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Evidence for Fe(IV)=O in the Molecular Mechanism of Action of the Trioxane Antimalarial Artemisinin

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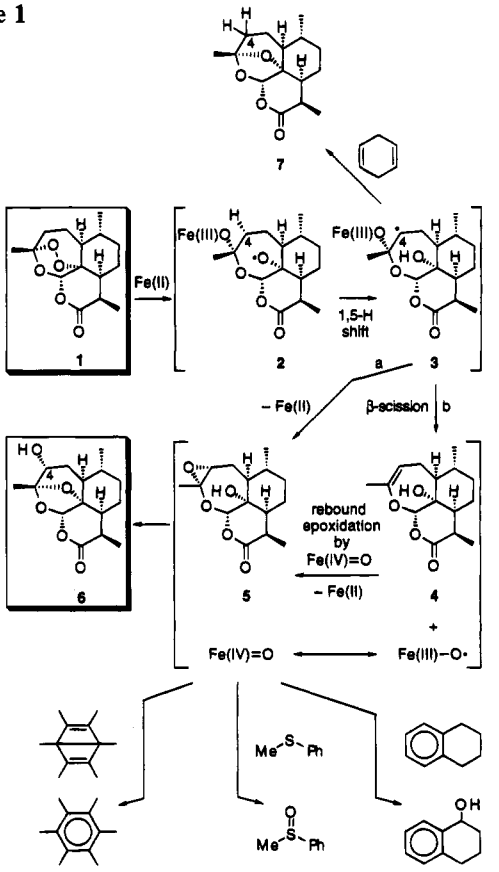
Among the 300–500 million people worldwide who are currently infected with malaria, about 2 million deaths, many of them children, occur each year.[1] As malaria parasites develop ever-increasing multidrug resistance to traditional alkaloidal antimalarial drugs,[2] artemisinin (quinghaosu, **1**), a non-alkaloidal endoperoxide natural product discovered in China, and related 1,2,4-trioxanes are increasingly being used for effective chemotherapy of malaria.[3,4] These organic peroxides, causing oxidative stress[5] to malaria parasites, apparently are reduced by the iron-rich parasites to form cytotoxic radical intermediates.[6] Using an oxygen-18-labeled trioxane[7] and some mechanism-based synthetic analogs,[8] we have shown that a carbon-centered radical, formed from an oxy radical *via* an intramolecular 1,5-hydrogen atom shift, is important for antimalarial activity.[9] We now report several kinds of evidence supporting the intermediacy of a high-valent, non-heme, iron–oxo species resembling that characteristic of monoxygenase metalloenzymes and known to cause oxidative damage to biological macromolecules.[10,11] It is proposed that such a high-valent iron–oxo species is formed *via* homolytic oxygen–carbon bond scission[12] from a β-ferryloxyethyl radical and that a highly electrophilic epoxide (*e.g.*, **5**, Scheme 1), a potent alkylating agent,[13] also is formed. A molecular mechanism representing these transformations and the types of evidence we have accumulated for a high-valent iron–oxo intermediate are summarized in Scheme 1. This molecular mechanism represents the *first report of generation of Fe(IV)=O during ferrous ion activation of a 1,2,4-trioxane* rather than, as usual, by heme protein (*i.e.*, cytochrome P_{450}) or metalloporphyrin model compounds activating dioxygen or hydrogen peroxide.[10,11]

Scheme 1



Evidence for a high-valent iron–oxo intermediate is provided by reactions characteristic of such a species, as follows: (1) hexamethyl Dewar benzene was rearranged into hexamethylbenzene (in 40% yield),[14,15] while the amount of C_4-hydroxylated artemisinin product **6** was diminished from 15–20% to 5–7% (Table 1); (2) methyl phenyl sulfide was oxygenated to the corresponding sulfoxide; and (3) tetralin (1,2,3,4-tetrahydronaphthalene) was oxidized into hydroxytetralin.[16] Three

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