QSPR ensemble modelling of the 1:1 and 1:2 complexation of Co^{2+}, Ni^{2+}, and Cu^{2+} with organic ligands: relationships between stability constants

Vitaly Solov'ev · Alexandre Varnek · Aslan Tsivadze

Abstract Quantitative structure–property relationship (QSPR) modeling of stability constants for the metal:ligand ratio 1:1 ($\log K$) and 1:2 ($\log \beta_2$) complexes of 3 transition metal ions with diverse organic ligands in aqueous solution was performed using ensemble multiple linear regression analysis and substructural molecular fragment descriptors. The modeling was performed on the sets containing 396 and 132 (Co^{2+}), 613 and 233 (Ni^{2+}), 883 and 257 (Cu^{2+}) $\log K$ and $\log \beta_2$ values, respectively. The models have been validated in external fivefold cross-validations procedure as well as on the external test set containing new ligands recently reported in the literature. Predicted $\log K$ and $\log \beta_2$ values were calculated as arithmetic means of several hundred individual models (consensus models) using their applicability domains in averaging. The root mean squared error of predictions varies from 0.94 to 1.2 ($\log K$) and from 1.2 to 1.4 ($\log \beta_2$) which is close to observed experimental systematic errors. Linear correlations between experimental $\log K$ values for pair of metal ions were evaluated. For all metal ions and ligands forming both 1:1 and 1:2 complexes the following ratio is observed: $\log \beta_2 / \log K = 1.8 \pm 0.1$, $n = 492$.

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Introduction

Binding of metal ions (M) by organic ligands (L) in solutions is of great importance in many chemical [1–3] and biological [4–11] processes. The thermodynamic quantities such as equilibrium constants and free energy are the most general and significant characteristics used in chemical speciation calculations of metal binding [12–18]. In the past decade, quantitative structure–property relationships (QSPR) linking the stability constant with the structure of organic ligands were reported [19–40] and reviewed [41, 42]. Developed QSPR models help to assess a selectivity of ligand for metal ions [40] which is a key parameter in biomedical, biological, and environmental applications, and in metal ion separations [43]. Technological importance of the Co^{2+}, Ni^{2+} and Cu^{2+} metal ions is well known, they are often widely used in materials for high-tech applications [44, 45] and objects of ion sequestering in biological systems [46]. Earlier, QSPR modeling of the stability constant $\log K$ for the 1:1 (M:L) complexes of Co^{2+} [20, 47, 48], Ni^{2+} [20, 25, 47, 48], Cu^{2+} [20, 25, 47–49] were reported on relatively small data sets and particular classes of ligands including from 6 (Cu^{2+}) [49] to 85 (Ni^{2+}) and 96 (Cu^{2+}) [25] ligands. These models were either not properly validated [49] or their validation have been performed on a single test sets [20, 25]. The models applicability domains (ADs) issue was never discussed in these studies [20, 25, 47–49]. In most of cases, QSPR

modeling of the Co^{2+}, Ni^{2+} and Cu^{2+} complexation was performed on the 1:1 complexes. At the same time, estimation of stability of the complexes with different stoichiometry is important for quantitative description of industrial and biological processes [50, 51], and for design of new materials [44]. In particularly, models for the stability constant ($log\beta_2$) of the 1:2 complexes could be an obvious step in stability assessment of multiligand and metallosupramolecular complexes.

In this paper, we describe QSPR modeling of both the stability constants for the 1:1 and 1:2 (M:L) complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with different classes of organic ligands in water at 298 K and an ionic strength 0.1 M. The models were obtained using ensemble multiple linear regression analysis (MLR) and substructural molecular fragment (SMF) descriptors. The modeling was performed on the biggest known data sets of the complexation containing 396 and 132 (Co^{2+}), 613 and 233 (Ni^{2+}), 883 and 257 (Cu^{2+}) organic ligands for $logK$ and $log\beta_2$, respectively. The models have been validated in external 5-fold cross-validations procedure and on an additional test set of the 23 complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with 13 organic ligands taking into account ADs of models. The root mean squared error (RMSE) of predictions varies from 0.94 to 1.2 ($logK$) and from 1.2 to 1.4 ($log\beta_2$) which is close to observed systematic experimental errors. Linear relationships linking $logK$ for pairs of metal ions and known ligands were evaluated. Sufficiently general linear relationship between $log\beta_2$ and $logK$ has been suggested. Developed QSPR models were applied for assessments of the stability constant $logK$ of the ML complexes of the ligands which form supramolecular metallogrid complexes.

Materials and methods

Data sets

The experimental values of the stability constants for the 1:1 and 1:2 (M:L) complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with various organic ligands in water were selected from the IUPAC Stability Constants Database (SC DB) (version 5.33, Academic Software) [52] at standard temperature 298 K and an ionic strength $I = 0.1$ M. Some $logK$ and $log\beta_2$ values (around 15 %) were corrected to specified temperature and an ionic strength using the procedures included in SC DB. Debye–Huckel theory and the Davies equation for the mean ionic activity coefficient were applied to adjust the stability constant from $I' = 0$–0.3 M to an ionic strength $I = 0.1$ M [52]. If an experimental enthalpy (ΔH) value of an equilibrium is available, and it is assumed that ΔH is independent of temperature, the van't

