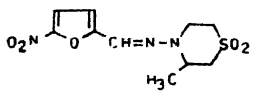
Electrochemical Behaviour of Nitrofurans

N. Y. SREEDHAR and S. JAYARAMA REDDY*

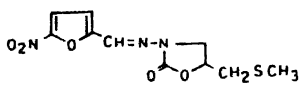
Department of Chemistry, Sri Venkateswara University, Tirupati-517 502

Manuscript received 18 June 1991, revised 6 September 1991, accepted 4 October 1991

NITROFURANS are known to be effective in experimental infection with *T. cruzi* and numerous congeners have been investigated for their chemotherapeutic usefulness. Recent work has proven promising that nifurtimox, [3-methyl-4-(5′-nitrofurfurylideneamino)tetrahydro-4*H*-1,4-thiazine-1,1-dioxide] (**1**) and nifurakel [5-methyl-thiomethyl-3-(5-nitrofurfurylideneamino)oxazolidin-2-one] (**2**) are effective clinically[1].



1



2

A review of the literature reveals that no attempt has been made to study the electrochemical behaviour of nifurtimox and nifurakel. However, several reports[2,3] pertaining to the electrochemical behaviour of various nitrofuran derivatives are available. The purpose of this work is to establish the experimental conditions that permit the study of the electrochemical behaviour of the said nitrofurans and their determination in pharmaceutical preparations.

Experimental

The details of the equipment used for most of the electro-reduction techniques and the DME and HMDE characteristics have been described elsewhere[4]. An AFRDE 4 potentiostat and MSRX speed control unit (Pine Instrument Company, U.S.A.) coupled with digital electronics *X-Y/t* recorder were used for rotating disk as well as rotating ring disk measurements with a glassy carbon ring disk electrode as the working electrode. In all the experiments platinum wire was employed as the auxiliary electrode. An Elico LI 120 pH meter was used for pH measurements. All experiments were carried out at 28.0 ± 1°.

Pharmaceutical grade nifurtimox and nifurakel (Sigma) were used as such. The stock solutions were prepared by dissolving the required amount of the drug in double-distilled dimethylformamide. The supporting electrolytes (pH 2.0–12.0) were prepared by using 0.2 *M* boric acid, 0.05 *M* citric acid and 0.1 *M* trisodium orthophosphate. The test solutions were prepared by dissolving the required quantity of the stock solutions and making up with the supporting electrolyte to the required volume to get the desired concentration and then purged with oxygen-free nitrogen gas for 10 min prior to each run.

Results and Discussion

Nifurtimox and nifurakel are found to exhibit two well-separated waves of almost equal height in the pH range 2.0–6.0. The first wave is due to the reduction of nitro group to the hydroxylamine in a four-electron process and the second to the simultaneous reduction of the azomethine and hydroxylamine groups consuming two electrons each. However, in alkaline solutions (pH 8.0–12.0) the said compounds are found to show a two-step reduction wave due to the four-electron reduction of nitro substituent followed by a mechanism corresponding only to the two-electron azomethine group reduction leading to saturation. Typical voltammograms are shown in Figs. 1–4. It is evident from Fig. 2 that in alkaline solutions the second peak has half the height of the first peak, as hydroxylamine is not reduced owing to the smaller availability of protons[3].

In cyclic voltammetry also, two cathodic peaks, C_1 and C_2 are observed in alkaline media for both the compounds due to the reduction of nitro and azomethine groups respectively. But an anodic peak (a_1) in the first reverse scan has been noticed at higher pH values (pH $\geqslant$ 10) as shown in Fig. 2. In the second scan, another small cathodic peak (C_3) at more positive potentials than C_1 is noticed. The anodic peak (a_1) may be due to the oxidation of hydroxylamine formed at C_1 to nitroso derivative and the cathodic peak (C_3) due to the reduction of the nitroso derivative to the hydroxylamine again[5]. The redox couple is observed to be irreversible as evidenced from the separation of their peak potential values.

