

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.

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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

the interaction of adriamycin and daunorubicin with Pd(II). In this communication we report the results of a detailed potentiometric and spectroscopic investigation undertaken to characterize Pd(II)-anthracycline complexes. Their stability constants have been determined as well as their interaction with DNA, their antitumor activity and their ability to catalyze the flow of electrons from NADH to molecular oxygen when they are inserted into the NADH-NADH dehydrogenase system.

Physico-chemical characterization

The addition of PdCl_4^{2-} to Adr (or Dr) at 1:1 molar ratio yields a complex with the concomitant release of two protons ($\text{pK}=2.4$). Our potentiometric and spectroscopic titrations strongly suggest that in this complex the four ligands of Pd(II) are i) one carbonyl and one phenolate oxygen forming a six membered chelate, ii) the deprotonated amine of the sugar portion, and iii), depending on pH, either a water molecule or OH^- group. The kinetics of formation of this complex is rather slow and follows a second order rate law with $k_2 = 3.9 \text{ s}^{-1} \text{ M}^{-2}$. The value of the constant of formation defined as $K = \frac{[\text{Pd}(\text{AdH}, \text{NH}_2)]}{[\text{Pd}][\text{AdH}, \text{NH}_2]}$ is 1.3×10^{22} . (AdH, NH_2)

stands for adriamycin with the anthraquinone moiety half deprotonated and the sugar amine deprotonated. Similar results have been obtained with daunorubicin.

Similar complexes are obtained when either $\text{Pd}(\text{NH}_3)_4^{2+}$ or $\text{cis-Pd}(\text{NH}_3)_2\text{Cl}_2$ is added to adriamycin instead of PdCl_4^{2-} ; however in that case the fourth position of the square of coordination is occupied by an amine group.

Interaction with DNA

The complex has been added to DNA at molar ratio $[\text{Nucleotide}]/[\text{Complex}] \approx 10$. A very slow evolution of the CD spectrum of the system is observed: in two weeks about 25% of the complex has disappeared suggesting that due to the high affinity of Adr and Pd^{2+} for DNA the complex partially dissociates.

Antitumor activity

The *in vitro* inhibition of P 388 leukemia cell growth by the complexes compares with that induced by the free drugs. They display antitumor activity against P 388 leukemia; no significant differences from the free drugs in terms of therapeutic efficacy were observed.

Effect of the complex on superoxide production by NADH dehydrogenase

Adr and Dr increased superoxide formation by NADH dehydrogenase in a dose-dependent fashion that appeared to follow saturation kinetics. On the contrary the Pd(II)-anthracycline complexes do not increase superoxide formation over control level.

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COPPER(II) BINDING BY MITOXANTRONE

The compound 1,4-dihydroxy-5,8-bis(2[(2-hydroxyethyl)amino]ethylamino)-9,10-anthracenedione dihydrochloride (Mitoxantrone (H_2MX), or No-