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Novel epoxide formation in the reaction of 2-bromo-3-methyl-1,4-naphthoquinone with 1,3-propanedithiol

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ABSTRACT

A novel epoxide **2** was formed as the major product in the reaction of 2-bromo-3-methyl-1,4-naphthoquinone with 1,3-propanedithiol in the presence of triethylamine in 92% yield. Molecular oxygen is suggested to be the source of the added oxygen in **2**, an oxidation product of its precursor **3**. A strong base such as triethylamine is required to abstract the methyl hydrogen of 1,4-naphthoquinones, leading to the formation of **3** as well as **2**.

The reactivity of 1,4-naphthoquinones toward a nucleophile is important for the understanding of their biological activities.[1–3] Various 1,4-naphthoquinone derivatives, including 2-methyl-1,4-naphthoquinone, have shown anticancer activity by inhibiting overexpressed tyrosine phosphatase of cdc25a in cancer cells.[4] These biological activities of 1,4-naphthoquinonoes are understood as the consequence of the covalent modification of a nucleophilic center such as cysteine residues in the active site of tyrosine phosphatase. The covalent modification of a nucleophile by 1,4-naphthoquiones is initiated with a conjugate addition reaction of a nucleophile to the qunonoid structure of 1,4-naphthoquinones. Due to the acidic nature of the methyl hydrogen of 2-methyl-1,4-naphthoquinones, a nucleophile could further react at the methyl group.

In this Letter, we describe the reaction of 2-bromo-3-methyl-1,4-naphthoquinone **1** with 1,3-propanedithiol in the presence of triethylamine. Depending upon the reaction setting, four different products are isolated (Fig. 1). Typically, 2-bromo-3-methyl-1,4-naphthoquinone (~20 mg) is reacted with 2 equiv of 1,3-propanedithiol in the presence of 2 equiv of triethylamine in methanol (10 mL). When the reaction is assisted by microwave[5] (at 80 °C for 20 min), the epoxide **2** is isolated in 92% yield, accompanied by two tricyclic products, **3** (3%), and **4** (3%) after purification on a silica gel column with chloroform as the eluent. From the reaction at room temperature for a week, dithiacyclooctene **3** is isolated (35%) as one of the major products, along with dithiacycloheptene **4** (39%). After reacting at −4 °C for two weeks, on the other hand, a spiro product, **5**, was found as the major product (45%) with the epoxide **2** as a minor product (18%).

Products **2** and **3** are formed in the presence of a strong base such as triethylemine due to the acidic nature of the methyl group.[6] The acidic nature of the methyl group of 2-halogeno-3-methyl-1,4-naphthoquinone as well as 2-alkylthio-3-methyl-1,4-naphthoquinone is demonstrated by the H–D exchange reaction in the presence of triethylamine in deuterated methanol, yielding the corresponding 3-duteriomethyl-1,4-naphthoquinone.[7] The reaction at the methyl group with a thiolate ion was reported in the reaction of 2-chloro-3-methyl-1,4-naphthoquinone with sodium methanethiolate.[8] Here, the primary product, 2-methyl-3-methylthio-1,4-naphthoquinone, is further converted to 2-methylthio-3-methylthiomethyl-1,4-naphthoquinone through a quinone methide, which is generated by the abstraction of an acidic methyl proton of 2-methyl-3-methylthio-1,4-naphthoquione. On the other hand, the formation of **4** is the result of a demethylation reaction. A similar demethylation reaction by a nucleophile was also found when 2-bromo-3-methyl-1,4-naphthoquinone was reacted with an alkylamine as a nucleophile, where the methyl group was replaced with the alkylamino group.[9]

In the reaction in chloroform as the solvent, instead of methanol, the epoxide **2** was also identified as the major product when assisted by microwave. Interestingly, however, under argon atmosphere, no epoxide formation was detected in either solvent. Thus, molecular oxygen is suggested as the source of oxygen for the formation of the epoxide **2**. The epoxidation of 2-methyl-1,4-naphthoquinone to the corresponding 2,3-epoxide is easily performed

