

## RESULTS AND DISCUSSIONS

The equilibrium analysis of the present system shows that the major aluminium-picolinate species are  $\text{AlL}_2^+$  and  $\text{AlL}_2(\text{OH})$  with  $\log(\beta_{120} \pm 3\sigma) = 8.27 \pm 0.02$  and  $\log(\beta_{12-1} \pm 3\sigma) = 17.668 \pm 0.008$  respectively in mixtures with excess of picolinate ( $\text{L}^-$ ).

In a 1:1 mixture the species  $\text{AlL}^{2+}$ ,  $\log(\beta_{110} \pm 3\sigma) = 4.497 \pm 0.007$  and  $\text{Al}_2\text{L}_2(\text{OH})_3$ ,  $\log(\beta_{22-3} \pm 3\sigma) = 39.27 \pm 0.02$  dominated. Minor species in the system are  $\text{AlL}(\text{OH})^+$  and  $\text{AlL}_2(\text{OH})$ .

The least squares computer calculations were performed with the program TITRER [4]. Distribution diagrams visualizing the relative amounts of the different species were produced using the program DISTPLOT.

The results of the present investigation show that competitive interaction between aluminium and zinc is possible.

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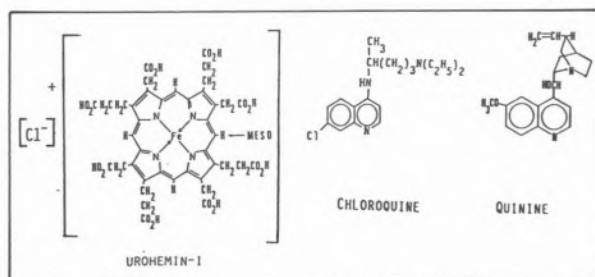
UROHEMIN INTERACTION WITH  
THE ANTIMALARIAL DRUGS  
CHLOROQUINE AND QUININE

## INTRODUCTION

Despite numerous years of research the actual mode by which antimalarial drugs operate remains obscure. Recently though, it has been proposed that drugs such as chloroquine and quinine form complexes with the protoporphyrin IX of hemoglobin inside red blood cells [1]. The precise mechanism is unknown, but presumably the complexes are formed with the heme that has been released from proteolytically digested hemoglobin. It has also been suggested that protohemin IX is a specific receptor for several malaria drugs and the cause of the rapid uptake of these drugs by the erythrocyte. Due to this implied high affinity of ferric porphyrins for antimalarial drugs, we have begun binding studies in aqueous solution. In this report we present some of our initial results concerning the interaction of chloroquine and quinine with iron porphyrins in aqueous solution. Urohemine-I was chosen due to its high solubility in aqueous solutions and because recent Raman and Nuclear Magnetic Resonance (NMR) work allowed us to thoroughly characterize its solution dynamics [2,3].

## EXPERIMENTAL

Urohemine was purchased from Porphyrin Products, Logan, Utah, and was further purified by column chromatography as previously described [2]. Chloroquine and quinine were purchased



from Sigma and were used without further purifications. Titrations of urohematin with the drugs were carried out at pH=6.0 (unbuffered) and at 20°C employing a Perkin Elmer 559A UV-Vis spectrophotometer with a thermostated cell compartment. pH was monitored throughout the experiment using a Beckman pH meter and a Fisher combination electrode. Ultraviolet-visible difference spectra were recorded in the Soret region of the visible spectrum. The differences here reflect the drug binding to urohematin. Data were handled using the Hill plot and Scatchard plot formalisms [4].