The reduction processes for the above two compounds are found to be diffusion-controlled and adsorption-free as evidenced from the linear plots of i_d vs $h^{1/2}$, i_p vs $v^{1/2}$, i_m vs $t^{2/3}$ and $I_{l\cdot d}$ vs $w^{1/2}$ passing through the origin. The current function $i_p/Cv^{1/2}$ is found to be fairly constant with respect to scan rate (v) indicating the electrode process to be free from any adsorption complications. The collection efficiencies calculated from rotating ring disk voltammetry (0.174 and 0.176 for nifurtimox and

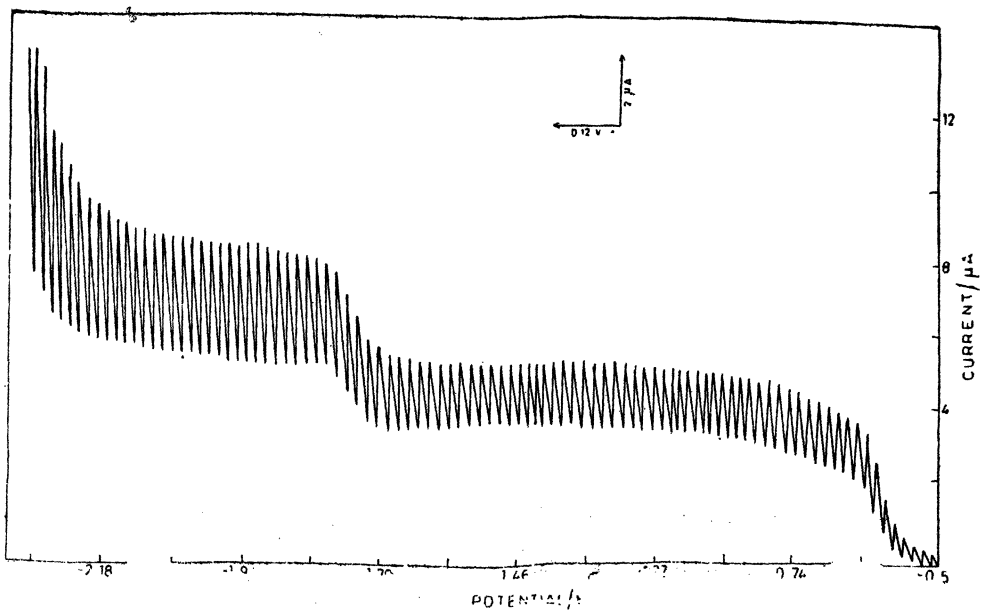


Fig. 1. Typical d.c. polarogram of nifurakel in pH=12.0; concn. =0.5 m*M*, drop time=3 s.

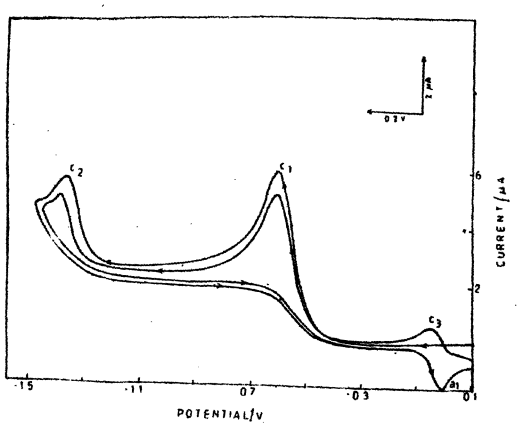


Fig. 2. Typical cyclic voltammogram of nifurtimox in pH=10.0; concn. =0.5 m*M*, scan rate=40 mV s^{-1}.

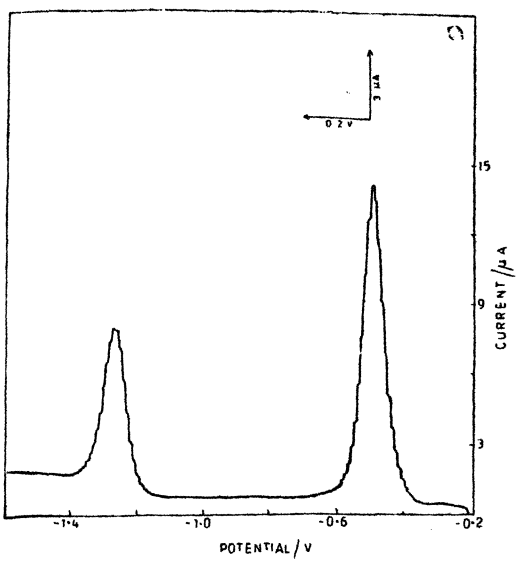


Fig. 3. Typical differential pulse polarogram of nifurakel in pH=10.0; concn. =0.5 m*M*, drop time=2 s.

