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Speciation of pyrithione in freshwaters

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Summary

Pyrithione (PT) is used as an active agent in some shampoos and other household products, and consequently may enter freshwaters following use. Dissolved metal (copper, zinc) salts of pyrithione are toxic to freshwater organisms, with toxicity dependent upon the metal. For this reason, the chemical speciation of pyrithione may be important in controlling its environmental toxicity. The objective of this work was to gather and assess data on the binding equilibria of pyrithione that could be used to assess its environmental speciation. Binding constants for the proton and a small number of metals were found in the literature. They were supplemented by binding constants for other metals estimated from constants for a ligand with an analogous structure to pyrithione. Using these tentative binding constants demonstration calculations of pyrithione speciation in a circumneutral freshwater were done. Pyrithione speciation was dominated by the binding of iron(III) with smaller contributions from aluminium, copper and zinc. Speciation was highly dependent upon water pH and the concentration of natural organic matter. These calculations demonstrate the feasibility of modelling to elucidate the speciation of pyrithione in freshwaters; for more robust calculations, experimental determination of more binding constants is needed. Knowledge of pyrithione speciation may be useful in other aspects of its risk assessment, specifically in understanding and predicting the rate at which it degrades in the natural environment.

1. Introduction

Pyrithione (PT) is an organic chemical that has been used for several decades in various forms as an industrial biocide, particularly as a marine ship antifouling agent. It is also used as an active agent in anti–dandruff shampoos, in the form of the compound zinc pyrithione. This latter use represen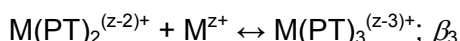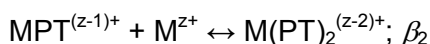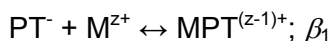ts the main s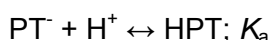ource of pyrithione to the natural environment [1]. Pyrithione compounds have been shown to be highly toxic to organisms (e.g. [2,3,4]) although previous risk assessment[1] has suggested that the effects may be limited by its tendency to undergo photolytic degradation in sunlight. Toxicity testing and risk assessment for pyrithione and metal salts has previously focused on the marine environment(e.g.[3,4]) with some limited testing of freshwater organisms (e.g. [2,5]). Where comparative testing was done with zinc and copper(II) pyrithione complexes, the latter was consistently found to be more toxic, indicating an important role of the complexing metal ion in exerting the overall effect. Although pyrithione is largely used commercially as a zinc or copper(II) compound, it is known (e.g.[6]) that it can form complexes with a range of metal ions such as manganese and iron(II). Pyrithione is known to be an ionophore for zinc and has also been shown to act as such for lead[7]; bioaccumulation of both uncomplexed and zinc–complexed pyrithiones has been demonstrated[8]. Therefore, knowledge of the distribution of pyrithione among its different chemical forms (speciation) in the environment is likely to be an important aspect of refining current assessments of its ecological risks. While measurement of different forms of a chemical in the environment may be theoretically possible it is frequently technically complex. For the purposes of risk assessment and prediction, modelling of the chemical speciation is a highly useful tool. In order to robustly model speciation it is necessary to know or to confidently estimate equilibrium constants for the reactions of the compound in question with the other components of the system under analysis. As well as trace elements such as copper and zinc, these components include the proton, major ions such as calcium and magnesium, and possible competing ions such as aluminium and iron. It is also necessary to know the constants for the other interactions (e.g. metal-ligand binding) within the system as these side-reactions will influence the speciation of the compound in question. In natural systems the most important class of ligands are those comprising natural organic matter (NOM), which is composed mainly of humic substances (humic and fulvic acids). The latest generation of speciation models (e.g. WHAM, ECOSAT) include models for the interactions of metals with humic substances and so are ideal for modelling the environmental speciation of specific ion–binding compounds such as pyrithione.

The purpose of the work described here is to assess the current state of knowledge with respect to modelling the speciation of pyrithione in natural systems, specifically:

1. To review the literature and identify stability constants for the binding of ions (e.g. zinc, copper) to pyrithione.

2. To assess whether a speciation model (such as WHAM) could be used to estimate the speciation of pyrithione in river waters.

