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Letters

Design of Self-Assembled Monolayers That Release Attached Groups Using Applied Electrical Potentials

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This Letter describes the design of a self-assembled monolayer of alkanethiolates on gold that can release attached groups when an electrical potential is applied to the gold. The design is based on monolayers that present a catechol orthoformate group that undergoes an irreversible two-electron oxidation with simultaneous release of the orthoformate substituent. Cyclic voltammograms (0.15 M NaCl, pH 7.4, 50 mV/s) of a monolayer presenting catechol orthoformate and hydroxyl groups showed an oxidation wave at 900 mV (versus Ag wire pseudo reference) for the quantitative conversion of the orthoformate group to the corresponding orthoquinone. The second cycle showed an oxidation wave at −75 mV and a reduction wave at −125 mV for the reversible oxidation of the catechol group.

Self-assembled monolayers (SAMs) of alkanethiolates on gold have provided an important and versatile class of model interfaces that are both structurally well-defined and synthetically flexible. These interfaces have been important for studies of electron transfer,[1] molecular recognition,[2] biomaterials interfaces,[3] and many other systems.[4] The introduction of strategies that can change the structure of an interface, in real time, will be important for expanding the utility of these model substrates. Whitesides, Wrighton, and co-workers, for example, described SAMs presenting electroactive groups to measure the pH of a contacting solution[5] and patterned monolayers presenting redox-active ferrocene groups to control the flow of fluids on surfaces.[6] In this Letter we describe a methodology for the preparation of monolayers that can selectively release attached molecules when electrical potentials are applied to the underlying gold.

The design is based on monolayers that present a catechol orthoformate group that undergoes an irreversible two-electron oxidation to produce the orthoquinone, with simultaneous release of the orthoformate substituent (Scheme 1). Whereas O,O-dialkylated catechols undergo a reversible one-electron oxidation[7] (presumably due to the stability of the radical cation), we believed that the corresponding orthoformates would hydrolyze and give the orthoquinone resulting from a two-electron oxidation. Our choice of the catechol orthoformate group as the redox-active moiety was based on several additional criteria: the potential for oxidation of the group had to be lower than 1 V (because alkanethiolate monolayers can oxidize and desorb at higher potentials); the reaction had to proceed with a near-quantitative yield and on a time scale comparable to a single voltammetric scan; the synthesis had to accommodate the preparation of alkanethiols having different substituents on the catechol group to

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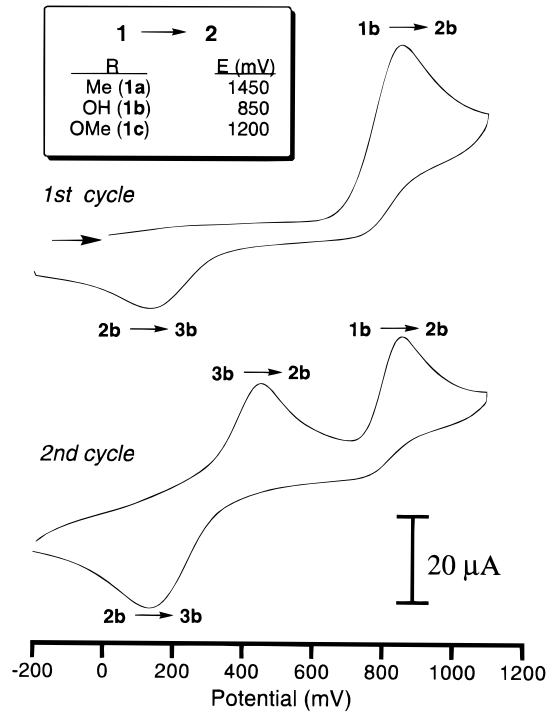
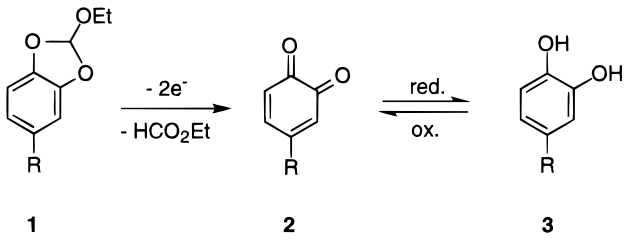


Figure 1. Cyclic voltammograms of catechol orthoformate **1b** for the first and second cycles in acetonitrile/water (9:1) (100 mV/s, Ag/AgCl reference). The arrow denotes the starting point and direction of the first scan. The inset shows the potentials at which oxidative cleavage occurred for three analogs.

Scheme 1



optimize the potential required for oxidation. The redox-activity of the resulting orthoquinone was an additional advantage because it permits the use of cyclic voltammetry (CV) to characterize the products and yield of the reaction.

