A QICAR approach for quantifying binding constants for metal–ligand complexes

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ABSTRACT

Relative metal–ligand complex stability is predicted by evaluating the relationships between physico-chemical properties of metal ions and their experimental biotic and abiotic binding constants, K. Linear regression analysis showed that the softness index (σ_p) and the covalent index ($\chi_m^2 r$) were especially useful in model construction for rainbow trout (*Oncorhynchus mykiss*), fathead minnows (*Pimephales promelas*) and crustaceansaquatic (*Daphnia magna*) based on RMSE and F-ratio criterion ($F_{observed}/F_{critical}$ of ≥ 4). The absolute value of the log of the first hydrolysis constant $|\log K_{OH}|$ correlated best with $\log K$ values for barley ($R^2 = 0.74$, $p = 0.02$) and earthworm ($R^2 = 0.82$, $p = 0.01$). In contrast, the ionic index Z^2/r explained most of the variability of $\log K$ values for the two clays kaolinite and montmorillonite, while $|\log K_{OH}|$ was a better predictor of the generic NICA-Donnan parameters for HA and FA ($0.67 < R^2 < 0.80$, $0.002 < p < 0.01$). This implies dissimilarity of the nature of the binding sites on biotic and chemical ligands and the different binding mechanisms between metal and ligands.

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1. Introduction

Thousands of chemicals per year are released into the environment, posing a threat to many living species (Mirsal, 2004). Only a few substances are empirically investigated due to financial, practical or ethical restrictions on animal testing. To allow extrapolation of data among compounds or among species, quantitative structure–activity relationships (QSARs) have been applied widely to predict bioactivity (e.g., toxicity or bioavailability) of organic compounds in pharmacology and toxicology (Hendriks et al., 2001; Hansch et al., 1989; Blum and Speece, 1990; Schunrmann, 1990). Newman et al. (1998) and Walker et al. (2003) created the terms quantitative ion character–activity relationships (QICARs) and quantitative cationic–activity relationships (QCARs), respectively, to predict metal toxicity. Although these relationships have been applied successfully to a wide range of effects, species, and media (Newman et al., 1998; Walker et al., 2003; Ownby and Newman, 2003; Kinraide and Yermiyahu, 2007; Mendes et al., 2010), the field of study continues to develop.

Equilibrium constants or stability constants are well known tools for biochemists and chemists and are always expressed by the mass action law relationship as shown in the following equation:

$$M + L \rightleftharpoons ML; \quad K = \frac{a_{ML}}{a_M a_L} \tag{1}$$

where K is the stability constant (often expressed as a logarithm), a_L is the activity of a specific chemical ligand, and a_M is the activity of the metal ion expressed in molar units. Thus, the magnitude of $\log K$ represents the relative affinity of the metal ion for the ligand; $\log K$ is a measure of the tendency toward formation of metal complexes and gives a quantitative measure of the relative stabilities of metal complexes when the constant refers to reactions with the exact same stoichiometry (i.e. $A + 2B = AB_2$). The ligand dependent binding constants may have predictive value for toxicity when comparing the interaction of several metals for a given ligand, as calculated in the Biotic Ligand Model (BLM) (Li et al., 2008; Di Toro et al., 2001).

Complexation of metal ions by abiotic ligands including organic and inorganic ligands regulates metal reactivity, bioavailability and transport in a variety of geochemical and environmental systems. Clay and organic matter are considered as

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important parameters influencing bioavailability and ecotoxicity of metals in soils. There are many types of clay and organic matter that are present in the environment, and these may have a different binding capacity for metals. Metal binding to organic and inorganic ligands has been studied for many decades, and the most recent comprehensive compilation of binding constants are available (Keizer and Van Riemsdijk, 2002; Milne et al., 2003). One may expect the binding constants of metal ions with an abiotic ligand to be related to metal characteristics. This may allow the prediction of binding constants for metals that have not been tested.

