Correlation Analysis of the Structures and Stability Constants of Gadolinium(III) Complexes

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To simplify the abstraction of descriptors, for the correlation analysis of the stability constants of gadolinium(III) complexes and their ligand structures, aiming at gadolinium(III) complexes, we only considered the ligands and ignored the common parts of the structures, i.e., the metal ions. Quantum-chemical descriptors and topological indices were calculated to describe the structures of the ligands. Multiple regression analysis and neural networks were applied to construct the models between the ligands and the stability constants of gadolinium(III) complexes and satisfactory results were obtained.

1. INTRODUCTION

Studies on quantitative structure−property relationships (QSPR) have suggested that properties are related to the corresponding structures. Thus if we can describe effectively a molecular structure, we can build a mathematical model to predict the properties for that compound and consequently it will be possible to define new compounds to be synthesized. In recent decades, enormous efforts have been made by many investigators to study various compounds in this field, but metal complexes have been involved only a little in these investigations.

NMR imaging contrast agents are adjuvant agents in magnetic resonance imaging (MRI) clinical diagnosis. In vivo, these drugs can enhance the image contrast between normal and diseased tissue and/or indicate the status of organ function or blood flow by decreasing the relaxation times of nearby proton nuclei. Stable complexes of gadolinium(III), manganese(II) or iron(III) are commonly used as contrast agents.

The general requirements for MRI contrast agents are as follows: (1) high relaxivity; (2) specific in vivo distribution; (3) in vivo stability and lack of toxicity; (4) considerable water solubility; and (5) excretability. In the required doses of contrast agents, free lanthanides and transition ions may induce obvious toxic effects in human and animal bodies.[1] There exists a balance in the body between stability, toxicity and relaxivity. As a result, the evaluation of these paramagnetic complexes has focused not only on their effectiveness but also, most importantly, on their stability in vivo. Toxic effects from a lanthanide complex can arise from[2] (a) a free metal ion, released by dissociation; (b) a free ligand which also arises from dissociation; and (c) the intact metal complex. Both metal ions and free ligands tend to be more toxic than metal chelates, thus MRI contrast agents must be kinetically and thermodynamically stable complexes. With classical organic ligand complexes, a thermodynamic stability constant of 10^{16} has been suggested as a minimum requirement.[2]

Table 1. Stability Constants for Various Cyclic and Acyclic Gd(III) Complexes[a]

no.	ligand	logK_{GdL}	no.	ligand	logK_{GdL}
1	DTPA-BMEA	16.84	15	DTPA-BAM	15.39
2	DTPA-BMMEA	17.68	16	DTPA-cis$^{C=C}$BAM	15.56
3	DTPA-BMA	16.85	17	DTPA-OAM	17.44
4	DTTA-BM	13.12	18	NOTA	13.70
5	DTTA-HP	23.65	19	DETA	15.10
6	DOTA	25.30	20	Me_2-DETA	10.40
7	DO3MA	25.30	21	PC2A	16.60
8	DO3A	21.10	22	BP2A	14.50
9	DOTP	28.80	23	N_3O_6-L_1	16.27
10	HP-DO3A	23.80	24	N_3O_5-L_1	11.49
11	HIP-DO3A	23.90	25	N_3O_6-L_2	18.07
12	HE-DO3A	22.30	26	N_3O_5-L_2	17.23
13	DTPA-EAM	11.15	27	TTAHA	19.00
14	DTPA-PAM	14.49	28	PEDTA	15.56

[a] The corresponding structures are given in Chart 1.

In last two decades, the most attention has been devoted to polyamino-polycarboxylate ligands for complexing gadolinium in regard to their potential applications as MRI contrast agents. Due to the toxicity of free gadolinium in vivo, the kinetic and thermodynamic stability of these complexes becomes an important factor in the possibility of their applications in clinical diagnosis. It has been reported that the stability of these gadolinium complexes is closely related to protonation constant of the ligands.[3] This paper describes studies of the relationships between the stabilities of gadolinium(III) complexes and the structures of their ligands.

