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Nitrooxyquinones: synthesis, X-ray diffraction and electrochemical studies

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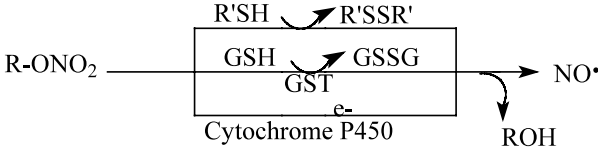
Abstract—2-Methyl-3-(nitrooxymethyl)-[1,4]-naphthoquinone and 2-(nitrooxymethyl)-[9,10]-anthraquinone, the first representatives of quinone-derived organic nitrates, potential hybrid drugs, were obtained and characterized through X-ray diffraction. Voltammetric studies showed that reductive elimination occurs, after quinone reduction. The NO_3^- release, leading to electrogenerated quinonemethide, would suggest a quinone-driven biological activity. © 2002 Elsevier Science Ltd. All rights reserved.

Organic nitrates are recognised as being able to relax vascular smooth muscle and represent the oldest class of NO donors that have been clinically applied.[1,2] NO is currently one of the most studied molecules in the biomedical sciences. This interest is driven by the multiplicity of roles that NO[2,3] plays. The NO release from organic nitrates requires either enzymatic or nonenzymatic bioactivation where a three-electron reduction thiol-dependent is involved (Scheme 1).[4] The biochemical mechanism of NO release from organic nitrates has not been fully defined.[4] Nitrosothiol formation and enzymatic conversion have been considered to explain the formation of nitric oxide from nitrates.[2,5] Specific thiols, for example, cysteine, interact with nitrates to give nitrites and NO in sequence.[2] Evaluation of NO release is possible through the measurement of NO_2^-, by the use of the Griess reaction.[6]



Scheme 1. Probable in vivo pathways of NO liberation from organic nitrates.[4] GST (glutathione transferase), GSH (reduced glutathione), GSSG (oxidized glutathione).

Additionally, numerous quinones play vital roles in the biochemistry of living cells and exert biological activities.[7] As the nitrate is a good leaving group, those quinones can alternatively generate quinonemethides after reduction[8] and eventually behave as bioreductive alkylating reagents.[9]

As seen, both processes, NO release or quinonemethide generation, would depend on a preliminary reduction. As such, one additional goal of the present work is to use electrochemical methods (cyclic voltammetry) to obtain information about the reduction behaviour of those hybrid compounds. Comparison of electrochemical data with results from in vitro released-NO_2^- quantification methods would be valuable and in case of a positive correlation, add value for the use of electrochemical methods as tools in the field of NO chemistry, apart from analytical determinations.[10]

In general, organic nitrates can be readily prepared from the esterification of the corresponding alcohols with nitric acid, in the presence of sulphuric acid, or by substitution between reactive alkyl halides and $AgNO_3$.[11]

In the present case, 2-methyl-3-(nitrooxymethyl)-[1,4]-naphthoquinone (**1**) and 2-nitrooxymethyl-[9,10]-anthraquinone (**2**) were prepared from the corresponding bromides through $AgNO_3$ displacement reactions.[12] Light yellow crystals suitable for X-ray analysis were obtained from **1** from a solution of hexane:ethylacetate (9:1). Compound **2** was prepared

Keywords: quinones; organic nitrates; redox potential; cyclic voltammetry; electrolysis; reductive elimination.

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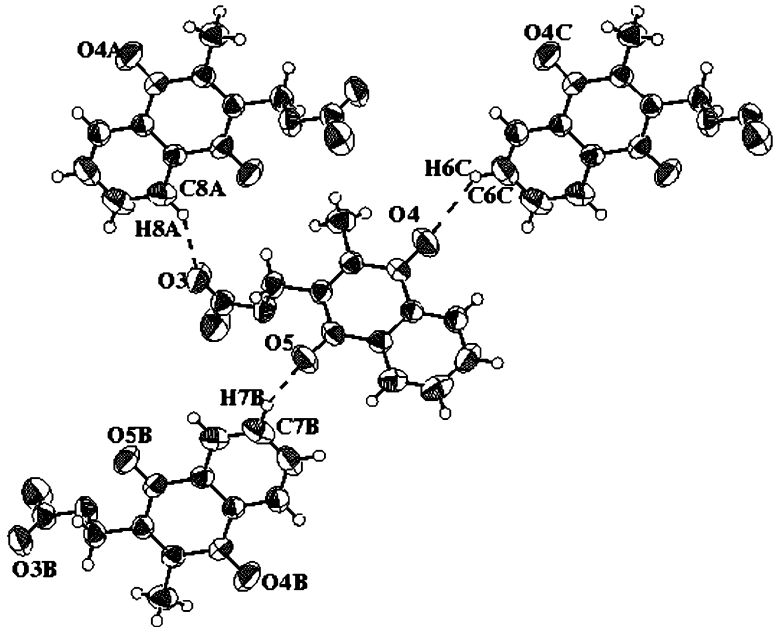


Figure 1. ORTEP3 view of **1** showing C–H···O interactions.