3. To outline data needs to carry out a detailed assessment of pyrithione speciation and refine current risk assessments.

2. Ion binding chemistry of pyrithione

Searches were initially done to identify possible equilibria of pyrithione with cationic entities (protons and metals) and to find literature containing determinations of binding constants for these reactions. Searches indicated that pyrithione undergoes a single proton dissociation reaction within the likely range of environmental pH values, and can potentially form 1:1, 1:2 and 1:3 complexes with metal ions ([6],[9]):

$PT^- + H^+ \leftrightarrow HPT$; K_a

$PT^- + M^{z+} \leftrightarrow MPT^{(z-1)+}$; β_1

$MPT^{(z-1)+} + M^{z+} \leftrightarrow M(PT)_2^{(z-2)+}$; β_2

$M(PT)_2^{(z-2)+} + M^{z+} \leftrightarrow M(PT)_3^{(z-3)+}$; β_3

where M is a binding metal ion of charge z. Thus for ions such as Zn^{2+} and Cu^{2+} the $M(PT)_2$ complex is neutral while for others such as Al^{3+} and Fe^{3+} it is the $M(PT)_3$ complex that is neutral. Two protonation equilibria have been identified ([6]) but only one (shown) is relevant at environmental concentrations.

Jones and Katritzky[10] measured a proton dissociation constant for pyrithione corrected to standard conditions (T = 298K and zero ionic strength). Sun and co–workers ([6]) measured metal binding constants at T = 298K and an ionic strength of 0.1M. These are summarised in Table 1. The metal binding constants have been corrected to standard conditions. No measurements of reaction enthalpies could be found in the literature.
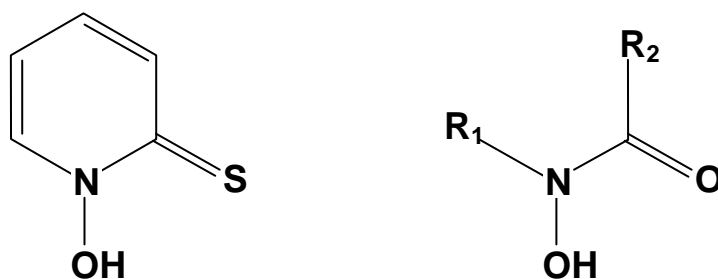
Table 1. Measured binding of pyrithione to protons and metals.

Binding ion	Reaction	log K_a/log β_1	log K^o_a/log β^o_1 [¶]	Reference
H^+	$PT^- + H^+ \leftrightarrow HPT$	4.67	4.67	10
Mn^{2+}	$PT^- + M^{2+} \leftrightarrow MPT^+$	3.1	3.5	6
Fe^{3+}	"	4.8	5.2	11
Co^{2+}	"	4.8	5.2	6
Ni^{2+}	"	5.1	5.5	6
Cu^{2+}	"	>8.5	—	6
Zn^{2+}	"	5.3	5.7	6

[¶] Constants corrected to standard conditions (T = 298K, ionic strength = 0).

Although these data are certainly useful they are rather limited in scope, since they do not include binding constants for other metal ions of possible importance (e.g. Al^{3+}), nor do they include constants for the formation of 1:2 and 1:3 complexes. Thus, the use of these binding constants alone in a speciation model might provide a misleading picture of pyrithione speciation. In order to estimate binding constants for other reactions, it is necessary to consider binding of metals to ligands having a binding site structure analogous to the HO–N–C=S binding site of pyrithione, which binds a metal ion by formation of a five-membered chelate ring. Unknown binding constants for the reaction of a metal ion with the ligand of interest can then be estimated from the constant for binding to the analogous ligand, given a regression relating binding constants for the analogous ligand to the ligand of interest. Such a family of ligands are the hydroxamic acids (Figure 1), which contain an OH–N–C=O

Figure 1. Structures of pyrithione (left) and a hydroxamic acid (right).

