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Prediction of Gd(III) Complexes Stability Constants for the Development of MRI Contrast Agents

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Abstract. Since free Gd(III) ion is extremely toxic at the concentrations needed for MRI studies, prediction of Gd(III) complexes stability constants and the use of stable complexes is very important. In this work, the quantitative structure–property relationships (QSPR) have been developed for the stability constants of Gd(III) complexes with 38 polyamino-polycarboxylic ligands. A good quality of model (Q^2=0.916 and R^2=0.935) enables reliable prediction of stability constants for unmeasured complexes.

Keywords: QSPR, Gadolinium complex, stability constant, Contrast agents, Imaging.

1. Introduction

Nuclear magnetic resonance imaging (MRI) has become a powerful tool for clinical diagnostics thanks both to the progress of the relevant technology and the development of a new class of pharmaceuticals administered to patients to enhance the contrast between normal and diseased tissues. Such contrast agents are mostly based on metal complexes of paramagnetic metal ions, since they enhance the relaxivity of water protons, the main factor determining the intensity of the 1H-NMR image [1–2].

Nowadays, several Gd(III) complexes are the active constituents of pharmaceuticals employed as contrast agents in clinical MRI diagnostics. Free Gd(III) ion is extremely toxic at the concentrations needed for MRI studies, for this reason it must be administered in the form of stable complexes, unable to release the metal ion before excretion. Furthermore, the use of synthetic ligands offers an additional advantage consisting of the possibility to prepare specific contrast agents that accumulate in target tissues or a physiological district.

Gd(III) is a typical hard metal ion and consequently it interacts preferentially with ligands bearing hard donor groups, such as carboxylate, while it demonstrates lower tendency to form complexes with softer ligands like amines. Nevertheless, polyamino-polycarboxylic ligands, containing both such functional groups, form very stable complexes with this metal ion.

Quantitative structure–property relationships (QSPR) studies are one of the most important areas in chemometrics, biological chemistry, medicinal chemistry and many other fields. This method has been successfully established to predict different important chemical and physical properties [3].

In this work, we established QSPR models for prediction of stability constants of Gd(III) complexes with polyamino-polycarboxylic ligands.

2. Methodology

2.1. Data set

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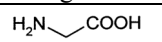
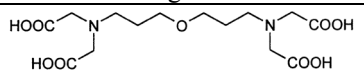
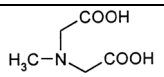
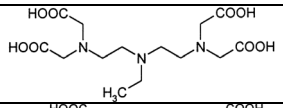
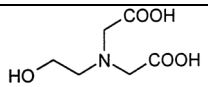
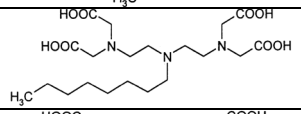
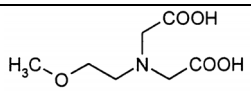
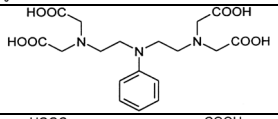
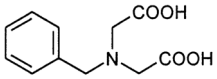
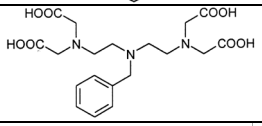
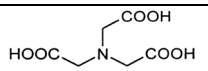
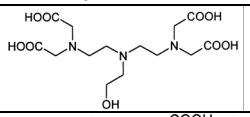
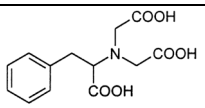
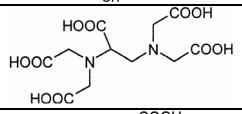
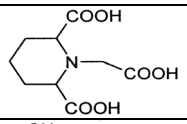
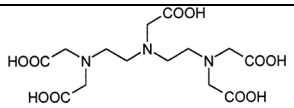
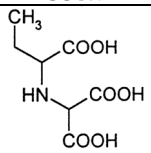
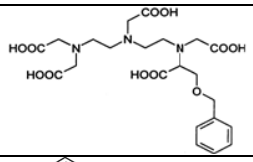
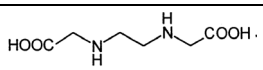
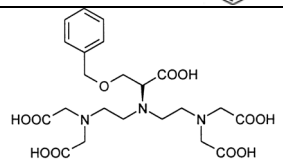
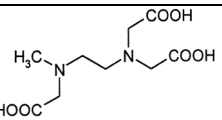
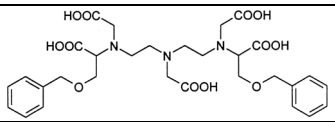
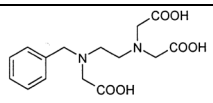
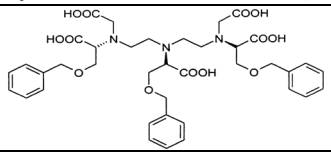
The data set of experimental stability constants of Gd(III) complexes was compiled from the literature (cf. references from Table 1). For the QSPR model development, the logarithmic constants $\log K_1$ were used, where K_1 is defined as follows:

