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CORRELATING METAL IONIC CHARACTERISTICS WITH BIOLOGICAL ACTIVITY USING QSAR MODEL. ELECTRONIC PROPERTIES

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ABSTRACT. Quantitative structure activity relationships (QSARs) were developed to predict toxicity of metal ions (from the aquatic environment and soil) by correlating the biological activity, $A=\log(1/EC_{50})$, values with four ion descriptors, chosen to represent the binding tendencies of metals to ligands, electronic and electrical effects: the electronegativity coefficient (χ), enthalpy of hydration (ΔH_{hyd}), the first hydrolysis constant (K_{OH}) and the $\log(Z^2/r\Delta E_0)$, where Z^2/r reflects the energy of an ion when interacting electrostatically with a ligand and ΔE_0 reflects the effects of atomic ionization potential. Most QSARs are developed for organic toxicants, with inorganic toxicants (metals) being under-represented. Successful predictive models for relative toxicity of metal ions (monovalent and divalent ones) using ion characteristics have been developed. Relative metal toxicity (Li^+, Na^+, K^+, Ca^{2+}, Ba^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Sr^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+} and Zn^{2+}) was predicted by least squares linear regression and several ion characteristics. Toxicity was most effectively predicted (R=0.84) with $\log K_{OH}$ (where K_{OH} is the first hydrolysis constant) and electronegativity, which reflects a metal ion tendency to bind to intermediate ligands such as biochemical functional groups with oxygen atom donors. These QSAR correlations could be useful in ecological risk assessment.

Keywords: *QSAR, binding tendency, correlation, biological activity, hydrolysis*

INTRODUCTION

Quantitative Structure-Activity Relationships (QSARs) are empirical models that relate experimental properties/activities of compounds with their molecular structures. The rapid development of quantum theory and ab initio computational methods made possible the prediction of molecular properties of small isolated molecules within experimental error. QSARs have been widely applied to predict the bioactivity (toxicity or bioavailability) of organic compounds in pharmacology and toxicology. In contrast, models

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correlating metal ionic characteristics with their bioactivity remain poorly explored. During the last one and a half century, many scientific researchers have tried correlations between physical and chemical properties of metal cations and their toxicity [1-5]. However, the majority of industrially and environmentally important chemical processes, and biochemical transformations in living organisms take place in heterogeneous condensed media and hence the use of QSARs that proceed directly from the endpoint of interest is an attractive and fast alternative to predict molecular properties in complex environments [6,7].

The direct prediction of properties is in general not feasible either due to the lack of computing resources or lack of knowledge about the relationship between the structure and property. QSAR predictions for inorganic toxicity (especially for the toxicity of metal ions) are, however, less developed. In 2000, a paper entitled, “QSARs for metals - fact or fiction?”, authored by Walker and Hickey [8] raised a number of issues.

Newman and co-workers [1,2,5,9,10] developed a novel quantitative ion character–activity relationship (QICAR) to predict the relative toxicity of metal ions, based on metal–ligand binding tendency. The metal-biological system interaction, in terms of the nature of reacting species and the types of formed products, needs to be characterized. Tatara et al. (1997) argued [11] that the first hydrolysis constant reflects the metal ion’s tendency to bind to intermediate ligands. McKinney et al. (2000) also analysed the biological activity of metal ions [12]. Ownby and Newman further demonstrated that the QICAR approach is also suitable for prediction of toxicity in binary metal mixtures [5].

Metal toxicity is largely determined by the functional ionic selectivity of proteins (e.g., complexation, coordination, chelation, ion exchange, adsorption, etc.). The QSAR methods offer a new way to explore the interaction between the absorbed metal ions and the functional groups on the biomass [4,13-16]. Metals can cause toxicity at the cellular level [15-17] in plants by affecting the membrane permeability, by inhibiting, inducing or increasing the activity of enzymes and by activating the defending mechanisms against the increased metal phytotoxicity.

RESULTS AND DISCUSSION

The objective of this study was to establish a QSAR model between the metal ionic properties and their biological activity (EC_{50}).

Ion characteristics used in modelling (Table 1) were obtained from a variety of sources: Ionic radii (r) are from Shannon and Prewitt [18,19] and *CRC Handbook of Chemistry and Physics* [20], the first hydrolysis constants ($\log K_{OH}$) are from Baes and Mesmer [21] and Brown and Allison [22], the ΔE_0 values were obtained from Kaiser [23], and average electronegativity values (χ) were taken from Allred [24]. The mean effect concentration values (EC_{50}) were taken from John T. Mccloskey [9].

