



Surface grafting of a π -conjugated amino-ferrocifen drug



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ABSTRACT

The electrochemical grafting of a π -conjugated amino-ferrocifen complex (**1**) at gold surfaces may be achieved through the direct electrochemical oxidation of the amino group (+0.9 V/SCE) but is prone to proceed also indirectly through the oxidation of the ferrocene moiety (+0.45 V). The modification and characterization of the gold electrode surfaces are demonstrated by cyclic voltammetry, ellipsometry, Infra-Red Reflection–Absorption Spectroscopy (IRRAS), Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS), and X-ray Photoelectron Spectroscopy (XPS). Combination of these techniques clearly demonstrates that (**1**) is covalently attached to the gold surfaces via an Au–NH bond. The crucial role played by the electrogenerated aminyl radical in the grafting process is highlighted. This transient species, which is responsible for the covalent grafting of (**1**) onto the gold surface was also found able to react with the amino-ferrocifen parent complex to form multilayers. This detailed characterization of the grafted electrode surface finally brings insight into the overall mechanistic frame related to the grafting of conjugated amino compounds and, consequently, allowing establishing definitively the occurrence of the intramolecular redox catalysis process which is key to their cytotoxic properties against cancer cells.

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1. Introduction

Presently, the most commonly used electrochemical procedures for derivatizing carbon and metal surfaces rely either on the electrochemical reduction of aryldiazonium salts [1–7] or on the electrochemical oxidation of amine-containing compounds [8–12]. In the second method, the attachment of the amino group was initially assigned to the radical-cation formed upon oxidation of the amine, but more recent investigations indicated that the radical obtained after deprotonation of the radical-cation is the grafting species which actually reacts with the electrode surface [10]. In general, the attachment of the amino group obtained by this procedure is evidenced through the observation of the electrochemical signal of redox substituents such as nitro [8–10], anthracene, anthraquinone [8], or hydroquinone [11]. Interestingly, it was demonstrated that the surface concentration of amino groups was lower with secondary amines than with primary ones whereas tertiary amines hardly graft at all [9,10].

On the other hand, the covalent attachment of organometallic complexes such as ferrocene has already been reported [13–15]. For instance, the reaction of 4-bromophenyl modified glassy

carbon electrode with a ferrocene derivative was investigated [15]. However, even if the presence of ferrocene moieties at the electrode was demonstrated by cyclic voltammetry and X-ray photoelectron spectroscopy, no definitive conclusion could be made about the nature of the attachment of the ferrocene moiety onto the surface. Its presence at the electrode surface could indeed be explained either by the nucleophilic displacement of bromine from the 4-bromophenyl grafted groups by the amine of the ferrocene derivative, or through involving π -stacking between the phenyl rings of the ferrocene derivative and the grafted phenyl group.

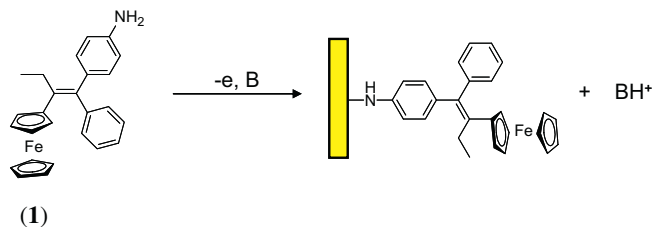
The covalent attachment of ferrocenemethylamine was also achieved on a glassy carbon electrode in a stepwise process consisting of the electrochemical reduction of the 4-carboxyphenyl diazonium salt to yield a stable monolayer to which ferrocenemethylamine was covalently attached via a condensation reaction [16]. In this case, the modified electrode was fully characterized and the covalent attachment of the ferrocene group was demonstrated [17,18].

Recently, we reported the original covalent grafting of a π -conjugated ferrocene–aniline complex (**1**) (Scheme 1) [19,20].

The grafting of compound (**1**) was electrochemically achieved either by the direct oxidation of the amino group or mediated via the oxidation of the ferrocene moiety in the presence of collidine (2,4,6-trimethylpyridine) as a base. In the first case, the

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Scheme 1. Covalent grafting of the amino-ferrocifen complex (**1**) (1-(4-aminophenyl)-1-phenyl-2-ferrocenylbut-1-ene).

modification consisted of oxidizing the amino moiety to its radical cation, at the aromatic amine oxidation potential, which upon deprotonation yielded an aminyl radical that added onto the electrode surface. Alternatively, the amine group could be indirectly oxidized through an intra-molecular electron transfer from the amino moiety to the ferricenium through the conjugated π system of the complex. This latter indirect grafting procedure incidentally impacts the mechanistic and the biological aspects of the oxidative metabolism of compound (**1**), which belongs to the class of “ferrocifen” anticancer drugs developed by Jaouen et al. and which we have been investigating mechanistically in full detail [21–28]. Ferrocifens involve a ferrocene group conjugated to tamoxifen derivatives skeleton, the standard reference drug for endocrine therapy related to breast cancer. These molecules combine endocrine modulating properties and cytotoxicity, such effects being namely related to the ability of (**1**) to undergo an intramolecular base-promoted electron transfer between the oxidized ferrocene center and the aminophenyl moiety. The oxidation sequence ultimately yields the biologically active form, viz., a quinone imine responsible for the cytotoxic activity [29–34]. In that context, (**1**) showed a strong antiproliferative effect on breast cancer cells (MBA-MB231), with a IC_{50} value of 0.8 μ M, making this compound even more cytotoxic than the analog ferrocenyl phenol (IC_{50} = 1.13 μ M) [20]. In both cases, the mechanism involves an intramolecular redox catalysis process through which the easily oxidized ferrocene moiety is reduced by the aniline or phenol groups. Such electronic communication between the amino group and the ferrocene “antenna” is a common and key-step of both the surface grafting of π -conjugated ferrocenyl aniline compounds and the activation of an antiproliferative drug. In this respect, the electrochemical grafting of (**1**) and then addressing of the covalently-grafted ferrocene group of (**1**) could set the intramolecular electron transfer from the amino group to the ferricenium as the initial step of the formation of highly reactive aminyl radicals, which may either graft onto surfaces or evolve to produce quinone imines.