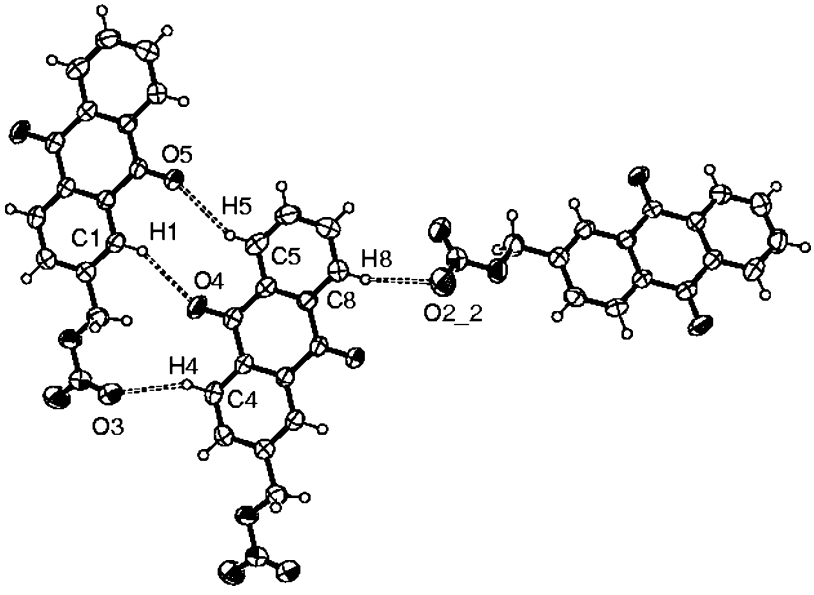
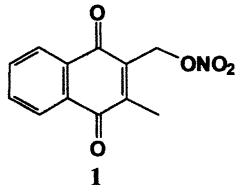
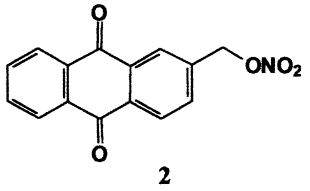


Figure 2. ORTEP3 view of **2** showing C–H···O interactions.

with a similar procedure. Light yellow crystals were obtained after silica gel chromatography, using 1:1 hexane:CH_2Cl_2.[12]



1



2

The single-crystal X-ray diffraction study of **1** and **2**, together with physical–chemical data analysis[12] allowed the structure elucidation.[15] ORTEP3 views of the molecular structures and the adopted numbering scheme are shown in Figs. 1 and 2.

The molecules are held together through van der Waals interactions, additionally there are three C–H···O weak hydrogen bondings for **1** and four hydrogen bondings for **2**: O4···H6C = 2.77 Å; C6C–H6C···O4 = 124.8°(2); O3···H8A = 2.48 Å; C8A–H8A···O3 = 144.6°(2); O5···H7B = 2.58 Å; C7–H7B···O5 = 155.6°(2) for **1** and O4···H1 = 2.51 Å; C1–H1···O4 = 151.2°(2); O5···H5 = 2.52 Å; C5–H5···O5 = 151.4°(2); O3···H4 = 2.67 Å; C4–H4···O3 = 155.3°(2); O2···H8 = 2.69 Å; C8–H8···O2 = 159.4°(2) for **2**, as shown in Figs. 1 and 2.