Table 1. Metal ion characteristics and biological activity (A^{obs}) used in regressions

No.	*Ion*	EC_{50} *(μM/L)*	A^{obs}= $\lvert log(EC_{50})\rvert$	χ	pKa= $\lvert logK_{OH}\rvert$	ΔH_{hyd} *(kJ/mol)*	SI= Z^2/r	ΔE_0 *(V)*	$log(SI/\Delta E_0)$
1.	Mn^{2+}	1.571	0.196176	1.55	10.6	–1845.6	4.82	1.03	-0.68305
2.	Cd^{2+}	27.000	1.431364	1.69	11.7	–2384.9	4.21	0.40	-0.62428
3.	Ca^{2+}	94.702	1.976359	1.00	12.7	–1592.4	4.00	2.76	-0.60206
4.	Li^{+}	294.13	2.468547	0.98	13.8	–514.1	1.35	3.05	-0.13033
5.	K^{+}	625.24	2.796047	0.82	11.6	–320.9	0.72	2.92	0.142668
6.	Sr^{2+}	235.52	2.372041	0.95	13.18	–1444.7	3.54	2.89	-0.549
7.	Ba^{2+}	95.455	1.979799	0.89	13.82	–1303.7	2.94	2.90	-0.46835
8.	Zn^{2+}	35.000	1.544068	1.65	9.60	–2044.3	5.33	0.76	-0.72673
9.	Cu^{2+}	1.620	0.209515	1.90	8.96	–2100.4	5.48	0.16	-0.73878
10.	Hg^{2+}	0.919	0.03668	2.00	3.40	–1853.5	3.92	0.91	-0.59329
11.	Na^{+}	401.00	2.603144	0.93	14.48	–405.4	0.98	2.71	0.008774
12.	Co^{2+}	874.00	2.941511	1.88	9.65	–2054.3	5.33	0.28	-0.72673
13.	Ni^{2+}	566.00	2.752816	1.91	9.86	–2105.8	5.8	0.23	-0.76343
14.	Mg^{2+}	87.242	1.940726	1.31	11.42	–1922.1	5.56	2.38	-0.74507
15.	Pb^{2+}	1.150	0.060698	2.33	7.80	–1479.9	3.39	0.13	-0.5302

Some data in Table 1 were calculated from the literature data, e.g., the biological activity $\boldsymbol{A^{obs}} = |\log_{10}(EC_{50})|$, the *polarizing power*, Z^2/r (where Z is the ion charge and ***r*** the ionic radius), the absolute difference in electrochemical potential between an ion and its first stable reduced state (ΔE_0), *electronegativity* (χ), the *acidity of metal ions pKa* like $|\log K_{OH}|$ and the *enthalpy of hydration* ΔH_{hyd} (kJ/mol).

Since the usual statistic analysis demands the *trial* and *test* stages in validation, the ions metal of Table 1 were classified accordingly based on the best fit of the normal distribution of input data (EC_{50}), as evidenced in Figure 1, such that each category of metal ions to be represented in both "trial" and "test" sets of toxicants.

We obtained structure activity relationships for all the possible correlation models considered for the data in Table I together with the corresponding statistics (simple correlation factor, standard error of estimation SEE). The results are given in Table 2. Data for the test set are given in Table 3.

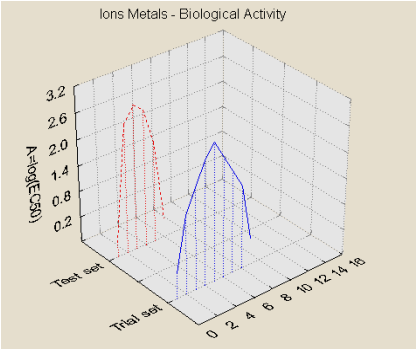

Figure 1. The plot of metal ions EC_{50} toxicities of Table 1.

Table 2. Structure activity relationships for the "Trial set" (9 ions metal) of Table 1 (No. 1, 2, 3, 4, 5, 6, 7, 8, 9)

No. Eq.	*Model*	*R*	*SEE*
1.	$A^{obs} = -2.7577 + 0.3755\ pK_a$	0.7140	0.6983
2.	$A^{obs} = 4.6933 - 0.9319\ \chi + 0.3923\ \chi^2$	0.8407	0.5731
3.	$A^{obs} = 2.7737 + 2.2807\ \log(SI/\Delta E_0)$	0.7328	0.6787
4.	$A^{obs} = -11.7454 + 0.4123\ pK_a + 0.0823\ \Delta H_{hyd}$	0.7505	0.7112
5.	$A^{obs} = 2.8364 + 0.0046\ pK_a - 0.6942\ \chi^2$	0.8467	0.5833
6.	$A^{obs} = -0.8472 + 1.0689 pK_a - 0.0432 pK_a^2 - 4.7761\chi + 1.1913\chi^2$	0.8531	0.6884

Table 3. Observed and predicted activity for the "Test set" metal ions of Table 1 (No. 10, 11, 12, 13, 14, 15) using model equations (1 to 6) from Table 2.

