Speciation of Plutonium in Biological Fluids*

JOHN R. DUFFIELD†, DAVID P. RAYMOND
and DAVID R. WILLIAMS

Department of Applied Chemistry, U.W.I.S.T., P.O. Box 13, Cardiff CF1 3XF, U.K.

Recent publicity concerning cancer incidence and mortalities in the vicinity of nuclear installations and the imminent requirement for radioactive waste disposal sites has highlighted the necessity for a clearer understanding of radionuclide migration pathways through the biosphere and into man [1]. Central to this issue will be the bioavailabilities and subsequent tissue distributions of these nuclides, particularly of the actinides, in man.

To date, risk assessments from actinides to man have been partially based upon gut uptake factors obtained from, and tissue distribution measurements made in, animal models [2]. Whilst there is little doubt as to the validity of such an experimental approach, the results are phenomenological such that extrapolation to man is difficult and, in some cases, of dubious value. A number of important and sometimes conflicting parameters must be taken into account when analysing such gut absorption and distribution studies. For example, the gastro-intenstinal tracts of neonates may be only partially formed and thus more permeable to actinide and other metal ions, whereas those of older animals may be damaged, which would also increase gut uptake. Similar conditions will also apply for humans. In addition, gut uptake factors and subsequent retention and distribution may vary widely depending upon the fasting state of the animal (or man), diet and initial chemical form of the radionuclide. Thus, a more general method of predicting gastro-intestinal absorption of actinides (and other radionuclides) would be highly desirable.

One possible approach to the above problem is to speciate the actinide in question under conditions pertaining to the relevant biofluids, e.g., duodenal fluids and blood plasma, using computer simulation programs [3]. Thus, providing the component concentration data are available in addition to thermodynamic formation constants for all possible metal–ligand interactions within the biofluid, the percentage species distribution of, say plutonium, can be determined. Uptake across hydrophobic membranes can then be predicted in terms of the passive diffusion of neutral low-molecular-weight (lmw) species via the duodenal walls and into blood plasma and cells.

Previous studies of plutonium(IV) speciation in blood plasma have indicated Pu(IV)–citrate species to be of major importance. Predictions made using the ECCLES (Evaluation of Constituent Concentrations in Large Equilibrium Systems [4]) computer program have shown approximately 30% of plutonium present in the lmw plasma pool to be bound as a neutral Pu·citrate·OH^0 species [5]. The formation constants for Pu(IV)–ligand interactions used in this model were, however, extrapolations from constants for Fe(III), which has been suggested as a possible biomimetic agent for Pu(IV) as the latter appears to follow certain components of the iron metabolic pathways in mammals. Such an extrapolation was, and is, unavoidable due to the paucity of thermodynamic data for Pu(IV) interactions. Nevertheless, the resulting predictions were useful and comprehensible in terms of Pu(IV) metabolism [5].

The work reported here extends this initial study and assesses the possibility and practicality of using thorium(IV) formation constant data to model Pu(IV) interactions in biofluids. The rationale behind this decision was that Th(IV) has been used successfully as an analogue for Pu(IV) under geochemical conditions [6]. In addition, data for Th(IV) are more extensive than for Pu(IV) and constants for Th(IV)–citrate have recently become available for comparison with Pu(IV)–citrate formation constants [7].

Method

Relevant formation constants for blood plasma–metal ion interactions were extracted from the U.W.I.S.T. Thermodynamic Database Library ($I = 0$) and converted to the ionic strength of blood plasma ($I = 150$ mmol dm^{-3} NaCl) using the Davies equation. All subsequent speciation simulations were performed using the ECCLES computer program. Thorium– and plutonium(IV)–ligand formation constants were compared by performing regression and correlation analyses on 1:1 metal–ligand formation constants measured at, or converted to, $I = 150$ mmol dm^{-3} NaCl.

