Reactive Species

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Trapping Unstable Benzoquinone Analogues by Coordination to a $[(\eta^5\text{-}C_5Me_5)Ir]$ Fragment and the Anticancer Activity of the Resulting Complexes**

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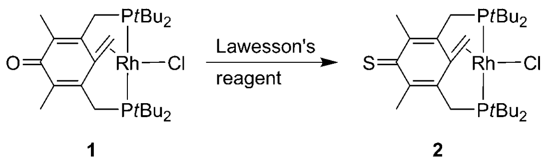
antitumor agents · bioinorganic chemistry · quinones · reactive intermediates · sandwich complexes

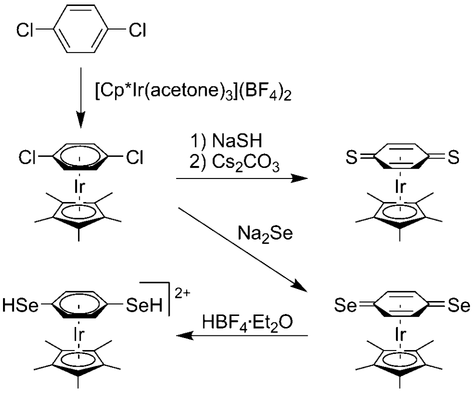
Quinonoids are important in biology and in industrial processes; they serve as synthons in organic synthesis and as building blocks for hormones and pigments, and many different derivatives are known.[1,2] In biology their major role is in electron transport in the respiratory chain and in photosynthesis, but their potential as anticancer drugs and as central components of antibiotics has also been noted.[1]

Only a few quinonoids with heavier elements have been reported because of the inherent stability of such species.[2,3] Several examples are known in which quinonoids and quinone methides were stabilized by coordination to a metal center. The coordination of quinonoid compounds to metals is characterized by their different binding modes: the π system of the aromatic ring can display η^2 as well as η^4 binding, and the aromatic ring can also form σ bonds directly.[2] For example, Vigalok and Milstein reported the synthesis of the thioquinone methide **2** by conversion of **1** with Lawesson's reagent (Scheme 1); the thioquinone methide unit, which undergoes rapid oligomerization in the free state, is stabilized by coordination to the metal.[2,4]



Scheme 1. The conversion of the metal-stabilized quinone methide **1** into its thio analogue **2**.[2,4]

Recently an η^4-coordinated [Cp*Ir] unit (Cp* = η^5-pentamethylcyclopentadienyl) was used to stabilize the elusive molecule 1,4-dithiobenzoquinone. Attempts to synthesize this quinonoid species go back to at least the start of the last century: in that first approach oxidation of 1,4-dimercaptobenzene resulted in polymeric species rather than in the desired product.[5] Later on, the compound was characterized spectroscopically at 10 K in an argon matrix.[6] However, when a template method was applied starting from [Cp*Ir(η^6-1,4-dichlorobenzene)], which was reacted with NaSH/Cs_2CO_3, the 1,4-dithiobenzoquinone ligand was obtained bound to a [Cp*Ir] unit (Scheme 2).[7]



Scheme 2. The synthesis of 1,4-dithio- and 1,4-diselenobenzoquinone analogues. The reaction of 1,4-diselenobenzoquinone with $HBF_4{\cdot}Et_2O$ gives rise to $[Cp^*Ir(\eta^6\text{-}1,4\text{-diselenohydroquinone})]^{2+}$.[7,8]

Considering the stability issues with such quinonoids, it is noteworthy that Amouri and co-workers recently reported another exotic molecule in this series, namely 1,4-diselenobenzoquinone.[8] This is one of the few selenoketones known because they are generally unstable.[9] By applying methodology similar to that used for the synthesis of 1,4-dithiobenzoquinone, the [Cp*Ir] fragment was utilized as a template to convert 1,4-dichlorobenzene with Na_2Se into 1,4-diselenobenzoquinone, which in a subsequent step was transformed to 1,4-diselenohydroquinone by treatment with $HBF_4{\cdot}Et_2O$ (Scheme 2).[8]

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Another aspect of quinonoids, besides their coordination chemistry and stability issues, is their role in biological systems and their potential as drugs in particular. Menadione, 2-methyl-1,4-napthoquinone, exhibits in vitro and in vivo anticancer activity against different tumor types.[10,11] Its mode of action appears to involve activation by cytochrome P450 reductase in a one-electron process to yield a semiquinone radical, which in turn is able to reduce dioxygen to the superoxide anion,[12] causing oxidative stress, depletion of glutathione, and induction of DNA single-strand breaks and eventually apoptosis.[11]

Organometallic species have attracted significant interest as anticancer agents in recent years.[13,14] On account of the remarkable stability of the [Cp*M(η^4-quinonoid)] compounds ($M = Rh$, Ir), they were assayed for their in vitro anticancer activity in A2780 human ovarian cancer cells.[8] The structure–activity relationships were probed by comparing the efficacy of the 1,4-diselenobenzoquinone complexes to that of the analogous *ortho*- and *para*-benzoquinone [Cp*Rh] and [Cp*Ir] complexes and to *ortho*- and *para*-dithiobenzoquinone [Cp*Ir] compounds.[8,15]

The rhodium compounds were inactive in this cell model, as was the iridium complex of 1,2-benzoquinone. The *ortho*-dithio-, *para*-dithio-, and *para*-benzoquinone [Cp*Ir] products exhibited moderate anticancer activity, whereas [Cp*Ir(η^6-1,4-diselenobenzoquinone)] was as active as cisplatin, the benchmark of metal-based anticancer agents. There is no obvious correlation between *ortho* or *para* substitution and anticancer activity; nevertheless it is clear that the selenium contributes positively to the biological effect. Other iridium and rhodium complexes have been reported to exhibit anticancer activity, though probably with a different mode of action which was often hypothesized as DNA (synthesis) targeting.[8,16,17] The mode of action of the benzoquinone compounds is not yet known, as for many anticancer agents, but a mechanism similar to that discussed for menadione might be in action. Also, further work may be required to determine the fate of the metal complex in biological media, in particular after administration to living systems: This is important information for their further (and eventually clinical) development.[18]

In summary, the synthesis of 1,4-diselenobenzoquinone on a [Cp*Ir] template stabilized an elusive species, and the promising anticancer activity of this metal complex may be the basis for further research. The determination of key elements of the mode of action, including the molecular targets, may help in the development of a new class of anticancer chemotherapeutics.

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