Metal Ion	*A observed*	*A predicted*					
		Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Hg^{2+}	0.03668	-1.481	4.3987	1.420583	-162.887	0.07524	-2.49933
Na^{+}	2.603144	2.67954	4.165933	2.793711	-39.1397	2.302594	2.161293
Co^{2+}	2.941511	0.86587	4.327873	1.116247	-176.836	0.42721	0.676256
Ni^{2+}	2.752816	0.94473	4.344521	1.032545	-180.987	0.349245	0.715898
Mg^{2+}	1.940726	1.53051	4.145737	1.074419	-165.226	1.697615	1.513348
Pb^{2+}	0.060698	0.1712	4.65173	1.564473	-130.325	-0.89646	0.201068
	R	0.7436	0.6684	0.0276	0.0519	0.5990	0.7121
	SEE	1.0014	1.1140	1.4972	1.4958	1.1993	1.0515

As can be seen in Table 2, we obtained useful information about the structure parameters in correlation with electronegativity, acidity, heat of hydration, the size of ions (SI) and biological activity. For the metal ion series, the maximum of R (0.8467) is given by the two-variable model using pK_a and χ^2 , A=f(pK_a, χ^2), (eq. 5, Table 2) this being the most reliable correlation across the A models of Table 2. This also shows the second lowest SEE (0.5833) value. The best one-variable model is that using the electronegativity like χ and χ^2 (R=0.8407; SEE=0.5731, eq. 2, Table 2) and next was the model using the size of ion (SI) and the absolute difference in electrochemical potential between an ion and its first stable reduced state (ΔE_0) with R=0.7328 (eq. 3, Table 2).

The significant relationships, above presented, indicates that the toxicity of all series of metal ions can be best described in terms of pK_a, pK_a^2, χ, and χ^2, by a regression model. The toxicity (EC_{50}) of the metal ion series could be also described by a multilinear regression model including the acidity and the electronegativity (eq. 6, Table 2) but the corresponding SEE is rather high. The best predictive ability (R=0,7437), is shown by the model 1, followed by the model 6 (R=0.7121).