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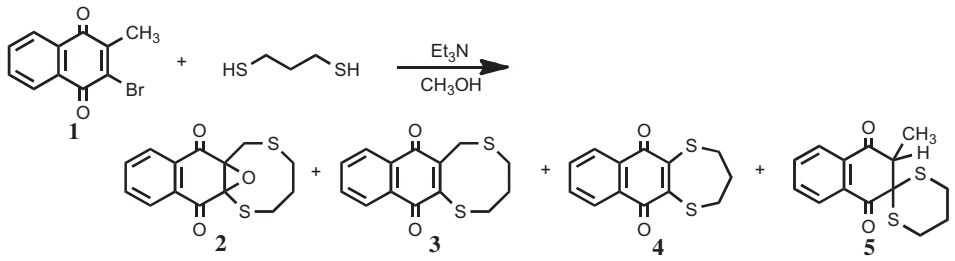
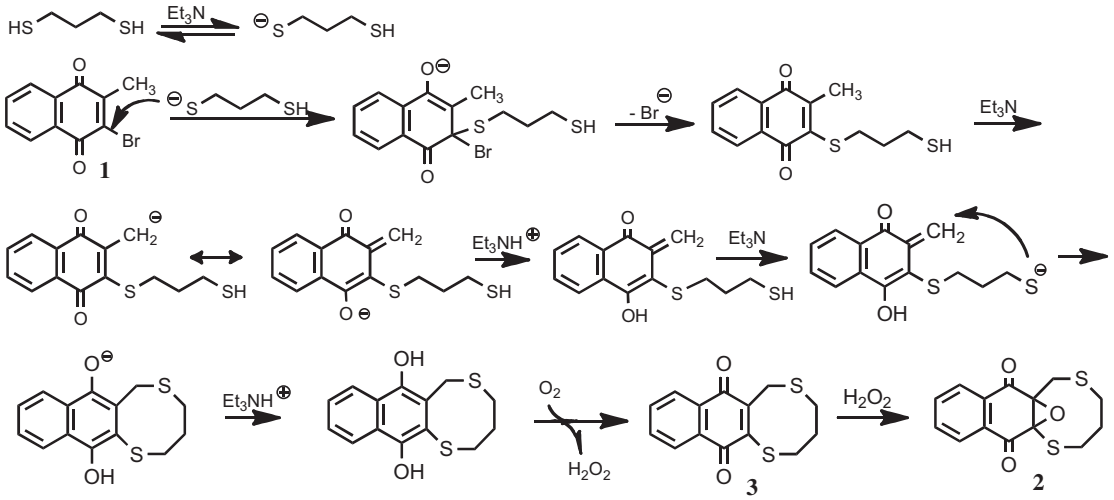


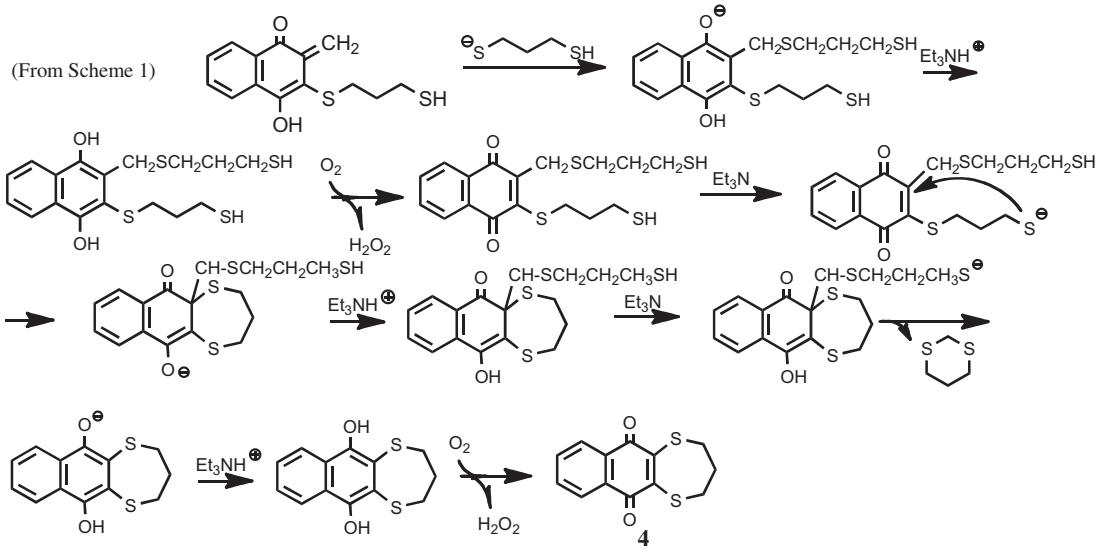
Figure 1. The reaction of 2-bromo-3-methyl-1,4-naphthoquinone with 1,3-propanedithiol.



