IIa}$ V
2.0	0.65	0.75	0.64	0.75
3.5	0.74	0.72	0.74	0.70
5.1	0.86	0.61	0.85	0.60
7.0	1.00	0.52	1.00	0.52
8.8	1.12	0.45	1.11	0.44
9.2	1.15	0.42	1.15	0.42
10.6	1.24	0.35	1.23	0.35
11.2	1.28	0.32	1.29	0.32

concluded that the processes of peaks lc and 11a are independent reactions and not related to each

other. The only difference in the cyclic voltammograms observed was that peak 11a becomes sharp when sweep was initiated in positive direction and peak 1c had a tendency to become broad. On the other hand peak 1c was sharp when sweep was initiated in the negative direction. When the potentials more negative to peak 1c were held for some time in cyclic voltammetry, the peak 11a decreased but did not disappear even when the potential was held for 20–30 min. It was thus believed that redox-reaction for peak 1c is not quantitative under cyclic voltammetric conditions.

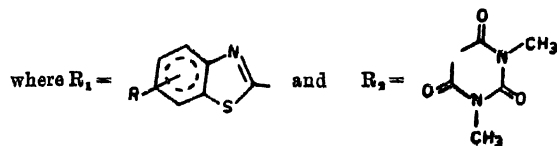
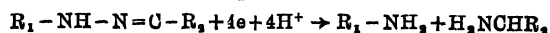
Controlled-potential electrolysis of these compounds was carried out to determine the number of electrons involved in reduction as well as in oxidation. The value of n was determined by the method of Lingane *et al.*¹¹ and was close to 4.0 for reduction at all the electrodes. This clearly indicated that the electrode process for reduction at d.m.e., platinum and PGE occurs by the same mechanism. The number of electrons involved in oxidation were found to be 1.0 ± 0.1 at PGE and platinum electrodes.

Product characterisation: The products of electroreduction for the parent compound 1 were characterised at pH 7.0 at all the three electrodes. It was interesting to observe that exhaustively electrolysed solution at mercury pool, PGE and platinum exhibited two clear spots in tlc. The R_f values of these spots were 0.77 and 0.95. Thus it is clear that two products are formed by electroreduction of these compounds at all the three electrodes studied. The spot corresponding to $R_f = 0.95$ was identified as 2-aminobenzothiazole. The second spot with $R_f = 0.77$ could not be completely identified at this stage, however, a comparison with 1,3-dimethylbarbituric acid, which has one amino group less than the product formed, indicated that product could be similar to it.

The products of electroreduction were further identified by separating the two products using Sephadex G-10 column (see Experimental). The fraction collected between 80–110 ml (peak-2) and 140–170 ml (peak-3) were separately freeze-dried and the resulting product was identified by m.p. and mass spectral studies. The fraction between 80–100 ml exhibited m.p. 128° which corresponds to 2-aminobenzothiazole (lit.¹² 128°). The mass spectra of this fraction exhibited a m/e 150, which corresponds to 2-aminobenzothiazole. The other major high mass peaks observed in the fragmentation pattern are m/e 134 (26.5%), 133 (11.6%), 132 (6.8%), 108 (19.2%), 107 (11.1%) and 90 (16.5%).

The second fraction (140–170 ml) on freeze-drying showed m.p. 185°. The mass spectra of this fraction indicated a m/e 171, similar to 5-amino-1,3-dimethylbarbituric acid. The other major high mass peaks in the fragmentation pattern were m/e 155 (51.8%), 154 (31.6%), 153 (11.9%), 57 (16.8%), 43 (19.3%) and 42 (18.6%). However, no attempt was made to explain the fragmentation pattern.

Thus it can be concluded that products of electroreduction of these compounds are 2-aminobenzothiazole and 5-amino-1,3-dimethylbarbituric acid at all the electrodes studied. The following 4e, 4H⁺ overall mechanism can be proposed for the reduction of these compounds.



A similar mechanism for the reduction of hydrazones has been proposed earlier^{13,14} in acidic and alkaline media. The one-electron oxidation of these compounds is probably similar to autooxidation of hydrazones as has been reported in literature¹⁵.

Substituents effect: The examination of Tables 1 and 2 clearly indicates that the electron donating substituent shift the $E_{1/2}$ or E_p towards more negative potentials and electron withdrawing substituents towards more positive potentials in comparison to compound 1.