binding site. Sun and co–workers measured binding of Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} to 2-hydroxypyridine-1-oxide (1,2–HOPO), the hydroxamic acid analogue of pyrithione (i.e. with an O atom replacing the S of pyrithione). The correlation between pairs of binding constant for each metal was significant ($r = 0.996$; $p < 0.001$), suggesting that 1,2–HOPO was a suitable analogue; however, a literature search indicated that there were insufficient

constants for the binding to 1,2–HOPO of metals for which constants for binding to PT were required. Therefore, a systematic search was conducted of the NIST Database of Critically Selected Binding Constants[12] for a hydroxamic acid having a suitably comprehensive

Table 2. Measured binding of acetohydroxamic acid (AHA) to protons and metals.

Binding ion	Reaction	$\log \beta_n$	$\log \beta^o{}_n$[¶]
Al^{3+}	$AHA^- + M^{z+} \leftrightarrow MAHA^{(z-1)+}$	8.0	8.6
Ca^{2+}	"	2.4	2.9
Mn^{2+}	"	4.0	4.5
Fe^{2+}	"	4.8	5.3
Fe^{3+}	"	11.4	12.1
Co^{2+}	"	5.0	5.4
Ni^{2+}	"	5.2	5.6
Cu^{2+}	"	7.9	8.4
Zn^{2+}	"	5.2	5.7
Cd^{2+}	"	4.5	5.0
Pb^{2+}	"	6.7	7.2
Al^{3+}	$AHA^- + MAHA^{(z-1)+} \leftrightarrow M(AHA)_2^{(z-2)+}$	7.3	7.8
Mn^{2+}	"	2.9	3.1
Fe^{2+}	"	3.7	3.9
Fe^{3+}	"	8.4	8.9
Co^{2+}	"	3.9	4.1
Ni^{2+}	"	4.1	4.3
Cu^{2+}	"	6.2	6.4
Zn^{2+}	"	4.9	5.1
Cd^{2+}	"	3.3	3.5
Pb^{2+}	"	4.0	4.2
Al^{3+}	$AHA^- + M(AHA)_2^{(z-2)+} \leftrightarrow M(AHA)_3^{(z-3)+}$	6.2	6.7
Fe^{3+}	"	7.1	7.6

[¶] Constants corrected to ionic strength = 0. For Co^{2+}, Ni^{2+}, Fe^{3+}, Zn^{2+}, Cu^{2+}, T = 298K, for the remainder, T = 293K.

database of metal binding constants. One ligand, acetohydroxamic acid (In Figure 2, R_1 = H and R_2 = CH_3), was found to have a reasonably comprehensive set of binding constants available; these are summarised in Table 2.

It was not possible to correct all the constants found to standard temperature (298K) since no enthalpy data were available. The constants found were all measured at T = 298K or T = 293K; the difference between the measured values at 293K and the values corrected to 298K is likely to be small for these simple binding equilibria.

With the dataset in Table 2, binding constants for the 1:1 reaction between PT and the ions Ca^{2+}, Al^{3+}, Fe^{2+}, Fe^{3+}, Cu^{2+}, Cd^{2+} and Pb^{2+} were estimated, from the expression for the regression between pairs of 1:1 binding constants for PT and AHA for Mn^{2+}, Co^{2+}, Ni^{2+} and Zn^{2+}. The 1:1 binding constant quoted in Table 1 for Fe^{3+} was excluded from these

calculations since it was significantly lower than would be expected given the binding constant for AHA, and appears to be highly suspect. The regression obtained was:

$$\log \beta_1 \text{ (PT)} = 1.819\log \beta_1 \text{ (AHA)} - 4.69; \text{ } R^2 = 0.997, \text{ } p < 0.001$$

which was used to estimate the missing b_1 values for PT. For the estimation of 1:2 binding constants (β_2 values) for PT, the solution was less clear. No 1:2 binding constants for PT were found in the literature so direct regression against β_2 values for AHA was not an option. However, inspection of the $\log \beta_1$ and $\log \beta_2$ values for AHA showed a very strong relationship:

$$\log \beta_2 \text{ (AHA)} = 0.775\log \beta_1 \text{ (AHA)}; \text{ } R^2 = 0.877; \text{ } p < 0.001,$$

Thus, constants for the stepwise binding of a second PT were estimated by assuming the same relationship between $\log \beta_1$ and $\log \beta_2$ for PT as was found for AHA.

