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Cisplatin and the Dissolution of Electrodes in Electrochemistry Experiments

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Abstract: Cisplatin and related compounds are important for the treatment of cancers. Here, we discuss the discovery of its biological action and how this is of importance to electrocatalysis today.

Keywords: Cancer · Cisplatin · Electrochemistry · Platinum

Pt as a Chemically Inert Electrode Material

Despite its rareness and the attributed high costs, Pt is one of the most important noble metals on Earth and is commonly used for various applications. Its highly noble character, described by one of the highest oxidation potentials for metals ($E^0_{Pt/Pt^{2+}} = 1.19$ V *vs.* SHE), is linked to the chemical inertness of Pt.[1] This character, combined with a high electrical conductivity, makes Pt attractive as a conducting material in electrochemical setups today. However, as discussed below, Pt must not be considered as an innocent electrode in electrochemical experiments.

The Discovery of Cisplatin

Cisplatin (*cis*-[Pt(NH_3)$_2$$Cl_2$], *cis*-diamminedichloroplatinum (II)) was first reported in 1844 by Michele Peyrone, becoming known as Peyrone's salt.[2] Later, in 1893, Alfred Werner proposed that the four ligands of cisplatin were directly bound to the Pt metal center in a square-planar configuration.[3] These square-planar Pt(II) complexes are more prone to ligand substitution than their octahedral Pt(IV) counterparts; this reactivity would later become extremely important to humankind.

How Does an Electric Field Impact Cell Growth and Proliferation?

Fast-forward to 1965, where Pt salts would unexpectedly appear. Rosenberg, Van Camp and Krigas attempted to address this question using the bacterium *Escherichia coli*.[4] Two different strains of *E. coli* were used to inoculate an electrochemical cell containing medium capable of supporting cell proliferation (aerobic cultivation on glucose). Once the bacteria had grown sufficiently, an electric current was passed between two Pt electrodes. Pt was chosen since, as we still learn today, Pt metal is *relatively* chemically inert. The current passed was limited to prevent significant electrolytic reactions occurring at the Pt electrodes while minimizing electrode polarization. After only one hour, the turbidity of the cell cultures had decreased. Microscopy confirmed that *E. coli* had ceased to divide, although the cells had begun to elongate. The cessation of current led to the eventual recovery of the expected division and proliferation of *E. coli*. Through rigorous control experiments, contributions from ultra-violet light, temperature, pH and Mg^{2+}, as well as spontaneous mutations, were eliminated. It was also determined that the electrolysis of the cultivation medium followed by its subsequent addition to *E. coli* cells also resulted in cell elongation, cementing the importance of electrolysis in the observed effect. A series of anticipated oxidizing agents including peroxide and perchlorate that could have been electrogenerated from the medium components (formed by oxidation at the Pt electrodes) were then tested, none of which resulted in elongation. However, electrolysis-dependent activity was observed with a series of NH_4^+ salts in the presence of Cl^-.

It turns out that chemically inert Pt electrodes are in fact not so inert under certain electrolytic conditions, particularly when Cl^- is present. Rosenberg *et al*. went on to demonstrate that filamentous growth of *E. coli* was linked to the presence of electrogenerated soluble Pt salts in the bacterial cultivation medium, where the addition of $(NH_4)_2[PtCl_6]$ to the fresh medium could duplicate the same effects. Thus, these Pt salts were formed *in situ* by the dissolution of the Pt electrodes during electrolysis. One likely explanation for the observations of Rosenberg *et al*. is that, through a series of steps, Pt complexes crosslink DNA strands and ultimately inhibit cell division.

Due to this serendipitous discovery, cisplatin and similar Pt drugs (with over 4'000 Pt compounds having been tested) are used for the treatment of certain cancers today, since cell proliferation of cancerous cells is expected to be fast.[5]

Pt as a Non-Inert Counter Electrode?