2. EXPERIMENTS

2.1. Data Set. The stability of gadolinium(III) complexes and the structures of their ligands were obtained from ref 4. The thermodynamic stability constant K_{GdL} is defined in eq 2. Table 1 shows the solution equilibrium data collected for

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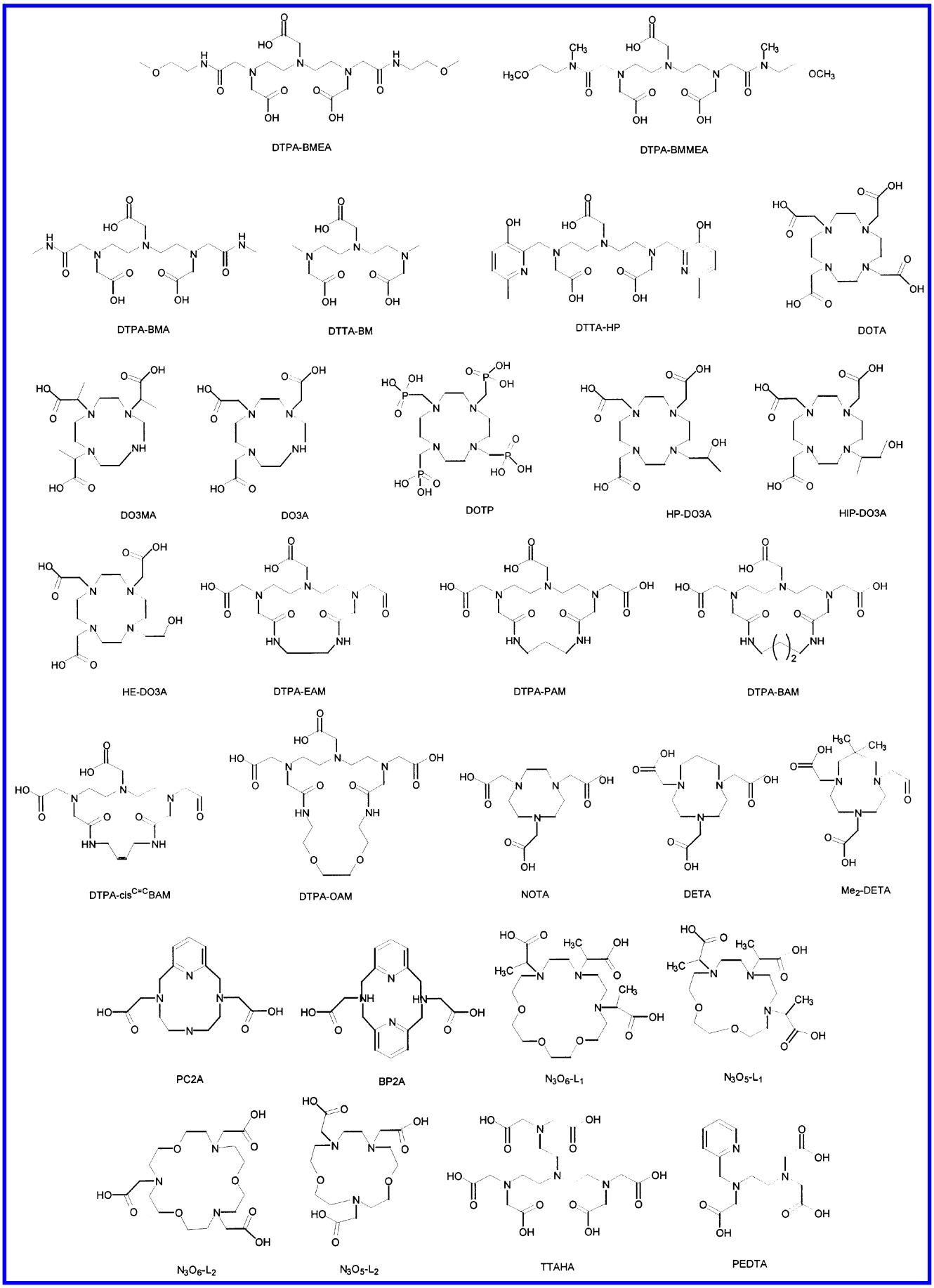
Chart 1


