



Selective detection of morphine in the presence of paracetamol with anodically pretreated dual layer Ti/tetrahedral amorphous carbon electrodes

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ABSTRACT

We investigated the effect of anodic treatment of titanium/tetrahedral amorphous carbon electrodes on the electrochemical detection of morphine and paracetamol. The anodic treatment caused both oxidation of the carbon and, more importantly, exposure and oxidation of the underlying Ti layer. This treatment anodically shifted the oxidation potential of paracetamol while that of morphine remained unaffected. The resulting electrode also showed better selectivity than a ta-C electrode without Ti. After anodic treatment at 2.5 V, selective detection of morphine with a physiologically meaningful detection limit of 9.8 nM and a linear range of 0.1–10 μM was obtained in the presence of 100 μM paracetamol.

1. Introduction

Morphine (MO, IUPAC name: (5 α ,6 α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol) is a strong opioid used for the treatment of moderate to severe pain. Its use is, however, associated with adverse effects including sedation, nausea, constipation, respiratory depression, and development of tolerance as well as dependence [1]. Morphine is also the active metabolite of the prodrug codeine, a weak opioid used to treat mild and moderate pain. Paracetamol or acetaminophen (IUPAC name: N-(4-hydroxyphenyl)acetamide) is one of the most widely used non-prescription medicines in the world [2]. It is a weak non-opioid analgesic and an antipyretic that is relatively safe when used at recommended doses [1]. Co-administration of paracetamol with morphine has been reported to decrease the need for morphine in patient-controlled analgesia (PCA) after major surgery [3]. Therefore, paracetamol (PA) is combined with codeine as a compound analgesic and co-administered with morphine in many countries. Consequently, a selective electrochemical sensor for direct determination of morphine without time-consuming separation is highly desirable.

Paracetamol and morphine are electroactive compounds that can be oxidized electrochemically [4,5]. However, they typically show overlapping oxidation peaks [4–7]. The peak plasma concentration following a therapeutic oral dose (1 g) of paracetamol ranges from 130 to

200 μM [2]. In contrast, plasma morphine concentrations usually range between only 7 and 100 nM [8–10]. However, higher concentrations of up to 1 μM have been reported for patients with advanced cancer [11]. The overlapping oxidation peaks and considerable differences in therapeutic concentrations make selective detection of morphine in the presence of paracetamol challenging. To our knowledge, only one report of the simultaneous voltammetric determination of morphine in the presence of paracetamol has been published [6]. That study, however, used a relatively complicated CdO nanoparticle ionic liquid modified carbon paste electrode.

Tetrahedral amorphous carbon (ta-C) is resistant to wear, corrosion and biofouling [12]. It is also patternable and can be deposited at room temperature. Ultrathin ta-C films have been shown to support facile electron transfer with Ru(NH₃)₆^{2+/3+} and Fe(CN)₆^{4-/3-} [13,14]. It has also been used recently for electrochemical detection of dopamine [15] as well as other catechols [16]. Previous studies have shown that the amount and type of oxygen-containing functional groups as well as the C–C bonding on the surface of carbon electrodes affect both the electron transfer kinetics and their sensitivity toward biomolecules [14,17–19]. Various mechanical, chemical and physicochemical pretreatments have been used to functionalize the surface of carbon materials [20–22]. Electrochemical pretreatments have been widely used to improve the electrochemical properties of carbon electrodes and

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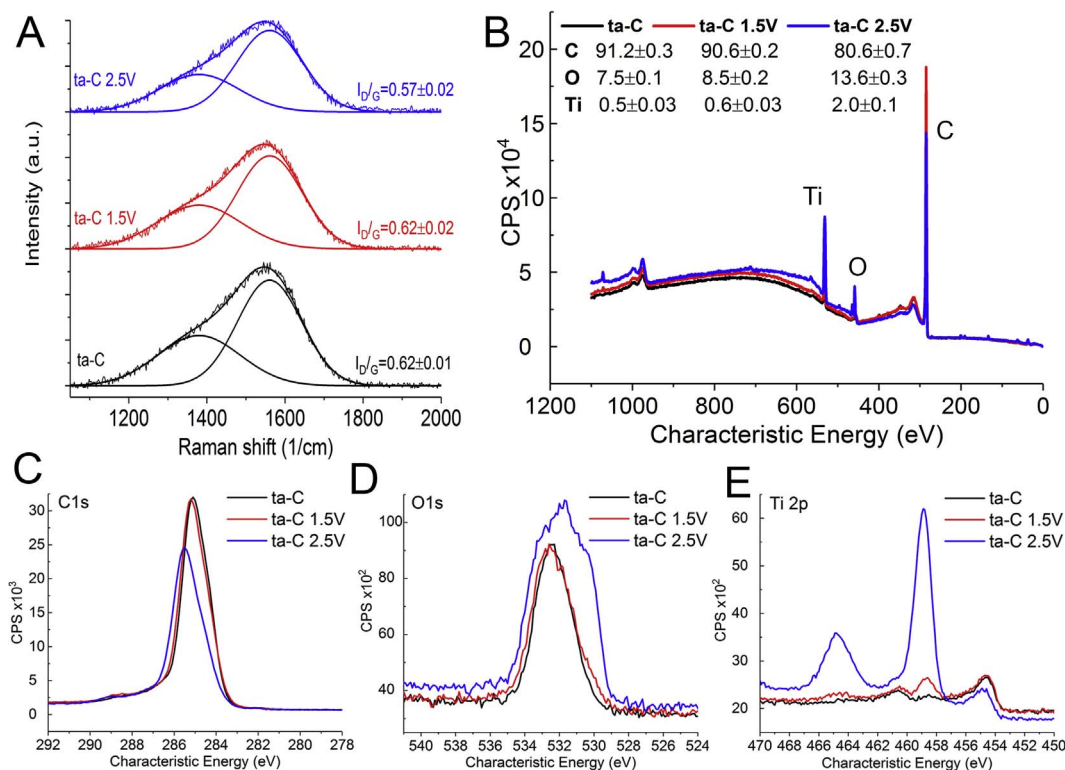


