

# Electrochemical behaviour of cis-platin at carbon paste and platinum electrodes

F. MEBSOUT, J.-M. KAUFFMANN and G. J. PATRIARCHE\*

*Free University of Brussels (U.L.B.), Pharmaceutical Institute, Campus de la Plaine 205/6, Bd. du Triomphe, B-1050 Brussels, Belgium*

---

**Abstract:** The electrochemical behaviour of a platinum(II) anti-tumour drug (cis-platin) has been investigated at the platinised platinum and carbon paste electrodes using cyclic voltammetry. Measurements performed in neutral aqueous media at the platinised platinum electrode as a function of free chloride ions have enabled the nature of oxidised species to be established and the sensitive determination of the molecule within the range of concentration  $1 \times 10^{-3}$ – $1 \times 10^{-5}$ M to be realised.

Use of the carbon paste electrode offers interesting insights into the redox stability of the molecule and allows the hydrolytic degradation of cis-platin to be followed as a function of time.

**Keywords:** *Anti-tumour platinum(II) agents; cis-platin; cyclic voltammetry.*

---

## Introduction

Cis-dichlorodiamineplatinum(II) (cis-platin, cis-DDP) has been used widely as a potent anti-cancer drug since its discovery in 1965 [1] and still plays the principal rôle among the metal-containing anti-tumour drugs [2–5].

From an electrochemical point of view, cis-platin as well as other platinum species have been submitted to several investigations at platinum [6–10], glassy carbon [11–14] and dropping mercury [15–17] electrodes for analytical and mechanistic purposes.

Until now, the study of this interesting molecule has not yet been carried out at carbon paste electrode and on stationary platinum electrodes preconditioned with fresh platinised platinum [18–19]. Using the carbon paste electrode which has a larger potential range than other electrodes, it has been possible to observe a cis-platin hydrated structure which was not described by previous authors nor by G. M. Schmid in a recent publication [14]. In a previous study [18] devoted to the redox behaviour in neutral aqueous media of a derived chemotherapeutic agent (JM8, carboplatin), it has been shown that the electroreduction is not feasible at platinum and carbon paste electrodes. However, oxidation proceeds readily permitting quantitative analysis of the molecule. Moreover, it has been shown that the reduction of the oxidised products does not regenerate the carboplatin molecule but gives rise to cis-platin structures.

---

\*To whom correspondence should be addressed.

Furthermore it was observed that the greater the number of halide ligands in the carboplatin(IV) derivatives, the easier is their electroreduction.

The present work is directed towards studying the redox behaviour of aqueous cis-platin solutions in the absence and in the presence of free chloride ions, insofar as these ions play a prominent part both biologically [20] and chemically [7] in the reactivity of the molecule.

Comparative investigations have been performed using platinum and carbon paste electrodes, the latter allowing interesting mechanistic observations due to its inherent surface inertness over a large potential range.

## Experimental

### *Instrumentation*

Voltammetric measurements were carried out using the same equipment as described earlier [18].

### *Reagents and solutions*

Cis-platin was a generous gift from the Bristol-Myers International Corp. (Brussels, Belgium). To minimise hydrolysis care was taken to prepare freshly the solutions to be analysed by direct dissolution in the supporting electrolyte. The measurements were carried out as soon as possible after making up the solutions.

Supporting electrolytes were either 0.1 M sodium perchlorate or 0.1 M sodium sulphate and were prepared with pure grade reagents (Merck, PA). Traces of oxygen were removed from the solution to be analysed by purging with purified nitrogen. The chloride effect on the cis-platin redox behaviour was investigated using sodium chloride.

