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Coordination Chemistry Reviews
185–186 (1999) 177–188

COORDINATION CHEMISTRY REVIEWS

Chemical speciation contributing to research knowledge and everyday life

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Received 13 May 1998

Contents

Abstract

The definition and determination of Chemical Speciation is described and how this parameter controls the behaviour of an element and its compounds. Examples are quoted in terms of the efficiency and biodegradability of ligands, trace metal complex migration in the environment, 'more for less' approaches to ligand usage, zinc and the common cold, the perception of toxicity of materials and healthcare such as dentistry. Definitions of 'safe' chemistry are discussed. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Environment; Healthcare; Perception; Speciation; Safe chemistry; Technology; Toxicology

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PII: S0010-8545(98)00267-7

1. Introduction

Metal complexes undeservedly receive a bad press. There are two reasons (i) the scientist's perception of chemistry is as a pivotal contributor to our well-being in terms of both bodily and financial health (UK exporting £327 billion and employing half a million workers) whereas the public are led to use the adjective 'chemical' to imply undesired food additive/contaminant, or to associate it with plume, spillage or contamination[1]. (ii) Secondly, names of elements or components are associated with a threat which implies that the element may never be useful or beneficial and that concentration, speciation, and threshold-dependence are not relevant: The larger the concentration, the greater the risk! In fact, causal links between a chemical and its environmental/healthcare influence are increasingly being shown to be related to the presence of a specific chemical species rather than to the total presence [2,3].

This review discusses the roles of different chemical species in technology, in the environment, toxicology and healthcare and then suggests ways in which scientists can influence the lay public concerning their perception of metal complex species.

2. Speciation

The IUPAC-accepted definition of 'speciation' refers to 'the chemical form or compound in which an element occurs in a living system or the environment. It may also refer to the quantitative distribution of an element' and is supported by the views of the OECD (NEA) that 'modelling the chemical speciation prevailing is essential when trying to understand complex systems and phenomena in order to take action on the information obtained' [4,5]. When chemical speciation data are obtained from computer simulation modelling based upon parameters such as formation constants, solubility products, etc. the strict criteria for model selection system definition, software selection, verification and validation as described by Grenthe and Puigdomenech should be closely followed [5]. Experimental determination of the speciation prevailing, provided that it does not disturb equilibria to an unknown extent, is necessary as part of the validation exercises as well as being highly desirable as an alternate to speciation modelling. Techniques for experimental determination and for computer simulation of speciation have been described elsewhere [6,7].

3. Technology

The technology embodied in the chemical industry is pivotal to the survival of Western economies. For the production of fine chemicals not only the quantity of product but also its purity is dependent upon the chemical species present in the reaction vessel rather than the total amounts of the reactants used. Similarly, the efficacy of using such chemicals can be optimised based upon speciation knowledge, thus improving cost-effectiveness and decreasing waste emissions.

A simple example may be seen in the use of EDTA, and of its more readily biodegradable replacement, EDDS – SS ethylenediaminedisuccinic acid to sequester copper ions from a copper, iron and nickel solution[8]. Table 1 refers to mildly alkaline pH = 9 where the CuEDDS species concentration accounts for 43% of the copper present which is a four-fold increase over its equivalent [CuEDTA] at approximately 9%. Clearly, the amount of residual unused ligand to be disposed of is far less with EDDS than with EDTA. There are many other examples in the literature where speciation knowledge has improved efficiency, yields and profits [9–11].

4. Environment

The environment contains a myriad of ligands and of metal complexes arising from both endogenous and exogenous sources. There are many challenges being faced by environmental research which are facilitated by a speciation knowledge. First, the environment is in a state of labile equilibrium (Fig. 1) and so the administration of an industrial/domestic-use ligand usually disturbs such an equilibrium as indeed may the removal of a sample for analysis [12].

Secondly, many of the timescales involved with the environmental roles of chemical species are beyond those easily researchable in the laboratory. For example, vaults under consideration and construction to hold radioactive waste are not intended to leak for 50 000 years or more. Thus much computer simulation and reference to naturally occurring extinct reactors which are now leaching radionuclides, are used instead.

