SYNTHESIS, SELF-ASSEMBLING AND REDOX PROPERTIES OF 2-[(ω-SULFANYLALKYL)AMINO]-1,4-NAPHTHOQUINONES

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The newly synthesized 1,4-naphthoquinones linked via nitrogen atom to a short chain with terminal sulfanyl group form self-assembled monolayers on gold. The main electrochemical parameters of the monolayers were determined by cyclic voltammetry. Combined voltammetric and in situ Fourier-transform surface-enhanced Raman spectroscopic studies of the Au electrode modified with the title compounds clearly evidence that naphthoquinone group transforms into naphthalenediol during a reduction process.

Keywords: 1,4-Naphthoquinone derivatives; Self-assembled monolayers; Electrochemistry; Fourier-transform surface-enhanced Raman spectroscopy; Cyclic voltammetry; Electroreductions.

Derivatives of 1,4-naphthoquinone (NQ) are known to play an important role in biological systems including electron transport in photosynthesis and the build-up of a proton gradient across the biomembrane. To gain a better insight into the redox functioning of natural NQ derivatives, it is very important to explore electrochemical properties of this aromatic quinone under conditions close to those prevailing in the lipid bilayer. The two-dimensional self-assembled monolayers (SAMs) on the electrode surface are particularly attractive among various possible models of biomembranes[1]. In addition, NQ-terminated SAMs are of particular interest because of their potential use for construction of chemically modified electrodes with pH-dependent electrocatalytic properties.

Self-assembling compounds, in general, are surface-active thiols or corresponding dialkyl disulfides. Hydroquinone-terminated SAMs are the most widely studied among the quinone derivatives[2–5]. However, only a few investigations of NQ-containing SAMs are available in the literature. Thus,

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Mukae et al.[6] anchored 2,3-dichloro-NQ through the SAMs of ω-aminoalkanethiols of various chain lengths (*m* = 2, 5 and 8, where *m* is the number of CH_2 groups) on the Au electrode, and studied their redox behavior by voltammetry. Panetta et al.[7] formed SAMs from 2-(decylamino)- and 3-chloro-2-(decylamino)-NQ disulfides and methyl sulfides. The self-assembling properties of dialkyl disulfides containing 2-chloro-3-alkylamino-NQ group with different lengths of spacer were studied by Ohtsuka et al.[8]. SAM-forming compounds containing 2-(alkylamino)-3-chloro- or 2-(alkylthio)-3-chloro-NQ groups were also used[9]. It should be noted that the NQ-ring in these compounds has additional substituents strongly affecting the redox characteristics. A complex electrochemical behavior is expected for the biologically relevant quinones possessing a bulky aromatic NQ group because of π–π stacking interactions and distortions in the monolayer packing induced by the large cross-sectional area of the terminal group.

EXPERIMENTAL

Electrochemistry

Electrochemical measurements were carried out on a EG&G Versastat computerized potentiostat system (Princeton Applied Research, Princeton (NJ), U.S.A.) in a three-electrode cell. The platinum plate served as an auxiliary electrode, sodium chloride saturated calomel electrode, SSCE (*E* = 239 mV vs standard hydrogen electrode), served as a reference electrode.

Polycrystalline gold disk electrode before modification with SAM-forming compound was pre-treated by the following procedure. The electrode was polished with a 0.05 μm alumina slurry, rinsed with water and ethanol, sonicated for 10 min in water/ethanol 1:1, followed by Millipore purified water, and electrochemically cleaned in 0.1 м H_2SO_4 by potential cycling between 0.4 and 1.6 V vs SSCE at a *E* scan rate of 0.1 V/s for 25 min. The prepared electrode was rinsed with water, ethanol, and immersed into a 1 mм ethanolic solution of compound **3a** or **3b** for 15–20 h. For the Fourier-transform surface-enhanced Raman spectroscopic (FT-SERS) measurements, the pre-treated gold electrode was additionally roughened by *E* cycling between –0.3 and 1.35 V in 0.1 м KCl at the *E* scan rate of 0.3 V/s for 10 min, similarly as reported previously[10,11].

Electrochemical measurements were performed in a 0.1 м $HClO_4$ solution purged with Ar at 25 °C. The real surface area of the electrode was determined by measuring the area of the gold oxide reduction peak in 1.0 м H_2SO_4 (ref.[12]). Electrochemical parameters were estimated from three independent measurements.