Fig. 1. (A) Raman and (B) XPS survey spectra of ta-C, ta-C 1.5 V and ta-C 2.5 V. High resolution XPS spectra of (C) C 1s, (D) O 1s and (E) Ti 2p for ta-C, ta-C 1.5 V and ta-C 2.5 V.

introduce oxygen-containing functional groups on the surface [20]. For example, anodic pretreatments of glassy carbon electrodes have been found to increase their sensitivity toward morphine [7] and decrease the sensitivity and oxidation kinetics of boron-doped diamond (BDD) electrodes toward paracetamol [23,24].

Little has been reported on the effect of electrochemical pretreatment of ta-C thin films and the implications for the electrochemical measurement of paracetamol and morphine. Here we report for the first time the effect of anodic pretreatment on the electrochemical performance of ultrathin Ti/ta-C electrodes. We studied the effect of the anodic treatment on the surface chemistry and electrochemistry of paracetamol and morphine. We also successfully demonstrate selective detection of morphine in the presence of paracetamol.

2. Experimental section

2.1. Reagents

Hexaammineruthenium(III) chloride and paracetamol were purchased from Sigma Aldrich. Morphine hydrochloride powder was obtained from the University Pharmacy, Helsinki, Finland. 1 and 5 mM solutions of hexaammineruthenium(III) chloride were prepared by dissolving in 1 M KCl (Merck Suprapur). 1 mM stock solutions of paracetamol and morphine in pH 7.4 phosphate-buffered saline (PBS) were prepared for injection into the cell. All aqueous solutions were prepared with water from a Millipore system ($> 18 \text{ M}\Omega \text{ cm}$).

2.2. Electrode preparation

Ti and ta-C films were deposited on p-type (100) Si wafers ($< 0.005 \Omega \text{ cm}$). A 20 nm Ti underlayer was deposited by direct current magnetron sputtering. A 7 nm ta-C surface layer was deposited using a pulsed filtered cathodic vacuum arc (p-FCVA). The deposition process is described in detail in [13]. Sample wafers were diced with an automated dicing saw into $5 \times 5 \text{ mm}$ electrodes. The electrodes were

placed on copper-clad FR4-PCB strips and covered with PTFE film (Saint-Gobain Performance Plastics, CHR 255-2) with pre-made 3 mm holes.

2.3. Instruments

Raman spectroscopy was carried out using LabRAM HR confocal Raman (Jobin Yvon Horiba) with an argon laser ($\lambda = 488 \text{ nm}$, power 10 mW) and BX41 (Olympus) microscope with a $100\times$ objective. X-ray photoelectron spectroscopy (XPS) was performed using an Axis Ultra electron spectrometer (Kratos Analytical, Manchester, UK) with monochromatic Al K α irradiation at 100 W under neutralization. Before analysis, pre-evacuation was carried out overnight. High-resolution spectra of C 1s, O 1s, and Ti 2p were recorded in addition to survey spectra of 3–4 locations for each sample. The data were fitted with CasaXPS software, assuming Gaussian line shapes. 100% filter paper (Whatman) was used as an in-situ reference for charge correction [25].

Electrochemical measurements were carried out with CH Instruments CHI630E and Gamry Reference 600 potentiostats. A three-electrode cell with an Ag/AgCl reference (+0.199 V vs RHE, Radiometer Analytical) and Pt counter was used for all measurements and anodic treatments. Before electrochemical measurements and anodic treatments, the cell was purged with N_2 for 15 min. During the measurements the cell was kept at N_2 overpressure. Prior to measurement and characterization, the electrodes were subjected to anodic treatment at 1.5 V (sample named ta-C 1.5 V) and 2.5 V (sample named ta-C 2.5 V) for 300 s in PBS of pH 7.4. For Raman and XPS analysis, separate electrodes were treated without Teflon film by partial immersion in PBS. These electrodes were rinsed in deionized water and cleaved for Raman and XPS spectroscopy. For EIS measurements, a 15 mV AC signal in the range 10 mHz to 100 kHz was used. The formal potential (around -0.165 V vs Ag/AgCl) determined by cyclic voltammetry (CV) was used as the DC potential. The EIS data was fitted with a Randles circuit and the apparent heterogeneous rate constant (k^0) was calculated as in ref [13].

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