DTPA-BMEA
DTPA-BMMEA
DTPA-BMA
DTTA-BM
DTTA-HP
DOTA
DO3MA
DO3A
DOTP
HP-DO3A
HIP-DO3A
HE-DO3A
DTPA-EAM
DTPA-PAM
DTPA-BAM
DTPA-cis$^{C=C}$BAM
DTPA-OAM
NOTA
DETA
Me_2-DETA
PC2A
BP2A
N_3O_6-L_1
N_3O_5-L_1
N_3O_6-L_2
N_3O_5-L_2
TTAHA
PEDTA

these complex compounds (see Chart 1 for cyclic and acyclic ligands).

$$M + L = ML \quad (1)$$

$$K_{ML} = \frac{[ML]}{[M][L]} \quad (2)$$

where [M] is the concentration of metal, [L] is the concentration of the ligand and [ML] is the concentration of intact metal complex.

2.2. Calculation of Descriptors. In this research, different types of descriptors have been examined. These include topological, geometric, electronic, and hybrid features. Topological descriptors yield information about the connectivity of compounds, such as path lengths of molecules,[11] count of atom types, types of bonds, and molecular paths and connectivity.[12−16] Geometric descriptors provide information about the shape of the compound. Examples include solvent-accessible molecular surface area, volume,[17] and principal moments of inertia,[18] etc. Charge information is encoded by electronic descriptors, such as dipole moments, electron density, the energies of the highest occupied molecular orbital, and the lowest unfilled molecular orbital. There are some descriptors that encode information about more than just one of the aforementioned types. In many attempts that have been made, the results revealed that better models can be obtained by using quantum-chemical and topological features. Thus, in this work, only two types of descriptors were calculated as follows.

2.2.1. Quantum-Chemical Descriptors. As we know, there are two main advantages applying the quantum-chemical descriptors in a QSAR study: (a) the compounds and their various fragments and substituents can be directly characterized on the basis of their molecular structure only and (b) the proposed mechanism of action can be directly accounted for in terms of the chemical reactivity of the compounds under study.[5] Quantum-chemical descriptors mainly encode the electronic and geometric features of each molecule, and these descriptors have the important influence for the biology activities and physical chemistry properties. Owing to the importance of quantum-chemical parameters for a QSAR/QSPR, 10 descriptors were calculated by using the MOPAC option of SYBYL version 6.1 (Tripos Associates, 1699 S. Hanley Road, Suite 303, St. Louis, MO 63144). These descriptors are heat of molecular formation, molecular total energy, electronic energy, nucleus-nucleus repulsive energy, ionization potential, energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment, the HOMO−LUMO gap and the square of dipole moment. They are denoted as H_f, E_t, E_e, E_p, E_i, E_L, E_H, μ, E_{H-L}, and μ^2, respectively.

2.2.2. Topological Descriptors. The molecular connectivity indices ${}^m x_t^6$: ${}^0x_p$, ${}^1x_p$, ${}^2x_p$, ${}^3x_p$, ${}^4x_{pc}$, ${}^5x_{pc}$, ${}^6x_{pc}$, ${}^3x_c$, ${}^4x_c$, ${}^5x_c$, and ${}^6x_c$, a total of 11, and the topological indices A_{m1}, A_{m2}, and A_{m3}, were calculated. Because the molecular connectivity indices suggested by Randić, and later extended by Kier and Hall, have been widely used, and well-known to researchers in the QSAR area, the algorithm is not presented in detail here. Indices A_{mi} were suggested by one of the authors based on the augmented path matrix and have been used for various kinds of compounds with satisfactory results.[7−9] For easy understanding, here we briefly introduce the algorithm of A_{mi} indices again. The three topological indices are generated from path matrices *A*, *B*, and *C*, respectively. These three matrices are defined as follows:

Table 2. Order of the 24 Variables

no.	label	no.	label
1	${}^0x_p$	13	A_{m2}
2	${}^1x_p$	14	A_{m3}
3	${}^2x_p$	15	H_f
4	${}^3x_p$	16	E_t
5	${}^4x_{pc}$	17	E_e
6	${}^5x_{pc}$	18	E_p
7	${}^6x_{pc}$	19	E_i
8	${}^3x_c$	20	E_L
9	${}^4x_c$	21	E_H
10	${}^5x_c$	22	μ
11	${}^6x_c$	23	E_{H-L}
12	A_{m1}	24	μ^2

$$A = (a_{ij}),\ a_{ij} = \begin{cases} 1 & path = 1 \\ 0 & others \end{cases} \quad (i, j = 1, 2, ..., n)$$

$$B = (b_{ij}),\ b_{ij} = \begin{cases} 2 & path = 2 \\ 0 & others \end{cases} \quad (i, j = 1, 2, ..., n)$$

$$C = (c_{ij}),\ c_{ij} = \begin{cases} 3 & path = 3 \\ 0 & others \end{cases} \quad (i, j = 1, 2, ..., n)$$

Augmented path matrices G_1-G_3 are obtained by adding two columns into matrices *A*, *B* and *C*, respectively. The elements in the first column of matrices G_1-G_3 are square roots of vertex degrees, and the elements in the second column represent the square roots of the van der Waals atomic radii. From matrices G_1-G_3, we can obtain matrices Z_1-Z_3

$$Z_1 = G_1 \cdot G_1';\quad Z_2 = G_2 \cdot G_2';\quad Z_3 = G_3 \cdot G_3'$$

where $G_1' - G_3'$ are the transpose matrices of G_1-G_3. The three new topological indices are defined as

$$A_{m1} = \lambda_{max1}/2;\quad A_{m2} = \lambda_{max2}/2;\quad A_{m3} = \lambda_{max3}/2$$

where $\lambda_{max1}-\lambda_{max3}$ are the largest eigenvalues of matrices Z_1-Z_3.

To sum up, a total of 24 descriptors were labeled from 1 to 24 according to the following order: ${}^0x_p$, ${}^1x_p$, ${}^2x_p$, ${}^3x_p$, ${}^4x_{pc}$, ${}^5x_{pc}$, ${}^6x_{pc}$, ${}^3x_c$, ${}^4x_c$, ${}^5x_c$, ${}^6x_c$, A_{m1}, A_{m2}, A_{m3}, H_f, E_t, E_e, E_p, E_i, E_L, E_H, μ, E_{H-L}, and μ^2 (see Table 2).

2.3. Selection of the Descriptors. It is known that increasing the number of descriptors in a regression equation will improve the fit to the training set, but inclusion of too many variables will often cause a substantial reduction in the predictive ability of the model to the predictive set. So it is necessary to select a set of descriptors that produces the most predictive model. There are some methods to this end, such as Leaps-and-bounds regression, principal component analysis, factor analysis, etc. In our research, Leaps-and-bounds regression method[10] was employed. This method can quickly produce different sizes of the best subsets of variables without examining all possible subsets. It is based on the fundamental inequality 3

$$RSS(A) \le RSS(A_i) \quad (3)$$

where RSS is the residual sum of squares, *A* is any set of independent variables and A_i is a subset of *A*. The number