0.177 and 0.180 for nifurakel respectively) are found to be in good agreement with the theoretical value (0.179), also indicating the electrode processes to be free from any kinetic complications.

The irreversible nature of the two peaks obtained for both the compounds are seen from log-plot analysis, disobedience of Tomes' criterion and non-linearity between i_m vs $1-\sigma/1+\sigma$ plots. From the slope of $E_{1/2}$ vs pH plots, the number of protons involved in the rate-determining step of nitro group reduction in both the compounds is found to be one. The n_a values for the reduction of nitro group is found to be about one, indicating that two electrons are involved in the rate-determining step. A similar stoichiometry of rate-determining step for the reduction of nitro group has been reported[6]. The value of n_a exceeding one should merely mean that the successive steps are too close together to be

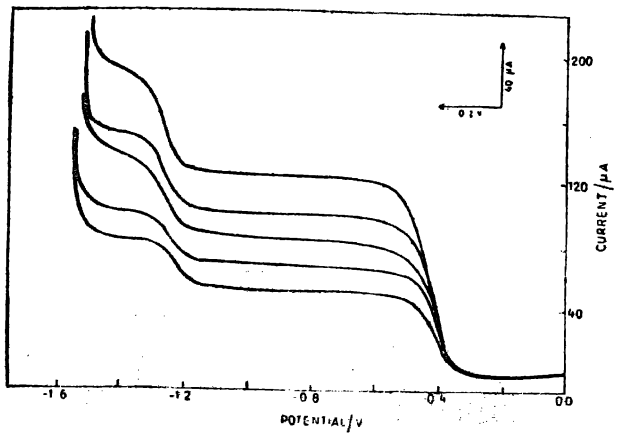


Fig. 4. Typical rotating disk voltammogram of nifurakel in pH=8.0 ; concn. =0.5 mM, sweep rate=50 mV s^{-1}.

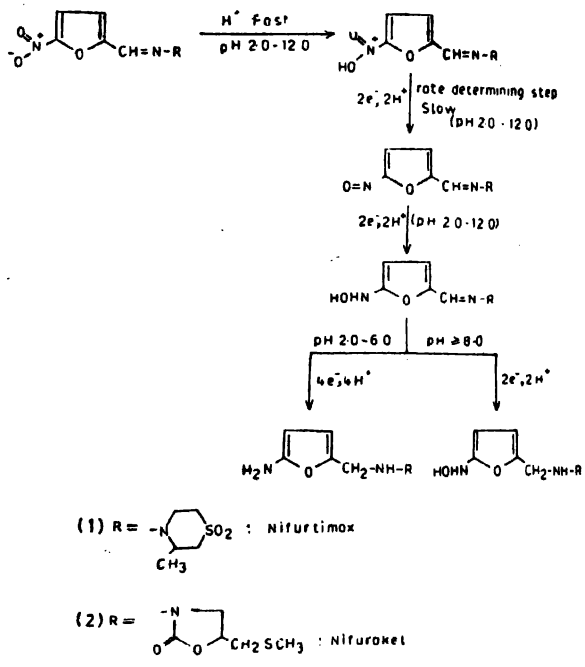
distinguished on the time scale implicit in the polarographic measurements[7].

The number of electrons (n) involved in the overall reduction process as determined by millicoulometry are found to be four for both the first and second waves of nifurtimox and nifurakel at pH 2.0, but n is observed to be four and two for the first and second waves respectively in basic media (pH 10). By comparing the heights of the first and second waves in acidic as well as basic media conclusion can be drawn about the number of electrons involved in the electrode process as given by millicoulometry. The same results are obtained through controlled potential electrolysis (CPE) experiments. The CPE carried out at pH 2.0 at -1.1 V for nifurtimox and at pH 10.0 at -1.5 V for nifurakel has given corresponding amine and hydroxylamine respectively as the products. The isolated products are confirmed by ir spectral studies (nujol : 3 400 and 1 600 cm^{-1} for nifurakel, and 3 350 and 1 625 cm^{-1} for nifurtimox).