Hoff equation in the integration form was used to assess $logK$ ($log\beta_2$) at 298 K from $logK$ ($log\beta_2$) measures at any other temperature T' (T' = 283–308 K) [52].
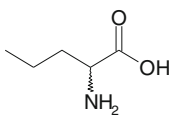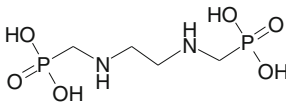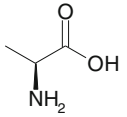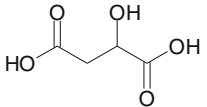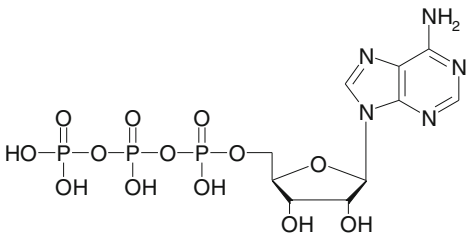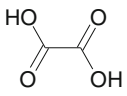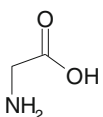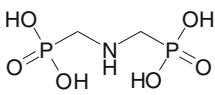
2D structures of ligands, names of metal ions and corresponding $logK$ and $log\beta_2$ values resulted from searching in SC DB were converted into structure-data files (SDF) served as an input in the MLR module of the ISIDA/QSPR program [53]. Chemical editor EdChemS [54] and the SDF manager EdiSDF [23, 55–57] were used to prepare data sets. If several values of $logK$ ($log\beta_2$) were available for a particular ligand, the most recent data or the data consistent with respect to different experimental methods were chosen. It should be noted that discrepancies in experimental $logK$ values reported for the same equilibrium by different authors may attain rather high values (more than 2.8 $logK$ unites, Table 1). At the pretreatment stage, some specific ligands were excluded if they bring fragments occurred less than in 3 ligands for different types of SMF descriptors and given metal ion. Finally, 396 and 132 (Co^{2+}), 613 and 233 (Ni^{2+}), 883 and 257 (Cu^{2+}) organic ligands were se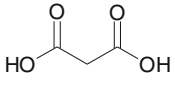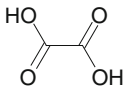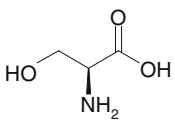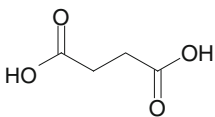lected for the modeling for the 1:1 and 1:2 complexes, respectively. For the studied complexes, the $logK$ values vary in the ranges of 0.8–19.1 (Co^{2+}), 0.4–20.5 (Ni^{2+}) and 1.2–23.0 (Cu^{2+}). The $log\beta_2$ values lie in the ranges of 2.8–15.4 (Co^{2+}), 3.0–20.6 (Ni^{2+}) and 6.9–22.3 (Cu^{2+}) (Fig. 1).

The datasets for three metal ions contain totally 1,237 ($logK$) and 423 ($log\beta_2$) organic ligands. The names of the ligands and experimental stability constant values are given as supporting information in SDFs. As a rule, an organic ligand has several functional groups. Studied molecules include derivatives of carboxylic and polycarboxylic acids; polyamines, (thio)ethers, various amino acids and aminocarboxylates; derivatives of phosphonous, phosphoric, (di)phosphonic and phosphinic acids; cyclic and acyclic polydentate ligands with the terminal carboxy and phosphoryl groups separated by various cyclic or acyclic spacers; various (di)sulfonic acids; ternary amines with phosphono and carboxy groups; mono- and dipodands of ternary amines; amide, (thio)phenol, imidazole, adenosine, inosine, uridine, uracil, cytidine, thymidine, adenine and guanosine derivatives; crown-ethers, thia-, and aza-crowns with neutral and acidic lariat groups, cryptands; pyridines; cyclodextrins; purine, phenanthroline, hydrazide derivatives, etc. (see supporting information: SD Files).

Machine learning methods

Quantitative structure–property relationship modeling was performed using MLR Analysis of the ISIDA/QSPR program [53] with combined forward [40] and backward [19] stepwise variable selection techniques.

Table 1 The log$K$ values for the 1:1 (M:L) complexes of several studied ligands with Co^{2+}, Ni^{2+} and Cu^{2+} in water at temperature 298 K and an ionic strength 0.1 M. The demonstration of a discrepancy in the experimental log$K$ values

No.	Ligand	Metal ion	Log$K$	References
1		Co^{2+}	4.15	[81]
			4.80	[82]
2		Co^{2+}	10.23	[83]
			9.72	[84]
3		Co^{2+}	4.33	[85]
			4.85	[86]
4		Co^{2+}	3.1	[87]
			5.65	[86]
5		Co^{2+}	5.1	[88]
			4.40	[89]
6		Ni^{2+}	3.46	[90]
			4.43	[91]
7		Ni^{2+}	5.49	[92]
			6.82	[93]
8		Ni^{2+}	8.32	[94]
			10.06	[95]
9		Ni^{2+}	2.83	[96]
			3.69	[97]
10		Ni^{2+}	4.58	[91]
			3.27	[98]
11		Cu^{2+}	6.67	[99]
			4.28	[100]
12		Cu^{2+}	8.38	[101]
			7.23	[102]
13		Cu^{2+}	3.98	[103]
			2.61	[104]