The AHA binding constants included values for the formation of 1:3 complexes with Al^{3+} and Fe^{3+}, and it is likely that these metals can form analogous complexes with PT. Scarrow and co–workers[13] synthesised the 1:3 complex of Fe^{3+} with 1,2–HOPO and calculated a β_3 of ~7.6. Based on these data, highly tentative estimates of 7.0 and 8.0 for the β_3 of Al^{3+} and Fe^{3+} were made. Given their nature, these constants were not used in the main demonstration calculations but were incorporated into a scoping calculation to consider their possible importance in the overall speciation of PT.

The full set of binding constants for PT is summarised in Table 3. All but five of the constants have been obtained by estimation using the binding constants for the analogue ligand AHA. Thus the robustness of these estimates relies upon the correctness of the assumption that AHA is a suitable analogue for PT in terms of relative metal binding strength, and the relative binding strengths of 1:1 and 1:2 complexes. Also, the PT binding strengths (β_1 values) from which the remainder of the binding constants have been derived cover a relatively small range of binding strengths (~2 log units), thus for some metal ions (particularly, Al^{3+} and Fe^{3+}) the estimated binding constants are extrapolations along the regression line. The constants should therefore be regarded as tentative. Nonetheless, the derived values should allow relative binding strengths and trends in metal-PT binding to be assessed.

The strength of metal binding varies in the order $Fe^{3+} > Al^{3+} > Cu^{2+} > Pb^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Fe^{2+} > Cd^{2+} > Mn^{2+} > Ca^{2+}$. This is broadly consistent with the expected order of binding strength for ligands that have binding sites comprising O(-II) moieties, and as such is consistent with the participation of O(-II) and S(-II) moieties in the binding of metals.

Table 3. Measured and estimated proton and metal binding constants for PT. Estimated constants are given in italics

Binding ion	Reaction	log K^o_a/log β^o_n[¶]
H^+	$PT^- + H^+ \leftrightarrow HPT$	4.67
Al^{3+}	$PT^- + M^{z+} \leftrightarrow MPT^{(z-1)+}$	*11.0*
Ca^{2+}	"	*0.6*
Mn^{2+}	"	3.5
Fe^{2+}	"	*5.0*
Fe^{3+}	"	*17.2*
Co^{2+}	"	5.2
Ni^{2+}	"	5.5
Cu^{2+}	"	*10.6*
Zn^{2+}	"	5.7
Cd^{2+}	"	*4.4*
Pb^{2+}	"	*8.4*
Al^{3+}	$PT^- + MPT^{(z-1)+} \leftrightarrow M(PT)_2^{(z-2)+}$	*8.5*
Ca^{2+}	"	*0.5*
Mn^{2+}	"	*2.7*
Fe^{2+}	"	*3.8*
Fe^{3+}	"	*13.4*
Co^{2+}	"	*4.0*
Ni^{2+}	"	*4.3*
Cu^{2+}	"	*8.2*
Zn^{2+}	"	*4.4*
Cd^{2+}	"	*3.4*
Pb^{2+}	"	*6.5*

[¶] Constants corrected to ionic strength = 0. For Co^{2+}, Ni^{2+}, Fe^{3+}, Zn^{2+}, Cu^{2+}, T = 298K, for the remainder, T = 293K.

3. Chemical speciation of PT in freshwaters

The next stage of assessment is to carry out speciation calculations for representative freshwaters. This was done using the WHAM (Windermere Humic Aqueous Model) model, version 6.1 (http://windermere.ceh.ac.uk/Aquatic_Processes/wham). WHAM includes a description of the chemistry of natural organic matter (humic substances), thus allowing a more realistic depiction of the speciation of natural waters.