Grenthe and Puigdomenech have produced an extensive review of why modelling of chemical speciation in environmental research is necessary and how best to undertake this task[5]. With large complex systems modelling is often the only way in which all of the controlling parameters may be considered simultaneously so that they can be understood more fully and the consequences of changes made to the

Table 1
Illustration of the ‘More For Less’ principle[a]

pH	7		9	
	$EDTA^{4-}$	$EDDS^{4-}$	$EDTA^{4-}$	$EDDS^{4-}$
Cu	37	82	9	43
Ni	58	18	91	57
Fe	5	0	0	0

[a] The use of a ligand for a process (a) may be optimised by judicious choice of speciation conditions by, for example, adjusting the pH, and (b) thus less ligand is left over to be a cost upon the environment. The table compares ethylenediaminetetraacetate ($EDTA^{4-}$) and ethylenediaminedisuccinate ($EDDS^{4-}$) for complexing Cu^{2+}at pH = 7 and 9 (expressed as percentage of metal ions complexed). All total concentrations are 1 mmol dm^{-3}.

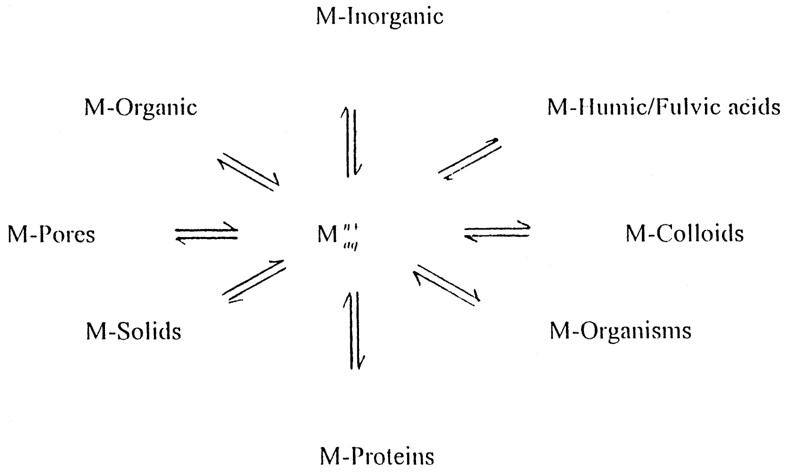

Fig. 1. Speciation scheme suggesting the possible distribution of metal ions (M) in the environment [3].

process be known, and importantly, be quantified in a language that is common to all of the disciplines who have a vested interest in the scenario. Modelling is now a widely used scientific discipline often known as system or operation analysis. Such features as performance criteria, decision making, verification (checking that the equations have been established accurately and the computer software solves them correctly) and validation (the assurance that the software and model reflects behavioural patterns in the real world).

The OECD(NEA) volume comprehensively lists sources of modelling software and of databases [5]. Topics discussed at length include aqueous system modelling, solubility considerations, humic and fulvic acids, groundwater and silicates, medium effects, temperature effects, transport processes, porous media, safety criteria, trace element modelling, and most importantly, the graphical representation of speciation systems [5].

Reports of the experimental determination of chemical speciation in the environment and in industry has produced an expanding literature as methods are adapted from analysing *total* amounts of components present to those of examining separate fractions and even individual species. The areas of greatest interest are environmental contamination (often associated with waste disposal) and preparative chemical technology in industry (for optimising yields). Caroli has edited a most useful book covering these areas [6].

Co-ordination compounds involve both ligands and metal ions and possibly too much emphasis has been placed upon the latter. An exciting new development involving ligands is that of replacing EDTA after 60 years of intensive and essential use [3,13].

Chelating agents in widespread use include polyphosphates (e.g. pentasodium tripolyphosphate), hydroxycarboxylates (e.g. citric acid), aminocarboxylates (e.g. NTA and EDTA) and phosphonates (e.g. aminotrimethylenephosphonate). The chemical industry produces 166 000 tonnes EDTA + NTA per annum. The majority of these chelates are discharged into sewers and they are not readily biodegradable therein. Environmental concerns, which have banned EDTA etc., in some states/countries, have led to drives to find readily biodegradable replacement ligands which have parity in terms of chelating power and are not considerably more expensive than traditional ligands [14,15]. Newly constructed chemical plant is now producing several thousand tonnes per annum. Front runners include EDDS and MGDA (ethylenediaminedisuccinate and methylglycinediacetate, respectively [16,17]). A major challenge is matching the extraordinary chelating ability of EDTA for calcium ions for use in the dairy industry for precipitate removal using cold water conditions.