Table 3. Results of Leaps-and-Bounds Regression Analysis

no.	best variable subset	R	F	S
1	23	0.65	18.88	4.05
2	2,23	0.72	13.31	3.70
3	7,8,23	0.80	14.35	3.18
4	6,7,16,20	0.88	19.33	2.55
5	6,7,16,19,23	0.92	25.38	2.04
6	6,7,8,16,19,23	0.93	23.01	1.93
7	6,7,8,15,17,19,23	0.94	21.52	1.82
8	1,5,6,7,8,16,19,23	0.95	22.06	1.66

of subsets evaluated in a search for the best subset regression can be restricted by the use of the inequality. For example, set A_1 contains three variables with RSS, 596; set A_2 contains four variables with RSS, 605. Thus all the subsets of A_2 will be ignored, because of these subsets with RSS greater than that for A_2 and also for A_1. The results using Leaps-and-bounds regression are given in Table 3.

3. RESULTS AND DISCUSSION

3.1. Simplification of Problem for Descriptor Abstraction. The thermodynamic stability constant K_{GdL} depends on three factors: the concentrations of free metal, free ligand, and complex compound from the definition of K_{GdL}. Clearly, K_{GdL} relies heavily upon the factor of the complex, GdL, and little, if any, free metal is present at equilibrium under conditions where the equation is valid. So we should consider mainly the complexes. Usually, the gadolinium(III) complex is a nine-coordinated structure, thus it is difficult to compute any type of descriptors including topological, geometric, electronic, and hybrid features as mentioned above. Fortunately, the metal ions in the complexes are the same, i.e., gadolinium(III), and this allowed us to ignore the ions, considering only the ligands. As mentioned in section 2.2, two types of descriptors, i.e., electronic and topological information, were extracted from the ligand in this study. The results (see sections 3.3 and 3.4) reveal that in this way useful information is not lost.

3.2. Best Subsets of the Descriptors. We report in Table 3 the best combinations for 8 variables. From a statistical viewpoint the ratio of the number of samples (N) to the number of variables (M) should not be too low. Usually, it is recommended that $N/M \geq 5$. In the situation of this study, with 28 samples, 5 variables were selected based on the above rule. In our study, the best one-variable selection is 23 (E_{H-L}, the HOMO−LUMO gap). The best two-variable selection is the combination of 2 (2 is ^1x_p) and 23, and the combination of 7, 8 (7 is $^6x_{pc}$ and 8 is ^3x_c), and 23 is the best for three-variable selection and so on. It is noteworthy to point out that the most important descriptor seems to be 23, i.e., the HOMO−LUMO gap, because descriptor 23 appeared in almost all the best subsets. The HOMO−LUMO gap, i.e., the difference in energy between the HOMO and LUMO, is an important stability index. A large HOMO−LUMO gap implies high stability for a molecule in the sense of its lower sensitivity in a chemical reaction.

3.3. Multiple Regression. As we mentioned above, 5 variables should be selected in this study. Table 3 shows that more descriptors evidently do not improve the regression results. The 5 descriptors are 6, 7, 16, 19, and 23, and the regression model is

$$\log K_{GdL} = 34.17 - 16.41\,{}^5x_{pc} + 15.75\,{}^6x_{pc} - 6.32*10^{-3}E_t - 2.26E_i - 2.48E_{H-L} \quad (4)$$

$$R = 0.92 \quad F = 25.38 \quad S = 2.04 \quad N = 28$$

where R is a correlation coefficient, F is the significance test, S denotes the standard deviation, and N is the number of samples. This equation shows that only $^6x_{pc}$ relates to the stability constant positively, whereas $^5x_{pc}$, E_t (molecular total energy), E_i (ionization potential), and E_{H-L} (the HOMO−LUMO gap) relate to the stability constant negatively. This means that compounds will possess higher stability with higher $^6x_{pc}$ or lower $^5x_{pc}$, E_t, E_i, and E_{H-L}. At the same time, we also know that the more easily the ligand ionizes, the more stable the gadolinium(III) complex will be. This allows us to explain and emphasize that a lower HOMO−LUMO gap implies its higher reactivity in chemical reactions. The results obtained using multiple regression are given in Table 4.