Table 1 continued

No.	Ligand	Metal ion	LogK	References
14		Cu^{2+}	4.22	[87]
			6.80	[90]
15		Cu^{2+}	4.10	[87]
			6.96	[90]
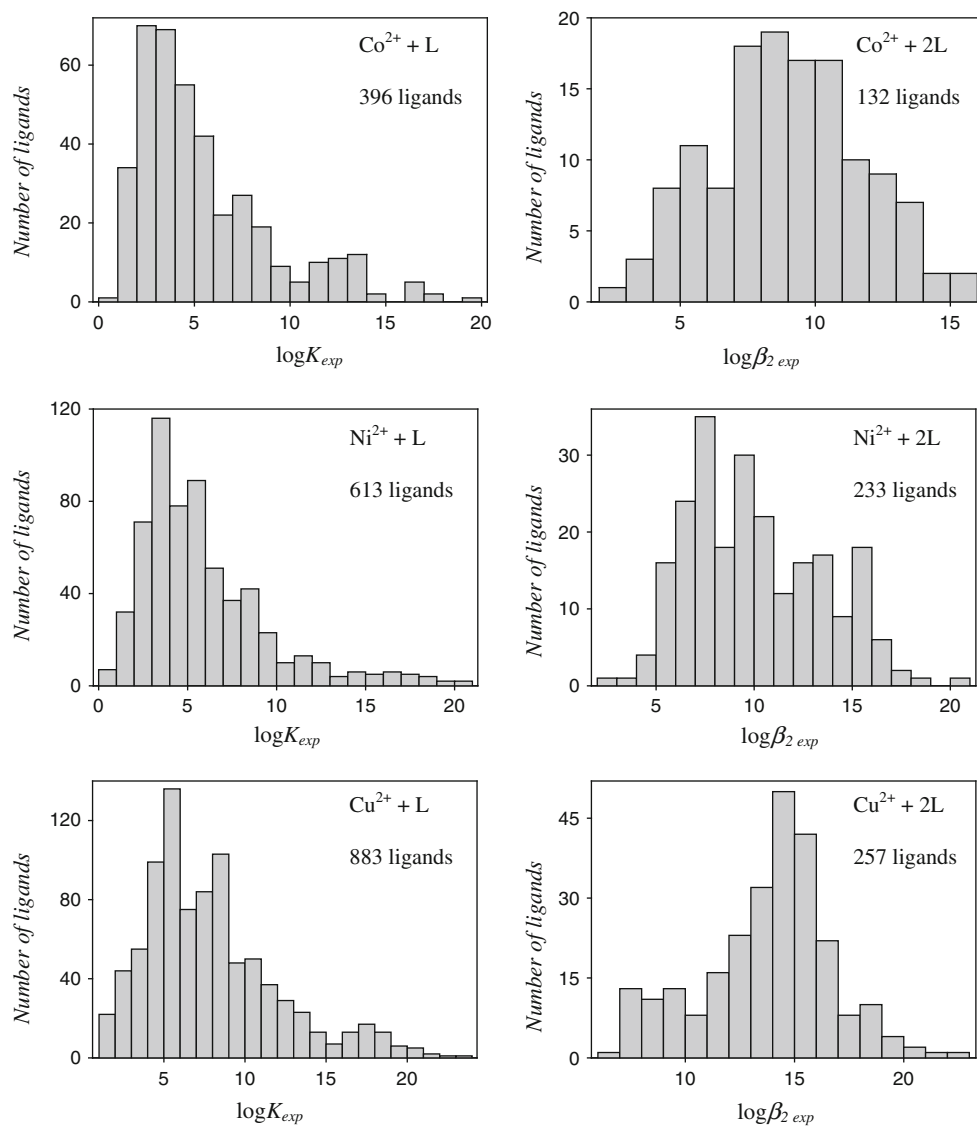
Fig. 1 Distribution of experimental values of the stability constants for the 1:1 (M:L) (*left*) and 1:2 (*right*) complexes of Co^{2+}, Ni^{2+}, and Cu^{2+} with organic ligands in water at temperature 298 K and an ionic strength 0.1 M

Ensemble multiple linear regression analysis

Multiple linear regression analysis is applied to build linear relationships between independent variables (SMF descriptors: X_i, $i = 1, 2,\dots$) and a dependent variable (here target property is $Y = \log K$ or $\log\beta_2$): $Y = c_0 + \Sigma c_i X_i$, where every descriptor value (SMF count x_{ij}, $j = 1, 2,\dots, n$; here n is the number of ligands) is associated with observed property value (y_j, $j = 1, 2,\dots, n$), c_i is descriptor contribution, and c_0 is the independent term which is omitted in a part of models. The singular value decomposition method [58, 59] is used to fit contributions c_i and to minimize the sum of squared residuals which are squared differences between the property values calculated by the model ($y_{j,calc}$) and observed values ($y_{j,exp}$) in the training set. Ensemble modeling was performed generating up to 840 MLR models each of them corresponds to particular type of the SMF descriptors and MLR equation ($c_0 = 0$ or $c_0 \neq 0$) and applied variable selection technique. Three sub-algorithms FVS-1, FVS-2 and FVS-3 for forward stepwise variable selection [40, 60] and the algorithm for backward stepwise variable selection [40, 61] have been applied. The efficiency of the FVS procedure was compared with an implementation of Genetic Algorithm (GA) on the QSPR modeling of different types of anti-HIV activities [61]. The results show similar predictive performance of computationally expensive GA-based approaches and FVS calculations. The leave-one-out (LOO) cross–validation correlation coefficient Q served as a criterion of model selection: the acceptable models were characterized by $Q^2 > 0.5$.

Consensus modeling

The $\log K$ ($\log\beta_2$) values for test set compounds were predicted by consensus models (CMs). CMs combines predictions issued from great number of selected individual models originated from different types of the SMF descriptors and variable selection algorithms [19, 23, 34, 60, 62]. Thus for each compound from the test set, the target property is computed as an arithmetic mean of values obtained by individual models excluding those leading to outlying values according to Tompson's rule [63]. If a test compound is identified as being outside combined AD of individual model, the prediction by given model for a given compound is not included in CM.

Applicability domain of models

Ensemble of three approaches for model AD has been applied: Bounding Box, Fragment Control [57] and "Quorum Control" [35]. The bounding box method considers as AD a multi-dimension descriptor space confined by minimal and maximal values of counts of SMF descriptors involved in an individual model. Fragment control rejects a prediction for a test compound containing SMF fragments which don't occur in the initial SMF pool generated for the training set. "Quorum Control" discards a test compound if CM includes less than n_Q % of the total number of selected individual models ("no consensus without quorum"). Here $n_Q = 15$ % was used.

Validation of models

In order to validate CM, the external 5-fold cross validation (5-CV) was applied [21, 60]. In this procedure, an entire dataset is divided in 5 non-overlapping pairs of training and test sets. Predictions are prepared for all molecules (n) of the initial dataset, since each of them belongs to one of the test sets. The descriptor selection and model acceptance procedures were performed only on the training folds. The compounds of test sets were not used for the model development. Predictive ability of CMs was additionally validated on the external test set of the 23 (M^{2+})L complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with 13 new organic ligands (see Supporting information, Additional_Test_Set.SDF) which were not studied in the initial data sets. Predictive performance of CM has been estimated using coefficient of determination (R^2_{det}) and RMSE for a combination of all five test sets

$$R^2_{\det} = 1 - \sum_{i=1}^{n} \left(Y_{\exp, i} - Y_{pred, i}\right)^2 \Big/ \sum_{i=1}^{n} \left(Y_{\exp, i} - <Y>_{\exp}\right)^2,$$

$$\text{RMSE} = \left[\sum_{i=1}^{n} \left(Y_{\exp, i} - Y_{pred, i}\right)^2 / n\right]^{1/2}$$

where Y_{exp} and Y_{pred} are, respectively, experimental and predicted values of the stability constant $\log K$ ($\log\beta_2$). The number of data points (n), the standard deviation (s) and the Pearson correlation coefficient (R_{corr}) also describe linear relationships.