The previous section, in discussing Table 1, describes how speciation studies have been used to produce a 'more for less' approach whereby a new ligand (EDDS) is up to four times as efficient as EDTA at sequestering the nominated metal ion and thus can be used at lower concentrations; in addition to enhanced efficiency this also reduces the environmental cost of disposal of unused ligands.

In the field of radioactive waste disposal, the vast majority of potential risks will come from doses of radiation arising from migration of radionuclides through the geosphere, (the minor risk is from airborne gases)[5,18]. The European Union has dedicated hundreds of millions of Euros to developing reliable internationally acceptable computer programs and databases for predicting the chemical speciation which controls the radionuclide migration characteristics of suggested radioactive waste disposal scenarios. There is now a general consensus of agreement concerning the choice of programs, and the acceptable increased doses permissible to some future generation of inhabitants from emissions from a vault. Generally, any increased dose must be less than one millionth of the background dose. The influence of ligands, such as cleansing agents used for decontamination, or such as naturally occurring humic and fulvic acids can speed up migration by factors of up to 10^6 (mainly because they influence the speciation through maintaining hydrolysable metal ions in solution rather than precipitating, giving conditions such that they can travel with the groundwater flow rather be stationary precipitates of oxides or hydroxides). The UK Government's rejection of planning permission to construct a rock characterisation facility needed to quantify some of this speciation near to the Sellafield site in Cumbria in the UK has set back progress to waste disposal by many years [19].

5. Toxicology

Increasingly, the toxicological effect of an administered agent is being correlated with the chemical speciation prevailing rather than with the total dose.

A recent example involves the correlation of the speciation in saliva for the administration of zinc (as gluconate) in throat lozenges for reducing the symptoms of the common cold. More than 600 volunteers were studied [20–27] and no correlation found between concentration of total zinc administered, whereas there was a clear correlation with the free zinc [Zn^{2+}] species computed to be present in saliva. As expected, the species was both pH, and lozenge-component, dependent (Fig. 2).

Briefly, the risk from an exposure to a chemical is:

$$\text{Risk} \propto \text{Dose} \propto \text{Speciation from dose} \propto \text{Sensitivity of target organ/biofluid}$$

Not only do such approaches permit an optimisation of the dose but they also suggest possible beneficial modifications, e.g. the influence of modifying saliva pH values, likely side effects such as the zinc species disturbing essential copper species; also they give leads towards alternative ligands to gluconate which may be administered with zinc in these trials.

The public, journalists especially, and even some scientists tend to oversimplify data interpretation and label an element or a compound as toxic, dangerous, etc. regardless of the circumstances. There are many examples of the oxidation state, the anion, the ligand and the target organ changing the agent from a beneficial to a toxic agent or modifying the risk by factors of thousands or more [11].

To illustrate how the toxicology of an element is both speciation and target organ-specific, we consider plutonium which the newspaper headline writers will have us believe is the most dangerous element known and as little as one atom can kill you! Table 2 lists route of exposure – inhalation, ingestion or wound contamination – for Pu compared with several other toxins[2]. The final column is the time

Table 2
The toxicity of plutonium compared with some other toxins expressed as lethal dose to fifty percent of the exposed persons and interval between exposure and death

Toxin or poison	Lethal dose (mg)	Time to death
Ingested (swallowed)		
Anthrax spores	<0.0001	–
Botulism	<0.001	–
Potassium cyanide	700	Hours to days
Reactor plutonium[a]	1150	Over 15 years
Injected		
North American coral snake venom	0.005	Hours to days
Indian king cobra	0.2	Hours to days
Reactor plutonium[a]	0.078	Over 15 years
Inhaled		
Reactor plutonium[a]	0.26	Over 15 years
Nerve gas (Sarin)	1.0	A few hours
Benzpyrene (1 packet of cigarettes per day for 30 years)	16.0	Over 30 years

[a] The plutonium is administered as a mixture of radioactive isotopes as oxides (the worst case scenario). Data have been selected from 'Nuclear Power and the Environment', American Nuclear Society, 1995.