Accordingly, it is crucial to establish the existence of a covalent Au–NH bond when the grafting of (**1**) is performed by its ferrocene moiety oxidation and to confirm the π -cross talk between the Fc center and the amine moiety. This could not be achieved in our previous report which characterized qualitatively the existence of the grafting [19].

Ellipsometry, IR surface spectroscopies (Infra-Red Reflection–Absorption Spectroscopy (IRRAS) and Attenuated Total Reflectance (ATR) spectroscopy), Time of Flight Secondary Ion mass Spectrometry (ToF-SIMS), and X-ray Photoelectron Spectroscopy (XPS) were thus used to provide a quantitative coherent set of unambiguous information about the nature of the grafting, the film composition as well as its thickness. This confirmed the covalent immobilization of (**1**) onto gold surfaces, provided structural information about the assembly, led to devise a mechanism for the grafting, and finally brought a strong indirect support about the facility of the intramolecular redox catalysis process essential to the cytotoxicity of the amino-ferrocifen complex.

2. Experimental

2.1. Chemicals

Lithium perchlorate (Aldrich) was used as the supporting electrolyte in methanol solutions. Methanol (Acros) and 2,4,6-trimethylpyridine (Acros, collidine) were used as received. *Caution: lithium perchlorate is a powerful oxidizing material, forms explosive mixtures with combustible organic or other easily oxidizable materials. It can decompose violently or explosively at high temperatures.*

The ferrocifen complex was synthesized by McMurry cross-coupling of the appropriate ketones as described elsewhere [19]. It was kindly supplied to us by Prof. G. Jaouen and his team. Gold coated plates used for electrografting (Aldrich, gold coated silicon wafer, 1000 angstrom coating) were cleaned with ‘piranha’ solution (1:3 v/v H_2O_2 : H_2SO_4 for 10 min) and then where rinsed through sonication during 10 min in ultrapure water (resistivity >18.2 M Ω cm) at 25 °C. Before modification, the plates were dried under a stream of nitrogen. *Caution: Piranha solutions are highly aggressive and should be handled with full protection, gloves, mask, etc.*

2.2. Instrumentation

2.2.1. Cyclic voltammetry and electrografting

Cyclic voltammetry and electrografting experiments were performed at room temperature under an argon atmosphere in a three-electrode cell using an Autolab potentiostat (PGSTAT 20). The reference electrode was an SCE (Tacussel) separated from the solution by a bridge compartment filled with the same solvent/supporting electrolyte solution as that used in the cell. The counter electrode was a gold wire. The voltammetric gold working electrodes (Goodfellow, 0.5 mm) were home-made by sealing the gold wire into a glass case.

2.2.2. IR spectra

IRRAS and ATR spectra of the modified plates were recorded using a purged (low CO_2 , dry air) JASCO FT/IR-6100 Fourier Transform Infra Red Spectrometer equipped with a MCT (mercury–cadmium–telluride) detector. For each spectrum 1000 scans were accumulated with a spectral resolution of 4 cm^{-1} . The background recorded before each spectrum was that of a clean bare substrate.

2.2.3. Ellipsometry

Thicknesses of the films on Au were measured with a mono wavelength ellipsometer (Sentech SE400), with a He–Ne laser λ = 6328 Å, angle = 70°. The following values were taken: ns = 0.153, ks = 3.567 were measured on clean gold surfaces before grafting, and we used ns = 1.46, ks = 0 for the polymeric layer. The thickness was determined from the same plate after modification. The uncertainty of the film thickness was determined from 15 points on each modified plates.

2.2.4. XPS (X-ray Photoelectron Spectroscopy)

XPS (X-ray Photoelectron Spectroscopy) analyses were performed with an ESCALAB 250 spectrometer (Thermo Electron Corporation), using a monochromatized focused Al $K\alpha$ X-ray source (1486.6 eV). The spectrometer was calibrated against the reference binding energies (BEs) of clean Cu (Cu 2 $p_{3/2}$ at 932.6 eV), Ag (Ag 3 $d_{5/2}$ at 368.2 eV) and Au (Au 4 $f_{7/2}$ at 84.0 eV) samples. Base pressure during analysis was 1×10^{-7} Pa. The analysed area had a diameter of about 500 μ m. In addition to the survey spectrum (pass energy of 100 eV, step energy: 1 eV), the following core levels were systematically recorded at higher energy resolution (pass energy of 20 eV): C 1s, O 1s, N 1s and Fe 2p (step energy: 0.1 eV), with

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