Descriptors

The SMF [34, 56, 64, 65] as subgraphs of molecular graphs of the ligands were descriptors in QSPR models. Molecules were represented with implicit hydrogen atoms. Two classes of the SMF descriptors were applied: shortest topological paths with explicit representation of atoms and bonds, and terminal groups as shortest paths but defined by length and explicit identification of terminal atoms and bonds [34, 65]. Single, double and triple bonds were considered different in acyclic and cyclic non-aromatic motifs. For every class of the sequences, the minimal ($2 \leq n_{min} \leq 4$) and maximal ($6 \leq n_{max} \leq 15$) numbers of constituent atoms are defined. The notations $IAB(n_{min}–n_{max})$ and $IAB(n_{min}–n_{max})t$ represent SMF types of two classes, which include all intermediate shortest paths with n atoms: $n_{min} \leq n \leq n_{max}$. 60 types of the sequences of two classes have been generated varying

the values of n_{min} and n_{max}. SMF descriptors of each particular type were used as an initial descriptors' pool in QSPR modeling to build several QSPR models using different variable selection technique. Concatenated fragments always occurring in the same combination in compounds of the training set were considered as one extended fragment.

Results and discussion

QSPR modeling

Quantitative structure–property relationship modeling was performed for the complexation of 1,237 (log$K$) and 423

(logβ_2) organic ligands. 840 (360), 120 (360) and 160 (360) individual structure–property models were built for the 1:1 (1:2) complexes of Co^{2+}, Ni^{2+} and Cu^{2+}, respectively, only the most stable models ($Q^2 > 0.5$) were selected to include in CMs. Obtained CMs demonstrate a reasonable predictive ability of log$K$ in 5-CV (Fig. 2): RMSE is 0.94 (Co^{2+}), 1.1 (Ni$^+$) and 1.2 (Cu^{2+}), whereas squared determination coefficient R^2_{det} changes from 0.907 (Cu^{2+}) to 0.929 (Co^{2+}). RMSE of predicted logβ_2 values varied from 1.2 to 1.4 and R^2_{det} varies from 0.780 to 0.838 as a function of metal ion (Fig. 2). Notice that similar performance for log$K$ predictions (RMSE = 1.1 (Cu^{2+}) and 1.3 (Ni^{2+}) [25]) was reported for the models built on small and structurally homogeneous datasets. On the Regression
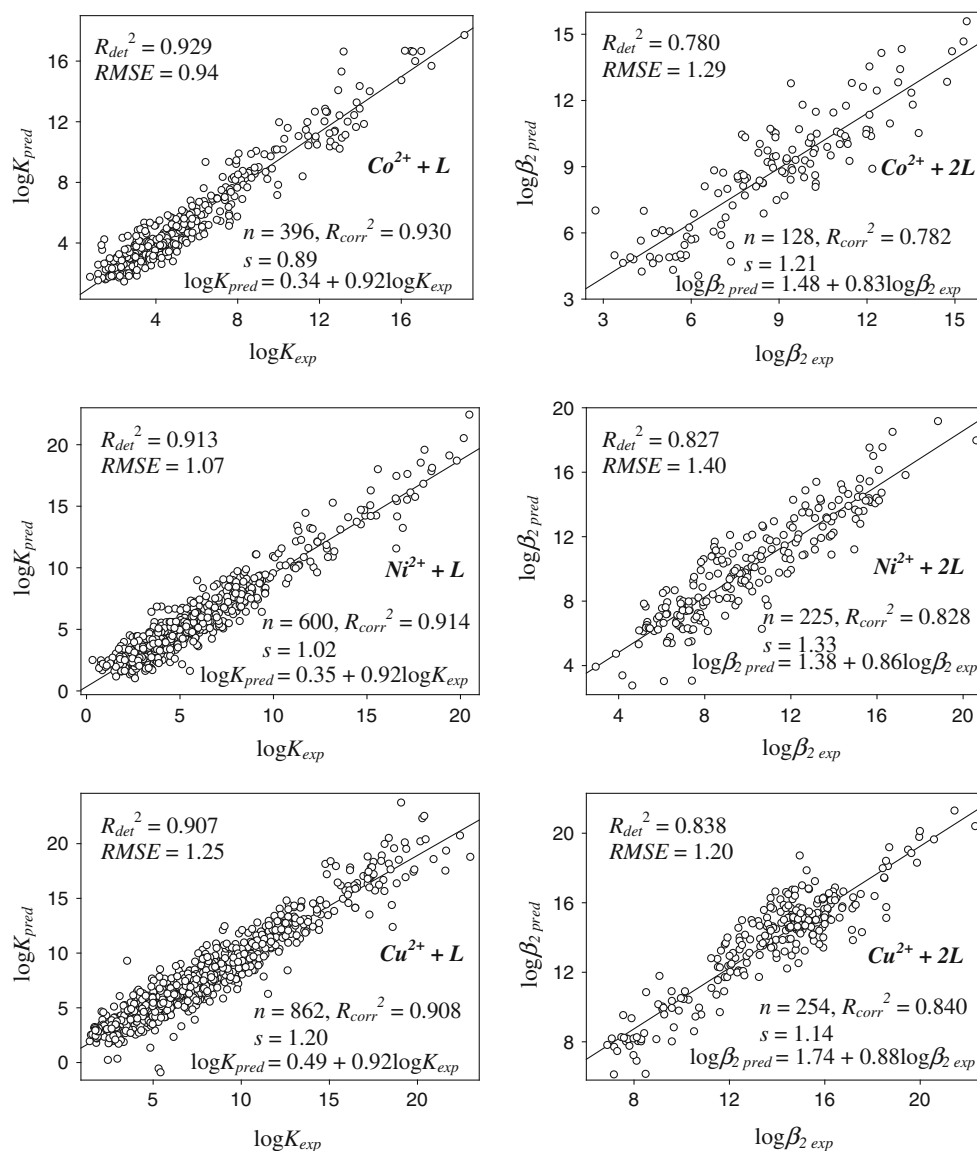
Fig. 2 Predicted versus experimental values of the stability constants for the 1:1 (M:L) (*left*) and 1:2 (*right*) complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with organic ligands in water at temperature 298 K and an ionic strength 0.1 M. The predicted data represent a combination of the five external test sets of the 5-CV procedure
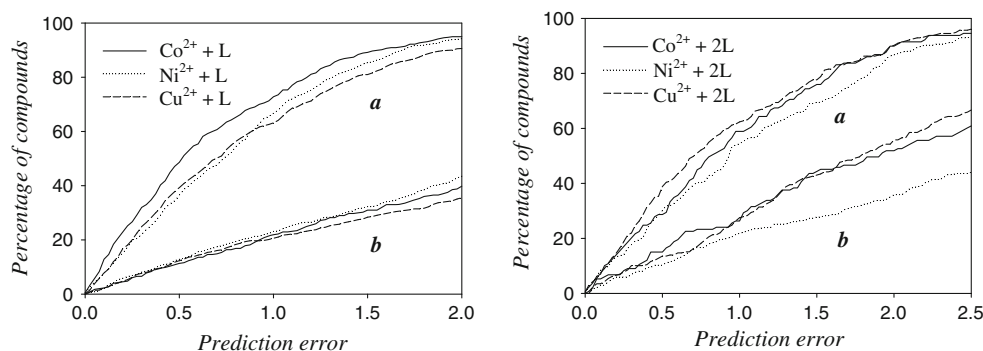
Fig. 3 Percentage of compounds versus absolute prediction error $|\log K_{exp} - \log K_{pred}|$ for the 1:1 (M:L) (*left*) and 1:2 (*right*) complexes of Co^{2+}, Ni^{2+}, and Cu^{2+} with organic ligands in water at 298 K and ionic strength 0.1 M.; the series of the lines (*a*) corresponds to CMs; the series of the lines (*b*) correspond to "no model": arithmetic means of experimental constant values of all ligands for given metal ion is as the predicted value for any ligand

