Research Article

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Antimalarial sulfide trioxanes: a revision of mechanism

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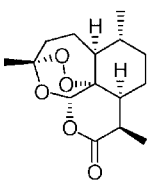
The mechanism by which an antimalarially inactive sulfanyl trioxane reacts with ferrous iron is revised. Although originally proposed to involve a short-lived high-valent iron-oxo intermediate, the revised mechanism involves $FeBr_2$ acting as a weak Lewis acid promoting intramolecular redox chemistry between the peroxide unit and the resident sulfanyl sulfur atom; one of the peroxide oxygen atoms is transferred intramolecularly to the neighboring sulfide sulfur atom, oxidizing it into a sulfoxide and reducing the trioxane into a non-peroxidic dioxolane. This facile ferrous iron-triggered conversion of the parent 1,2,4-trioxane sulfide into the corresponding 1,3-dioxolane sulfoxide accounts for the observed lack of antimalarial activity of the parent sulfanyl trioxane without invoking the intermediacy of a high-valent iron-oxo species. Copyright © 2008 John Wiley & Sons, Ltd.

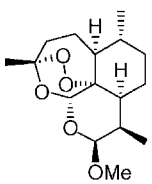
Keywords: peroxides; mechanism of action; intramolecular redox chemistry

INTRODUCTION

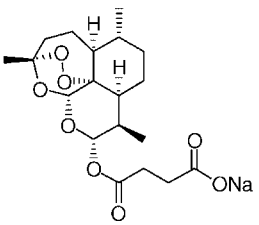
Ancient herbal remedies in China have led to modern antimalarial drugs characterized chemically by a peroxide pharmacophore.[1,2] Ferrous (e.g., heme) iron-triggered reductive cleavage of such O—O bonds in antimalarial 1,2,4-trioxanes like natural artemisinin (**1**) and its derivatives artemether (**2**) and sodium artesunate (**3**) initiates a cascade of chemical steps producing cytotoxic reactive intermediates which kill the malaria parasites in infected human red blood cells.[3–5] Such cytotoxic intermediates include carbon-centered radicals,[6] electrophilic epoxides,[7] and putative high-valent iron-oxo species.[8–10] Evidence supporting the intermediacy of high-valent iron-oxo species includes Fourier transform infrared spectroscopic data,[11] rearrangement of hexamethyl Dewar benzene into hexamethylbenzene, oxidation of toluene into benzyl alcohol, and oxidation of thioanisole into methyl phenyl sulfoxide.[12]



artemisinin (**1**)



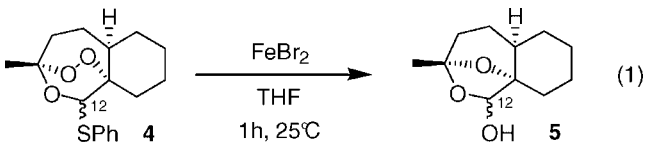
artemether (**2**)



sodium artesunate (**3**)

DISCUSSION

Years ago, we reported synthesis of simplified stable 12-phenylthiotrioxanes **4** designed to react with ferrous iron to form a putative high-valent iron-oxo intermediate.[13] Ferrous bromide-induced room temperature cleavage of phenylthiotrioxanes **4** is summarized in Eqn (1). Although the sulfones corresponding to sulfides **4** were shown *in vitro* to have potent antimalarial activity ($IC_{50} = 33–59$ nM), only the 12β-sulfide **4** was comparably active ($IC_{50} = 56$ nM); the 12α-sulfide **4** was not antimalarially active. We interpreted these results as shown in Scheme 1 in which release of Fe(IV)=O from the α-face of the C4-radical intermediate would be followed immediately by its oxidation of the nearby 12α-oriented sulfide sulfur atom. Ferrous bromide-promoted hydrolysis of the C12-sulfinyl monothioacetal functional group in intermediate **8** would then form the observed lactol **5**.