To run WHAM, a chemical composition for the water of interest was required. This would ideally comprise measurements of pH, temperature, dissolved organic matter (DOC) and concentrations of major ions, Fe, Al, trace metals and any ligands considered significant (for our purposes this will comprise PT). For our purposes, demonstration calculations using a generic river water composition were used, rather than using specific water compositions.

The basic water composition used for the demonstration calculations is given in Table 4. The composition represents a moderately hard water typical of a large lowland river. Trace metal concentrations are set to levels typical of moderately contaminated UK lowland systems.

Table 4. Basic water composition for WHAM calculations

Determinand	Value	Units
pH	7.5	—
Temperature	298	K
DOC	5	mg/l
Dissolved Na	11.5	mg/l
Dissolved Mg	1.2	mg/l
Dissolved Al	Controlled by $Al(OH)_3$ solubility.	
Dissolved K	2.0	mg/l
Dissolved Ca	40	mg/l
Dissolved Mn	100	µg/l
Dissolved Fe(III)	Controlled by $Fe(OH)_3$ solubility.	
Dissolved Cu	5	µg/l
Dissolved Zn	20	µg/l
Dissolved Cd	0.1	µg/l
Dissolved Pb	2	µg/l
Dissolved Cl	19.5	mg/l
Dissolved SO_4	24	mg/l
Alkalinity	155	mg/l $CaCO_3$

Aluminium and iron(III) concentrations are not specified; rather, the activities of their free ions are calculated assuming them to be controlled by the metal hydroxide. Recent work[14,15] has shown this to be a reasonable assumption and a more reliable way to speciate these metals than to use measured dissolved concentrations. Standard solubility products of 8.5 and 2.7, respectively, are used in calculations. The dissolved organic carbon concentration was set to that of a typical temperate lowland system. A temperature of 298K was assumed for the calculations. While not representative of temperate systems, it can be considered sufficient for these demonstration calculations since no information on the temperature dependence of PT binding constants was available. In order to simplify calculations and reduce the number of outputs, some relatively weakly binding trace elements (Fe(II), Co, Ni) were not included in the composition.

The concentration of PT was set to 100nM (12.7 µg/l), based on the measurement of Mackie and co–workers[16] in the Mersey Estuary, UK. This was the only measurement of PT concentration in a natural environment identified in the literature and so was taken as broadly representative, although it was most likely derived mainly from ship anti–fouling agent use.

Initially, a set of predictions of PT speciation was made for a range of pH from 5 to 8, by adjusting Ca concentration from the default value given in Table 4. Prediction results are

shown in Figure 2. The top chart shows the proportional distribution of the major predicted forms of PT, i.e. those having an abundance of 0.1% or greater, for at least one pH value. The lower chart shows the complete predicted speciation. Complexes with metals dominated the predicted speciation although a non–negligible amount of the dissociated species PT^- was predicted to form when pH > 7. Metal complexes are strongly dominated by Fe(III), particularly the $Fe(III)(PT)_2^-$ complex. Small amounts of copper(II) complexes were predicted to form when pH > 6.5 and some aluminium complex when pH < 6. Zinc complex made a small (<1% of the total) contribution when pH > 7.5.

The full predicted speciation is also shown in Figure 2. This presents a complex picture containing a large number of PT species. Many species were predicted to comprise only a negligible proportion of the total PT, including all the uncharged species (HPT and $M(PT)_2$ where M has a charge of +2) with the exception of $Cu(PT)_2$.

Allowing the formation of 1:3 complexes with Al^{3+} and Fe^{3+} had little overall effect on the predicted speciation. $Al(PT)_3$ formed <0.1% of the total PT at all pH values. $Fe(PT)_3$ formed up to ~8% of the total PT at pH 8 but overall the change in Fe(III)–bound PT was negligible.

Dissolved organic carbon (DOC) is an important ligand for trace metals in natural waters and as such is expected to be an important competitor for metals with PT. In order to assess the likely importance of this competition, a sensitivity calculation was performed, using the same water composition but setting the DOC concentration to half the original value. The computed distribution of major PT forms is shown in Figure 3.