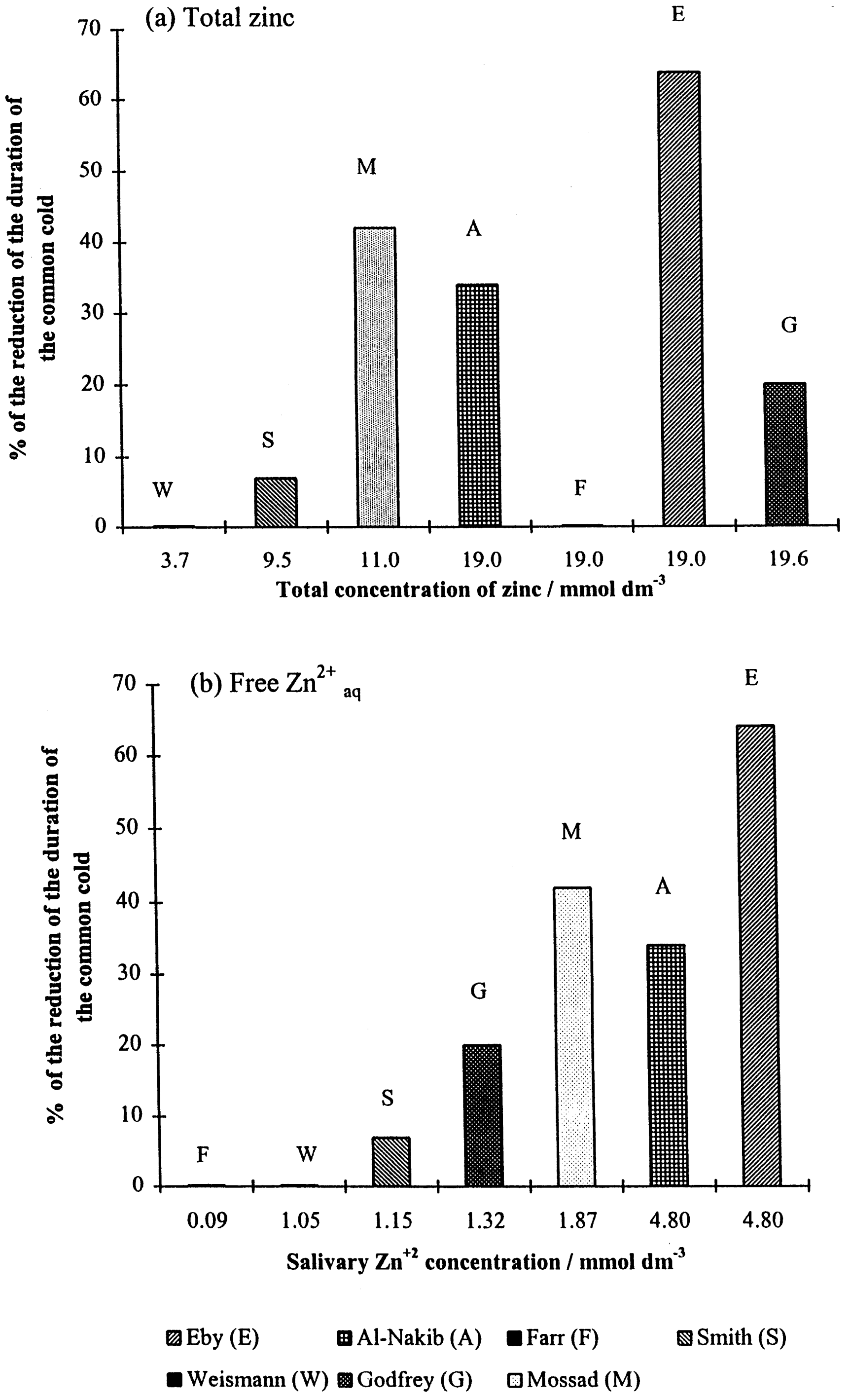

Fig. 2. Percentage reduction in symptoms of the common cold plotted versus (a) total zinc administration, and (b) the chemical speciation as expressed as free aquated zinc ions. The data are computed from references [21–27].