Error Curves' plots (Fig. 3), the curves corresponding to $\log K$ lay higher than those of $\log \beta_2$ relative to the compared lines of "no model" as arithmetic means of experimental constant values of all ligands for given metal ion (Fig. 3). Absolute prediction error of $\log K$ is below 1.0 for 70 % (Co^{2+}, Ni^{2+}) and 60 % (Cu^{2+}) of the ligands (Fig. 3). Thus, *RMSE* values for $\log K$ are appreciably lower than those for $\log \beta_2$ in line with the observed trend in experimental errors of stability constants [52, 66–69]. The RMSE values are close to observed experimental systematic errors (Table 1) showing that predictive performance of QSPR models is appropriate.

Particular types of the SMF descriptors enabled to build the individual models with high squared LOO cross-validation correlation coefficient ($Q^2 = 0.91$–0.98), and low standard deviation ($s = 0.37$–1.1) for all training sets of 5-CV. In most of cases, these are shortest topological paths and terminal groups containing from 2 to 12 atoms (Table 2).

The SMF types providing the best predictions in 5-CV have been used to build and validate the models on the entire modeling data set. The final CMs include the 601 (190) (Co^{2+}), 117 (254) (Ni^{2+}) and 160 (188) (Cu^{2+}) individual models for $\log K$ ($\log \beta_2$). Predictive ability of CMs was validated on the additional external test set of the 23 (M^{2+})L complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with 13 new organic ligands (see Supporting information, Additional_Test_Set.SDF) [70–76] which were not studied in the initial data sets. New ligands include acetyl phosphate, acetonylphosphonate, (2-phosphonoethoxy)ethane, 9-[2-(2-phosphonoethoxy)ethyl]adenine, 2,9-bis(hydroxymethyl)-1,10-phenanthroline, N,N′-bis(2-hydroxycyclohexyl)ethane-1,2-diamine, N,N′-bis(2-hydroxycy-clohexyl)propane-1,3-diamine, 1,7-bis(2-hydroxycyclohexyl)-1,4,7-triazaheptane, 1,4,8,11-tetraazacyclotetradecane-1,8-bis(methylphosphonic acid)) and aminocarboxylate derivatives (Table 3). Statistical parameters of correlations (Fig. 4, $R_{det}^2 = 0.918$ and RMSE = 1.97) demonstrate an acceptable agreement between the experimental and predicted $\log K$ values, which is similar to that obtained in 5-CV on the modeling sets (Fig. 2).

The SMF descriptors enable detection of ligand moieties with important contributions into $\log K$. Thus, we detected several individual models involving common fragments whose contributions into $\log K$ slightly vary from one model to another one. For instance, these are $O=C-C-N_c-C_c-C_c-O_c-C_c-C_c-N_c-C-C=O$ (Co^{2+}), $C-C-O-P-O-P=O$ (Co^{2+}), $N_c-C_c-C_c-N_c-C_c-C_c-O$ (Ni^{2+}), $C_{ar}-N_{ar}-C_{ar}-C_{ar}-N_{ar}-C_{ar}$ (Ni^{2+}), $O-N-C=O$ (Cu^{2+}), $O-N=C-C=O$ (Cu^{2+}) fragments which are involved in 13–126 models and contribute from 2.1 to 6.0 $\log K$ units into the stability (see Table 4). These fragments occur in derivatives of 1,7-di- and 1,4,7-triazacyclododecane with acetate pendant arms

Table 2 The statistical parameters of the best individual MLR models and optimal descriptor types according to the five training sets of the 5-CV procedure[a]

