$$E_J = -\sum_i \frac{RT}{Fz_i} \int_0^1 \frac{|Z_i| \left\{ \lambda_i^A + \left[ \frac{\left[ I^A + x\left( I^B - I^A \right) \right]^{1/3} - I^{A\,1/3}}{I^{B\,1/3} - I^{A\,1/3}} \right] \left( \lambda_i^B - \lambda_i^A \right) \right\}}{\sum_j |Z_j| \left\{ \lambda_j^A + \left[ \frac{\left[ I^A + x\left( I^B - I^A \right) \right]^{1/3} - I^{A\,1/3}}{I^{B\,1/3} - I^{A\,1/3}} \right] \left( \lambda_j^B - \lambda_j^A \right) \right\} \left[ M_j^A + x\left( M_j^B - M_j^A \right) \right]} \times$$

$$\left\{ \left\{ \left[ \frac{\left( \ln \gamma_i^B - \ln \gamma_i^A \right) \left( I^B - I^A \right)}{\left( I^{B\,1/3} - I^{A\,1/3} \right) 3 \left[ I^A + x\left( I^B - I^A \right) \right]^{2/3}} \right]_s \left[ M_i^A + x\left( M_i^B - M_i^A \right) \right] \right\} + \left( M_i^B - M_i^A \right) \right\} dx$$

Para a resolução da equação desenvolveu um programa computacional que recorre a integrações numéricas. Para aplicação deste programa é necessário um tratamento preliminar dos dados onde deparámos com grande número de dificuldades de ordem prática.

Dada a incapacidade de ultrapassar estas limitações, em tempo útil não foi possível prosseguir o referido tratamento.

A ausência de dados bibliográficos posteriores ao trabalho original sobre a aplicação da equação de Harper, limitou as nossas possibilidades de interpretação dos resultados, sendo neste momento difícil fazer recomendações sobre qual a metodologia experimental ou teórica a seguir para a obtenção de valores de potencial de junção líquida de melhor qualidade em sistemas de pontes mistas.

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# ELECTROCHEMICAL STUDY OF A GROUP OF ANTI-CANCER DRUGS

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## ABSTRACT

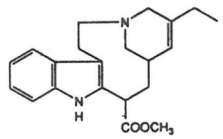
The electrochemical oxidation mechanism of a group of dimeric *Vinca* alkaloid type antineoplastic agents showed that homogeneous chemical reactions are coupled with a multistep electron transfer process that is also dependent on pH. The irreversibility of the process leads to final products that form an unreactive film that strongly adsorbs on the electrode surface. The differences encountered in the anodic oxidation mechanisms of the compounds studied can be explained in relation to their toxic effects.

## INTRODUCTION

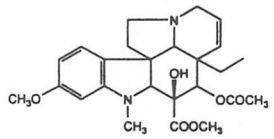
The search for new anti-cancer drugs through chemical synthesis and the isolation of plant extracts has yielded many unusual cytotoxic compounds, but few of these products have had significant impact on clinical chemotherapy due to their very high toxicity. The group of chemotherapeutic drugs studied are used in the treatment of various neoplastic diseases, e.g., Hodgkin's disease, leukemia and solid tumours. They are dimeric indole alkaloid type compounds.

Two of them, vincristine and vinblastine, are naturally occurring alkaloids [1,2] extracted from the ornamental shrub *Vinca rosea* and the other two, 4-desacetylvinblastine and 5'-noranhydrovinblastine are semisynthetic derivatives of vinblastine [3,4]. They were synthesised using a biomimetic-type reaction between the two likely biogenetic precursors of the vinblastine-type compounds, i.e. catharanthine and vindoline [5]. They are linked together in a basic structure comprising an indole and a dihydroindole nucleus and, although the compounds are

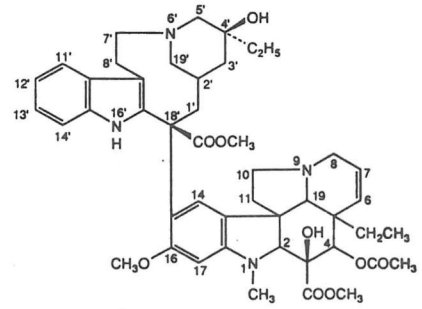
structurally very similar, they differ significantly in their clinical usefulness and clinical toxicity.



Catharanthine



Vindoline



Vinblastine

The cytostatic activity of these bisindole alkaloids is associated with high neurotoxicity and myelosuppressive effects. In order to explain the effect of the minor structural changes on the experimental activity and toxicity observed clinically, a systematic electrochemical study of these compounds was carried out.

## EXPERIMENTAL

### *Chemicals and solutions*

*Vinca* alkaloid solutions were prepared from the comercially available sulphates of vinblastine "Velbe®" (Lilly), 4-desacetylvinblastine "Gesidine®" (Lilly), 5'-noranhydrovinblastine "Navelbine®" (Pierre Fabre) and vincristine "Oncovine®" (Lilly) and were used without any further purification. A stock solution of the alkaloids was prepared in 0.2M NaCl and kept in the fridge (2-8°C). All other reagents were AnalaR grade, the water used for the solutions was tridistilled, once over alkaline



permanganate, and all the experiments were done at room temperature (T=19-22°C) and carried out in buffer solutions.

