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Concise synthesis and voltammetric studies of dielsiquinone, a cytotoxic azaanthraquinone

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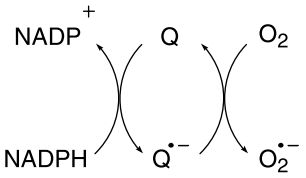
Abstract—We have developed a concise synthesis of dielsiquinone **1**, a potent cytotoxic agent related to anthraquinones. Electrochemical studies have shown that dielsiquinone is reduced to a semiquinone radical that does not react with O_2 to generate toxic reactive oxygen species. These results strongly suggest that **1** should be less cardiotoxic than anthracyclines used in clinic and may therefore provide the basis for the development of safer anticancer drugs.

In 1986, Maia and co-workers reported the isolation of dielsiquinone **1** from the plant *Gutteria dielsiana*.[1] However, it is only in 1999 that its cytotoxicity was reported, with a DE_{50} in a 0.1–1 μM range on many cancer cell lines.[2] The planar polycyclic aromatic structure of this compound presents some similarities with that of anthracyclins, such as doxorubicin and daunorubicin, which display their cytotoxicity by binding to DNA and stabilizing the topoisomerase II–ADN complex. The use in clinic of these chemotherapeutic agents is limited by their cardiotoxicity.[3] This adverse effect is caused by their ability to catalyze the formation of toxic superoxide anion radicals, through a process that involves their reduction by NADPH into a semiquinone radical that is reoxidized by oxygen (Scheme 1).[3,4] This process has been well characterized by electrochemical studies.[5,6] Many analogs of daunorubicin have been synthesized over the last two decades to obtain safer drugs. Few of these compounds have emerged into clinic, such as mitoxantrone or idarubicin.[3] However, the search for less cardiotoxic compounds remains a major aim in chemotherapy.[7]

The presence of a methoxy group on the pyrimidone moiety makes dielsiquinone very original and should stabilize the semiquinone radical **2** by captodative effect (Fig. 1).[8,9] If this were the case, **2** might not be able to react with O_2 to generate toxic superoxide anion radicals. To test this hypothesis, we have synthesized dielsiquinone and investigated its electrochemical properties.



Scheme 1. Catalytic production of superoxide by anthraquinones (Q).

Dielsiquinone had been synthesized in more than 13 steps.[10] We have developed a more concise approach based on the N-oxidation of **3** with the urea–hydrogen peroxide complex[11], followed by an in situ rearrangement (Scheme 2). Compound **3** was conveniently prepared, according to the procedure described by Kitahara et al.[12]

We have studied dielsiquinone's electrochemical properties by cyclic and stationary voltametry, according to the conditions established for daunorubicin and related anthraquinones.[5,6] Cyclic voltammogram of dielsiquinone displays a reversible reduction at $E_{1/2} = (E_{pa} + E_{pc})/2 = -0.64$ V/SCE (Fig. 1). In addition, the measured value $\Delta E = E_{pa} - E_{pc} = 60$ mV corresponds to the theoretical value for a one-electron process.

Keywords: Cancer; Anthraquinone; Voltametry.
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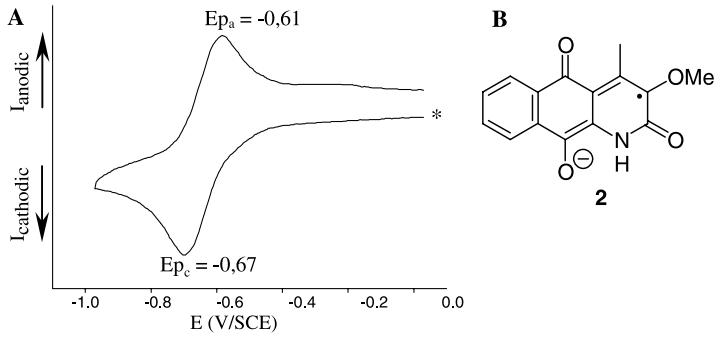
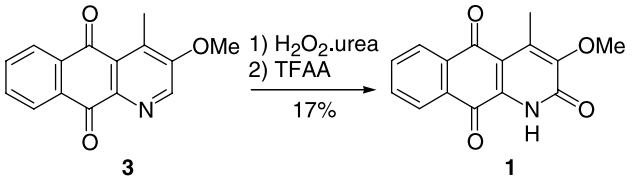


Figure 1. (A) Cyclic voltammogram of dielsiquinone in 0.1 M $TBAPF_6$/DMF. Working electrode : Pt Scan: 2 V s^{-1}. *, start of the scan. (B) Proposed structure of the radical anion **2** generated by a one-electron reduction.



Scheme 2. Synthesis of dielsiquinone.

This potential value suggests that **2** cannot be oxidized by O_2.[13]

Spectroelectrochemical experiments were carried out at this potential to determine whether O_2 could react with radical anion **2** (Fig. 2). When air is introduced, we observe the disappearance of the radical anion **2**. The product(s) of the reaction of **2** with O_2 display(s) a spectrum different from that of dielsiquinone (compare c with a).

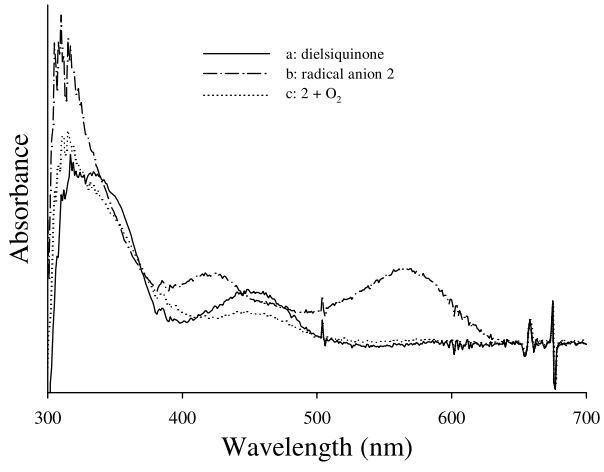


Figure 2. Spectroelectrochemical reduction of dielsiquinone in DMF ($C = 2.5 \times 10^{-3}$ mol l^{-1}). Data were recorded during a slow linear potential sweep (scan rate = 10 mV s^{-1}). Curve a: solution of dielsiquinone in 0.1 M $TBAPF_6$/DMF before reduction (continuous line); curve b: after one-electron reduction (dashed-dotted line); curve c: after placing the latter solution in contact with air (dotted line). Working electrode : Pt.

This evolution differs from the behavior observed by Anne and Moiroux for daunomycin[5,6] and suggests that the catalytic production of superoxide depicted in Scheme 1 does not occur with dielsiquinone.

These results indicate that dielsiquinone should be less cardiotoxic that anthraquinones used in clinic and may therefore provide the basis for the development of safer antineoplasic agents.

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13. $O_2^{\cdot-}/O_2$: $E_{1/2} = -0.80$ V/SCE in DMF.