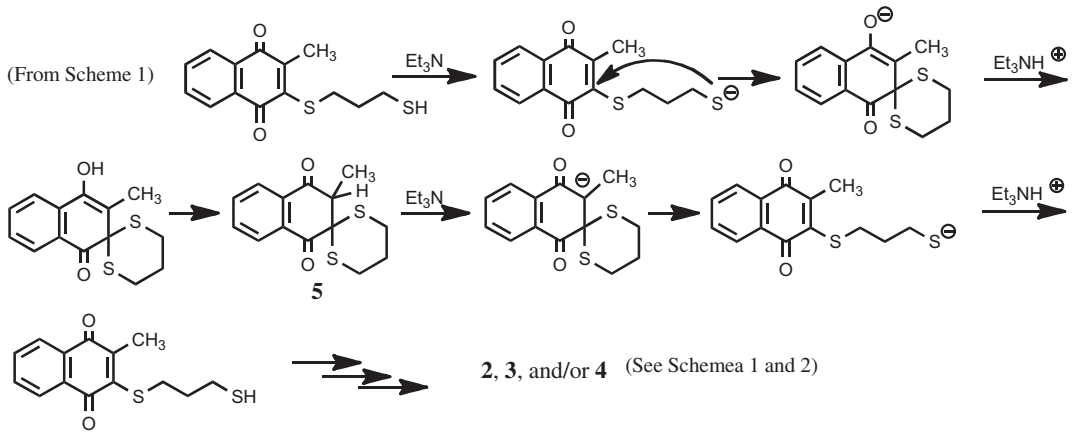
Scheme 1. A proposed pathway to **3** and **2**.

by the reaction with hydrogen peroxide in aqueous sodium carbonate solution.[10] In our reaction, molecular oxygen is anticipated to oxidize 1,4-naphthohydroquinone intermediates to the corresponding 1,4-naphthoquinones, generating hydrogen peroxide (see Schemes 1 and 2).[11] Thus, the formation of the epoxide **2** can be explained as the secondary reaction product from the cyclic product **3** with hydrogen peroxide, which is generated during the reaction. The mechanisms leading to two cyclic products, **3** and **4**, as well as the epoxide **2** are tentatively suggested in Schemes 1 and 2. The presence of a strong base such as triethylamine is crucial for the production of a quinone methide, and thus, **3** and **2**.

The spiro product, **5**, is the major product in the reaction at −4 °C and is transformed to cyclic products, **3** and **4**, upon the addition of excess 1,3-propanedithiol and triethylamine in methanol at



Scheme 2. A proposed pathway to **4**.



Scheme 3. A proposed pathway to **5** and its transformation to **3** and **4**.

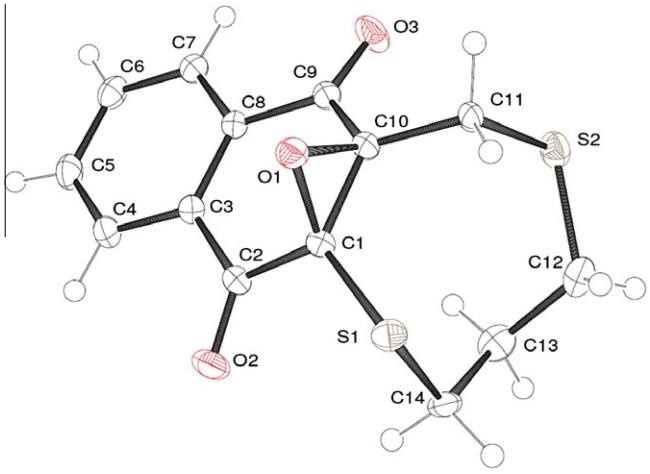


Figure 2. ORTEP drawing of the epoxide **2**.

room temperature. Thus, it is suggested that the spiro product, **5**, is a kinetic product in the reaction, whereas the cyclic products, **3** and **4**, are the thermodynamic products.

A mechanism is proposed for the formation of the spiro product **5** and its conversion to the thermodynamic products **3** and **2** in the presence of triethylamine (Scheme 3).