(1)

12α 53%
12β 0%

We now reinterpret these results without postulating the intermediacy of a short-lived high-valent iron-oxo species in this case. Scheme 2 summarizes our new current mechanistic understanding. *In silico* Hartree–Fock calculations of the ground state structure of 12α-sulfide **4** show that the sulfide sulfur atom is significantly closer to O2 (3.06 Å) than O1 (3.22 Å).[14] Assisted by

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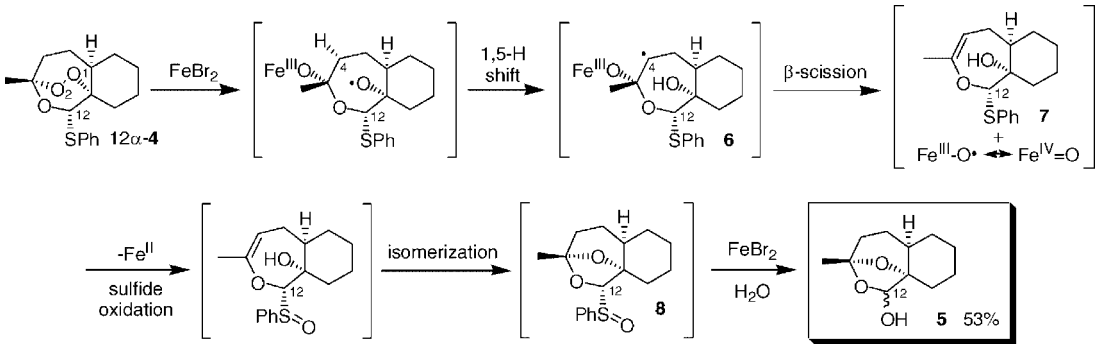
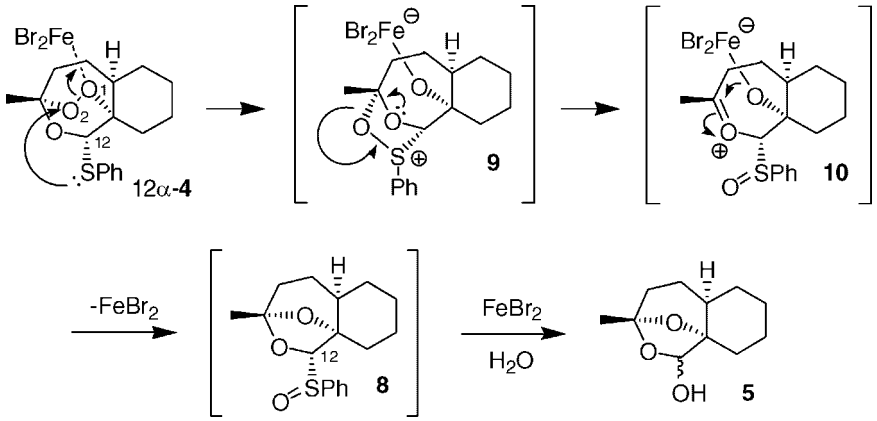


Scheme 1.



Scheme 2.

coordination of the hard but weak Lewis acid ferrous bromide to O1,[15] neighboring sulfide sulfur atom nucleophile attack on the proximal O2 atom would form, via a favorable 5-centered transition state, peroxide-cleaved intermediate **9** and then oxonium intermediate **10**; release of ferrous bromide from oxonium intermediate **10** and dioxolane ring closure would form C12-sulfinyl thioacetal **8** in which the original O2 peroxide oxygen atom is now located in the sulfoxide functionality. Ferrous bromide-promoted aqueous hydrolysis of C12-sulfinyl thioacetal **8** would then form the observed lactol **5**. This mechanism invokes O2 atom transfer to (i.e., oxidation of) the polarizable 12α-sulfide sulfur atom, in this case without the originally proposed intermediacy of a high-valent ion-oxo species.

In conclusion, we propose here that ferrous bromide acts catalytically as a weak Lewis acid promoting neighboring group participation by the resident polarizable 12α-sulfide sulfur atom to mono-deoxygenate (i.e., reduce)[16] the peroxide unit in 12α-SPh trioxane **4** and thus to render this trioxane antimalarially inactive. Deoxygenated 1,3-dioxolane versions of antimalarial 1,2,4-trioxane peroxides are known to be antimalarially inactive.[9] In sharp contrast, the diastereomeric 12β-SPh trioxane **4**, which cannot undergo such sulfide anchimeric assistance (i.e., peroxide deoxygenation) because the resident sulfide sulfur atom is remote from the peroxide unit, is antimalarially potent. Likewise, the 12α-SO_2Ph trioxane sulfone, in which the sulfur atom is close to the peroxide unit but is not nucleophilic and thus not able to participate in peroxide deoxygenation, is antimalarially potent.

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