Compounds **1** and **2** have two reduction-activated pharmacophoric groups[4,7] as well as two electroactive groups.[16,17] The electrochemistry of quinones have been extensively reviewed[16] while for organic nitrates, the

information about electrochemical redox processes are quite scarce.[17] Such esters are reduced in a pH independent two-electron wave to nitrite ion and alcohol.[17,18]

$$R–O–NO_2+2e^-\rightarrow RO^-+NO_2^-$$

In organic medium, benzyl nitrate is reduced and the formed anion radical loses nitrite.[17]

The Griess reaction is largely used for determination of NO release through spectroscopic quantification of nitrite ion.[6]

In this work, **1** and **2** were assayed through Griess reactions,[19] in the presence and absence of cysteine, and submitted to cyclic voltammetry[20] experiments, in aprotic medium, in order to verify eventual release of NO_2^- and to study the electrochemical reduction process, respectively, to observe similarity or complementarity between the two methods. When considering such mechanisms, some questions arise, in particular, which group is more easily reduced, which are the structure'

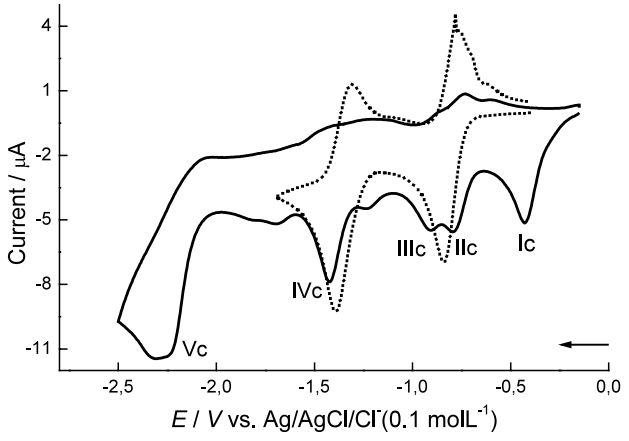


Figure 3. Cyclic voltammogram of (___) **1** and (.....) **3**. Hg electrode. DMF/TBAP 0.1 mol L^{-1}. $v=0.100$ V s^{-1}.

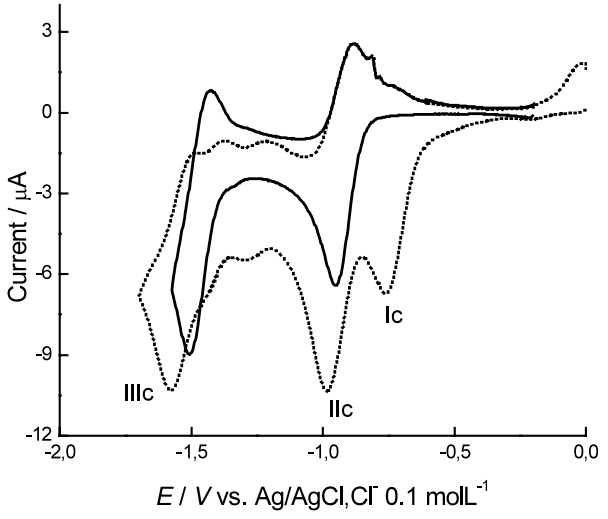


Figure 4. Cyclic voltammogram of (___) **2** and (.....) **4**. Hg electrode. DMF/TBAP 0.1 mol L^{-1}. $v=0.100$ V s^{-1}.

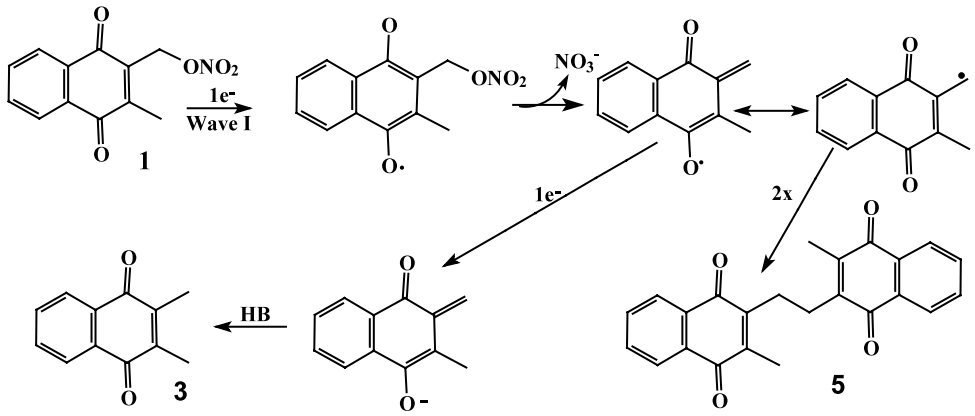
modifications after uptake of an electron and how many electrons can be transferred.