Results and Discussion

Figure 1 shows the correlation between a selection of Pu(IV) and Th(IV) formation constants for 1:1 metal–ligand complexes taken from the U.W.I.S.T. Database. The regression line can be described by eqn. (1):

*Paper presented at the Second International Conference on the Basic and Applied Chemistry of f-Transition (Lanthanide and Actinide) and Related Elements (2nd ICLA), Lisbon, Portugal, April 6–10, 1987.

†Author to whom correspondence should be addressed.

0020-1693/87/$3.50

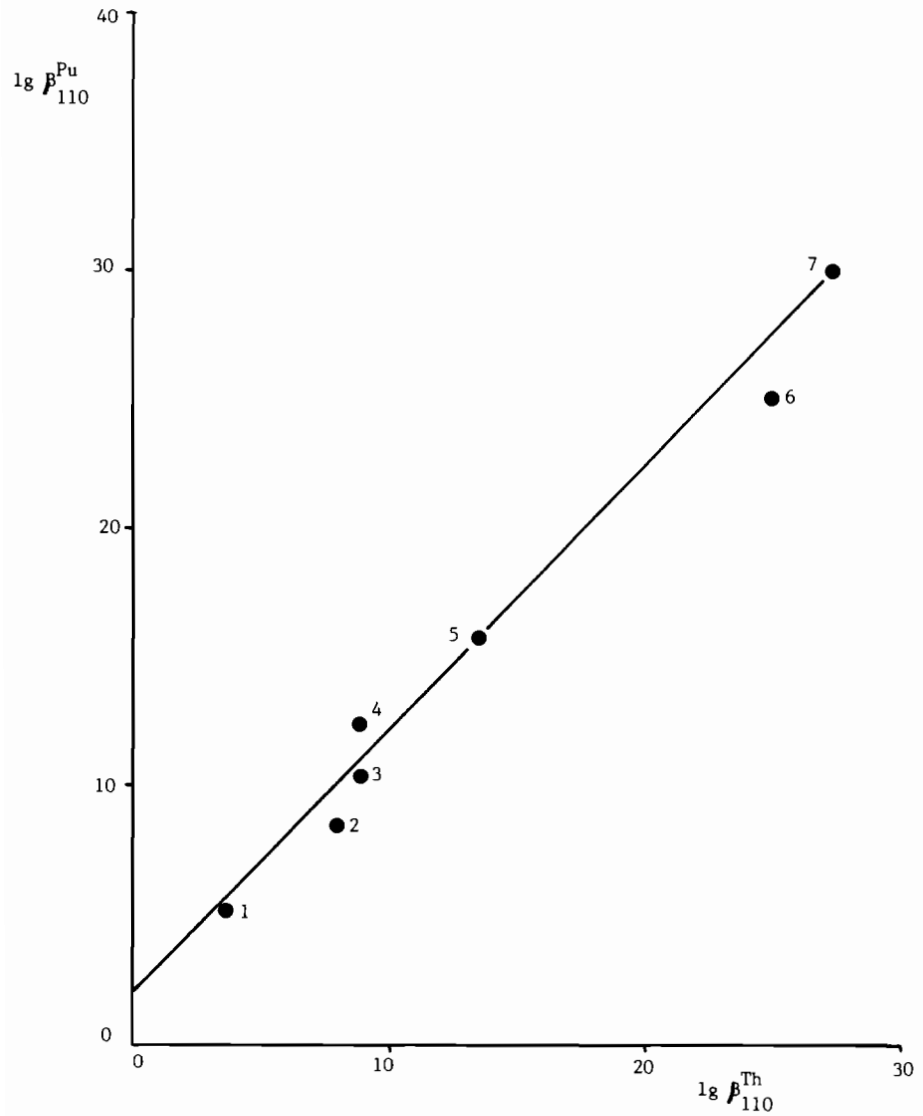

Fig. 1. Correlation of Pu(IV) and Th(IV) formation constants (Key: 1, acetate; 2, oxalate; 3, acetylacetone; 4, benzohydroxamate; 5, citrate; 6, ethylenediaminetetraacetate; 7, diethylenetriaminepentaacetate).

$$\log \beta_{110}^{Pu} = 0.997 \log \beta_{110}^{Th} + 1.92 \quad (1)$$

where

$$\beta_{110} = \frac{[ML]}{[M][L]}$$

from the more generalized eqn. (2).

$$pM + qL + rH \rightleftharpoons M_pL_qH_r \quad (2)$$

The overall correlation coefficient was determined to be 0.991.