The work of Rosenberg *et al*. exemplifies how the unexpected dissolution of Pt electrodes can lead to deleterious effects. Such effects must not be ignored in our efforts to identify and characterize new electrode materials for reactions such as electrochemical dinitrogen reduction to ammonia or the hydrogen evolution reaction (HER), the latter for which Pt is arguably the best electrocatalyst. Nevertheless, Pt counter electrodes (CE) remain prevalent in many electrochemical experiments today. The potential dissolution of Pt CEs has the possibility to lead to false positives, as illustrated in Fig. 1, especially when performed in strongly acidic or alkaline media.[6] This issue has also been discussed in an editorial of *ACS Catalysis*.[7]

During studies of different electrochemical systems for the HER, independent reports by the groups of Ho,[8] Tang,[9] Ramasamy[10] and Kowalewski[11] show incredibly high activity exclusively while using a Pt CE. Based on electron microscopy data and XPS analysis, deposition of Pt nanoparticles on the respective working electrode (WE) could be detected, which originated from anodic Pt CE electrodissolution. Ultimately, the high activity could be attributed to the deposited Pt nanoparticles, which reached activities similar to those of commercially available Pt/C.

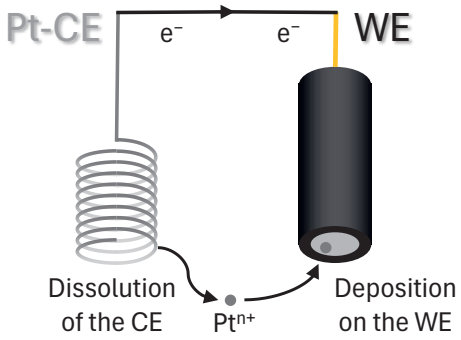

Fig. 1. Schematic representation of the anodic dissolution of a Pt counter electrode (CE) and subsequent Pt deposition on working electrodes (WE) during electrochemical experiments (reference electrode(s) omitted for clarity).

The anodic electrodissolution of Pt in acidic media was found to occur not only by direct Pt cation formation.[12] The formation of hydroxide (OH^-) and oxide (O^{2-}) layers on the Pt surface form passivated Pt-oxides, which accelerate the dissolution. The processes of surface passivation (1), dissolution of reduced Pt (2) and chemical dissolution of Pt-oxide (3) can be expressed by the following equations and their equilibrium defines the electrode processes.

$$Pt + H_2O \rightleftharpoons PtO + 2H^+ + 2e^- \quad (1a)$$

$$PtO + H_2O \rightleftharpoons PtO_2 + 2H^+ + 2e^- \quad (1b)$$

$$Pt \rightleftharpoons Pt^{2+} + 2e^- \quad (2)$$

$$PtO + 2H^+ \rightleftharpoons Pt^{2+} + H_2O \quad (3)$$

If Pt dissolution cannot be avoided, the separation of the anodic and cathodic cell compartments as well as additional control experiments are vital. To prevent the transfer of Pt cations a membrane, which allows for the transfer of charge but not dissolved Pt cations, can be incorporated. Studies by the group of Walsh indicate that membranes like Nafion or glass frits indeed might reduce Pt cation diffusion to some extent, however they do not completely prevent Pt deposition on the WE.[13] To fully avoid Pt deposition on the WE, an alternative CE should be chosen. This statement is in agreement with reports of Liu,[1b] Jerkiewicz[14] and Sheng.[15] Thus, the choice of the CE should be carefully considered when setting up an electrochemical experiment, depending on the setup conditions, and the following criteria should be met: i) chemical and electrochemical stability of the CE, ii) a sufficiently fast reaction in the CE compartment to ensure electron flow and enable the reaction at the WE, iii) larger size than the WE (at least 10 ×) to overcome energetic barriers, iv) requirement of a membrane to separate anodic and cathodic compartments. On the other hand, the dissolution and deposition of thin layers of Pt on a WE can be useful as an alternative approach to produce effective and stable HER electrodes. Indeed, the group of Schäfer prepared highly active HER electrodes by Pt transfer from the CE to a stainless steel WE, with negligible amounts of Pt left in the electrolyte and a low amount of total transferred Pt, making this approach cost-effective.[16]

In conclusion, data interpretation when using Pt CEs should always be carried out with caution, especially when the HER is studied. Although Pt is seen as an inert electrode material, its dissolution and redeposition on the WE can lead to false activity assumptions. Alternative electrodes should be considered, depending on the reaction studied and electrode environments. For the HER, carbon CEs were suggested to be a reliable alternative, although these might also show redox non-innocent character in different systems.[17]

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