### *Apparatus and procedures*

The working electrode was a glassy carbon disc of 3.50mm radius, the reference electrode a saturated calomel electrode (SCE) and the auxiliary electrode a platinum foil. Electrode potentials were controlled and currents were measured using a Princeton Applied Research Corp. (PAR) Model 174A Polarographic Analyser with a PAR RE0074 X-Y recorder.

## RESULTS AND DISCUSSION

The electrochemical oxidation of this group of dimeric indole alkaloids at a glassy carbon electrode consists of a multistep electron transfer process coupled with fast proton transfer.

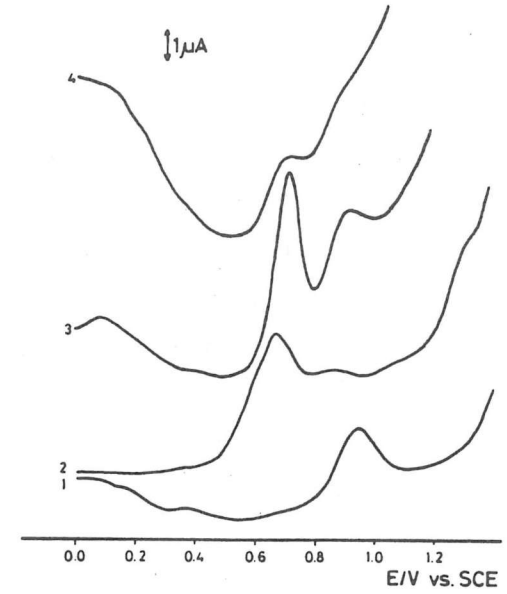



Fig.1 Differential pulse voltammograms in 0.2M NaOAc/ 0.2M HOAc buffer, pH = 4.5, pulse amplitude 50mV, scan rate 5mV $s^{-1}$, of the *Vinca* alkaloids, $10^{-5}$M: (1) vincristine; (2) vinblastine; (3) 4-desacetylvinblastine; (4) 5'-noranhydrovinblastine.

In fact, when studied in different buffer supporting electrolytes, differential pulse voltammograms of this group of *Vinca* alkaloids showed that the anodic oxidation mechanism depends on the pH. The mechanism is a succession of one electron transfer steps with one of thse with a much higher rate constant, perhaps corresponding to the oxidation of the nitrogen of the eight-member ring. Cyclic voltammograms showed that all the steps were irreversible and the products of oxidation adsorb strongly at the electrode surface, as the second cycle could never be observed. The electrochemical results show similarities between the vinblastine derivatives, but differences between these and vincristine. This could account for some of the differences in the pharmacokinetics in patients: vincristine has superior antitumour effects than the others as well as much greater neurotoxicity and myelosuppression side effects.

## CONCLUSIONS

The differences in the electrochemical mechanism observed between the members of this group of alkaloids will help in understanding the mechanism of drug action of this type of compounds and possibly lead to the search for novel chemotherapeutic drugs with an expanded activity spectrum and/or reduced toxicity.

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# VOLTAMETRIC STUDIES OF Co(III) COMPLEXES

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**Abstract**

Voltametric studies of the octahedral Co(III) complexes with a pentadentate ligand (PICDIEN) and a ligand X (X= $Cl^-$, $Br^-$, $H_2O$) in aqueous solution of 0.1M in $KNO_3$, pH 7 at Pt electrode were performed and the corresponding results are presented in this paper.

Experimental values of $E^O$ for the complexes under study were estimated.

Peaks A'/ A at potentials between -0.4 e +0.4 V *vs* e s c were attributed to the reduction and oxidation of Co(III), while peaks B/B' at $E^O$= +0.90 V *vs* e s c are most probably due to the oxidation of $Br^-$.

## 1-INTRODUÇÃO

A quantidade e diversidade de estudos efectuados com compostos cuja esfera de coordenação apresenta ligandos de denticidade cinco tem versado essencialmente sobre dois aspectos; por um lado o estudo das suas reacções de hidrólise com vista a aprofundar o conhecimento dos mecanismos reaccionais, por outro lado desenvolver um aspecto interessante destes compostos, largamente estudado por Martell *et al*[1,2] que consiste na interação dos ligandos deste tipo, em que o átomo doador é exclusivamente o azoto, com iões metálicos da primeira série de transição, concluíndo que os complexos de cobalto (II), apresentavam uma tendência excepcional para a captação, a valores de pH baixos, de oxigénio molecular.

Martell *et al*, estabeleceram uma relação qualitativa entre o potencial de oxidação do complexo e a sua tendência para uma ligação reversível ao oxigénio molecular. Estes estudos revelaram-se bastante úteis para a compreensão do processo de transporte de oxigénio, a nível biológico, apesar dos sistemas naturais utilizarem

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