In an earlier study of the correlation between Fe(III) and Pu(IV), a regression line of

$$\log \beta_{110}^{Pu} = 0.982 \log \beta_{110}^{Fe} + 1.362 \quad (3)$$

was found, with a correlation coefficient of 0.997 [8].

From the limited data available, eqn. (1) predicts Pu(IV)–lmw formation constants for ML-type species to be approximately two orders of magnitude greater than those for equivalent Th(IV) complexes. This increased stability does not seem unreasonable from the point of view of ionic size as, for 6-fold coordination, the ionic radii for Th^{4+} and Pu^{4+} are 0.94 Å and 0.86 Å, respectively [9].

For initial speciation modelling of Pu(IV) in plasma, the Th(IV)–citrate (cit) data of Raymond *et al.* [7] were used to model citrate interactions after correction to an ionic strength of 150 mmol dm^{-3} and use of eqn. (1) (see Table I). Use of these corrected formation constants with the Pu(IV) blood plasma model predicted all of the metal ion to be bound as $Pu{\cdot}cit_2{\cdot}(OH)_2^{4-}$, a species which, being charged, would not traverse lipid membranes.

TABLE I. Pu(IV)–Citrate Species used in the ECCLES Blood Plasma Model (corrected to I = 150 mmol dm^{-3} NaCl and from Th(IV) and Fe(III) data using eqns. (1) and (3), respectively)

Species			Charge	log β_{pqr}		
p	q	r[a]		Based on Fe(III)[b]	Pu(IV)[c]	Based on Th(IV)[d]
1	1	0	+1	11.67	11.90	13.21
1	1	1	+2	13.22	13.68	
1	2	0	−2	17.07	16.41	22.64
1	2	1	−1	18.06		25.08
1	2	2	0	23.95	25.30	
1	1	−1	0	10.20	6.40	(11.51)[e]
1	1	−2	−1	2.84	2.38	
1	2	−2	−4	4.31	7.95	14.26
2	2	−2	0	19.59		
1	1	2	+3		14.75	
1	2	4	+2		27.34	
1	2	5	+3		27.91	
1	3	0	−5			27.74
1	3	1	−4			31.88

[a]Defined in eqn. (2). [b]From the U.W.I.S.T. Thermodynamic Database. [c]From ref. 10. [d]From ref. 7. [e]Rejected from the experimental model as although inclusion of this species improved the statistical output slightly, there was no overall improvement in fit.

These predictions were then compared with those made using the Pu(IV)–citrate data of Metivier and Guillaumont [10] (Table I). Once again, all the plutonium was found as a Pu·cit$_2$(OH)$_2^{4-}$ species.

Overall, therefore, these two models predict that Pu(IV) is bound, in the lmw fraction of serum, to citrate which is also found experimentally [11]. However, all the lmw Pu(IV) is present as a charged complex which would be confined to the extracellular spaces. Such a prediction is in conflict with experimental evidence where plasma clearance of Pu(IV) to the liver and skeleton is relatively fast [2]. In addition, cell uptake of Pu(IV) does not appear to take place with its serum binding protein, transferrin. Therefore, at least some fraction of Pu(IV) must enter the tissues as an uncharged lmw species.

An explanation of this apparent anomaly may be obtained from an examination of Table I. Here, it can be seen that the formation constants for Pu(IV)–citrate extrapolated from the Fe(III)–citrate data are, on the whole, closer in magnitude and predicted species to the formation constants of Metivier and Guillaumont, than those obtained from Th(IV)–citrate. However, both extrapolations would predict a neutral MLOH species of stability at least 10^4 orders of magnitude greater than that found by Metivier and Guillaumont. If these extrapolated β_{11-1} values are used in place of the original MLOH formation constant, the speciation of Pu(IV) in blood plasma changes markedly as shown in Table II.