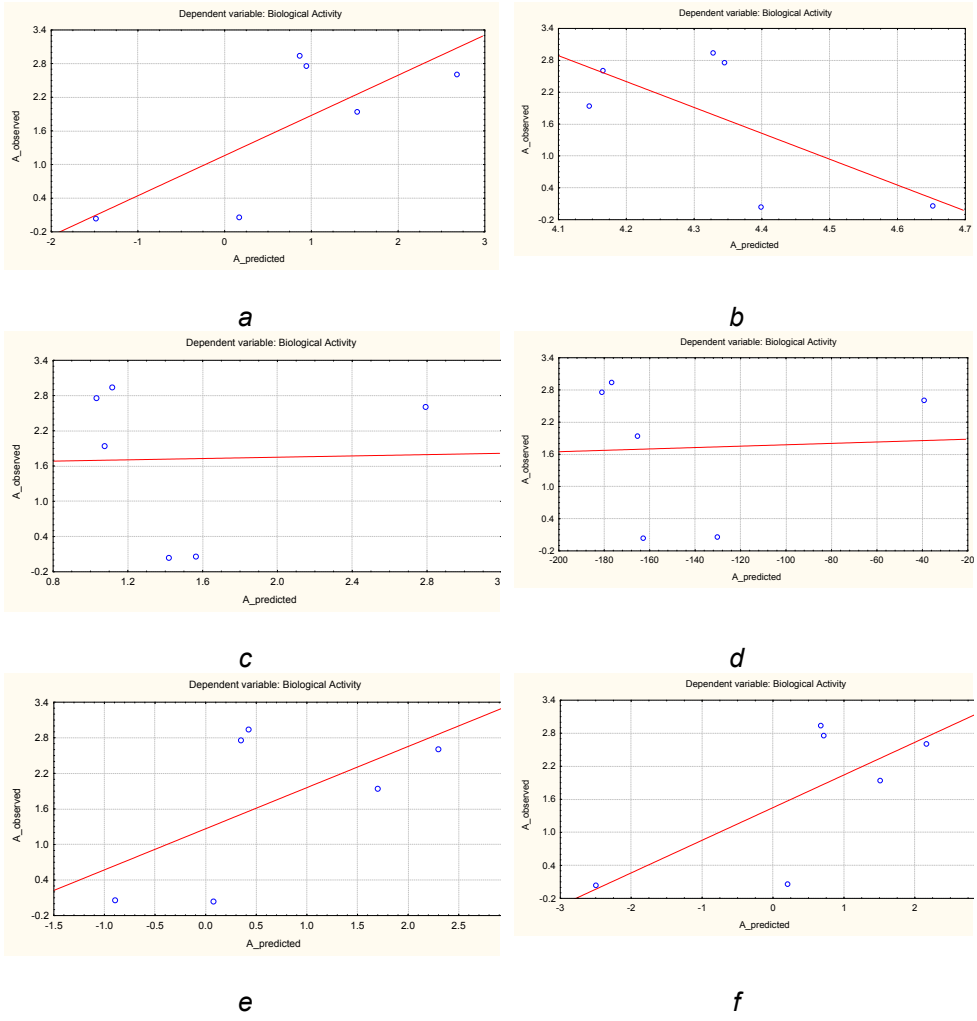

Figure 2. Correlation between observed and calculated activity for the test compounds (NonGaussian) of Table1, cf. data in Table 2 for:
a) model (I) of Eq. (1); b) model (II) of Eq. (2); c) model (III) of Eq. (3).
d) model (IV) of Eq. (4); e) model (V) of Eq. (5); f) model (VI) of Eq. (6).

These predictive models, if developed, could be very useful in areas where data on metal toxicity or sublethal effects are lacking or incomplete. Once a model has been developed with representative metals for a particular organism under certain environmental conditions, the relative effect of additional metals could be predicted.

The present analysis showed the parabolic dependence of activity on the acidity and electronegativity, as the most reliable model (the model 5) on a collection of QSAR trial equation.

Relatively high correlation coefficients were obtained in the present study between ion characteristics and biological activity. These types of information could be extremely useful in ecological risk assessment.

CONCLUSIONS

Our results (models of metal ion toxicity using ion characteristics) agree with the theory on toxicants interaction with the living organisms. Actually, for a group of metal ions (monovalent and divalent), the trial set of compounds provided a good parabolic dependency of the activity by means of the chemical transport index of electronegativity and first constant of hydrolysis, even the predictive ability did not support the trial test (due, maybe, of a limited data set). Such a behaviour is susceptible for further generalization in the future studies and will be reported in the subsequent communications.

METHODS

In predictive toxicology, we exploit the toxicological knowledge about a set of chemical compounds in order to predict the activity of other compounds [25].

Ion characteristics of inorganic species can be used to predict the relative toxicity or sublethal effects of metal ions. Many of these characteristics reflect the binding tendency of metals to ligands. For example, *polarizing power*, Z^2/r (where Z is the ion charge and $\boldsymbol{r}$ is the ionic radius), is a measure of strength of the electrostatic interaction between a metal ion and a ligand; the ΔE_0 (where ΔE_0 is the absolute difference in electrochemical potential between an ion and its first stable reduced state) reflects the ability of an ion to change its electronic state; *electronegativity* (χ) is correlated with the energy of an empty valence orbital and reflects the ability of a metal to accept electrons, combining electronegativity with the ionic radius yields an index that quantifies the importance of covalent interactions relative to ionic interactions [14]; the *acidity of metal ions pKa* like $|\log K_{OH}|$, where K_{OH} is the first hydrolysis constant: $[M(H_2O)_n]^{x+} + HOH \rightarrow [M(H_2O)_{n-1}OH]^{(x-1)+} + H_3O^+$ (metal ions in aqueous solution behave as Lewis acids); the *enthalpy of hydration* ΔH_{hyd} of an ion is the amount of energy released when a mole of the ion dissolves in a large amount of water forming an infinite dilute solution in the process.

Multilinear models have been in use since a long time. As linear equations, they are easy to use and relatively straightforward to interpret. For n instances they are defined as the coefficients that minimize the error on a system of n linear equations [26, 27, 28]:

$$y_i = b_1 x_{i1} + b_2 x_{i2} + ... + b_m x_{im} + d \qquad i \in \{1, ..., n\},$$

or in a more compact notation, $y = (\langle X, b \rangle + d)$ where $\langle ..., ... \rangle$ denotes the normal dot product and b and d are the coefficients to learn. Multilinear models assume linear relationships between features and activities [26]. The prediction $f(x_q)$ is obtained by [25]:

$$f(x_q) = (\langle x_q, b \rangle + d).$$

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