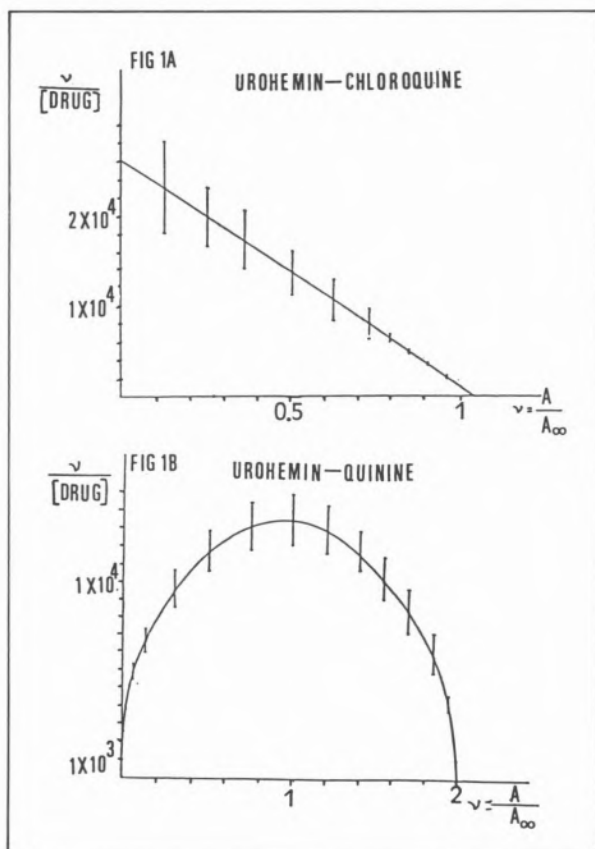


Fig. 1

Scatchard plots for drug binding to urohematin-I

## RESULTS AND DISCUSSIONS

Figs. 1A and 1B show Scatchard plots for the association of urohematin to chloroquine and quinine, respectively. These results indicate that chloroquine associates in a noncooperative manner with urohematin, exhibiting a Hill coefficient of 1.0 and a  $K_{\text{ass}} = (3.6 \pm 0.3) \times 10^4 \text{ M}^{-1}$  while quinine displays a cooperative association, a Hill coefficient of two, and a  $K_{\text{ass}} = (1.5 \pm 0.2) \times 10^8 \text{ M}^{-2}$ .

These results are interesting in view of the similar structures of the two drugs. Both possess quinoline rings with side chains at the fourth position. Since proton NMR data do not indicate axial coordination at the urohematin iron ion [4], it seemed reasonable to expect that both drugs would have similar stoichiometries. Furthermore, from our UV-Vis and proton NMR data we can conclude that urohematin forms  $\pi$ -complexes with both drugs [5].

Further work on malaria drug interaction with free hemins and heme proteins is in progress in our laboratory.

## ACKNOWLEDGEMENTS

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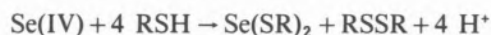
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### SELENIUM-MERCURY INTERACTIONS IN PRESENCE OF SULFHYDRYL COMPOUNDS: POSSIBLE MODEL SYSTEM FOR SELENIUM DETOXIFICATION OF MERCURY

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.



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

$\text{Hg}^{2+}$ , not coordinated to thiol, and  $\text{Hg(SR)}^+$  react with  $\text{Se(SR)}_2$  by abstracting one of the Se-bound thiols. The thiol in  $\text{Se(SR)}^+$  now reduces it to  $\text{Se}^{2-}$ . 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  $\text{Hg}_2\text{Se(SR)(SO}_4\text{)}_{0.5}$ . This interaction means that the  $\text{RS}^-$  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  $\text{Hg(SR)}_2$ . Se(IV), however, has no action on Hg(II) bound to a single thiol as in  $\text{Hg(SR)}^+$ .

There is interaction between  $\text{Se(SR)}_2$  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 $\text{Hg}^{2+}$	$\text{Se}^{\text{II}}(\text{SR})_2$	$\text{Hg}_2\text{Se(SR)(SO}_4\text{)}_{0.5}$
1 4 1	aquo $\text{Hg}^{2+}$	$\text{Se(SR)}_2$	"
1 5 1	$\text{Hg(SR)}^+$	$\text{Se(SR)}_2$	"
*1 2 1	$\text{Hg(SR)}_2$	Se(IV)	"
*1 1 1	$\text{Hg(SR)}^+$	Se(IV)	no reaction
1 8 1	$\text{Hg(SR)}_2$	$\text{Se(SR)}_2$	HgSe
1 4 1	$\text{HgCl}_2$	$\text{Se(SR)}_2$	$\text{Hg}_2\text{Se(SR)Cl}$
1 4 0.1	aquo $\text{Hg}^{2+}$	$\text{Se(SR)}_2$	Se(O)

Sodium selenite and RSH were mixed in 1N  $\text{H}_2\text{SO}_4$ . Hg(II) solution was added to the  $\text{Se(SR)}_2$  solution at room temperature.

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