Compounds **1** and **2** do not release NO_2^-.[19]

Electrochemical studies, cyclic voltammetry[20] and electrolysis,[22] were performed in aprotic medium[20–22] and the unsubstituted quinones 2,3-dimethyl-1,4-naphthoquinone (**3**) and 2-methyl-9,10-anthracenedione (**4**) were used as standards. Compounds **3** and **4** showed behavior typical of quinones in aprotic medium. They are reduced in two pairs of diffusion-controlled peaks ($Ip\propto v^{1/2}$) corresponding to two sequential reversible and quasi-reversible one-electron transfer processes. E_{pIc} and E_{pIIc} were, for **3**, −0.838 and −1.393 V and, for **4**, −0.949 and −1.502 V ($v=0.100$ V s^{-1}) furnishing their radical anions and dianions, respectively (Figs. 3 and 4). The presence of the nitrooxy group in the allylic (**1**) and benzylic (**2**) positions modifies drastically the voltamogramms, with the observation of at least six waves for **1** (Fig. 3). The first cathodic wave ($E_{pIc}=-0.428$ V) has no anodic counterpart and, compared to the unsubstituted quinone **3**, suffers an intense anodic shift ($\Delta E_{pIc}=0.410$ V). The E_{pIc} dependence on v ($\partial E_{pIc}/\partial \log v=36$ mV) is indicative of an EC mechanism (electronic transfer with a coupled chemical reaction), probably an electronic transfer to the quinonoid group followed by the cleavage of C–ONO_2 bonding, releasing NO_3^-.

The quinonoid radical, generated after cleavage, can suffer dimerization, furnishing dimer **5**[23] or a second electron transfer, leading to the anion that can be protonated by trace amounts of residual water in the supporting electrolyte to give 2,3-dimethyl-1,4-naphthoquinone (**3**) (Scheme 2), both products prone to suffer additional reductions at E_{pIIc} and E_{pIIIc} at potentials close to E_{pIc} of **3** (Fig. 3). Additional waves suggest further reductions of the anion-radicals formed (E_{pIVc}). Waves Vc and shoulders are probably related to the resulting electrogenerated quinone methide and its reaction giving electroreducible dimers. Those are not examined in the present paper and complete electrochemical study will be published elsewhere. Electrolysis held at potential close to the first wave[22] ($E_{app}=-0.5$ V) led to the consumption of 1 mol electrons mol^{-1} and after workup furnished a complex mixture, where the presence of nitrate anion, **3** and **5** was evident.[22]

Concerning **2**, the first reduction wave has also an irreversible nature (no anodic counterpart) and occurs at $E_{pIc}=-0.764$ V, higher than the one for the standard **4** ($\Delta E_{pIc}=0.185$ V). Its height (I_{pIc}) is similar to the first wave of **4**, being related then to the transfer of one electron, as also proved by controlled potential electrolysis.[22] In addition, waves IIc and IVc with a more reversible character and similar heights were observed and are also related to successive monoelectronic transfers. IIc ($E_{pIIc}=-0.987$ V) is close to the first reduction wave of **4** ($E_{pIc}=-0.949$ V); while IVc is shifted to more negative potentials ($E_{pIVc}=-1.580$ V). Except for the first wave, the cyclic voltammogram follows the typical



Scheme 2. Probable pathway for the reduction of **1**.

behavior of quinones.[16,21] Electrolysis held at the first wave ($E_{app} = -0.800$ V)[22] furnished the original quinone **4** as the major product after consumption of 1 mol electrons mol^{-1}, as reported for acetate-derived anthraquinones.[24] Electrochemical studies of both nitrooxy-derived quinones showed that reductive cleavage occurs, with release of the nitrate anion, instead of nitrite anion, which corroborate results obtained from Griess reaction.

In summary, two new organic nitrates were synthesized and properly identified, using spectroscopic and X-ray diffraction methods. They belong to a class of bifunctional compounds not yet investigated from the biological point of view.

They are promising biologically active compounds and can belong to the class of 'hybrid drugs', that combine different pharmacophoric groups in a single molecule.[25] The use of hybrids could solve pharmacokinetic problems and replace the use of mixture of drugs.[25]

Voltammetric studies showed that reductive elimination occurs, after quinone reduction. The NO_3^- instead of NO_2^- release, leading to electrogenerated quinonemethide, would suggest a quinone-driven biological activity, more than a NO donor characteristic.