The effect of substituents in case of reduction was determined quantitatively by using Hammett equation. The various substituted compounds exhibited the $dE_{1/2}/d\rho_H$ and $dE_p/d\rho_H$ values in the same range and also the values of α_n (Table 1) were practically constant; hence, it was considered worthwhile to apply Hammett equation to these compounds. The substituents in these compounds are not present in the benzene ring directly attached to site of reduction ($-NH-N=C-$). Thus the system can be represented as [X-Benzo-Het-R], where X represents substituents and R, the reducible sidechain. The values of Hammett substituent constants for the various groups in such systems has been successfully used by a large number of workers^{16,17}, and are found to give satisfactory correlation. Hence, positions 4', 5' and 6' are considered as *ortho*, *meta* and *para* positions, respectively, with respect to hydrazono group. The linear plots observed for $E_{1/2}$ vs σ and E_p vs σ are presented in Fig. 2. It is interesting to observe that the substituents fit well in the straight line for $E_{1/2}$ vs σ in comparison to E_p vs σ plot. The *ortho*-substituted derivatives (2, 5 and 8), which usually deviate from the regression line due to steric hindrance to co-planarity do not deviate much in these plots. The possible reason for non-deviating nature is that the substituents are remote from the reaction centre and hence the steric hindrance does not play a significant role. The values of specific reaction constant (ρ) are found to be 0.27 and 0.28, respectively, for both the plots and are in good agreement with the values reported in the literature¹⁷⁻¹⁹.

It is thus clear from these studies that the electrode process for the reduction of these com-

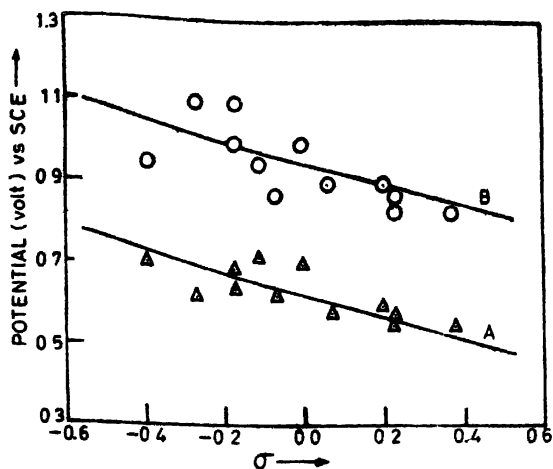


Fig. 2. Variation of (A) $E_{1/2}$ vs σ , and (B) E_p vs σ for barbiturates at pH 7.0.

pounds at various electrodes is more or less same. Theoretically it is expected that the slopes of $E_{1/2}$ vs pH and E_p vs pH plots should be the same. The difference of about 20–30 mV/pH may be due to the nature of electrodes. The solid electrodes are generally not free from adsorption complications and also does not permit the free orientation of the species undergoing reduction and hence, the reduction potentials expected are slightly more negative in comparison to d.m.e.

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References

1. H. G. GARG and R. A. SHARMA, *J. Pharm. Sci.*, 1970, 59, 1691.
2. R. N. GOYAL and G. DRYHURST, *J. Electroanal. Chem.*, 1982, 135, 75.
3. J. L. OWENS, H. A. MARSH and G. DRYHURST, *J. Electroanal. Chem.*, 1978, 91, 231.
4. W. U. MALIK, R. N. GOYAL and P. N. DUA, *Electrochim. Acta*, 1982, 27, 25.
5. W. U. MALIK, R. N. GOYAL and P. N. DUA, *Indian J. Chem., Sect. A*, 1982, 21, 114.
6. P. N. DUA, Ph. D. Thesis, University of Roorkee, 1982.
7. R. N. GOYAL, R. BHUSHAN and A. AGARWAL, *J. Electroanal. Chem.*, 1984, 171, 281.
8. R. N. GOYAL, S. K. SRIVASTAVA and R. AGARWAL, *Bull. Soc. Chim. Fr.*, 1985, 4, 656.
9. L. MÉRITS, "Polarographic Techniques", Interscience, New York, 1967, p. 232.
10. G. D. CHRISTIAN and W. C. PURDY, *J. Electroanal. Chem.*, 1962, 3, 863.
11. L. MÉRITS, "Polarographic Techniques", Interscience, New York, 1967, p. 232.
12. J. J. LINGANE, C. G. SWAIN and M. FIELDS, *J. Am. Chem. Soc.*, 1943, 65, 1348.
13. H. KRALL and R. D. GUPTA, *J. Indian Chem. Soc.*, 1935, 12, 629.
14. U. EISNER and E. K. EISNER in "Encyclopedia of the Electrochemistry of Elements", eds. A. J. BARD and H. LUND, Marcel Dekker, New York, 1979, Vol. XIII.
15. H. LUND, *Acta Chem Scand.*, 1964, 18, 563.
16. K. H. PAUSACKER, *J. Chem. Soc.*, 1950, 3478.
17. J. TIROUFLLET, R. ROBIN and M. GUYARD, *Bull. Soc. Chim. Fr.*, 1956, 571.
18. W. E. WHITMAN and L. A. WILES, *J. Chem. Soc.*, 1956, 3016.
19. P. ZUMAN, "Substituent Effects in Organic Polarography", Plenum Press, New York, 1967, p. 248. 5