The values obtained for the transfer coefficient, diffusion coefficient and heterogeneous forward rate constant at various pH values for the different techniques used are furnished in Tables 1 and 2. Diffusion coefficients evaluated for the two compounds are found to be almost equal, the reason being attributed to the almost equal molecular weights of the two compounds under investigation.

The heterogeneous forward rate constant values obtained for the reduction of the title compounds are found to decrease with the increase in pH of the solution as expected. The forward rate constant values for the reduction of nitro group are found to be high when compared to azomethine since the reduction of nitro group is facile as evidenced from the less negative reduction potentials. From the comparison of $k^{o}_{f,h}$ values for both the compound, nifurakel is noticed to be reduced somewhat easier than nifurtimox because nifurtimox has electron-donating methyl group at C_3-position.

On the basis of the results, the proposed reduction mechanism for nifurtimox and nifurakel in different pH zones is presented in Scheme 1.



Scheme 1

Well resolvable and reproducible wave obtained for nitro group in both the compounds is used for analysis by employing differential pulse polarography. It is observed that with buffers of pH $\leqslant$ 2.0, the nitro group reduction appears at the lower potential (i.e. around 0.0 V). Similarly in alkaline solutions (pH $\geqslant$ 8), the reduction of nitro group is not easily facilitated owing to the less availability of protons. The optimum pH range for obtaining well-resolved peaks for the determination of the title compounds is found to be between 4 and 6. The peak current is found to vary linearly with the concentration of the drugs over the range 1.0×10^{-5} to 2.3×10^{-7} M for nifurtimox and 1.5×10^{-5} to 2.5×10^{-7} M for nifurakel, and the lower detection limits are found to be 2.0×10^{-7} and 2.35×10^{-7} M for the two respectively.

Recommended analytical procedure : Standard solutions of the title compounds (1.0×10^{-5} M) are prepared in DMF. 1 ml of the unknown solution is transferred into a polarographic cell and made up with 9 ml of the supporting electrolyte of pH 4.0 and then deoxygenated with nitrogen gas for 10 min. After recording the polarogram, small increments (0.2 ml) of standard solution are added and the polarograms recorded after each addition under similar experimental conditions. The optimum conditions for the title compounds are given in Table 3.

TABLE 1—TYPICAL KINETIC DATA OF NIFURTIMOX

Concen. = 0.5 m*M*

Supporting electrolyte pH		D.C. polarography Drop time=3 s			Cyclic voltammetry Scan rate=40 mV s^{-1}			A.C. polarography Drop time=3 s			Differential pulse polarography			Rotating disk volatmmetry Sweep rate=50 mV s^{-1}	
		$-E_{1/2}$ V	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}	$-E_p$ V	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}	$-E_s$ V	$D\times10^5$ cm^2s^{-1}	k_s cm^{-1}	$-E_m$ V	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}
2.0	(a)	0.07	5.32	1.34×10^{-4}	0.09	5.45	2.56×10^{-4}	0.07	5.13	1.28×10^{-2}	0.06	5.23	3.33×10^{-5}	6.90	8.09×10^{-3}
	(b)	0.96	4.92	6.59×10^{-9}	0.96	4.91	1.52×10^{-9}	0.93	4.71	9.47×10^{-5}	0.93	4.82	4.91×10^{-8}	5.35	7.99×10^{-7}
4.0	(a)	0.14	5.28	1.37×10^{-5}	0.16	5.30	6.46×10^{-5}	0.16	5.05	9.20×10^{-3}	0.11	5.16	5.66×10^{-6}	6.85	5.30×10^{-4}
	(b)	1.08	4.35	5.21×10^{-9}	1.10	4.49	3.24×10^{-10}	1.07	4.23	7.43×10^{-6}	1.06	4.25	1.02×10^{-10}	5.26	2.09×10^{-8}
6.0	(a)	0.29	5.11	8.10×10^{-7}	0.30	5.14	9.15×10^{-6}	0.27	4.99	3.55×10^{-5}	0.26	4.91	2.85×10^{-7}	6.62	5.60×10^{-5}
	(b)	1.24	4.12	4.27×10^{-11}	1.24	4.21	2.96×10^{-11}	1.25	4.00	2.24×10^{-8}	1.23	4.04	1.79×10^{-12}	5.19	4.01×10^{-10}
8.0	(a)	0.40	5.06	6.28×10^{-8}	0.42	5.08	1.05×10^{-7}	0.42	4.90	2.07×10^{-7}	0.39	4.89	2.06×10^{-8}	6.18	9.00×10^{-7}
	(b)	1.31	3.91	1.99×10^{-14}	1.35	3.98	1.85×10^{-13}	1.34	3.96	1.14×10^{-10}	1.29	3.53	3.89×10^{-14}	5.00	2.80×10^{-12}
10.0	(a)	0.57	4.85	2.11×10^{-10}	0.60	4.95	1.56×10^{-9}	0.56	4.85	3.59×10^{-8}	0.57	4.62	7.68×10^{-9}	5.85	3.08×10^{-8}
	(b)	1.41	3.54	1.79×10^{-17}	1.39	3.58	1.85×10^{-16}	1.42	3.00	1.52×10^{-11}	1.45	3.29	4.82×10^{-15}	4.91	4.19×10^{-15}
12.0	(a)	0.68	4.82	7.44×10^{-12}	0.69	4.88	5.70×10^{-12}	0.71	4.73	4.32×10^{-9}	0.63	4.68	1.42×10^{-11}	5.79	8.61×10^{-10}
	(b)	1.47	3.01	3.41×10^{-19}	1.44	3.12	4.03×10^{-18}	1.46	2.82	2.40×10^{-12}	1.47	2.89	2.98×10^{-18}	4.80	6.08×10^{-19}