It is thus apparent that the value of the formation constant of the Pu·citrate·OH^0 species is critical in the modelling of Pu(IV) in biological fluids. Such

TABLE II. The Distribution of Pu(IV) in Blood Plasma as Influenced by Variations in the Value of β_{11-1} in the Metivier and Guillaumont Pu(IV)–Citrate Model

Model	Species formed	Charge	% Total lmw Pu(IV)
Metivier	Pu·cit$_2$·(OH)$_2$	−4	99.9
Guillaumont	Pu·cit·(OH)$_2$	−1	0.1
Original model	Pu·(OH)$_2$	+2	0.0
	Pu·cit·OH	0	0.0
Original model	Pu·cit$_2$·(OH)$_2$	−4	91.9
+ log β_{11-1} = 10.20	Pu·cit·(OH)	0	5.9
	Pu·cit·(OH)$_2$	−1	2.2
Original model	Pu·cit·OH	0	56.1
+ log β_{11-1} = 11.51	Pu·cit$_2$·(OH)$_2$	−4	42.9
	Pu·cit·(OH)$_2$	−1	1.0

a species is not found for Th(IV) as, indeed, is the case for a number of other citrate complexes. Formation constants extrapolated from Th(IV)–citrate data also give rise to β values which are larger than real Pu(IV)–citrate constants by many orders of magnitude. In biological systems, therefore, Th(IV) is not to be recommended as a chemical analogue for Pu(IV). However, in groundwaters where inorganic anions are dominant, Th(IV) is probably the best analogue likely to be found for Pu(IV).

With regard to the Pu(IV)–citrate data of Metivier and Guillaumont, whilst this is the best available at present, the value of the MLOH species must be treated with caution as it is not consistent with other models. In addition, the system was studied by solvent extraction techniques at an ionic strength of 1.0 mol dm^{-3} ($NaClO_4$) which is far removed from conditions found in biological fluids and, for that matter, groundwaters. There is, thus, an urgent need for a re-appraisal of Pu(IV)–citrate equilibria.

Acknowledgement

One of us (D.P.R.) would like to thank S.E.R.C. (Science and Engineering Research Council) for a maintenance grant.

References

1 P. J. Cook-Mozaffari, F. L. Ashwood, T. Vincent, D. Forman and M. Alderson, 'Cancer Incidence and Mortality in the Vicinity of Nuclear Installations, England and Wales 1959–80', Her Majesty's Stationery Office, London, 1987.
2 International Commission on Radiological Protection, 'The Metabolism of Plutonium and Related Elements', Pergamon, Oxford, 1986.
3 G. L. Christie, J. R. Duffield and D. R. Williams, *1986 Summer Computer Simulation Conference*, Reno, Nevada, 28–30 July, 1986, p. 405.
4 P. M. May, P. W. Linder and D. R. Williams, *J. Chem. Soc., Dalton Trans.*, 588 (1977).
5 J. R. Duffield, P. M. May and D. R. Williams, *J. Inorg. Biochem., 20*, 199 (1984).
6 K. B. Krauskopf, *Chem. Geol., 55*, 323 (1986).
7 D. P. Raymond, J. R. Duffield and D. R. Williams, *Inorg. Chim. Acta, 140*, 309 (1987).
8 J. R. Duffield and D. R. Williams, *Chem. Soc. Rev., 15*, 291 (1986).
9 R. D. Shannon, *Acta Crystallogr., Sect. A, 32*, 751 (1976).
10 H. Metivier and R. Guillaumont, *J. Inorg. Nucl. Chem.* (Suppl.), 179 (1976).
11 F. Planas-Bohne, D. M. Taylor and J. R. Duffield, *Cell Biochem. Funct., 3*, 217 (1985).