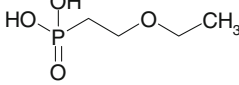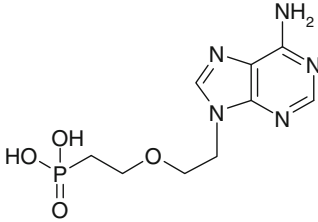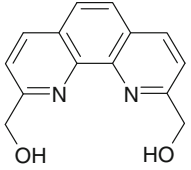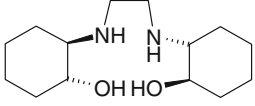| No.	SMF type[b]	n	m	s	Q^2
Co^{2+}					
1	IAB (3–10)	316–317	89–106	0.40–0.46	0.963–0.977
2	IAB (3–12)	316–317	96–109	0.37–0.44	0.960–0.977
3	IAB (2–8)	316–317	53–106	0.40–0.70	0.952–0.969
Ni^{2+}					
4	IAB (2–11)t	490–491	57–74	0.84–1.0	0.912–0.937
5	IAB (3–13)t	490–491	56–65	0.88–0.96	0.913–0.934
6	IAB (3–11)t	490–491	59–64	0.87–0.97	0.912–0.933
Cu^{2+}					
7	IAB (2–11)	706–707	71–160	0.61–1.1	0.907–0.966
8	IAB (2–12)	706–707	77–169	0.64–1.1	0.911–0.960
9	IAB (2–10)	706–707	70–161	0.64–1.1	0.906–0.964
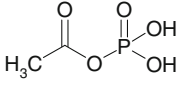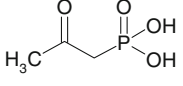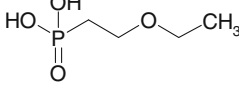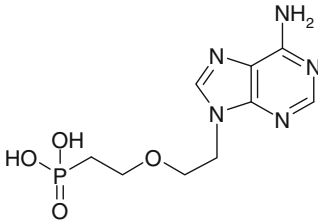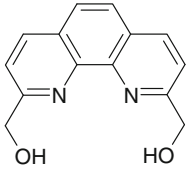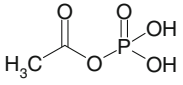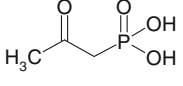
[a] Statistical parameters of the MLR models: the number of data point in training set (n), the number of SMF variables (m), standard deviation (s), squared LOO cross-validation correlation coefficient (Q^2)

[b] SMF type: see the notation in Methods section: descriptors

Table 3 Experimental and predicted stability constant values log$K$ of the 1:1 (M:L) complexes of Co^{2+}, Ni^{2+} and Cu^{2+} for the additional test set[a]

No.	Ligand	Cation	Log$K$		
			exp.	*pred.*[b]	N_m^c
1		Co^{2+}	1.83[d]	3.18 (0.29)	110
2		Co^{2+}	2.19[d]	2.46 (0.80)	256
3		Co^{2+}	2.24[e]	1.85 (0.89)	214
4		Co^{2+}	2.21[e]	5.32 (0.71)	168
5		Co^{2+}	6.36[f]	4.31 (0.74)	206
6		Ni^{2+}	1.75[d]	4.1 (1.2)	54
7		Ni^{2+}	2.14[d]	3.52 (0.53)	34
8		Ni^{2+}	2.18[e]	2.51 (0.36)	38
9		Ni^{2+}	2.41[e]	4.34 (0.49)	31
10		Ni^{2+}	7.42[f]	7.46 (0.58)	51
11		Ni^{2+}	7.77[g]	8.42 (0.83)	44

Table 3 continued

No.	Ligand	Cation	Log$K$		N_m^c
			exp.	pred.[b]	
12		Cu^{2+}	2.86[d]	5.36 (0.65)	54
13		Cu^{2+}	3.36[d]	4.89 (0.79)	59
14		Cu^{2+}	3.44[e]	3.00 (0.22)	40
15		Cu^{2+}	3.98[e]	4.60 (0.31)	37
16		Cu^{2+}	21.43[h]	18.54 (0.92)	122
17		Cu^{2+}	19.47[h]	17.63 (0.77)	77
18		Cu^{2+}	24.9[i]	22.7 (1.4)	43
19		Cu^{2+}	11.47[g]	9.8 (1.7)	68
20		Cu^{2+}	12.67[g]	11.7 (1.4)	67
21		Cu^{2+}	16.74[g]	12.2 (1.5)	60

Table 3 continued

No.	Ligand	Cation	Log$K$		N_m^c
			exp.	*pred.*[b]	
22		Cu^{2+}	5.13[j]	7.66 (0.91)	60
23		Cu^{2+}	5.64[j]	7.78 (0.52)	65
R_{det}^2	*0.918*				
RMSE	*1.97*				

[a] Experimental data are given at 298 K and an ionic strength (*I*) 0.1 M excepting: for the ligand 18 *I* = 1.0 M, for the ligands 22 and 23 *I* = 0.2 M

[b] Predicted stability constant values logK_{pred} are computed by the MLR CMs, standard deviations are given in parentheses

[c] The number of individual models in CM using AD for the given ligand

[d] Ref. [70]

[e] Ref. [71]

[f] Ref. [72]

[g] Ref. [73]

[h] Ref. [74]

[i] Ref. [75]

[j] Ref. [76]
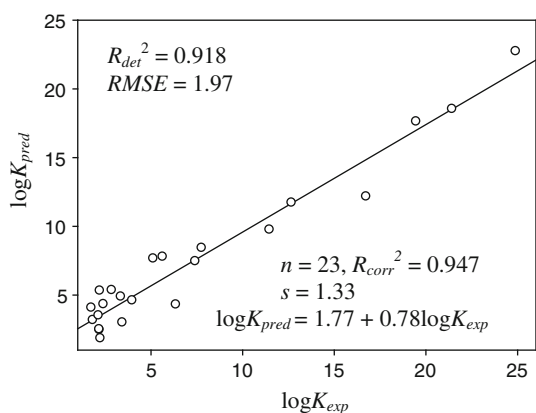
Fig. 4 Experimental versus predicted stability constant values log$K$ of the 1:1 (M:L) complexation for the additional external test set

(Co^{2+}, Ni^{2+}), diphosphoric acid (Co^{2+}), 1,10-phenanthroline (Ni^{2+}), hydroxamic acid and 2-hydroxyiminopropanamide (Cu^{2+}) (Table 4). As we earlier demonstrated [34,

62, 77], SMF and their contributions could become convenient building blocks for compounds' design.