Figure 1 shows cyclic voltammograms of 2-ethoxy-5-hydroxy-1,3-benzodioxole (**1b**).[8] Because of the poor solubility of the catechol orthoformates in water, electrochemistry was performed in a mixture of acetonitrile and water (9:1) containing tetrabutylammonium hexafluorophosphate (100 mM). On the forward scan of the first cycle **1b** was irreversibly oxidized to orthoquinone **2b** at a potential of 850 mV; on the return scan, **2b** was reduced to catechol **3b**. The second cycle showed two oxidation waves which represent the conversion of both catechol (**3b**) and orthoformate (**1b**) to orthoquinone (**2b**). Although the potential of 850 mV required for oxidation of **1b** was compatible with SAMs on gold, the molecule was not stable in air; it underwent decomposition to give a dark paste over a period of 1 day. We next examined analogs having different substituents (Figure 1). 2-Ethoxy-5-methyl-1,3-benzodioxole (**1a**) underwent electrochemical oxidation at a potential of 1450 mV and was not suitable for incorporation into a monolayer. 2-Ethoxy-5-methoxy-1,3-benzodioxole (**1c**), however, underwent oxidation at 1200 mV. We believed that the potential required for oxidation of **1c** in aqueous solution would be lower still and that this group would be well-suited for incorporation into the monolayer.

Figure 2 shows the structure of a SAM presenting the 2-ethoxy-5-methoxy-1,3-benzodioxole group mixed with hydroxyl groups.[9,10] Hydroxyl-terminated alkanethiols were used as the background component of the monolayers because this functional group is electrochemically inert and because it is hydrophilic and well-suited for use in contact with aqueous media. Cyclic voltammograms of this SAM showed an oxidation wave at 900 mV for the forward scan of the first cycle (Figure 3A).[11] Several observations support the interpretation that the orthoformate underwent oxidation to produce the orthoquinone. The return scan of the first cycle showed a wave at −125 mV for the reduction of the orthoquinone to the catechol; the integrated area under this wave was the same (to within 5%) as that for the original wave at 900 mV. The second voltammetric cycle (Figure 3B) showed an oxidation at a lower potential (−75 mV) and again a reduction at −125 mV on the return scan; the next five cycles were indistinguishable and showed that the monolayer did not desorb. We do not know what process gave rise to the small wave at ∼350 mV; this wave did not continue to grow in size with repeated cycling, and it accounted for less than 5% of the total current. The voltammogram shown in Figure 3B is also identical to that of a SAM presenting catechol groups mixed with hydroxyl groups (Figure 3C)[12] and provided direct evidence for cleavage of the orthoformate group. The absence of an oxidation wave at 900 mV on the second cycle shows that the orthoformate was efficiently converted to the orthoquinone in a single scan. The integrated areas for the waves representing oxidation of the orthoformate (Figure 3A) and reduction of the orthoquinone (Figure 3B) were the same (to within 5%) and provided additional evidence for an efficient conversion. Under the conditions of the experiment, the catechol orthoformate was stable and did not undergo hydrolysis or decomposition. A control experiment showed,

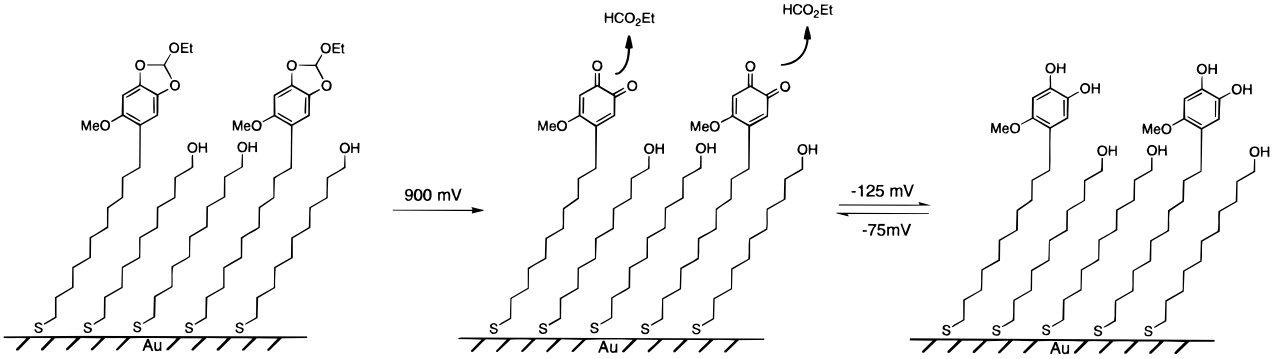


Figure 2. Design of monolayers that present the catechol orthoformate group. An applied potential causes irreversible oxidation of the group to give a monolayer terminated in the orthoquinone. Reversible reduction gives the catechol-terminated monolayer.

