

Cyclic voltammetric study of biologically active metal ions with norfloxacin

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The interaction of biologically active metal ions:Co(II), Cr(III), Fe(III), Mn(II) and Cu(II) with Norfloxacin (NRF) has been studied using cyclic voltammetric technique, in the potential range +1.5 to -1.0V with DMF and NaClO₄ as supporting medium and platinum as working electrode. The voltammetric pattern shows characteristic peaks with NRF, however, the peaks of the free metal ions are influenced by the presence of NRF indicating complexation with the metal ions. The results show that NRF forms complexes with metal ions (M-NRF) in 1:2 ratio. The values of stability constant (K_C) and thermodynamic parameters ΔG° , ΔH° and ΔS° for complex formation are evaluated. These findings reveal the possible use of various metal ions for analytical and chemotherapeutic investigations with NRF.

The chemistry of metal ions in biological system can be better explained in terms of their co-ordination chemistry. In recent years, there is an increasing interest in the use of metal complexes in medicine for therapeutic applications. Most of the transitional metals are present in very low concentrations *in vivo* and their environment can be considerably altered when a therapeutically effective dose of drug is administered. It has been observed that the formation of a complex between the metal ions and the drug has a remarkable effect on the activity of the drug¹.

Norfloxacin[1-ethyl(-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperaziny)) quinoline-3 carboxylic acid] [NRF], is a synthetic broad-spectrum fluoroquinolone antibacterial agent for oral administration. It has carboxylic, 4-oxo and three basic nitrogen sites. It is likely that any of these could be the potential binding sites with metal ions. It has been reported that the activity of the metal-norfloxacin complex is stronger than that of NRF itself².

Determination of trace amounts of Fe(III) in presence of NRF by spectrophotometric method³ has been reported. However, the study on interaction of other biologically active metal ions with NRF by electroanalytical methods has not been done. Cyclic voltammetric technique is used in the present study to investigate the behaviour of various metal ions in the presence of NRF.

Experimental Procedure

Materials—NRF (Plama lab, India) was purified by CH₂Cl₂ / CH₃OH (m.p.227-228°C) before use. All

reagents used were of analytical grade (Merck) and the solutions were prepared by using double distilled water. The stock solutions [5×10^{-3} M] of Co(II), Cr(III), Fe(III), Mn(II) and Cu(II) were prepared.

Cyclic Voltammetry—Cyclic voltammograms were obtained in undivided glass cell of 50 mL capacity with three electrodes system consisting of a platinum wire (0.05cm²), platinum foil (1cm²) and a saturated calomel as working, counter and reference electrodes respectively. Cyclic voltammetric experiments were carried out using definite concentration of NRF [1×10^{-3} M] and metallic ions [5×10^{-4} M] in DMF-water mixture (1:1 v/v) with NaClO₄ [1×10^{-2} M] as supporting electrolyte at a scan rate of 50mV s⁻¹. Experiments were also conducted at different temperatures (288-318K). After each run, the working electrode was rinsed with water and electrically pre-treated to obtain reproducible results. The solutions were purged with purified nitrogen gas⁴ for 8-10 min before each experiment. Voltammograms were recorded with a scanning potentiostat (EG & G 326A, U.S.A). All experiments were repeated to ensure reproducibility. Fresh solution was used for each experiment.

Results

Fig.1 represents the cyclic voltammogram on platinum in DMF-water mixture containing NaClO₄ as supporting electrolyte and 1×10^{-3} M NRF scanned from +1.5 to -1.0V at a scan rate 50mVs⁻¹. The forward scan exhibits a cathodic peak C_N at -0.097V. The reverse scan showed anodic peak (OX) at +1.0V. The blank medium (DMF/NaClO₄) did not show any significant peak during the anodic and cathodic scans in the selected potential range.