Acknowledgements

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12. 2-Methyl-3-(nitrooxymethyl)-[1,4]-naphthoquinone (**1**): 2-Bromomethyl-3-methyl-1,4-naphthoquinone[13] (0.200 g; 0.75 mmol) was mixed up with silver nitrate (0.250 g; 1.5 mmol) in 5 mL of acetone and the mixture was stirred, at room temperature for 2 h. The precipitate (AgBr) was removed through filtration and washed with ether (3×10 mL). The ethereal fractions were concentrated and the resulting mixture was chromatographed in silica gel column, eluted with hexane:ethylacetate (9:1), furnishing a yellow solid, mp 108.2–111°C, with 80% yield. IR (KBr) cm^{-1}: 1664 (νC=O), 1624 (ν_{as}O–NO_2), 1594 (νC=C), 1338, 1279 (ν_sO–NO_2), 961, 869, 701; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.14–7.78 (m, 4ArH); 5.59 (s, 2H, CH$_2$); 2.35 (s, 3H, CH$_3$). $C_{58.22\%}H_{3.72\%}N_{5.55\%}$, calcd $C_{58.30\%}H_{3.67\%}N_{5.67\%}$. 2-(Nitrooxymethyl)-[9,10]-anthraquinone (**2**): 2-Bromomethyl-[9,10]-anthraquinone (0.200 g; 0.66 mmol)[14] and silver nitrate (0.230 g; 1.3 mmol) in 5 mL of acetone were stirred for 3 h at room temperature. The precipitate (AgBr) was removed and washed several times with $CHCl_3$ (3×10 mL). The chloroform fractions were combined, evaporated at reduced pressure and chromatographed in silica gel, eluted with 1:1 hexane:methylenechloride, furnishing a light yellow solid, mp 177.0–177.8°C, with 80% yield. IR (KBr) cm^{-1}: 1680 (νC=O), 1620 (ν_{as}O–NO_2), 1595 (νC=C), 1338, 1280 (ν_sO–NO_2), 960, 869, 701. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.2–8.3 (m, 4ArH); 7.74–7.85 (m, 3ArH), 5.62 (s, 2H,

$C\underline{H}_2$ benzylic). MS (EI): m/z 284 (6), 283 (5), 237 (85), 236 (100%), 235 (46), 221 (19), 209 (82), 207 (24), 193 (14), 181 (67), 169 (14), 153 (44), 152 (68), 151 (70). $C_{63.46\%}H_{3.61\%}N_{4.61\%}$, calcd $C_{63.61\%}H_{3.20\%}N_{4.95\%}$.

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15. X-Ray crystallographic data for the two structures were recorded on an Enraf–Nonius CAD-4 diffractometer using graphite monochromated CuKα radiation (λ= 1.5418 Å) for **1** and MoKα radiation (λ=0.71070 Å) for **2** and $\omega/2\theta$ scan mode at room temperature (293 K). Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 188722 for **1** and CCDC 188723 for **2**. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CH2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk or hppt://www. ccdc. cam.ac.uk).
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19. Solutions (0.1 mmol L^{-1}) of **1** and **2** were prepared at 37°C, using 50 mmol L^{-1} phosphate buffer, pH 7.4 (diluting 10 mmol L^{-1} DMSO stock solutions) in the presence or absence of 5 mmol L^{-1} L-cysteine.[6]
20. Cyclic voltammetry (CV) of **1**–**4** was carried out as described[21] in DMF/TBAP 0.1 mol L^{-1}, on Hg.
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22. The electrolyses of **1** and **2** were carried out, as described.[21] Conventional divided glass cells (20 mL) were used with the anode and cathode compartments separated by medium porosity sintered glass. This solution was electrolysed on an Hg pool cathode held at –0.500 and –0.800 V versus Ag/AgCl, Cl^- 0.1 mol L^{-1} for **1** and **2**, respectively, under N_2, and after consumption of 1 mol electrons mol^{-1} and workup,[21] furnished 1,2-bis-(1,4-naphthoquinon-2-yl)-ethane (**5**):[23] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.13 (s, $C\underline{H}_3$, 6H), 2.8 (s, $C\underline{H}_2$, 4H), 8.2–7.5 (m, 8 Ar$\underline{H}$). ^{13}C NMR: 185, 184 (C=O), 147 (-C-), 132, 133 (-CH, ArH), 126 (-CH, ArH), 25 ($-CH_3$), 12.8 ($-CH_2$-CH_2). MS m/z (%) (5): 370 $M^{+\bullet}$ (100%), 355 ($M^{+\bullet}$–15), 341 ($M^{+\bullet}$–CHO), 327 ($M^{+\bullet}$–28), 299, 281, 265, 252, 237, 211, 186, 128, 115, 77.
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