Changing the amount of DOC present in the system had a notable effect on the speciation at pH > 6.5, with a greater degree of copper binding to PT predicted. The extreme case of zero DOC resulted in extensive formation of $CuPT^+$ at higher pH although it must be noted that this is not a physically realistic simulation but instead illustrates the importance of DOC in competing with PT to bind copper.

Figure 2. Speciation of Pt in a model river water with DOC = 5 mg/l. Top: % distribution of PT among its major forms. Bottom: complete calculated speciation of PT.
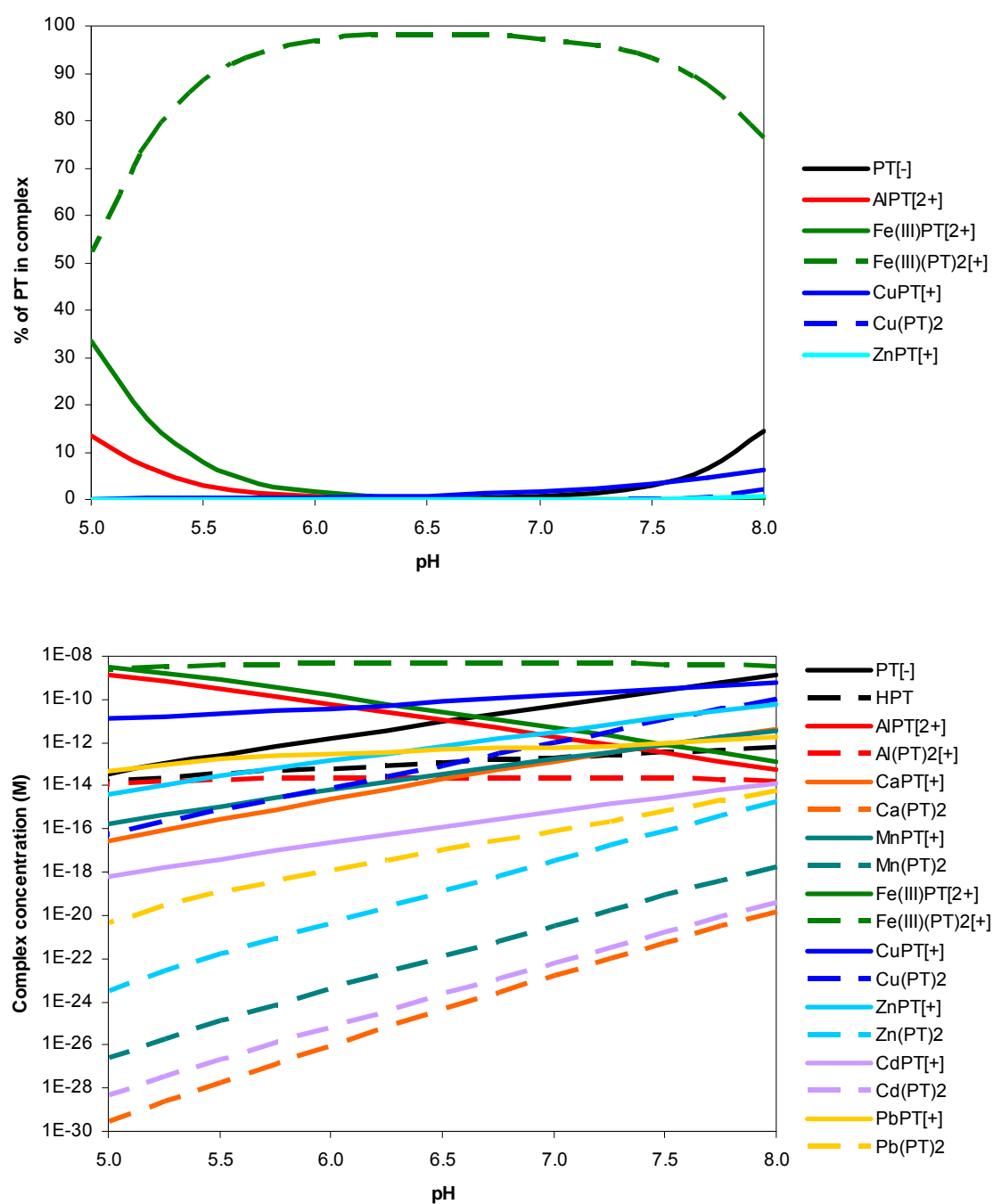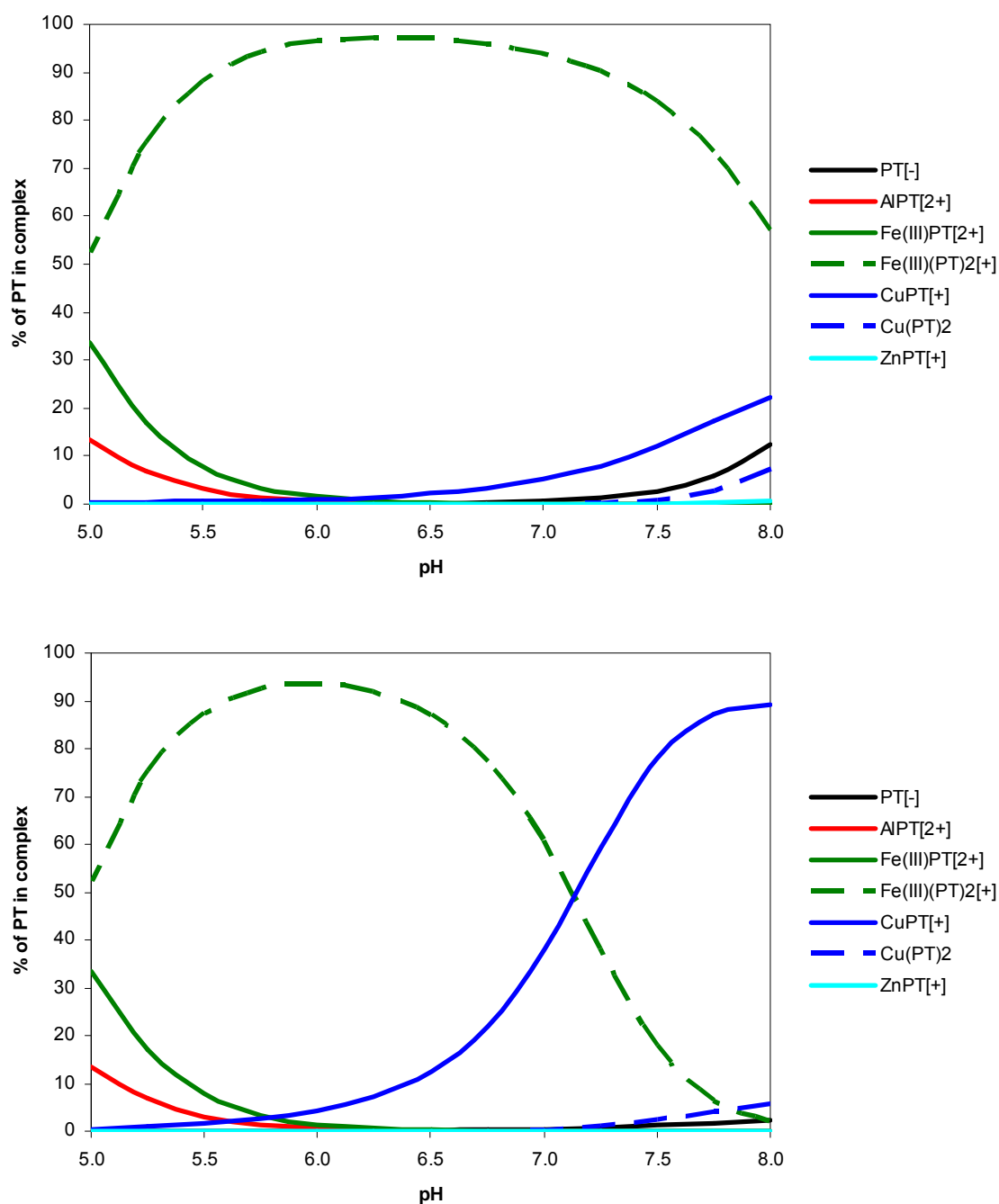
Figure 3. % distribution of PT among its major forms in a model river water with DOC = 2.5 mg/l (top) and 0 mg/l (bottom).