(a)=first wave/peak ; (b)=second wave/peak.

TABLE 2—TYPICAL KINETIC DATA OF NIFURAKEL

Concn. = 0.5 m*M*

Supporting electrolyte pH		D.C. Polarography Drop time=3 s			Cyclic voltammetry Scan rate=40 mV s^{-1}			A.C. polarography Drop time=3 s			Differential pulse polarography Drop time=2 s			Rotating disk voltammetry Sweep rate=50 mV s^{-1}	
		$-E_{1/2}$ V	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}	$-E_p$ V	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}	$-E_s$ V	$D\times10^5$ cm^2s^{-1}	k_s cm^{-1}	$-E_m$ V	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}	$D\times10^5$ cm^2s^{-1}	$k^\circ_{f,h}$ cm^{-1}
2.0	(a)	0.06	5.44	2.44×10^{-4}	0.09	5.55	3.08×10^{-4}	0.07	5.33	2.79×10^{-2}	0.06	5.29	4.32×10^{-5}	6.99	9.32×10^{-3}
	(b)	0.83	4.76	3.06×10^{-7}	0.85	4.94	8.56×10^{-8}	0.90	4.68	7.44×10^{-4}	0.88	5.18	5.62×10^{-8}	5.17	3.24×10^{-6}
4.0	(a)	0.12	5.33	1.45×10^{-5}	0.17	5.39	4.98×10^{-5}	0.15	5.29	3.56×10^{-3}	0.08	5.25	6.14×10^{-6}	6.91	5.59×10^{-4}
	(b)	0.98	4.62	4.72×10^{-9}	0.98	4.82	4.74×10^{-10}	0.98	4.50	4.02×10^{-6}	0.97	5.13	8.82×10^{-9}	5.10	1.37×10^{-7}
6.0	(a)	0.28	5.23	7.38×10^{-6}	0.29	5.29	9.08×10^{-6}	0.30	5.21	9.05×10^{-4}	0.27	5.18	3.80×10^{-7}	6.70	2.31×10^{-5}
	(b)	1.12	4.20	8.36×10^{-11}	1.18	4.32	5.76×10^{-12}	1.18	4.17	8.14×10^{-7}	1.19	5.05	1.08×10^{-10}	5.05	4.97×10^{-9}
8.0	(a)	0.39	5.08	4.59×10^{-8}	0.36	5.09	5.80×10^{-7}	0.42	4.99	3.59×10^{-5}	0.35	5.04	5.11×10^{-8}	6.07	5.80×10^{-7}
	(b)	1.25	2.92	5.33×10^{-12}	1.24	3.01	3.84×10^{-13}	1.25	2.97	2.46×10^{-9}	1.20	4.90	6.72×10^{-11}	4.93	8.33×10^{-10}
10.0	(a)	0.48	4.99	8.50×10^{-9}	0.49	4.96	2.31×10^{-9}	0.53	4.91	7.65×10^{-7}	0.48	4.93	7.78×10^{-9}	5.95	7.05×10^{-8}
	(b)	1.37	2.80	3.18×10^{-14}	1.36	2.95	1.96×10^{-15}	1.38	2.38	8.01×10^{-11}	1.34	4.86	2.15×10^{-14}	4.90	2.01×10^{-12}
12.0	(a)	0.63	4.91	2.05×10^{-11}	0.63	4.92	6.75×10^{-11}	0.61	4.97	3.33×10^{-9}	0.58	4.89	7.90×10^{-10}	5.88	6.73×10^{-8}
	(b)	1.50	2.73	1.02×10^{-18}	1.51	2.83	9.01×10^{-18}	1.50	2.01	4.21×10^{-14}	1.47	4.84	3.43×10^{-18}	4.85	9.80×10^{-16}

