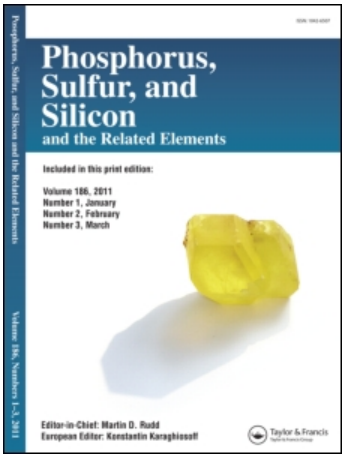

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ONE- VERSUS TWO-ELECTRON TRANSFERS: CYTOTOXIC AND CYTOPROTECTIVE EFFECTS OF SELENO-ORGANIC CATALYSTS

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Reliable predictions of cytotoxic effects are often missing in the design of selenium-containing mimics of glutathione peroxidase (GPx). Our data support the concept that a major factor of toxicity is the ability of either alkyl-selenolates, arylselenolates or arylselenenylsulfides to behave as catalysts for the reductive activation of dioxygen. Model studies of selenocystamine and 7-nitro-3,3-dimethyl-benziso-(2H)-selenazoline demonstrate that undesirable one-electron transfers to dioxygen can arise either from the production of electron-rich selenolates, or from the monovalent reduction of electron-deficient selenenyl-sulfide species by flavin enzymes or by ascorbate, in the presence of glutathione GSH. We have compared the effects of five selenoaromatic GPx mimics on Jurkat cells, and we conclude that toxic effects increase with GSH oxidase activity, whereas protective effects increase with GPx activity. Thus, minimizing 1-electron transfers to dioxygen while maximizing 2-electron transfer from selenolates to hydroperoxide, would help in the design of cytoprotective catalysts.

Keywords Selenium toxicity; glutathione peroxidase mimics; oxygen reduction; superoxide; hydrogen peroxide; glutathione; ascorbate.

A few years ago [1], we demonstrated that the alkyldiselenide selenocystamine behaved as a glutathione oxidase catalyst in the presence of excess GSH and ambient oxygen. Based on the glutathione reductase-coupled assay, we found that selenocystamine catalyzed the fast production of GSSG in the absence of exogenous hydroperoxide. At neutral pH, an excess of GSH reduces the diselenide to the selenolate RSe^-, with RSe-SG as a transient intermediate. This rate-limiting process is followed by a three-step reduction of dioxygen to water. The first step is a one-electron transfer from RSe^- to dioxygen which yields superoxide $O_2^{\bullet -}$ and the selenyl radical $RSe^\bullet$. The second step is another one-electron transfer from RSe^- to superoxide which yields hydrogen peroxide. The third step is a two-electron transfer from RSe^- to hydrogen peroxide H_2O_2.
Catalytic recycling of RSe-SeR or RSe-SG is insured by the very fast recombination of $RSe^\bullet$ and by nucleophilic scavenging of RSeOH. Therefore, a GSH oxidase cycle and a GSH peroxidase cycle are simultaneously observed. This results in the consumption of GSH, the accumulation of GSSG and the continuous production of toxic peroxides which may hit other targets in a biological medium.

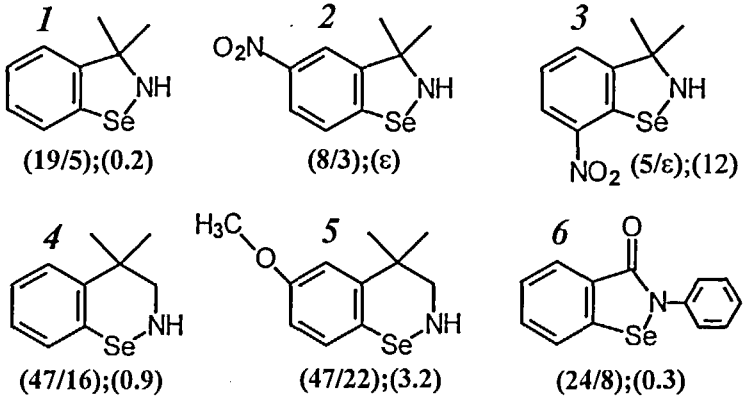
Such properties are also involved in the toxicity of other alkyl-diselenides [2]. They underline the ambivalent nature of electron-rich selenolates: In the peroxidase cycle, a powerful nucleophile performs two-electron transfers, while in the oxidase cycle, a species which has some metallic character easily performs one-electron transfers.
In our view, there should be special features at the selenocysteine active site of the enzyme Se-GPx to avoid one-electron transfers. A decreased electron density on Se through concerted protonation is one possibility.