For many decades people have noticed that binding strength was related to physical properties and to the position of the element in the periodic table (Filov et al., 1978). Most studies were conducted using the concept of metal-classifications based on physicochemical properties of metal ions (Newman et al., 1998; Walker et al., 2003; Ownby and Newman, 2003; Kinraide and Yermiyahu, 2007; Tatara et al., 1998). The present paper focuses on the possibility of abandoning the concept of metal classes and the objective is to describe, for both chemical and biological ligands, a relationship between complex stability constants and physicochemical properties of metal ions.

2. Materials and methods

2.1. Metal characteristics

A literature review of papers correlating metal characteristics to observed toxicities (Newman et al., 1998; Walker et al., 2003; Ownby and Newman, 2003; Kinraide and Yermiyahu, 2007; Tatara et al., 1998) found seven characteristics of interest. These characteristics included the Pauling ionic radius (r) (Shannon and Prewitt, 1970), ion electronegativity (χ_m) (Allred, 1961), metal softness index (σ_p) (Pearson and Mawby, 1967), the absolute value of the first hydrolysis constant ($|\log K_{OH}|$) (Baes and Mesmer, 1976; Turner et al., 1981) and ionic charge (Z) (Nieboer and Richardson, 1980). The electronegativity (χ) and Pauling ionic radius (r) were combined to produce a covalent index ($\chi_m^2 r$). The ionic charge (Z) and Pauling ionic radius were combined to generate ionic index (Z^2/r). Ion characteristics used for modeling were obtained from previous references where necessary and are shown in Table S-1(Supporting Information).

2.2. Equilibrium binding constant for biotic ligands

Biotic ligand stability constants for metal ions have been recently estimated on the basis of the Gill Surface Interaction Model (GSIM) (Pagenkopf, 1983) and the Biotic Ligand Model (BLM) (Di Toro et al., 2001) approach. Fish gills were one of the first biotic ligand examined systematically in the context of the BLM (Hollis et al., 2000a, 2000b; MacRae et al., 1999; Taylor et al., 2000; Alsop and Wood, 2000; Schwartz and Playle, 2001; MacDonald et al., 2002). Overall, we evaluated 50 conditional binding constants (K) for biotic ligands determined in 27 studies to accommodate the necessary variety of metals and organisms. The studies comprise data on several aquatic and terrestrial species, belonging to different phyla including two fish species, rainbow trout (Oncorhynchus mykiss) (Hollis et al., 2000a, 2000b; MacRae et al., 1999; Taylor et al., 2000; Alsop and Wood, 2000; Schwartz and Playle, 2001; MacDonald et al., 2002) and fathead minnows (Pimephales promelas) (Di Toro et al., 2001; Meyer et al., 1999; Santore et al., 2002; Playle et al., 1993a, 1993b; Santore et al., 2001), one crustaceans (Daphnia magna) (Santore et al., 2002; Borgmann et al., 1991, 2004; Paquin et al., 1999; Keithly et al., 2004; De Schamphelaere and Janssen, 2002, 2004; Heijerick et al., 2002; Bury et al., 2002), one plant, barley (Hordeum vulgare) (Thakali et al., 2006a; Lock et al., 2007) and one soil invertebrate, earthworm (Eisenia fetida) (Li et al., 2008; Lock et al., 2006; Thakali et al., 2006b). Species were included if the conditional binding constants were available for at least six different metals. For each species, the K-values determined for similar exposure conditions and response types (i.e., immobilization, root growth inhibition, cocoon production, mortality) were combined to calculate mean ligand-specific conditional binding constants (K). However, for the terrestrial species (i.e., barley, earthworm), this selection criterion appeared to be too strict since most data have been gathered for aqueous solutions of metals. Consequently, a single conditional binding constant for each metal was included in the model construction for terrestrial species (Thakali et al., 2006a,b; Lock et al., 2006, 2007). Different published versions of the BLMs have used different means to estimate the binding of the metal to the biotic ligand (Paquin et al., 2002). Many of the K-values that are used for binding to the biotical ligand were fit to describe the toxicity data and are not the result of direct

measurement of metal accumulation at the site of toxic action (i.e. the biotic ligand). It is not possible to directly evaluate metal accumulation at some biotic ligand, such as in very small invertebrates (e.g. D. magna or C. dubia). The conditional stability constants for the binding of metal to biotic ligands and experimental details are shown in Table S-2 (Supporting Information).