Table 3
An example of a trace element audit from a metal ion impregnated alginate wound dressing at pH = 7.4, released to wound fluid from whence the net-neutral species pass into healing tissue[a]

Sample	Zinc	Copper	Units
Alginate dressing	0	0	μmol g^{-1}
Impregnating solution	2000	500	μmol dm^{-3}
Impregnated dressing	3.5	26.5	μmol g^{-1}
Released from dressing	3.1	18.5	μmol g^{-1}
Wound fluid as metal ions	0.2	0	% of total metal
Wound fluid as net-neutral	8.4	81	% of total metal
Wound fluid as +ve complexes	1.5	8.7	% of total metal
Wound fluid as −ve complexes	89.6	10.3	% of total metal

[a] Adapted from references [31] and [32].

to death for half the persons exposed and the penultimate column is the dose taken. Although exposure to a whole gram of Pu by ingestion is not to be recommended, the speciation in the stomach and intestine from reactions between biochemical ligands such as phosphate, hydroxide, etc. render the Pu virtually insoluble and thus not bioavailable, being several orders of magnitude less of a risk than some naturally occurring poisons. Similarly, the target organ has a pivotal role in toxicology calculations as does both the *chemical* toxicology (Pu(IV) is similar to Fe(III) in vivo and tends to overload iron biochemistry) as well as the radiotoxicology of this emitter of α-particles which can damage stem cells if located in bone marrow [28].

6. Healthcare

We give descriptions of the use of chemical speciation in just three of many areas in which healthcare and nutrition benefits from a knowledge of the topic.

A recent review has described wounds and their decontamination and healing based upon speciation considerations [29]. The benefits of impregnating alginate dressings with essential trace element species that are a necessary component in efficient wound healing have been described and experimental techniques developed (a) for auditing the *total* amounts of trace elements transferred from dressing to wound fluid to tissue – this involves concentrations at parts per billion level in some instances,[30,31] and (b) for speciating these trace element concentrations in order to estimate those which are potentially bioavailable (as low molecular mass net-neutral species) and those which remain solvated in the aqueous wound fluid (as charged species) [32]. Examples are shown in Table 3. There is much scope for research in speeding up the analyses (so that the patient can benefit from treatment as soon as possible) and in speciating chronic wound samples which sometimes reflect underlying suppressed circulation, lack of muscular activity, or poor nutrition. Because of the inherent dryness of such wounds, this may require analyses to be achieved on samples less than 1 cm^3 volume [33].

Teeth and their healthy survival are dependent upon saliva and the biochemistry therein. This involves more than a hundred different types of bacteria and a multitude of metal ions and both low and high molecular mass ligands. The contents of saliva are dependent upon what is eaten and what is excreted from the salivary glands, the salivary contents differing between resting (an hour or two after eating or drinking) and stimulated (during the eating process) states [34]. Both can be analysed and speciated using computer simulation of the chemical equilibria prevailing. As with other biofluids, it is the low molecular mass metal complexes which dictate the chemistry at the surface of tooth enamel and in contact with gums. We have researched and reviewed the benefits of phosphate, zinc citrate and other inorganic components in dentifrices [35–37].

A sophisticated model of the thermodynamics of hydroxyapatite formation and dissolution has been published [38]

$$Ca_5(PO_4)_3OH \underset{\text{Remineralisation}}{\overset{\text{Demineralisation}}{\rightleftharpoons}} 5Ca^{2+} + 3PO_4^{3-} + OH^-$$