It should be noticed that developed in this work QSPR models outperform previously reported ones (Co^{2+} [20, 47, 48], Ni^{2+} [20, 25, 47, 48], Cu^{2+} [20, 25, 47–49]) in respect to both diversity and the size of the ligand sets, and rigorous cross-validation procedure.
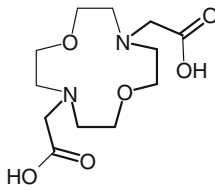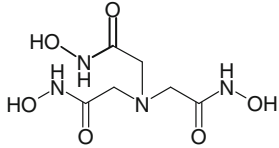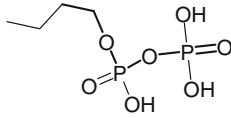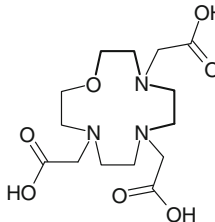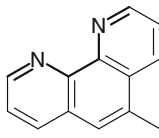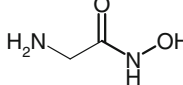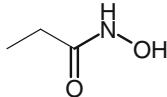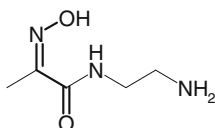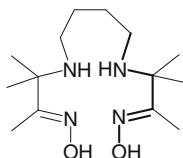
Relationships between stability constants

Analysis of available experimental data allowed us to detect several linear correlations between experimental log$K$ values for one same ligand with different metal ions and between log$K$ and logβ_2 for one same metal ion.

For known ligand, the stability constant log$K$ for one metal ion can be predicted by means of the stability constant for a second metal ion using the equations:

$$\log K_{CoL} = 0.867 \log K_{NiL}, \tag{1}$$

Table 4 Selected SMF and their mean contributions into log$K$ according to the sets of individual MLR models[a]

No.	SMF[b]	$<a_i>$	N_{model}	N_{mol}	Ligand[c]
Co^{2+} + L, 396 ligands					
1	O=C–C–N$_c$–C$_c$–C$_c$–O$_c$–C$_c$–C$_c$–N$_c$–C–C=O	6.05 (0.35)	30	3	
2	O–N–C=O	2.11 (0.41)	126	11	
3	C–C–O–P–O–P=O	2.16 (0.19)	39	10	
Ni^{2+} + L, 613 ligands					
4	N$_c$–C$_c$–C$_c$–N$_c$–C$_c$–C$_c$–O$_c$	3.36 (0.69)	35	13	
5	C$_{ar}$–N$_{ar}$–C$_{ar}$–C$_{ar}$–N$_{ar}$–C$_{ar}$	4.65 (0.56)	25	4	
6	O–N–C=O	2.67 (0.14)	13	12	
Cu^{2+} + L, 883 ligands					
7	O–N–C=O	6.50 (0.60)	54	7	
8	O–N=C–C=O	5.63 (0.61)	35	5	
9	C–N–C–C=N–O	3.62 (0.45)	35	6	

[a] $<a_i>$ is fragment contribution (arithmetic mean) and its standard deviation (in parentheses) according to the N_{model} individual models and the N_{mol} ligands

[b] Substructural molecular fragments (SMF): shortest topological paths with explicit representation of atoms and bonds; bonds: '–' and '=' are single and double in chain, N$_c$–C$_c$ is single bond in non-aromatic cycle; C$_{ar}$–N$_{ar}$ is aromatic bond

[c] Example of ligand including corresponding SMF which bonds are accented by thickness
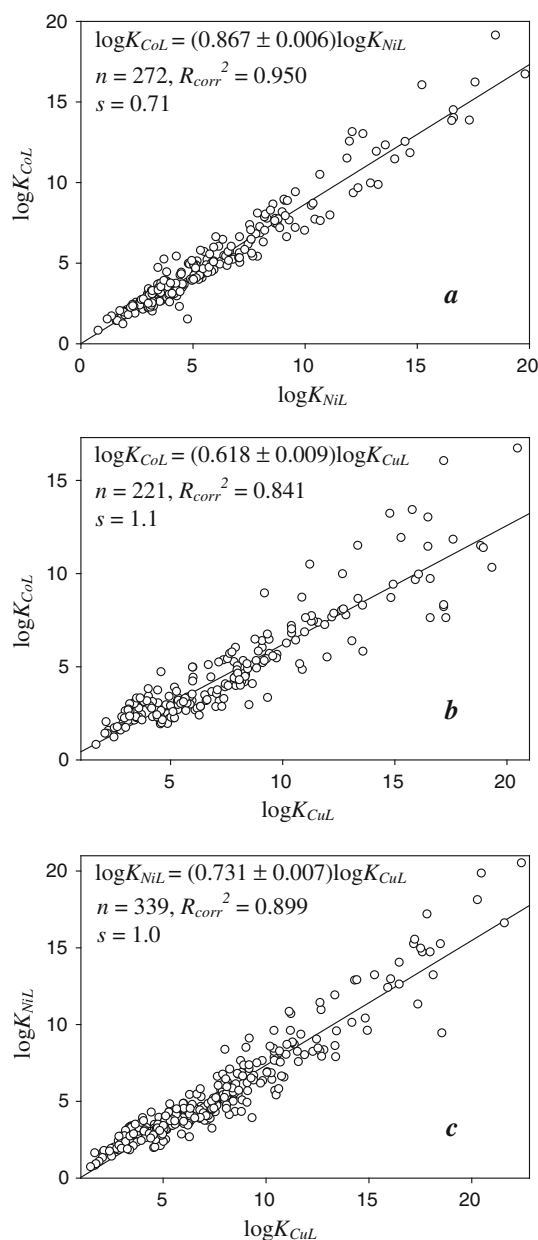
Fig. 5 The linear relationships $\log K_{CoL}$ versus $\log K_{NiL}$ (*a*), $\log K_{CoL}$ versus $\log K_{CuL}$ (*b*) and $\log K_{NiL}$ versus $\log K_{CuL}$ (*c*) for the complexation $M^{2+} + L = (M^{2+})L$ of the Co^{2+}, Ni^{2+} and Cu^{2+} (M^{2+}) ions with diverse organic ligands (L) in water at 298 K and an ionic strength 0.1 M