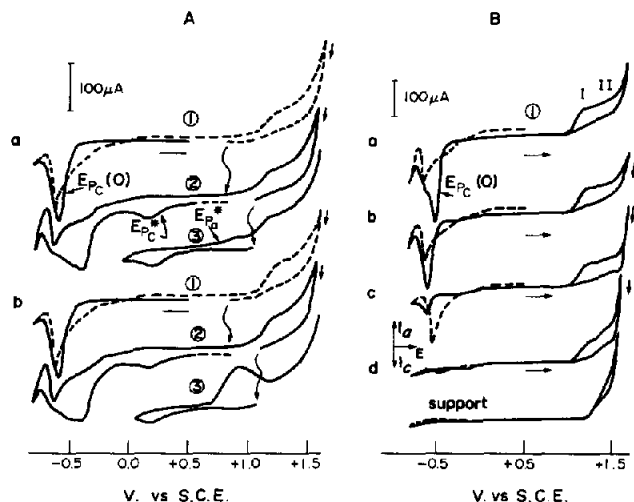
### *Cleaning and pretreatment of the working electrodes*

The platinum electrode was chemically [18] and electrochemically [10, 18, 21] cleaned in order to obtain reproducible current-potential curves characteristic of a clean electrode. Modification of the carbon paste electrode (CPE) involved the electro-deposition of platinum from cis-platin onto the carbon surface. The procedure involved the use of cyclic voltammetry with a  $1 \times 10^{-3}$  M cis-platin-0.1 M sodium perchlorate solution cycled between  $-0.8$  V and  $+1.5$  V at a sweep rate of  $20 \text{ mV s}^{-1}$  during 12 min. The electrodeposition time was carefully selected and carefully controlled in order to avoid too large an amount of platinum particles being deposited. The electrodes were thoroughly rinsed with doubly-distilled water and used as soon as ready. The platinum surface activation was as described earlier [18].

## Results and Discussion

### *Cyclic voltammetry at the CPE*

In contrast to JM8 [18], reduction of cis-platin occurs at the CPE. In Fig. 1 are reported the curves obtained for  $1 \times 10^{-3}$  M cis-platin in the presence and in the absence of free chloride ions as a function of initial scan direction. Investigations of cathodic potentials, with an initial potential of  $+0.5$  V, reveals a sharp reduction peak  $E_{p_c}(0)$  the intensity of which is diffusion controlled in the scan rate range of  $1-10 \text{ mV s}^{-1}$ . The relationship however deviates from the linearity at higher scan rates (Fig. 1A). With increasing chloride ion concentration, the peak potential remains constant but the



**Figure 1**

Cyclic voltammograms of  $1 \times 10^{-3}$  M cis-platin in 0.1 M NaClO<sub>4</sub> at the CPE as a function of initial scan direction. Starting potential = +0.5 V, scan rate  $\nu = 20 \text{ mV s}^{-1}$ . 1 = first run, 2 = second run, 3 = third run. A, initial cathodic scan; B, initial anodic scan. a, [Cl<sup>-</sup>] = 0; b, [Cl<sup>-</sup>] =  $4 \times 10^{-3}$  M; c, [Cl<sup>-</sup>] =  $1 \times 10^{-1}$  M; d, [Cl<sup>-</sup>] = 1 M.

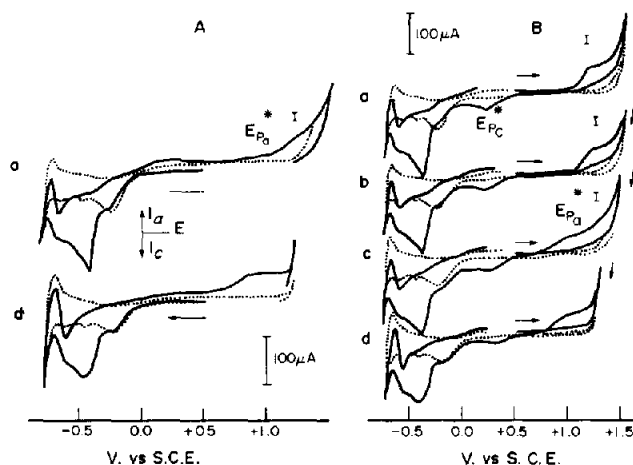
intensity decreases progressively. Maintaining the potential at  $E_{p_c}(0)$ , the formation of bubbles at the electrode surface is observed. Reversing the scan direction after  $E_{p_c}(0)$  produces hysteresis phenomena related to surface heterogeneity giving rise to overlapping curves. However the peak  $E_{p_c}(0)$  appears to be irreversible in the range of scan rates investigated ( $5\text{--}500 \text{ mV s}^{-1}$ ).