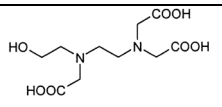
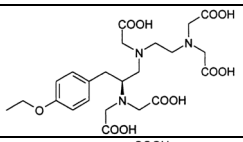
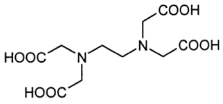
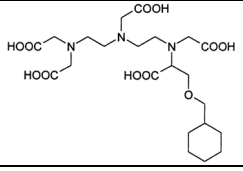
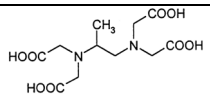
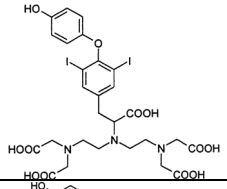
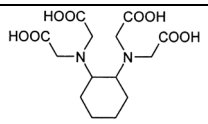
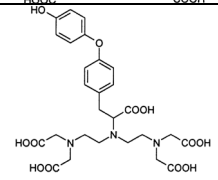
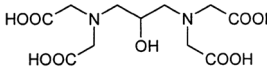
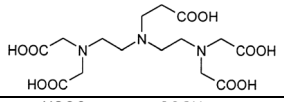
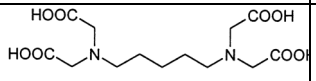
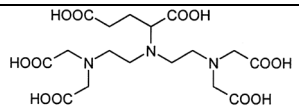
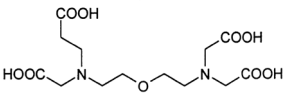
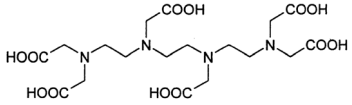
$$K_1 = \frac{[LnL^{n+3}]}{[Ln^{3+}][L^n]}$$

All stability constants correspond to aqueous solutions at the ionic force $\mu = 0.1$ and temperature 25ºC.

Table 1 gives the list of the 38 polyamino-polycarboxylic ligands(31 train and 7 test) that were selected for the present QSPR study.

Table 1. Stability constants for Gd(III) complexes with polyamino-polycarboxylic ligands

No.	Ligand	Logk	Ref.	N0.	Ligand	Logk	Ref.
1		3.4	4	20		11.74	21
2		7.02	5	21		17.79	22
3(t)		9.01	6	22		16.23	23
4		7.88	7	23		15.42	22
5(t)		7.04	5	24		17.50	23
6		11.54	8	25		15.44	24
7		8.97	5	26		15.93	25
8		10.66	9	27		22.46	26
9		8.71	10	28		22.58	27
10		8.13	11	29		22.23	27
11		12.98	12	30 (t)		21.72	27
12 (t)		12.4	13	31		22.18	27

13		15.22	14	32		22.76	27
14 (t)		17.1	15	33		21.73	27
15		18.21	16	34 (t)		21.87	27
16		18.8	17	35		22.30	27
17 (t)		13.94	18	36		16.71	28
18		10.37	19	37		21.66	27
19		15.21	20	38		28.4	29

(t): test

2.2. Descriptors calculation and selection

The first step to obtain a QSAR model is to encode the structural features of the molecules, which are named molecular descriptors. The molecular descriptors that were used to search the best model for the Logk of the studied compounds were calculated with the DRAGON program on the basis of the minimum energy molecular geometries. These geometries were optimized with the aid of the HYPERCHEM package, based on the AM1 semiempirical method. The calculated descriptors were first analyzed for the existence of constant or near-constant variables. The detected ones were then removed. In addition, to decrease the redundancy existing in the descriptor data matrix, the descriptors correlation with each other and with the Logk values of the molecules was examined. Afterwards, the collinear descriptors (i.e. $r > 0.9$) were detected and the one presenting the highest correlation with the Logk values was retained while others were removed from the data matrix. Then, the remaining descriptors were collected in an n×m data matrix (D), where n and m are the numbers of the compounds and the descriptors, respectively.