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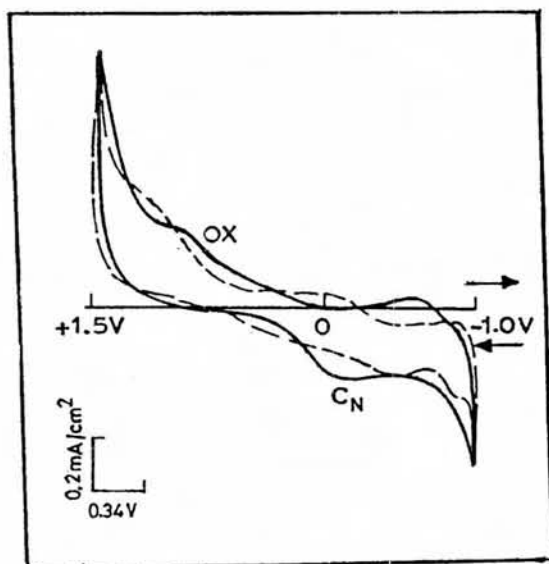


Fig. 1—Cyclic voltammogram of NRF [1×10^{-3} M] at platinum electrode in the potential range +1.5 to -1.0V at the scan rate 50 mV s^{-1} . --- DMF+NaClO₄ (blank), — DMF+NaClO₄+NRF *

Biologically active metal ions: Fe(III), Cu(II), Mn(II), Cr(III) and Co(II) were chosen for detailed study to know their interactions with NRF at constant temperature ($298 \pm 0.1 \text{ K}$). Voltammograms of metal ions in the absence and presence of NRF are shown in Fig. 2 with different metal to NRF ratios. It is observed that all the metal ions show their respective redox peaks, but in the mole ratio of 1:1 (M-NRF), the peak currents (I_p) are lowered and the peak potentials (E_p) are shifted. When the mole ratio of M-NRF is increased to 1:2, the voltammogram peaks further get reduced. The peaks at c_1 and a_1 are disappeared and emerged at c_{II} and a_{II} . In all these cases, the anodic peak is less distinct than the cathodic peak in the potential region of -0.3 to -0.4V. In the cases of Fe, Mn and Cr, the E_p values are shifted cathodically while in case of Cu, it is shifted anodically. The peak potentials of the free metal ions E_{pf} (free) and the complexed ions E_{pc} (Complex) are presented in Table 1.

Discussion

NRF has many active sites of which the carboxylic and the carbonyl groups are more susceptible to oxidation. When the voltammogram of NRF is recorded from +1.5 to -1.0V, only one reduction peak C_N is observed. This may be due to quinolone group which on reduction gives a radical species⁵ as shown in scheme (i).

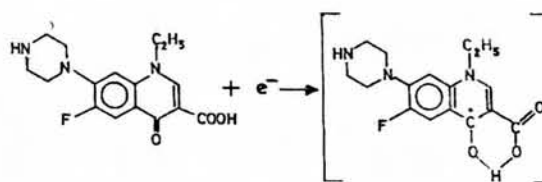
The radical species is stabilized due to the resonance of the electron in the aromatic ring. The increasing currents at extreme negative and positive

Metallic ions	Peak Potentials (V)			
	Free metal ions (E_{pf})		Complex (E_{pc})	
	Cathodic	Anodic	Cathodic	Anodic
Fe(III)	0.336	0.576	-0.318	0.198
	-0.417	-0.280		
Cu(II)	-0.041	0.336	0.233	0.644
			-0.383	
Mn(II)	0.840	1.257	-0.300	0.712
	0.111	0.840		
Cr(III)	0.215	0.458	0.047	0.689
			-0.410	
Co(II)	-0.177	-0.797	-0.193	0.790
	-0.781	-0.244		

Table 2—Values of K_c for metal -NRF complexes (1:2) at 298K

Complex	Colour	K_c
Co(II)-NRF	Dark Pink	0.6×10^1
Cr(III)-NRF	Green	4.25×10^8
Cu(II)-NRF	Greenish Blue	3.74×10^{11}
Mn(II)-NRF	Yellow	8.10×10^{13}
Fe(III)-NRF	Red	7.76×10^{32}

potentials is due to the hydrogen and oxygen evolution respectively.