If the study of the oxidation of cis-platin is performed at an initial potential of +0.5 V, two anodic peaks  $E_{p_a}(I)$  and  $E_{p_a}(II)$  are detected, the second being embedded in solvent evolution (Fig. 1B). The electrooxidative process is diffusion controlled, moreover peak intensity and potential are independent of chloride ions concentration. Reversing the scan direction produces no well-defined corresponding cathodic peak. Indeed reduction of the oxidised species occurs in a slight and spread out cathodic current starting at about +0.2 V, which is followed by a sharp reduction peak located at potentials corresponding to cis-platin reduction [ $E_{p_c}(0)$ ]. The presence of chloride ions produces only a slight increase of the first reduction step but drastically limits  $E_{p_c}(0)$  formation at concentrations higher than  $1 \times 10^{-1}$  M.

Several cycles conducted on the same surface, scanning first in the cathodic region, enabled the detection of new peaks formed as a consequence of the surface modification. During the second run a well-defined cathodic peak  $E_{p_c}^*$  related to  $E_{p_a}(I)$  was detected (Fig. 1A). By reversing the scan direction immediately after  $E_{p_c}^*$  a corresponding catalytic oxidation peak  $E_{p_a}^*$  appears. The shape of this quasi-reversible couple is particularly well-marked in the presence of chloride ions. With continued cycling, peak intensity of the newly developed pair increases as well as the reversibility of the reaction whilst potential ranges are narrowed.

#### *Cyclic voltammetry at the modified carbon paste electrode (MCPE)*

As for JM8, cyclic voltammetry at the MCPE exhibits shapes attributed to the heterogeneous nature of the Pt/C surface [18]. Cyclic voltammograms obtained with the



**Figure 2**

Cyclic voltammograms of  $1 \times 10^{-3}$  M cis-platin in 0.1 M NaClO<sub>4</sub> at the MPCE as a function of initial scan direction. Starting potential = +0.5 V, scan rate  $\nu = 20 \text{ mV s}^{-1}$ , dotted lines = supporting electrolyte. A, initial cathodic scan; B, initial anodic scan. a, [Cl<sup>-</sup>] = 0; b, [Cl<sup>-</sup>] =  $4 \times 10^{-3}$  M; c, [Cl<sup>-</sup>] =  $1 \times 10^{-4}$  M; d, [Cl<sup>-</sup>] = 1 M.

supporting electrolyte show the typical current–potential curves of the platinum deposit; with, in the negative region, a peak at  $-0.2 \text{ V}$  corresponding to surface oxide reduction [21] followed by the characteristic reversible hydrogen adsorption–desorption peaks. Anodically it is possible to detect surface oxide formation (Fig. 2, dotted lines).

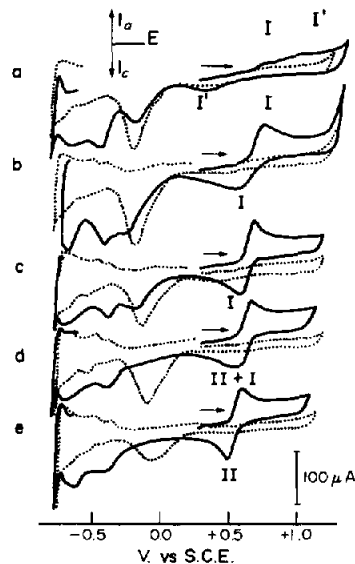
Reduction of cis-platin at the MCPE shows, additionally to the oxide reduction peak a broad current increase in the hydrogen evolution region (Fig. 2A). On the reverse scan, oxidation of cis-platin occurs in two distinct peaks  $E_{p_a}^*$  and  $E_{p_a}(\text{I})$ , peak  $E_{p_a}(\text{II})$  being masked owing to the restricted oxidative range available. As the concentration of chloride ions increases, the intensity of cathodic current is decreased slightly whilst  $E_{p_a}^*$  increased.