Finally, the MLR method provided equations linking the structural features to the logarithm stability constant values of the Gd(III) complexes:

$$\text{Log } k = a_0 + a_1x_1 + \cdots + a_nx_n \quad (1)$$

In this work, GA-MLR and the other calculations were performed in MATLAB.

3. Result and Discussion

The selected GA-MLR model between the stability constant as the dependent variables and dragon descriptors as independent variables was presented in Table 2.

Table 2. Selected GA-MLR model [a]

Descriptor	Coefficient	Mean effect (%)
nN	3.047	28.61
GGI1	2.112	59.77
JGI9	-380.556	11.62
Constant	-2.917	

[a] Statistics of the model: $n = 31$, $R^2 = 0.935$, Q^2=0.916, S.E. = 1.4 and $F = 130.8$.

According to Table 2, the three descriptors appeared in this model consist of number of nitrogen atoms (nN), topological charge index of order 1(GGI1) and mean topological charge index of order 9(JGI9).

The proposed model indicates a direct relationship between the stability constant and nN and GGI1 descriptors. As seen, GGI1 with the mean effect of 59.77 is the most effective factor and JGI9 descriptor (ME%=11.62) is the less effective on the stability constant.

Internal validation of proposed MLR model resulted in one or more measures of robustness of the model parameters such as q^2 (0.916), Y-scrambling ($a(r^2) = 0.043$, $b(q^2) = -0.273$) and internal predictability such as $q^2_{bootstrap}$ (0.913). There are no chance correlations because of the low Y-scrambling parameter values, since they satisfy the criteria $a(r^2) < 0.3$ and $b(q^2) < 0.05$. The value of $q^2_{bootstrap}$ is fairly close to q^2 confirming the internal predictability and stability of the model. The difference between r^2 and q^2 is not large. In view of these observations, we conclude that the 3D-QSAR model is fairly robust.

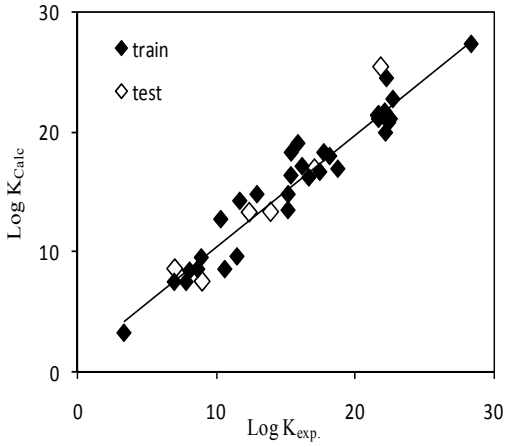


Fig.1

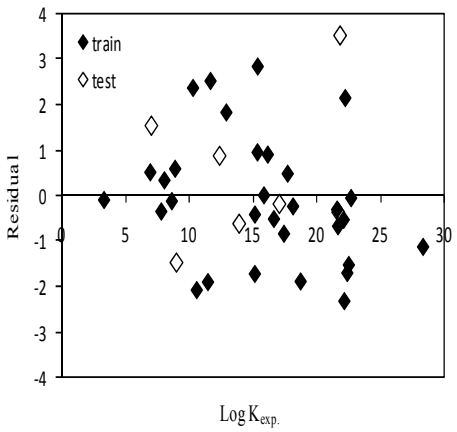


Fig.2

A plot of the calculated against the experimental stability constants (Figure 1) indicates an excellent correlation between the experimental and predicted values.

In Figure 2 are plotted the residuals of MLR predicted values of stability constants against the experimental values. As the calculated residuals are distributed on both sides of the zero line, one may conclude that there is no systematic error in the development of the MLR.

4. Conclusion

We have demonstrated that the theoretical molecular descriptors can been successfully applied in the development of predictive QSPR models for the stability constants of Gd(III) complexes with polyamino-polycarboxylic ligands. This study is interesting because the stable Gd(III) complexes are used for human MRI study. The QSPR results indicated the applicability of the model for prediction of the stability constants of the Gd(III) complexes.

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