Reactions of D-penicillamine with Some Metals and Alloys

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Received June 16, 1984

In recent years, joint replacement has become widespread for patients with arthritis. Materials used in these replacements have included metal alloys, plastics and ceramics. The bio-compatibilities of the materials used have been tested *in vivo* and *in vitro* with naturally occurring compounds. However, with some patients, in particular those with rheumatoid arthritis, drug therapy continues. This introduces into the blood a significant concentration of a foreign species. Many non-steroidal antiinflammatory drugs contain carboxylic acid groups, potential complexing sites for metal ions. However, these groups are fairly common in blood (*e.g.*, in amino acids) and thus the effect of the drugs is likely to be small in terms of solution of metals. With D-penicillamine, a commonly used second-line drug, three potential metal-complexing sites are available, including a thiol (RS^-) group. The natural concentration of thiol groups in extracellular fluids is low [1]; thus, the effect of added D-penicillamine could be more pronounced. Penicillamine is also often significantly different in its reactions compared to those of its close structural relative, the naturally occurring thiol amino acid cysteine. As, for example, with gold, D-penicillamine stablises gold(III) whereas L-cysteine stablises gold(I) [2].

Experimental

The metal or alloy in the form of turnings was added to 200 ml of a 0.01 M solution of D-penicillamine in distilled water. The progress of the reactions was monitored by inspection and by UV-visible and C.D. spectrometry. The stainless steels used were numbers 69, 70, 72 of formula

	C	Si	S	P	Mn	Cr	Ni	Mo
69	0.29	0.36	0.02	0.02	0.41	12.4	0.37	–
70	0.18	0.35	0.02	0.02	0.38	16.3	0.40	–
72	0.18	0.92	0.02	0.03	0.91	16.1	2.16	0.69

Results and Discussion

The results given in Table I show that D-penicillamine will react with chromium, iron, copper, zinc, and with the three stainless steels examined. With chromium, the spectrum of the original solution suggested the formation of an octahedral chromium(III) complex with typical transitions $^4A_{2g} \rightarrow {}^4T_{2g}$, $^4A_{2g} \rightarrow {}^4T_{1g}$ at 560 and 490 nm, respectively. With

TABLE I.

Metal	Time (days)	Colour	UV/Visible (NM)	Cd (nm)
V	5	–	–	–
Cr	1	purple	690 560	(–)320(+)350(–)380(–)430(+)500
	6	red ppte		(–)280
Fe	1	purple	360 480 580	(–)360(–)430(+)500
	3	yellow ppte		(–)280
Cu	5	blue	610	(–)320(+)600
Zn	5	white ppte		
Stainless Steel (69)	5	purple (brown ppte)	500	(–)380(–)430(+)500
(70)	5	purple (brown ppte)	500	(–)380(–)430(+)500
(72)	5	purple (brown ppte)	500	(–)380(–)430(+)500

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iron, the UV and CD of the solutions obtained were identical to those produced by iron(II) with D-penicillamine. After several days, air oxidation appeared to take place and a precipitate of iron(III) hydroxide resulted. With copper, a blue solution of a copper(II) penicillamine complex was obtained, whereas with zinc a white precipitate of hydrated zinc oxide resulted.

The three stainless steels reacted in a similar manner to iron, with the formation of an iron(II) penicillamine complex followed by oxidation to iron(III) hydroxide in each case.

As mentioned above, the concentration of free thiols in extra-cellular fluids tends to be low. For example, in blood serum, the concentration is about 50 μmol l^{-1}, most of which is accounted for by the thiol group on albumin [3], with smaller concentrations on the globulins and low-molecular-weight species such as cysteine and glutathione accounting for the rest. Of these, albumin, γ-globulin and glutathione have little effect on the metals and alloys examined above [4]. This is perhaps due to the sterically restricted site of the thiol [5]. L-cysteine, on the other hand, reacts similarly to D-penicillamine but at a much slower rate.

These results suggest that some care must be exercised in the use of metal-solubilising drugs such as D-penicillamine on patients who have undergone joint replacement. Although the corrosion is slow, over a period of years it could be significant. Another problem that could arise is the *in vivo* effect of the metal complexes formed, particularly if the patient is allergic to certain metals. Stainless steels often contain a range of transition-metal irons, including nickel and chromium, both of which are known to cause allergic responses.

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