(a)=First wave/peak ; (b)=second wave/peak.

TABLE 3

Compd.	Peak potential V	Supporting electrolyte pH	Pulse amplitude	Drop time s
Nifurtimox	−1.06	4.0	50	2
Nifurakel	−0.97	4.0	50	2

The relative standard deviation and correlation coefficients (for 10 replicants) are found to be 1.35% and 0.947 for nifurtimox and 1.42% and 0.996 for nifurakel respectively.

The above described procedure was successfully employed for the determination of the title compounds in different pharmaceutical dosage forms without any separation. The assay results are presented in Table 4. The results of the proposed method agree well with the manufacture's assay values. Further, the recoveries which are in the range 97.99−98.85%, indicate the high accuracy and reproducibility of the proposed method.

TABLE 4—ASSAY OF NIFURTIMOX AND NIFURAKEL DOSAGE FORMS (TABLET) BY DIFFERENTIAL PULSE POLAROGRAPHY

Pulse amplitude=50 mV, drop time=2 s.

Compd.	Trade name	Labelled amount mg	Amount found mg	Recovery %	Standard deviation
Nifurtimox	Lampit	10	9.98	99.80	0.019
	Lampit	15	14.77	99.50	0.024
Nifurakel	Magmilor	10	9.06	99.60	0.015
	Maimiror	15	14.70	97.99	0.031
	Inimur	10	9.985	99.85	0.027

References

1. M. BOCK, A. HABERKORN, H. HERLINGER, K. H. MAYER and S. PATERSEN, *Trypanosma Cruzi*, *Arzneim. Forsch.*, 1972, **22**, 1564 ; M. C. DODD and W. B. STILMAN, *J. Pharm. Exp. Ther.*, 1944, **82**, 11 ; D. L CR\MER, *J. Bacteriol.*, 1947, **54**, 119 ; E PITZUS, *J. Int. Med. Res.*, 1978, **6**, 414 ; A. WILDMEVER, *Arzneim-Forsch.*, 1974, **24**, 937.
2. J. STRADINs and R. GAVARS, *Vses. Naichm Konf. Khim. Technol. Furanovgk. Soedin.*, 1978, **3**, 22 ; W. KEMULA and ZAWADOWSKHA, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.*, 1975, **23**, 275 ; E. V. GORCHEVIKOVA and L. YA. PAVLIENKO, *Frmatsiya*, 1981, **30**, 26 ; S. J. REDDY and C. S. REDDY, *Indian J. Environ. Protec* , 1989, **9**, 598 ; S. J. REDDY and C. SRIDEVI, *Electroanalysis*, 1991, **3**, in the press ; F. SUMMA, *J. Pharm. Sci.*, 1965, **54**, 442.
3. A. K. MISHRA and K. D. GODE, *Analyst*, 1985, **110**, 1373.
4. S. J. REDDY and C. SRIDEVI, *Bull. Electrochem.*, 1990, **6**, 847.
5. A. MORALES, R. PABLA and M. I. TORAL, *Analyst*, 1987, **112**, 971.
6. A. K. MISHRA and K. D. GODE, *Analyst*, 1985, **110**, 31.
7. B. G. LEVICH, *Acta Physicochim. URSS*, 1942, **17**, 257 ; L. VIGNOLI, B. COISTAU, F. GOUEZO and C. FABRE, *Chim. Anal. (Paris)*, 1963, **45**, 439.