All products, **2**–**5**, were isolated by silica gel column chromatography and spectroscopically characterized.[12–15] The structure of the novel epoxide **2** is also confirmed by X-ray analysis (see Fig. 2, CCDC-720472).[16]

Other halogeno-1,4-naphthoquinones such as 2-chloro-, 2-bromo-, 2,3-dichloro-, and 2,3-dibromo-1,4-naphthoquinonoes, lacking the acidic methyl group, form cyclic product **4** in good yields in the reaction with 1,3-propanedithiol in the presence of triethylamine.[17] Further detailed study of the reactions of 1,4-naphthoquinones toward nucleophiles is under way to help better understanding biological activities of 1,4-naphthoqunones. The reaction caused by the acidic nature of the α-hydrogen, for example, leading to the formation of **2** and **3**, could result in another biological consequence of 2-methyl-1,4-naphthoquinones. It is not acidic enough to be easily ionized in solution. In the active site of an enzyme, however, due to the nature of the local environment, a particular pK_a value could be quite altered from the one in solution as in the lysine residue in the active site of acetoacetate decarboxylase.[18]

Acknowledgments

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5. A microwave reactor, Discover 1 by CEM Corporation (NC, USA) was used.
6. A weaker base such as *N*-methylimidazole does not abstract the hydrogen atom from the methyl group and thus does not yield **2** and **3**.
7. Further study on the acidity of the methyl hydrogen is currently in progress (Iverson, C. P.; Wenker, E.; Kim, T. T.; Otsuki, T.). For example, deuterated 2-bromo-3-methyl-1,4-naphthoquinone is detected by ^{1}H NMR spectroscopy in the deuterated methanol solution of 2-bromo-3-methyl-1,4-naphthoquinone in the presence of triethylamine.
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12. 1,2,3,4-Tetrahydro-2,3-epoxy-1,4-dioxonaphtho[*b*-2,3]-1,5-dithiacyclooctane (**2**): HR-CIMS *m/z*: 293.0299 (M+H)$^+$ (calcd for $C_{14}H_{13}O_3S_2$, 293.0306); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 1.63 (1H, m), 2.55 (2H, m), 2.85 (2H, m), 3.31 (1H, d, J = 14.8), 3.38 (1H, m), 3.91 (1H, d, J = 14.8), 7.79 (2H, m), and 8.09 (2H, m); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 30.67, 30.84, 31.08, 32.75, 69.26, 72.20, 127.83, 128.18, 131.56, 131.80, 134.98, 187.98 and 189.24; IR (KBr): 1689 and 1591 cm^{-1}.
13. 1,4-Dihydro-1,4-dioxonaphtho[*b*-2,3]-1,5-dithiacyclooctene (**3**): ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 2.35 (2H, m), 2.80 (2H, t, J = 5.7), 3.47 (2H, *t*, J = 5.9), 4.22 (2H, s), 7.74 (2H, m), and 8.13 (2H, m); ^{13}C-NMR [$CDCl_3$, 100 MHz]: δ 27.23, 27.57, 33.99, 36.52, 125.05, 127.07, 127.28, 132.19, 133.80, 134.38, 141.10, 145.80, 180.75 and 189.29; IR (KBr): 1651 and 1666 cm^{-1}.
14. 1,4-Dihydro-1,4-dioxonaphtho[*b*-2,3]-1,4-dithiacycloheptene (**4**): ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 2.17 (2H, quintet, J = 6.0), 3.63 (4H, t, J = 6.0), 7.67 (2H, dd, J = 4.2, 2.0), and 8.04 (2H, dd, J = 4.2, 2.0); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 26.62, 30.48, 127.05, 131.93, 133.92, 144.59, 180.42; IR (KBr): 1655 cm^{-1}.
15. 1′,3′-Dithiacyclehexane-spiro-2-2,3-dihydro-3-methyl-1,4-naphthoquinone (**5**): ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 1.49 (3H, d, J = 6.9), 1.88 (1H, m), 2.15 (1H, m), 2.60 (2H, m), 3.25 (1H, m), 3.37 (1H, m) 3.41(1H, q, J = 6.9), 7.74 (2H, m), and 7.97 (2H, m); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 13.22, 23.89, 27.34, 28.27, 53.27, 58.42, 126.40, 128.01, 132.24, 132.36, 134.11, 134.46, 189.31, and 195.74; IR (KBr): 1694 and 1591 cm^{-1}.
16. The X-ray analysis of epoxide **2** was performed at Center of Molecular Structure, California State University at Fullerton. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-720472. Copies of the data can be obtained free of charge via

www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.

17. The replacement of halogen with a thiolate ion is initiated by conjugate addition of thiolate, then, eliminating halide ion as in the first step in Scheme 1. The addition of thiolate at the unsubstituted position of 2-chloro- or 2-bromo-1,4-naphthoquinone is assumed to go through a sequence of conjugate addition, keto-enol tautomerization to a 1,4-naphthohydroquinone derivative, followed by oxidation. The mechanistic study on the details is under way.
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