Spectroscopy

The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, on a Varian Unity Inova 300 spectrometer in $CDCl_3$ unless stated otherwise. The NMR chemical shifts are expressed in δ (ppm) to tetramethylsilane; coupling constants (*J*) in Hz. Infrared spectra (ν in cm^{-1}) were recorded for KBr disks on a Perkin–Elmer Spectrum GX FT-IR spectrometer, and FT-Raman spectra of crystals (Δν in cm^{-1}) were acquired on a Perkin–Elmer NIR

Spectrum GX FT-Raman spectrometer. Raman spectra were excited with a Nd-YAG laser operating at 1064 nm wavelength. FT-SERS spectra were recorded on the same instrument. In order to reduce photo- and/or thermoeffects, the spectroelectrochemical cell, together with the working electrode, was moved linearly with respect to the laser beam (ca. 20 mm/s)[13]. The experiments were carried out in the 180° geometry.

All reactions were carried out under dry nitrogen atmosphere. Melting points were determined with an electrothermal apparatus and are uncorrected.

Synthesis of 2-[(ω-Haloalkyl)amino]-1,4-naphthoquinones (**1a**–**1c**). General Procedure

To a refluxed mixture of 1,4-naphthoquinone (6.3 mmol) and (ω-haloalkyl)amine hydrohalogenide (7.3 mmol) in acetonitrile (20 ml), a solution of $(C_2H_5)_3N$ (7.3 mmol) in acetonitrile (20 ml) was added dropwise during 0.5 h, and the mixture was refluxed for additional 0.5 h. The reaction mixture was cooled, water (100 ml) was added, and the product was collected by filtration, washed with water, methanol and ether, and recrystallized from acetonitrile.

2-[(2-Bromoethyl)amino]-1,4-naphthoquinone (**1a**). Orange crystals. Yield 0.5 g (28%), m.p. 174–176 °C. For $C_{12}H_{10}BrNO_2$ (280.1) calculated: 51.45% C, 3.60% H, 28.53% Br; found: 50.95% C, 3.43% H, 28.50% Br. ^{1}H NMR: 8.12–7.61 m, 4 H (C_6H_4); 6.17 br s, 1 H (NH); 5.77 s, 1 H (CH); 3.8–3.4 m, 4 H (CH_2CH_2). ^{13}C NMR: 28.9 (CH_2), 43.7 (CH_2), 101.5 (CH), 126.1 (CH), 126.3 (CH), 130.4 (C), 132.2 (CH), 133.2 (C), 134.8 (CH), 147.3 (C-N), 181.4 (C=O), 183.1 (C=O). IR: 1677 (C=O), 3348 and 3266 (N–H). Raman: 1677 (C=O), 3265 (N–H).

2-[(3-Bromopropyl)amino)-1,4-naphthoquinone (**1b**). Orange crystals. Yield 0.6 g (32%), m.p. 169–171 °C. ^{1}H NMR: 8.12–7.60 m, 4 H (C_6H_4); 5.97 br s, 1 H (NH); 5.79 s, 1 H (CH); 3.49 t, J = 6.2, 2 H (CH_2Br); 3.43 q, J = 6.5, 2 H (CH_2N); 2.23 m, 2 H (CCH_2C). ^{13}C NMR: 30.0 (CH_2), 30.5 (CH_2), 40.7 (CH_2), 101.2 (CH), 126.2 (CH), 126.3 (CH), 130.4 (C), 132.0 (CH), 133.4 (C), 134.8 (CH), 147.7 (C-N), 181.7 (C=O), 182.9 (C=O). IR: 1671 (C=O), 3338 (N–H). Raman: 1668 (C=O), 3343 (N–H).

2-[(2-Chloroethyl)amino]-1,4-naphthoquinone (**1c**). Orange crystals. Yield 0.4 g (27%), m.p. 163–165 °C.; lit.[14] gives 148 °C. ^{1}H NMR: 8.13–7.62 m, 4 H (C_6H_4); 6.17 br s, 1 H (NH); 5.78 s, 1 H (CH); 3.79–3.75 m, 2 H (CH_2Cl); 3.62–3.56 m, 2 H (CH_2N). IR: 1678 (C=O), 3262 (N–H). Raman: 1673 (C=O), 3263 (N–H).

Synthesis of *S*-{ω-[(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)amino]alkyl}isothiouronium Bromides (**2a**, **2b**). General Procedure

Thiourea (12.25 mmol) was dissolved in boiling ethanol (30 ml), the appropriate 2-[(ω-bromoalkyl)amino]-1,4-naphthoquinone (**1a** or **1b**; 3.5 mmol) was added and the mixture was refluxed for 2.5 h. The precipitated product was collected by filtration, washed with acetone, CH_2Cl_2 and dried.