2.3. Equilibrium binding constant for abiotic ligands

Two thermodynamic data sets for synthetic (nitriloacetic acid, NTA) and natural organic ligands (humic acid, HA and fulvic acid, FA), respectively were used in this work. Thermodynamic stability constants for NTA were calculated using the computer program ECOSAT (Keizer and Van Riemsdijk, 2002) (Table S-3, Supporting Information). The generic NICA-Donnan parameters (carboxylic and phenolic sites) for HA and FA were derived by Milne et al. (2003) using ion-binding data for a large variety of humic acids (Table S-4, Supporting Information). The Gibbs free binding energy (ΔG_{bi}) of seven metals (Ca, K, Cu, Zn, Pb, Cd, Cr) with two clay minerals (kaolinite and montmorillonite) was evaluated based on measurement of the Wien effect (increased electrical conductivity at strong electrical fields) (Li et al., 2005; Wang et al., 2008). The derived Gibbs free binding energy (ΔG_{bi}) was used to determine the thermodynamic stability constants of kaolinite and montmorillonite for the studied metals (Table S-5, Supporting Information) (Wang, 2007).

2.4. Model development

For each type of ligand, metal binding constants (K) were related to the four ion characteristics ($\chi_m^2 r$, σ_p, $|\log K_{OH}|$, Z^2/r) using linear regression analysis. All constants were log transformed prior to regression analysis to normalize their distribution. The level of significance was set at $\alpha = 0.05$. The contribution of a variable (ionic characteristic) to each equation was first tested for statistical significance (F-statistic). Multiple variable regressions were not calculated because of the low number of data points. Second, the predictive potential of models was estimated with more rigorous criteria (F-ratio approach) (Draper and Smith, 1981) and root mean square deviation (RMSE). The most stringent $F_{observed}/F_{critical}$ of ≥ 4 was adopted in the present study.

3. Results

3.1. Relating conditional binding constants for biotic ligands to the physicochemical properties of the ions

Evaluation of metal ion characteristics and $\log K$ values by linear regression analysis gave several statistically significant models. Table 1 lists the QICARs for five different biotic ligands with the physicochemical characteristics of metals. The regressions showed that metal sorption for the five biotic ligands were correlated to different metal ionic characteristics. The softness (σ_p) produced the best relationships ($0.82 < R^2 < 0.89$) between $\log K$ and metal characteristics for all the aquatic species (Fig. 1). Note that a positive correlation was obtained between $\log K$ and $\chi_m^2 r$, while a significant, negative relationship was found between $\log K$ and σ_p for both aquatic and terrestrial species.

For the two tested terrestrial species, barley Hordeum vulgare and earthworm Eisenia fetida, $|\log K_{OH}|$ gives the best description of the variation ($R^2 = 0.74$, $p = 0.02$; $R^2 = 0.82$, $p = 0.01$). Also, the slopes and the intercepts of the regressions lines are very similar (Fig. 2).

3.2. Relating conditional binding constants for abiotic ligands to the physicochemical properties of metal ions

For NTA, only the $|\log K_{OH}|$ showed a statistically significant relationship to $\log K$ for six metals tested ($R^2 = 0.88$, $p = 0.005$, Table 2). The σ_p and $\chi_m^2 r$ showed no significance ($0.32 < R^2 < 0.46$, $0.13 < p < 0.24$). Similar to the results of NTA, a significant, negative relationship ($0.67 < R^2 < 0.80$, $0.002 < p < 0.01$) was found for generic NICA-Donnan parameters values of HA and FA and the $|\log K_{OH}|$ (Fig. 3), except for the carboxylic sites of FA. The σ_p and $\chi_m^2 r$ regressions with HA and FA were not statistically significant ($0.11 < R^2 < 0.35$, $0.12 < p < 0.43$).