Oxidation of cis-platin at the MCPE as a function of free chloride ions is illustrated in Fig. 2B. Peak  $E_{p_a}(\text{I})$  is still present and occurs at the same potential as the CPE, whilst peak  $E_{p_a}(\text{II})$  is masked by rapid solvent oxidation. Additionally to  $E_{p_a}(\text{I})$ , peak  $E_{p_a}^*$  appears to a significant extent only when chloride ion concentrations exceed  $1 \times 10^{-2}$  M. On the reverse scan, the catalytic reduction of  $E_{p_a}(\text{I})$  and  $E_{p_a}^*$  is observed giving  $E_{p_c}^*$ , the process is followed by a surface oxide reduction peak and a broad intense current situated in the hydrogen adsorption region. Increasing chloride ions concentration produces no significant cathodic peak modification.

#### *Cyclic voltammetry at the platinised platinum electrode*

Careful control of the surface state as well as immediate use of the electrode are two essential parameters in order to yield high electron transfer and reproducible current–potential curves [22]. In Fig. 3, voltammograms of  $1 \times 10^{-3}$  M cis-platin in 0.1 M NaClO<sub>4</sub> as a function of chloride ions concentration are shown. In the absence of free halide ion, two anodic peaks are obtained:  $E_{p_a}^*(\text{I})$  and  $E_{p_a}^*(\text{I}')$ . On the reverse scan, a cathodic peak  $E_{p_c}^*(\text{I}')$  related to  $E_{p_a}^*(\text{I}')$  is detected and in the negative potential side, surface oxide reduction and hydrogen adsorption peaks are observed. The presence of chloride ion produces a marked increase in peak  $E_{p_a}^*(\text{I})$  intensity as well as in the

**Figure 3**  
Cyclic voltammograms of  $1 \times 10^{-3}$  M cis-platin in 0.1 M NaClO<sub>4</sub> at the platinised platinum electrode as a function of chloride ions concentration. Scan rate  $\nu = 20 \text{ mV s}^{-1}$ , dotted lines = supporting electrolyte. a,  $[\text{Cl}^-] = 0$ ; b,  $[\text{Cl}^-] = 4 \times 10^{-3}$  M; c,  $[\text{Cl}^-] = 1 \times 10^{-2}$  M; d,  $[\text{Cl}^-] = 1 \times 10^{-1}$  M, e,  $[\text{Cl}^-] = 1 \text{ M}$ .



reversibility of the reaction, whilst  $\text{Ep}_a^*(\text{I}')$  is no longer observed. Measurements realised as a function of scan rate indicate a diffusion controlled redox process in the range  $5\text{--}500 \text{ mV s}^{-1}$ . The cathodic peak  $\text{Ep}_c^*(\text{I})$  corresponding to  $\text{Ep}_a^*(\text{I})$  appears once free chloride ions are present. A new reduction peak  $\text{Ep}_c^*(\text{II})$  appeared at chloride ion concentration greater than  $1 \times 10^{-1}$  M at the expense of peak  $\text{Ep}_c^*(\text{I})$  and by 1 M chloride concentration peak  $\text{Ep}_c^*(\text{II})$  alone is observed.

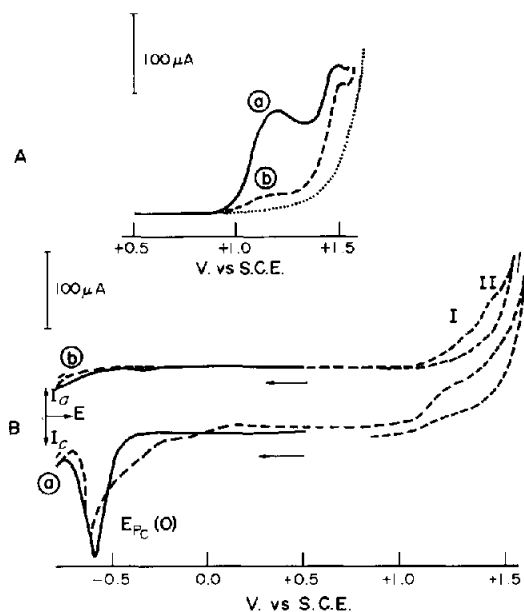
#### *Study of the degradation of cis-platin solutions as a function of time*