S-{2-[(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)amino]ethyl}isothiouronium bromide (**2a**). Orange crystals. Yield 1.0 g (80%), m.p. 230–233 °C. ^{1}H NMR ($(CD_3)_2SO$): 9.08 br s, 4 H (NH_2 and NH_2^+); 8.03–7.73 m, 4 H (C_6H_4); 7.63 br t, 1 H (NH); 5.85 s, 1 H (CH); 3.56–3.40 m, 4 H (CH_2CH_2). IR: 1678 (C=O), 1655 (C=N, NH_2 def.), 2698, 2728 and 2766 (NH^+), 3187, 3334 and 3437 (N–H). Raman: 1676 (C=O), 3348 (N–H).

S-{3-[(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)amino]propyl}isothiouronium bromide (**2b**). Orange crystals. Yield 1.1 g (82%), m.p. 225–230 °C. ^{1}H NMR ($(CD_3)_2SO$): 9.04 br s, 4 H (NH_2 and NH_2^+); 8.02–7.72 m, 4 H (C_6H_4); 7.68 br t, 1 H (NH); 5.76 s, 1 H (CH); 3.34–3.19 m, 4 H (CH_2N and CH_2S); 1.96 m, 2 H (CCH_2C). IR: 1678 (C=O), 1655 and 1633 (C=N, NH_2 def.), 2727 (NH^+), 3255 and 3330 (N–H). Raman: 1680 (C=O), 3334 (N–H).

Synthesis of 2-[(ω-Sulfanylalkyl)amino]-1,4-naphthoquinones (**3a**, **3b**). General Procedure

To a mixture of $Na_2S_2O_5$ (1.8 mmol), water (50 ml) and $CHCl_3$ (70 ml), an appropriate isothiouronium bromide **2a** or **2b** (1.0 mmol) was added, and the reaction mixture was vigorously stirred and refluxed for 3 h under argon. The organic layer was separated, washed with water (2×), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from a mixture hexane/CH_2Cl_2 (3:1).

2-[(2-Sulfanylethyl)amino]-1,4-naphthoquinone (**3a**). Orange crystals. Yield 0.16 g (70%), m.p. 142–147 °C (dec.). For $C_{12}H_{11}NO_2S$ (233.3) calculated: 61.78% C, 4.75% H, 13.74 S; found: 62.07% C, 5.13% H, 13.62% S. ^{1}H NMR: 8.12–7.60 m, 4 H (C_6H_4); 6.17 br s, 1 H (NH); 5.76 s, 1 H (CH); 3.43 q, J = 6.4, 2 H (CH_2N); 2.82 dt, J = 6.6 and 8.5, 2 H (CH_2S); 1.49 t, J = 8.5, 1 H (SH). ^{13}C NMR: 22.9 (CH_2), 45.1 (CH_2), 101.3 (CH), 126.1 (CH), 126.2 (CH), 130.4 (C), 132.1 (CH), 133.4 (C), 134.7 (CH), 147.5 (C-N), 181.6 (C=O), 183.0 (C=O). IR: 1682 (C=O), 2550 (S–H), 3242 and 3346 (N–H). Raman: 1680 (C=O), 2559 (S–H), 3245 (N–H).

2-[(3-Sulfanylpropyl)amino]-1,4-naphthoquinone (**3b**). Orange crystals. Yield 0.18 g (72%), m.p. 152–156 °C (dec.). For $C_{13}H_{13}NO_2S$ (247.3) calculated: 63.13% C, 5.30% H, 12.97 S; found: 63.53% C, 5.26% H, 12.58% S. ^{1}H NMR: 8.12–7.60 m, 4 H (C_6H_4); 5.96 br s, 1 H (NH); 5.77 s, 1 H (CH); 3.40 q, J = 6.5, 2 H (CH_2N); 2.65 dt, J = 6.8 and 7.9, 2 H (CH_2S); 2.03 m, 2 H (CCH_2C); 1.42 t, J = 7.9, 1 H (SH). ^{13}C NMR: 21.9 (CH_2), 31.8 (CH_2), 40.8 (CH_2), 101.0 (CH), 126.1 (CH), 126.2 (CH), 130.4 (C), 132.0 (CH), 133.5 (C), 134.8 (CH), 147.8 (C-N), 181.8 (C=O), 182.9 (C=O). IR: 1672 (C=O), 2532 and 2560 (S–H), 3338 (N–H). Raman: 1670 (C=O), 2567 (S–H).