4. Discussion

Clearly the very strong binding of Fe(III) to PT is predicted to exert an important control on the speciation of the ligand in freshwaters. Based on these results, we would expect PT discharged into freshwaters as a salt of another metal to transform predominantly into Fe(III) complexes, although at circumneutral pH copper binding may be important if DOC

concentrations are low. Aluminium may become more important at relatively low pH, and copper at relatively high pH, depending upon the relative concentrations of metals and PT in the system. Complexes of other metals, including zinc, do not appear to be significant unless their dissolved concentrations are elevated above those used for the calculations. This has important implications for risk assessment as it implies that Predicted Environmental Concentrations for metal pyrithiones may be flawed by not taking shifts in PT speciation into account. Such shifts in speciation, and the resulting changes that may occur in the toxicity characteristics of the PT, need to be incorporated into risk assessments. This requires more knowledge on the toxicity of different species of PT and on the extent to which PT transforms into different complexes on entering the environment. The set of tentative binding constants that we have derived here represents a start to gathering such knowledge but more experimental work is required to validate the approach taken. There is a need for firmer knowledge of the metal complexation chemistry of PT as a means to further understanding of its effects in the environment. In the first instance, binding constants for iron(III), copper and aluminium, and possibly zinc, need to be better understood. Knowledge of the temperature dependence of binding constants would also be highly useful.

Clearly, toxicity studies on PT should be interpreted in terms of the speciation of the ligand and any associated metals. Currently there has been little comprehensive work done and most has focused on the relative abundances of zinc and copper complexes in artificial test systems. Doose and co–workers[9] studied the effects of mixtures of PT with zinc, copper and iron(III) on rat leukemic cells, finding that the toxicity was relatively similar and concluding that PT binding to metals was a relevant aspect of it toxicity that required further study.

Although not part of the original scope of this work, the possibility of a relationship between PT speciation and its photolytic degradation requires consideration, as the literature suggests that degradation may well be a crucial aspect of the environmental behaviour of PT. Literature reports that metal pyrithiones can be rapidly degraded in the presence of ultraviolet light (e.g.[16,17]) with half lives of the order of minutes to hours reported, but there are studies reported where pyrithione appears to be more stable (e.g.[18]). It is plausible that the speciation of the PT has an influence on its stability and hence the potential for harm to the environment. Galvin et al.[19] reported that only the undissociated fraction of PT (i.e. HPT) can be photolysed; in our speciation calculations, this form consistently represents <0.1% of the total PT. There is a need to investigate the stability of PT in freshwaters as a function of its speciation.

5. Conclusions and recommendations

1. A set of tentative binding constants for pyrithione can be derived from the literature and by the use of an analogous ligand to estimate missing values. The binding constants can be used to estimate the equilibrium speciation of pyrithione in freshwaters.

2. Pyrithione is predicted to complex strongly to metals in circumneutral freshwater. Binding is particularly strong to iron(III), aluminium and copper. The extent of binding depends upon the pH, concentrations of metals and of competing ligands in natural organic matter.

3. Binding constants for PT complexation, particularly to the strongly binding metals noted in 2., need to be determined experimentally in order to perform more robust and detailed assessments of pyrithione speciation in the environment. Concentrations of pyrithione in the freshwater environment need to be measured, particularly in locations where high concentrations might be expected.

4. The speciation of pyrithione has not been fully considered in previous toxicity testing. More focused approaches to testing are needed, that take the speciation in natural waters into account and seek to relate toxic effects to specific forms of PT. The relationship between the photolysis and degradation of PT in natural systems and its speciation also needs investigation so that if such a relationship exists it can be incorporated into risk assessment methods.

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