The series of voltammograms in Fig. 2 shows the redox behaviour of the metal ions. The shift in the E_{pc} and decrease in the I_p with the addition of NRF (1:1 ; M-NRF) shows that the complex formation is not complete under this condition. On increasing the ligand ratio (M:NRF ; 1:2), the metal ion peaks which are less distinct disappear showing the complete complex formation. However, most of the cyclic voltammograms of metal-NRF complexes, consist of a common cathodic peak in the region -0.3 to -0.4V which is similar to the free NRF under comparable experimental conditions. The persistence of this peak could be due to quinolone group present in NRF molecule which remain free, even after complexation. The probable site of complexation at the ligand could be through the oxygen atoms of the two carboxylic groups as shown in scheme (ii).

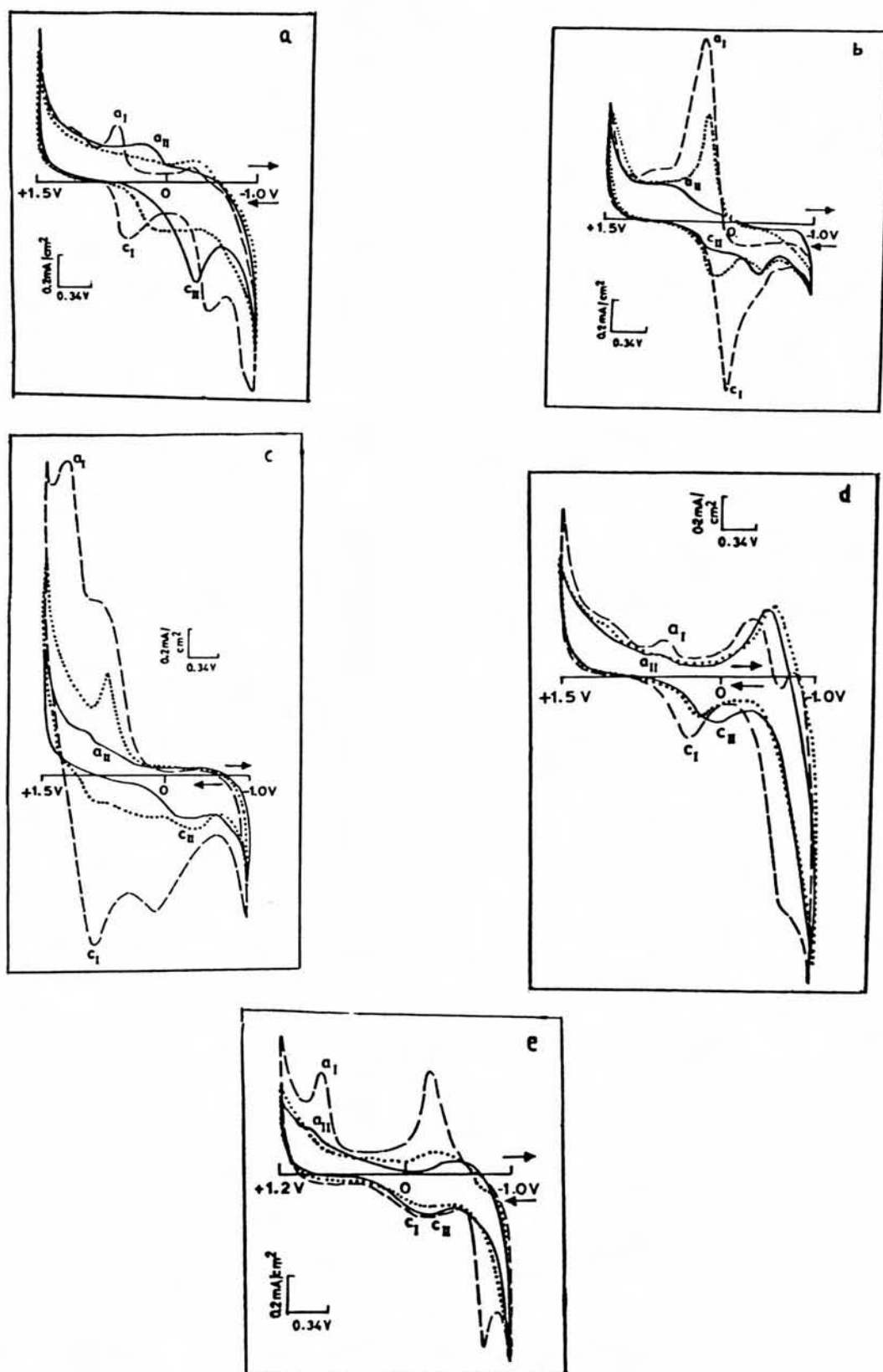
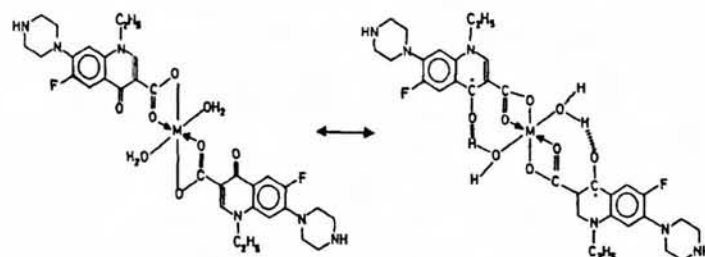


