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Letter to the Editor

Solution Chemistry Studies of Adriamycin–Iron Complexes Present *in Vivo*

P. M. MAY, G. K. WILLIAMS and D. R. WILLIAMS
Department of Chemistry, University of Wales Institute of Science and Technology, Cardiff CF1 3NU, United Kingdom

GOSÁLVEZ recently reported a new iron derivative of the antitumor agent adriamycin [1]. The lyophilized, freeze dried, mixture of three ferric chlorides and an adriamycin was called quelamycin. It has undergone clinical trials and aroused considerable research interest [2, 3].

We have used our established bio-inorganic techniques to investigate the binding constants for adriamycin–iron and other metals and considered which binding sites are involved. We also considered whether quelamycin dissociates into its components in plasma and whether adriamycin forms metal complexes *in vivo* [4–6].

The stability constants were determined potentiometrically and spectrophotometrically and are listed in Table 1.

Table 1. Log formation constants for adriamycin, $-H^+$, $-Fe^{3+}$ and $-Cu^{2+}$ systems at 37°C

Species	Log β
AdH^-	11.21
AdH_2°	19.29
AdH_3^+	21.43
$FeAd^+$	17.98
$FeAd_2^-$	29.03
$FeAd_3^{3-}$	33.41
$FeAd(OH)^\circ$	14.69
$CuAd^\circ$	12.72
$CuAd_2^{2-}$	19.27
$CuAd_3^{4-}$	23.21
$CuAd(OH)^-$	5.74

$I = 150$ mmole dm^{-3} [7].

Our results indicate that adriamycin has three good donor sites—the two-O^- groups on the naphthacene rings in positions 6 and 11, and the sugar amino moiety. Of the metal ions studies, adriamycin had its strongest binding affinity for ferric iron ($K \doteqdot 10^{18}$ $mole^{-1}$ dm^3). Our studies involved adriamycin and ferric ions at equilibrium. Under these circumstances the 3:1 Fe(III)–adriamycin complex called quelamycin is not formed upon administering adriamycin to blood plasma whereas a calcium–adriamycin complex is probably formed.

Turning to non-equilibrium conditions, our data leads us to believe that quelamycin persists in plasma for several hr and should not be simply regarded as just a source of readily labile ferric ions and adriamycin. It may be regarded as a new agent rather than a simple derivative of adriamycin because the former is orally absorbed, has lower cardiotoxicity, and can pass the blood brain barrier [1–3].

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