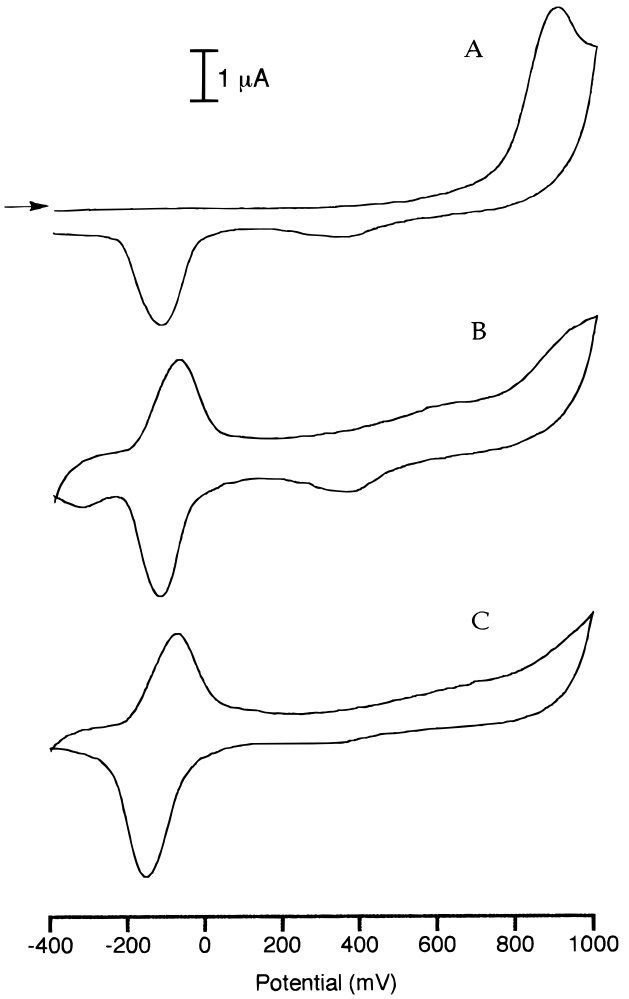


Figure 3. Cyclic voltammograms for the first (A) and second (B) cycles of a SAM terminated in catechol orthoformate groups. C shows the first cycle for a SAM presenting catechol groups. The arrow denotes the starting point and direction of the first scan (50 mV/s).

however, that immersion of the SAM in aqueous 1 M $HClO_4$ for 15 min caused complete hydrolysis of the orthoformate to give the catechol.[13]

This work provides a methodology for the design of substrates that can release immobilized groups. The focus of this Letter is on the design and demonstration of an appropriate electrical reaction and on the characterization of a monolayer that incorporates this reactive group. When compared to strategies that use polymers for the release of attached groups,[14] the monolayers described here have the advantages that they present groups in a homogeneous environment, they are synthetically flexible, and they are structurally well-defined. This methodology is general in that it can create substrates that release a variety of groups, including molecules, polymers, and mammalian cells: it only requires the synthesis of an alkanethiol terminated in the catechol orthoformate that is appropriately substituted. Because SAMs can be prepared from two or more alkanethiols, it will be possible to create substrates that present multiple groups but selectively release only a fraction of these groups. The compatibility of these tailored substrates with aqueous environments at neutral pH makes them useful for fundamental studies in cell biology and for applications in biotechnology.

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(8) Cyclic voltammetry was performed with a Bioanalytical Systems CV-50W potentiostat using a cell fitted with a carbon working electrode, Pt counter electrode, and Ag/AgCl reference electrode. All scans were performed at 100 mV/s with the electroactive molecule at a concentration of 1 mM.

(9) Substrates were prepared by electron-beam evaporation of an adhesion layer of titanium (2.5 nm) and then gold (80 nm) onto silicon wafers (Silicon Sense). The substrates were immersed in solutions of 2-ethoxy-5-methoxy-1,3-benzodioxole terminated undecanethiol (χ = 0.3) and 11-mercapto-1-undecanol (Aldrich) in ethanol (1 mM total) for 12 h to give mixed SAMs.

(10) The 2-ethoxy-5-methoxy-1,3-benzodioxole terminated alkanethiol was synthesized in eight steps; all intermediates gave satisfactory ^{1}H NMR spectra. Details will be described in a subsequent full report.

(11) All cyclic voltammograms were performed with a fabricated cell fitted with the gold/SAM working electrode, platinum counter electrode, and silver wire pseudo-reference electrode. All scans were performed at 50 mV/s in aqueous 0.15 M NaCl at pH 7.4 (phosphate buffer).

(12) SAMs were prepared from a mixture of catechol terminated alkanethiol (χ = 0.5) and hydroxyl-terminated alkanethiol. The catechol-terminated alkanethiol was an intermediate in the synthesis of the corresponding orthoformate (see ref 10).

(13) A SAM (see footnote 9) was immersed in 1 M aqueous $HClO_4$ for 15 min, thoroughly rinsed with water and then with ethanol, and dried with a stream of nitrogen. The monolayer was electrochemically cycled from −300 to 1000 mV and produced voltammograms that were indistinguishable from those for a monolayer presenting catechol and hydroxyl groups (as in Figure 3C).

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