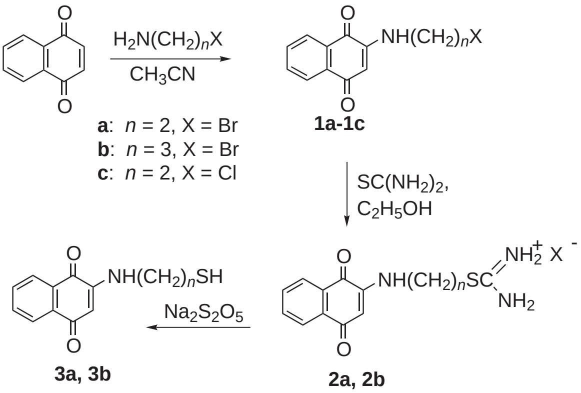
RESULTS AND DISCUSSION

Synthesis, Electrochemistry and Spectroscopy

Considering the problems discussed above, our objective was to synthesize NQ derivatives bearing the redox-active moiety attached to the NQ ring via nitrogen atom and containing thiol-functionalized alkyl chains of short lengths for SAM-forming. Recently we have demonstrated that 2-methyl-1,4-naphthoquinone (2-MeNQ) derivatives containing surface active (ω-sulfanylalkyl)alkanoate group with 5–12 atoms in the side chain form stable self-assembled monolayers on gold[15]. Herein, we present the synthesis of the novel NQ derivatives with a shorter side chains containing (2-sulfanylethyl)amino or (3-sulfanylpropyl)amino groups at C-2 of NQ, and an introductory study of their interfacial properties on gold.

The strategy used to obtain the title derivatives of NQ was based on direct functionalization of the quinone ring with the corresponding terminal substituted alkylamines. Direct interaction of bifunctional reagents with NQ is complicated due to multiple reaction pathways, e.g. intramolecular reaction of the reagent, attack of the NQ ring at different positions, further cyclization, etc., that may lead to complex mixtures of products. In general, derivatives of the amino group linked to the NQ ring are obtained via substituted NQ as for example halo derivatives of NQ [16]. One should have in mind that direct reaction of amines with NQ proceeds as addition to the double bond of the NQ ring with simultaneous rearrangement to naphthalene-1,4-diol, which is subsequently oxidized with a second molecule of NQ [17]. Thus, the yield is usually low, and separation as well as purification of the reaction mixture is quite tedious.

The synthesis of the 1,4-naphthoquinones linked with a short chain via nitrogen atom to terminal thiol group was accomplished using the pathway presented in Scheme 1. 2-Bromo- or 2-chloro-substituted alkylamines **1a**–**1c** were obtained by direct functionalization of 1,4-naphthoquinone with the corresponding bromo- or chloroalkylamines in acetonitrile. Yields of these reactions were moderate due to the side reactions mentioned above. Synthesis of the respective chloro derivative **1c** is described in the literature using reaction pathway which involves opening of the aziridine ring with 10% HCl solution[14]. However, formation of isothiouronium chloride from chloro derivative **1c** proceeded very slowly, therefore this compound was not used for further synthesis. In addition, the purification of target compounds was tedious reducing the yield.



SCHEME 1

The subsequent steps included synthesis of isothiouronium salts **2a**, **2b**, which were obtained by refluxing **1a**, **1b** in ethanol with an excess of thiourea. Decomposition of the isothiouronium salts in water/chloroform heterogenous mixture containing $Na_2S_2O_5$ under argon smoothly afforded thiols **3a**, **3b** in good yields. The ordinary procedure of the decomposition of isothiouronium salts with aqueous sodium hydroxide could not be used in this work due to the instability of NQ ring under these conditions.

The structure of the synthesized compounds was confirmed by ^1H and ^{13}C NMR, IR and FT-Raman spectroscopies, showing characteristic features of the NQ ring system and attached substituents, namely NH and SH groups.

Compounds **3a** and **3b** were tested for the formation of self-assembled monolayers on Au by cyclic voltammetry and Fourier-transform surface-enhanced Raman spectroscopy methods.

Cyclic voltammograms of the Au electrode modified by compound **3a** (Fig. 1) clearly show reduction and oxidation waves the parameters of which depend on the potential (*E*) sweep rate (*v*). Cathodic and anodic peak-currents depend linearly on *v* confirming irreversible coupling of the compound to gold.

