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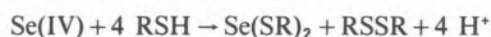
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SELENIUM-MERCURY INTERACTIONS IN PRESENCE OF SULFHYDRYL COMPOUNDS: POSSIBLE MODEL SYSTEM FOR SELENIUM DETOXIFICATION OF MERCURY

Since PARIZEK and OSTADALOVA [1] first demonstrated that selenite markedly decreased the toxicity of mercuric chloride in rats, it has been shown that mercury too counteracted selenium toxicity [2]. However, the mechanism of their mutual detoxification has not been studied. Both mercury and selenium are closely linked to the soft sulfhydryl donor groups in amino acids in the metabolism and therefore this phenomenon might likely be associated with such compounds. We have studied the interactions of selenite, Hg(II) and the sulfhydryl compounds, cysteine and

3-mercaptopropionic acid, $\text{HS}(\text{CH}_2)_2\text{COOH}$ (3-MPA). The results are presented in Table 1. Reactions were carried out in sulfuric acid medium to eliminate complications such as hydrolysis of mercury at higher pH in absence of chloride. A wide spectrum of products, depending upon the molar ratios of the reactants, was obtained. Similar products were formed with 3-MPA and cysteine proving the involvement of the sulfhydryl group in these interactions. The products contained selenium in several oxidation states. Formation of mixed metal complexes, featuring sulfhydryl bridging between Hg and Se in positive oxidation states, was noticeably absent. RSH reduces selenite to the unstable Se(II) and stabilises it by complexation.



Se(SR)_2 has been isolated and characterized for both 3-MPA and cysteine [3]. In most cases we studied, Se(SR)_2 is the interacting selenium species.

Hg^{2+} , not coordinated to thiol, and Hg(SR)^+ react with Se(SR)_2 by abstracting one of the Se-bound thiols. The thiol in Se(SR)^+ now reduces it to Se^{2-} . Reaction between selenide and $[\text{Hg(SR)}_x]^{2-x}$ ($x \leq 2$) leads to the formation of a complex product with the empirical formula $\text{Hg}_2\text{Se(SR)}(\text{SO}_4)_{0.5}$. This interaction means that the RS^- complexes of Hg(II) and Se(II) have comparable first formation constants. Further evidence for this is in the formation of this product when Se(IV) is added to Hg(SR)_2 . Se(IV), however, has no action on Hg(II) bound to a single thiol as in Hg(SR)^+ .

There is interaction between Se(SR)_2 and even

Table 1
 Results of Selenite — RSH — Hg(II) Interactions

Mole ratio of Se(IV):RSH:Hg(II)	Interacting Hg(II) species	Interacting selenium species	Product
1 4 3	aquo Hg^{2+}	$\text{Se}^{\text{II}}(\text{SR})_2$	$\text{Hg}_2\text{Se(SR)}(\text{SO}_4)_{0.5}$
1 4 1	aquo Hg^{2+}	Se(SR)_2	"
1 5 1	Hg(SR)^+	Se(SR)_2	"
*1 2 1	Hg(SR)_2	Se(IV)	"
*1 1 1	Hg(SR)^+	Se(IV)	no reaction
1 8 1	Hg(SR)_2	Se(SR)_2	HgSe
1 4 1	HgCl_2	Se(SR)_2	$\text{Hg}_2\text{Se(SR)}\text{Cl}$
1 4 0.1	aquo Hg^{2+}	Se(SR)_2	Se(O)

Sodium selenite and RSH were mixed in 1N H_2SO_4 . Hg(II) solution was added to the Se(SR)_2 solution at room temperature.

* Sodium selenite was added to a mixture of Hg(II) and RSH.

coordination-saturated Hg(II) ! Hg(SR)_2 reacts with Se(SR)_2 in presence of excess RSH , yielding HgSe . Higher mercapto complexes of Hg , higher than the bis-complex, were not observed to be formed [3]. The only plausible mechanism seems to be a direct interaction between Hg(II) and Se(II) themselves. The Hg...Se interaction causes the shift of the electronic equilibrium between S (bound to Se) and Se towards Se(II) which results in the reduction of the latter to selenide.

When HgCl_2 is the reacting species, some $\text{Hg}_2\text{Se(SR)Cl}$ was formed. However, higher chlorocomplexation of mercury affects its reactivity with Se(SR)_2 markedly. Reactions were very slow and the yields obtained, very poor.

Addition of a very small amount of Hg(II) brings about the quantitative reduction of much larger amounts of Se(SR)_2 to elemental selenium. This destabilization is most probably caused by the formation of free Se(II) and its interaction with Se(SR)_2 in a sequence of reactions.

Our studies of Hg(II) , selenite and thiol interactions provide by no means an unravelling of the exact mechanism behind the mutual antagonism between mercury and selenium in biological systems. But the broad spectrum of results obtained only suggests that the complexity of these interactions in the biological systems could be of much greater magnitude.

REFERENCES

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PS6.7 — MO

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METAL ANTHRACYCLINE COMPLEXES AS NON CARDIOTOXIC ALTERNATIVES TO ANTHRACYCLINE ANTICANCER AGENTS. PHYSICO-CHEMICAL CHARACTERISTIC AND ANTITUMOR ACTIVITY OF Pd(II) -ANTHRACYCLINE COMPLEXES

Adriamycin (Adr) and Daunorubicin (Dr) are anthracycline antibiotics widely used in the treatment of various human cancers. However their clinical use is limited due to clinical and histopathological evidence of cardiotoxicity [1]. Recent studies have suggested that the cardiac toxicity of anthracyclines may be related to the formation of semiquinone free radical intermediates *in vivo* [2] and it has been demonstrated that a component of mitochondrial NADH dehydrogenase actively reduces Adr [3].

Thus the hope of finding a non cardiotoxic but yet active anthracycline has prompted the development of a large number of semisynthetic analogues [4].

We have recently demonstrated that Fe(III) anthracycline complexes retain antitumor activity against P 388 leukemia on one hand, and unlike the free drugs does not catalyze the flow of electrons from NADH to molecular oxygen through NADH dehydrogenase on the other [5,6]. These results suggest that iron-anthracycline complexes and more generally metal-anthracycline complexes could be non cardiotoxic alternatives to other currently available anthracycline anticancer agents.

In this context we have focused our attention on