It is well known that when cis-platin dissolved in water, chloride ions are displaced in a stepwise manner by water molecules [20]. As this hydrolysis reaction proceeds readily in aqueous media [25] and may influence the voltammetric behaviour, measurements have been performed on 4-day-old solutions containing  $1 \times 10^{-3}$  M cis-platin in 0.1 M NaClO<sub>4</sub>.

Figure 4A shows that the shape of the curves at the CPE is markedly different after solution ageing. Indeed, due to hydrolysis of cis-platin we observe progressive  $\text{Ep}_a(\text{I})$  diminution while  $\text{Ep}_a(\text{II})$  is increasing. As the pH of the aged solution has dropped to 4, a study as a function of pH has been carried out. Measurements realised at various acid concentrations have shown no pH incidence on the anodic shape. On the cathodic side, reduction of the hydrated cis-platin species is markedly inhibited (Fig. 4B).

At the platinised platinum electrode, oxidation of cis-platin occurs readily, peak  $\text{Ep}_a^*(\text{I})$  increases during ageing of the solution masking peak  $\text{Ep}_a^*(\text{I}')$ . Such an increase in peak  $\text{Ep}_a^*(\text{I})$  intensity as a function of time may be related to the catalytic properties of free chloride ions liberated by hydrolysis of cis-platin [10].

The interpretation of the results reported above suggested a significantly different voltammetric behaviour of cis-platin compared to JM8 [18]. Indeed reduction of cis-platin, giving rise in a common step to platinum particles deposition and hydrogen evolution [ $\text{Ep}_c(0)$ ], is observed on the CPE in contrast to JM8. At elevated scan rates the amount of platinum deposited diminishes resulting in a decreased peak of  $\text{Ep}_c(0)$ .



**Figure 4** Differential pulse voltammograms,  $\nu = 5 \text{ mV s}^{-1}$  (A) and cyclic voltammograms  $\nu = 20 \text{ mV s}^{-1}$  (B) of  $1 \times 10^{-3} \text{ M}$  cis-platin in  $0.1 \text{ M NaClO}_4$  at the CPE. a, cis-platin fresh solution; b, cis-platin aged solution.

Reproducibility of peak  $E_{p_c}(0)$  intensity is poor, the coefficient of variation calculated on different surfaces ( $N = 10$ ) is 10%, a phenomenon related to the CPE inherent porous nature [23]. Study of the function of cis-platin ageing, supports the evidence that peak  $E_{p_a}(I)$  corresponds to the oxidation of cis-platin and  $E_{p_a}(II)$  to the oxidation of a cis-platin hydrated species with formation of platinum (IV) products.

Reduction of the oxidised molecules at the CPE as a function of chloride ion concentration is not as well-defined as in the case of JM8, permitting no mechanistic interpretations. At the MCPE, reduction of the oxidised products to the corresponding platinum(II) molecules occurs at the particulate platinum deposit in step  $E_{p_c}^*$ . The cathodic process is only slightly influenced by the presence of free chloride ions and proceeds readily even in the absence of free halides, a phenomenon which might be explained by the in-plane bridging effect [10]. The second cathodic step giving rise to platinum electrodeposition is disturbed by concomitant surface oxide reduction but a broad current is observed which might correspond to a catalytic hydrogen evolution at the platinum deposit [24, 12].

At the CPE surface, the influence of free chloride ions is negligible, however, if platinum has been deposited the reactivity of cis-platin is greatly enhanced; oxidation occurs preferentially on deposited platinum at  $1 \times 10^{-1} \text{ M}$  in chloride ions and the reversibility of peaks  $E_{p_a}^*/E_{p_c}^*$  is increased. In the cathodic mode, at high chloride ion concentrations the cis-platin(II) reduction step is inhibited but reduction of platinum(IV) species is observed continuously, a phenomenon which has been reported previously [8] and illustrated here at the CPE.