Fig. 6 $\log\beta_2$ versus $\log K$ for the complexations of the Co^{2+}, Ni^{2+} and Cu^{2+} ions with organic ligands in water at 298 K and an ionic strength 0.1 M

$$\log K_{CoL} = 0.618\ \log K_{CuL}, \qquad (2)$$

$$\log K_{NiL} = 0.731\ \log K_{CuL}. \qquad (3)$$

These linear relationships were derived using the $\log K$ values for 272, 221 and 339 ligands, respectively (Fig. 5). The standard deviations of the $\log K$ estimations vary from 0.7 to 1.1 (Fig. 5). For given ligand, the order of stability of complexes is $(Co^{2+})L < (Ni^{2+})L < (Cu^{2+})L$. The Cu^{2+} cation forms most stable complexes compared to

those of Co^{2+} and Ni^{2+}. The coefficient of Eq. 1 is more close to one than those of Eqs. 2 and 3 indicate larger chemical similarity between Co^{2+} and Ni^{2+} than that for other metal pairs.

Figure 6 shows, that a linear relationship between $\log\beta_2$ and $\log K$ is observed for every metal ion. The squared correlation coefficient varies from 0.826 (Cu^{2+}) to 0.954 (Co^{2+}), and the standard deviation changes from 0.63 (Co^{2+}) to 1.26 (Cu^{2+}). The relationships (Fig. 6) give possibility to estimate $\log\beta_2$ ($\log K$) from the knowledge of $\log K$ ($\log\beta_2$) for given ligand. For all ligands forming both

Table 5 Predicted stability constant values $\log K$ of the 1:1 (M:L) complexes of Co^{2+}, Ni^{2+} and Cu^{2+} with the ligands which can form metallosupramolecular grid complexes in water

No.	Ligand[a]	$\log K$		
		$(Co^{2+})L$	$(Ni^{2+})L$	$(Cu^{2+})L$
1		9.5	10.6	12.6
2		9.6	11.1	14.4
3		7.5	8.8	10.0

[a] The ligands are **33**, **28** and **11** from Ref. [44]

1:1 and 1:2 complexes with the Co^{2+}, Ni^{2+} and Cu^{2+} ions, the following ratio is observed:

$$\log\beta_2/\log K = 1.8 \pm 0.1; n = 492. \qquad (4)$$

Thereby, stepwise stability constant $\log K_2 = \log\beta_2 - \log K$ constitutes 80 % of $\log K$, and the free energy of coordination of second ligand molecule is weaker by 20 % in comparison with coordination of first ligand molecule to metal ion.

Linear correlation between stability constants of ML and ML$_2$ complexes may have an interesting interpretation in the context of metal-containing supramolecular architectures (grids). Thus, one may suggest that L forms stable metallo-grid complexes M_nL_n, if stability of its 1:1 complex is large enough. To illustrate this suggestion, developed QSPR models were applied to assess $\log K$ for $(Co^{2+})L$, $(Ni^{2+})L$ and $(Cu^{2+})L$ complexes of the 44 ligands [44] which form metallogrid complexes (see their structures in Supporting information: Metallogrid_forming_ligands.SDF). Three ligands forming most stable ML complexes are shown in Table 5. One may suggest that they, indeed, may form metallogrid complexes with Co^{2+}, Ni^{2+} and Cu^{2+} in water. There are some experimental proves of these suggestion: the $(Co^{2+})_4L_4$ complex of ligand 1 (Table 5) has been formed at the air-aqueous solution interface [78], and grid complex of Co^{2+} with ligand 2 was synthesized in the CD_3CN and D_2O solution [79]. For ligand 3, the synthesis of the $(Zn^{2+})_4L_4$ complex in MeCN was reported [80].

Conclusions

This article reports predictive QSPR models for the stability constants $\log K$ and $\log\beta_2$ of the 1:1 and 1:2 (M:L) complexes of transition metal ions (M = Co^{2+}, Ni^{2+} and Cu^{2+}) with different classes of organic ligands (L) in aqueous solution at 298 K and an ionic strength 0.1 M. The models have been built using ensemble MLR and SMF descriptors on big data sets of 396 (Co^{2+}), 613 (Ni^{2+}), 883 (Cu^{2+}) ligands for $\log K$ and 132 (Co^{2+}), 233 (Ni^{2+}), 257 (Cu^{2+}) ligands for $\log\beta_2$. They have reasonable prediction performance: RMSE is 0.94–1.2 ($\log K$) and 1.2–1.4 ($\log\beta_2$) which is close to observed experimental systematic errors. The $\log K$ and $\log\beta_2$ values were predicted by CMs as arithmetic means of several hundreds of individual models taking into account their combined ADs. The SMFs enable detection of ligand moieties with important contributions into stability constants and they can be used as building blocks of new ligands. Detected relationships between stability constants for pair of metal ions demonstrate that the order of stability of complexes is $(Co^{2+})L < (Ni^{2+})L < (Cu^{2+})L$, and the $\log K_{CoL}$ and $\log K_{NiL}$ values average 62 and 73 % of the $\log K_{CuL}$ value, respectively. For all ligands forming both 1:1 and 1:2 complexes the following ratio is observed: $\log\beta_2/\log K = 1.8 \pm 0.1$, $n = 492$. We believe that this relationship could be useful in design of new ligands for metallosupramolecular complexes.

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