Many selenoaromatic GPx mimics - whose Se is not bioavailable - unfortunately also exhibit such properties. Assuming that the oxidase activity of $ArSe^-$ increases with the electron density on Se, should we design selenoaromatic GPx mimics with electron-withdrawing substituents ? What follows suggests that the answer is no.

Compound *1* (see scheme 1) is a selenazoline which protects endothelial cells from the toxicity of hydroperoxides [3]. It exhibits moderate GPx activity, but its oxidase activity and its toxicity are both very weak. The selenolate $ArSe^-$ which is produced by excess GSH is indeed a poor monovalent reductant of oxygen, probably because of a decrease in

electron density through electrostatic interaction or through 6-membered hydrogen bonding.

Scheme 1: Structures discussed and their catalytic activities *(GPx:H_2O_2 / GPx:t-butyl-OOH);(GSH oxidase:ambient PO_2) nmol NADPH oxidized/min; pH 7.3, 37°C, 2 mM GSH; 20μM Se.*



The para-nitro derivative *2* has undetectable oxidase activity, but its GPx activity is also much smaller than that of *1*. Here, ring opening by GSH is fast, but it yields a dead-end product $ArSe^-$, due to electron-withdrawing effects.

More unexpectedly, we found that the ortho-nitro analog *3* had a very high glutathione oxidase activity at neutral pH and was very toxic, with an LC-50 close to 1μM in human leukemia cells of the HL-60 line.

In the presence of NADPH and GSSG reductase, *3* is a significant catalyst of NADPH oxidation, but the oxidation rate is markedly increased by excess GSH, and it is not affected by iodoacetamide, which means that the selenolate derivative $ArSe^-$ is not involved. This oxidation is catalytic, it increases linearly with the concentration of Se catalyst, and it is due to O_2 reduction.

Our interpretation is that the GSH-mediated heterolytic scission of the Se-N bond yields an electrophilic ArSe-SG intermediate whose NO_2-Se interaction prevents SN-2 displacement of the selenium substituent by GSH. In fact, this intermediate is rapidly reduced to the radical anion $[ArSe\text{-}SG]^{\bullet-}$ by a variety of one-electron donors, including GSSG reductase/NADPH, ascorbate, 4-amino-thiophenol, or more slowly by GS(H) itself.

$[ArSe\text{-}SG]^{\bullet -}$ is a fast reductant of O_2 to $O_2^{\bullet -}$, whose dismutation or other reactions drive the equilibrium to the right.

In conclusion, the selenoorganic intermediates which can generate superoxide as "GSH oxidase" catalysts in aerobic medium, include electron-rich selenolates as well as free radical anions derived from hindered electrophilic selenenyl-sulfides. The toxicological significance of GSH oxidase activity is illustrated in figure 1, where five GPx mimics (numbering of scheme 1) have been compared.

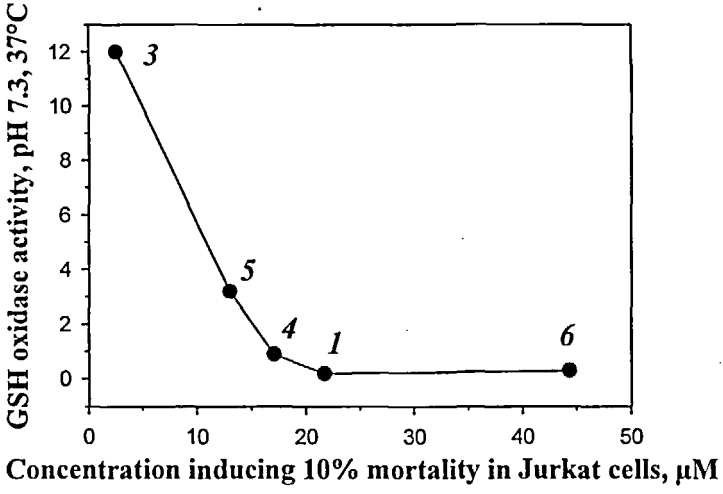


Figure 1. Correlation between LC-10 values and GSH oxidase activities of GPx mimics.

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