At the platinised platinum electrode, in contrast to the behaviour at the CPE, oxidation is highly influenced by the presence of free chloride ions due to the axial



*Acknowledgements:* We express our thanks to the Bristol Company for generously providing samples and to the "Fonds National de la Recherche Scientifique" (F.N.R.S. Belgium) for support to one of us (G.J.P.).

## References

- [1] B. Rosenberg, L. Van Kamp and T. Krigas, *Nature* **205**, 698–699 (1965).
- [2] S. J. Lippard, *Science* **218**, 1075–1082 (1982).
- [3] J. Reedijk and P. H. M. Lohman, *Pharm. Weekbl.* **7**, 173–180 (1985).
- [4] R. Dagani, *Science* **219**, 20–22 (1985).
- [5] S. J. Lippard, in *Platinum, Gold and other Metal Chemotherapeutic Agents*, (S. J. Lippard, Ed.). A.C.S. Symposium Series (1982).
- [6] C.-N. Lai and A. T. Hubbard, *Inorg. Chem.* **11**, 2081–2091 (1972).
- [7] A. L. Y. Lau and A. T. Hubbard, *J. Electroanal. Chem.* **33**, 77–93 (1971).
- [8] A. L. Y. Lau and A. T. Hubbard, *J. Electroanal. Chem.*, **24**, 237–249 (1970).
- [9] A. T. Hubbard and F. C. Anson, *Anal. Chem.* **38**, 1887–1893 (1966).
- [10] J. P. Cushing and A. T. Hubbard, *J. Electroanal. Chem.* **23**, 183–203 (1969).
- [11] W.-H. Kao and T. Kuwana, *J. Am. Chem. Soc.* **106**, 473–476 (1984).
- [12] R. D. Gilles, J. H. Harrisson and H. R. Thirsk, *J. Electroanal. Chem.* **20**, 47–60 (1969).
- [13] M. Fujihira and S. Poosittisak, *J. Electroanal. Chem.* **199**, 481–484 (1986).
- [14] G. M. Schmid and D. R. Atherton, *Anal. Chem.* **58**, 1956–1959 (1986).
- [15] M. Fleischmann and G. Sundholm, *J. Electroanal. Chem.* **30**, 4–6 (1971).
- [16] P. W. Alexander, R. Hoh and L. E. Smythe, *Talanta* **24**, 543–548 (1977).
- [17] S. J. Bannister, L. A. Sternson and A. J. Repta, *J. Chromatogr.* **273**, 301–318 (1983).
- [18] F. Mebsout, J.-M. Kauffmann, G. J. Patriarche, *J. Pharm. Biomed. Anal.* **5**, 223–231 (1987).
- [19] R. N. Adams, in *Part I: Fundamentals of electrochemical methods at solid electrodes* (A. J. Bard, Ed.), pp. 191–204. M. Dekker Inc., NY (1969).
- [20] R. B. Martin, Hydrolytic equilibria of cis-diamine dichloro platinum(II), in *Platinum, Gold and other Metal Chemotherapeutic Agents* (S. J. Lippard, Ed.). A.C.S. Symposium Series (1982).
- [21] J. B. Benziger, F. A. Pascal, S. L. Bernasek, M. P. Soriaga and A. T. Hubbard, *J. Electroanal. Chem.* **198**, 65–80 (1986).
- [22] A. M. Felthman and M. Spiro, *Chem. Rev.* **71**, 177–193 (1971).
- [23] J.-M. Kauffmann, A. Laudet, G. J. Patriarche and G. D. Christian, *Anal. Chim. Acta* **135**, 153–158 (1982).
- [24] J. A. Harrison and J. Thompson, *Electrochim. Acta* **18**, 829–834 (1973).
- [25] I. S. Krull, X. D. Ding, S. Braverman, C. Selavska, F. Hochberg and L. A. Sternson, *J. Chromatogr.* **21**, 166–173 (1983).

[Received for review 7 July 1986; revised manuscript received 30 October 1986]