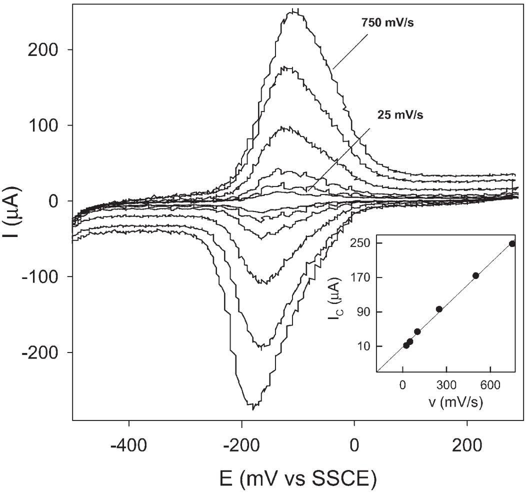


FIG. 1
Cyclic voltammograms of the electrochemically roughened Au electrode, modified with compound **3a**, recorded in 0.1 M $HClO_4$ at different potential (*E*) scan rates (25, 50, 100, 250, 500 and 750 mV/s). Inset: plot of the cathodic peak-current, I_c, vs potential scan rate, *v*

The main electrochemical parameters obtained in 0.1 M $HClO_4$ solution at 25 °C are given in Table I.

The estimated Γ values are about 2.2 times lower than the expected value of 6.1×10^{-10} mol/cm^2 for the close-packed assembly, considering that one vertically oriented NQ group occupies ca. 0.27 nm^2 (estimated using the semi-empirical PM3 method[18]). This result shows that the monolayers are not close-packed, as expected for such short-chain thiol molecules. However, the experimental Γ value is larger by about 1.7 times as compared with the flat lying model monolayer (1.59×10^{-10} mol/cm^2), assuming that

TABLE I
Formal redox potentials ($E^{0'}$ vs SSCE), peak separation (Δ*E*) and surface coverage (Γ) of compounds **3a** and **3b** self-assembled on the gold surface

Compound	$E^{0'}$, mV	Δ*E*, mV	$\Gamma \times 10^{10}$, mol/cm^2 [a]
3a	–146 ± 11	41 ± 6	2.6 ± 0.2
3b	–138 ± 20	62 ± 10	2.8 ± 0.3

[a] Estimated taken into account the 2 e, 2 H$^+$ reduction mechanism.

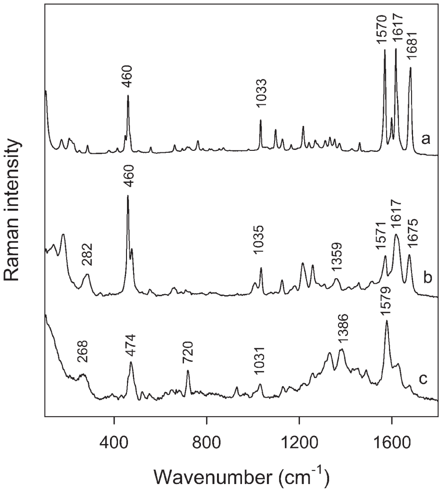


FIG. 2
FT-Raman and FT-SERS spectra of compound **3a**: FT-Raman spectrum of solid compound (a); FT-SERS spectra of self-assembled **3a** on gold in 0.1 M $HClO_4$ solution at *E* = 0.2 V vs SSCE (b), and at *E* = –0.35 V (c). Laser power at the sample: a 200 mW, b and c 300 mW

one NQ group occupies ca. 1.04 nm^2. The $E^{0'}$ values are more negative by about 100 mV as compared with those reported previously for monolayers self-assembled on Au from short-chain 2-MeNQ derivatives containing (ω-sulfanylalkyl)alkanoate groups[15].

On the formation of SAM, the band of S–H stretching vibration observed in the FT-Raman spectrum of solid **3a** at 2559 cm^{-1} (not shown in Fig. 2) disappears and a new band emerges in the FT-SERS spectrum at 282 cm^{-1} (Fig. 2, trace b). This new band is attributable to the stretching vibration of Au–S (ref.[19]).

These results clearly point out that chemisorption of compound **3a** proceeds through S atom. When the potential of the Au electrode is switched to more negative values than the peak-potential of the cathodic process in Fig. 1, the band at 1675 cm^{-1}, characteristic of C=O stretching in the quinone ring[20], significantly decreases in intensity, and new bands at 1386 and 720 cm^{-1}, characteristic of the substituted naphthalene ring[21], become apparent in the FT-SERS spectrum (Fig. 2, trace c). This indicates that the NQ group transforms to naphthalenediol during the reduction process.

In conclusion, the obtained results demonstrate that the synthesized 1,4-naphthoquinones linked via nitrogen atom through the short chain to the terminal sulfanyl group form self-assembled monolayers on Au. Cyclic voltammograms combined with in situ Fourier-transform surface-enhanced Raman spectra of the Au electrode modified with the title compounds clearly evidence that the naphthoquinone moiety transforms into naphthalenediol during the reduction process.

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