Fig. 2—Cyclic voltammograms of metal-NRF in the ratio 1:1 and 1:2 obtained using platinum electrode in the potential range +1.5 to -1.0V at the scan rate 50 mV s^{-1} .

(a). ---Fe(III), [Fe:NRF] ... (1:1), — (1:2); (b). ---Cu(II), [Cu:NRF] ... (1:1), — (1:2); (c). ---Mn(II), [Mn:NRF] ... (1:1), — (1:2); (d). ---Cr(III), [Cr:NRF] ... (1:1), — (1:2); (e). ---Co(II), [Co:NRF] ... (1:1), — (1:2)



Scheme (iii)

Using the values of cathodic peak potentials, the stability constant (K_C) for each complex at 1:2 molar ratio (M-NRF) is evaluated from the cyclic voltammetric data⁶ using the equation,

$$\log K_C = 0.434 ZF / RT \Delta E_p$$

Z is the charge of the metal ions, F is the faraday, R is the gas constant, T is the temperature and ΔE_p is the difference in the peak potentials without and with NRF. The values of stability constant of complexes are given in Table 2. K_C of the Fe(III) has maximum value showing better complexation while Co(II) has the least. For each complex, the values of ΔG^0 is calculated from the equation,

$$\Delta G^0 = -2.303 RT \log K_C$$

Voltammograms were also obtained for some of the complexes at different temperatures (288-318K). ΔS^0 values for complexation are evaluated from the dependence of ΔG^0 on temperature. ΔH^0 values are calculated from the Gibbs Helmholtz's equation. ΔG^0 , ΔS^0 and ΔH^0 values are given in Table 3. These thermodynamic parameters (Table 3) show that NRF

can form stable complexes with some of the biologically active metal ions.

Conclusion

The cyclic voltammetric studies revealed the complexation of NRF with biologically active metal ions⁷ and also oxidation-reduction behaviour of complexes. The thermodynamic parameters for complex formation revealed the relative stability of each complex under the selected experimental conditions.

References

- 1 Fei Gao, Pin Yang, Jun xie & Hongfei wang, *J Inorg Biochem*, 60 (1995) 61.
- 2 Buckingham D A, Clark C R, & Nangia A, *Aust J Chem.*, 43 (1990) 301.
- 3 Bhowal S K & Das T K, *Anal Lett*, 24(1) (1991) 25.
- 4 Kulkarni C L, Scheer B J & Rusling J F, *J Electroanal Chem*, 140 (1982) 57.
- 5 Dosol D, *A Handbook for Electrochemists in Industry and Universities* (Elsevier Scientific Publishing Company, New York), 1975, 255.
- 6 Hamada M Killa, *J Chem Soc, Faraday Trans*, 1,81 (1985) 2659.
- 7 Chen, Liang, Hu & Yuxian, *Bopuxue Zazhi*, 4 (2) (1987) 155.