In practice, hydroxyapatite (and fluorapatite) and tricalcium phosphate are kinetically slow to form and usually occur as aged versions of dicalcium phosphate dihydrate or octacalcium phosphate and so formation constants and solubility data for all are used in the chemical speciation modelling. Clearly, the ability to mineralise or demineralize is dependent upon the concentration of species such as $[Ca^{2+}]$, $[PO_4^{3-}]$, $[OH^-]$ and isoelectronic $[F^-]$ in saliva. The outer layer of teeth – the dentine layer – is thermodynamically similar to a layer of cells which charged ions do not readily traverse unless made lipophilic by use of counter ions or by enveloping metal ions with ligands. Schemes have been published for remineralising teeth using remineralisation solutions and their efficacy at rebuilding dental enamel correlated with data reported by Featherstone et al. reflecting the hardness of remineralised teeth [39]. Remineralisation using mouthwashes is supplementing that which occurs naturally from saliva in the resting state between meals and uses chemicals normally involved in saliva and thus avoids the suggestion that this is mass medication using chemicals (which produced the public pressure which has discouraged the use of fluoridated water supplies).

Demineralisation occurs when saliva bacteria such as *Strept mutans* consume glucose from food and drink and excrete acids such as lactic acid which withdraw the hydroxide from within the solid $Ca_5(PO_4)_3OH$ thus causing the early stages of dental caries. Reducing the activity of such bacteria by both physical (e.g. brushing with a mild abrasive) and chemical means reduces the acid excreted to challenge teeth. The bacterial cell activity can be either attacked by absorption onto cell membranes or by overloading the bacteria with one of the essential elements for their growth. These are the modus operandi of tin compounds (such as tin fluoride) and of zinc, (such a zinc citrate), both used as components in toothpaste. The former give cationic species in saliva and are bacteriostatic through membrane inhibition. The latter are bacteriocidal since they penetrate through the cell membranes and overload the zinc-dependent cell biochemistry. Chemical speciation data are being used to direct formulators towards more effective dentifrices involving different, and cheaper, sources of materials for the developing world [40].

7. Perception of 'safe chemistry'

The scientist and the public have entirely different interpretations of the word 'safe' and much opposition arises to most of the outstanding breakthroughs in chemistry, many of which depend on chemical speciation.

In theory, and by dictionary definitions, 'safe' implies 'protection from harm', 'free from danger', etc. [41,42]. In practice, safety is firmly linked to risk and a compromise state is sought involving risk, cost and benefits (see Fig. 3). It is often the scientist's determination and communication of risk that repels the public [2].

First, hard data are immensely difficult to obtain. Cause of death data are often too blunt an instrument. Thus, the effects of nuclear radiation upon humans which have been mega-funded over the last 30 years and studies such as the Royal Society of Chemistry monitoring of members' deaths and exposure over 25 years of working in the chemical industry are all mortality based [2,42].

Secondly, the ability to analyse statistical data and to distinguish between 'causal' and 'casual' links between risks and events has improved markedly, paralleling the growth in computing power. However, the wise, professional interpretation of such data still deserves more attention to enhance objectivity and transparency.

The public, often encouraged by the press, perceive healthy, stimulating, scientific debate as implying uncertainty. Coupled with the requirement to involve politicians in the legislation and funding of chemical projects and the public's ubiquitous distrust in them, it is not surprising that the chemical industry has so few friends.

There are now the order of 75 000 chemicals in ordinary everyday use. It is important to make more widely known (a) the manifold benefits of chemistry; for example, the almost doubling of the life expectancy at birth over the last century and a half, largely based on chemical research and innovation leading to improved nutrition and healthcare, (b) that 'chemical' disasters such as Flixborough, Bhopal, and Thalidomide were really management flaws, and (c) that chemical speciation can change an element from a 'high' to a 'very low' risk.

Let us accept that science and coordination chemistry, which are central to our culture are extremely difficult to grasp and to accept by non-scientists. We must do far more to contribute towards the public understanding of our researches by having a better understanding of public concerns and spending more time communicating. A social reconstruction of science is required accepting that modern

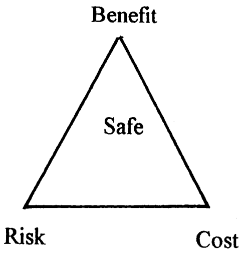

Fig. 3. 'Safety' is a situation based upon risk, benefits and costs. From reference [2].

technology may frighten many lay-persons, but life would be even more frightening without it! There is need for a rethink of risk, safety and communication at undergraduate and postgraduate levels.

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