The above eq 4 is not sufficiently robust to allow confident prediction because the correlation coefficient R is not high. Thus, neural networks were employed, since this approach always gives better results than those obtained by multiple regression.

3.4. Neural Networks. In recent years, artificial neural networks have been used widely. Among the neural network learning algorithms, the back-propagation (BP)[19] method is one of the most commonly used methods. The drawback of BP is that the training processes slowly, because the gradient-descent algorithm is usually used for minimizing the sum-of-squares error. In this research, the BFGS quasi-Newton method[20−24] was used. The advantages of using the BFGS method are that specifying rate or momentum is not necessary and training processes are much more rapid.[25,26]

The input nodes of the neural network are the same as in multiple regression, i.e., $^5x_{pc}$, $^6x_{pc}$, E_t, E_i and E_{H-L}. The number of output neurons is one. To avoid overtraining, the test set was used to monitor the training process for networks; that is during the training of the network, the performance was monitored by predicting the values for the compounds in the test set. As long as test set results were improving, training was continued but when the test set results ceased to improve, the training was stopped. The results indicated that this method is an effective approach to avoiding overtraining.

Consequently, the entire data set was divided into two groups: 20 compounds as the training set and 8 compounds as the test set. The usual rule of thumb is that the weights and bases should be fewer in number than the samples so that the model achieved by the network is stationary. The number of the hidden neurons should not therefore be greater than 3, and better results could be obtained by using 2 hidden neurons. So the architecture of an over network was 5:2:1. The results obtained by the neural network, also given in Table 4, are $R = 0.95$, $F = 251.58$, $S = 1.60$. Obviously, the results are better than those obtained by using multiple regression analysis.

4. CONCLUSIONS

From the results in this paper, the following conclusions can be drawn. (1) For some macromolecule compounds, it

Table 4. Comparison of the Results Obtained by Two Different Methods

no.	logK_{GdL} (obs)	logK_{GdL} (MLR)	logK_{GdL} (diff)	logK_{GdL} (ANN)	logK_{GdL} (diff)
1	16.84	18.66	−1.82	16.31	0.53
2	17.68	17.62	0.06	17.73	−0.05
3	16.85	17.95	−1.10	17.79	−0.94
4	13.12	10.62	2.50	11.67	1.45
5[a]	23.65	22.90	0.75	23.07	0.58
6[a]	25.30	24.15	1.15	25.29	0.01
7	25.30	21.27	3.93	22.97	2.33
8	21.10	22.34	−1.24	22.90	−1.80
9	28.80	28.33	0.47	27.47	1.33
10	23.80	22.42	1.38	23.38	0.42
11[a]	23.90	21.80	2.10	23.17	0.73
12	22.30	24.11	−1.81	25.16	−2.86
13	11.15	13.36	−2.21	13.44	−2.29
14[a]	14.49	15.94	−1.45	16.79	−2.30
15	15.39	13.06	2.33	13.51	1.88
16[a]	15.56	13.43	2.13	13.86	1.70
17	17.44	16.37	1.07	17.63	−0.19
18	13.70	15.71	−2.01	13.09	0.61
19[a]	15.10	16.84	−1.74	15.05	0.05
20	10.40	11.52	−1.12	11.99	−1.59
21	16.60	17.42	−0.82	16.20	0.40
22	14.50	15.52	−1.03	14.86	−0.36
23[a]	16.27	15.14	1.13	15.35	0.92
24	11.49	13.83	−2.34	13.40	−1.91
25	18.07	16.30	1.77	16.47	1.60
26	17.23	17.34	−0.11	16.80	0.43
27	19.00	22.18	−3.18	19.21	−0.21
28[a]	15.56	14.36	1.20	13.02	2.54

[a] Samples of the test set.

is very difficult to abstract the descriptors because the structures are complicated. In our study, although gadolinium(III) complexes are nine-coordinated structures, the metal ions in the complexes are common to all of them. Thus we were able to ignore the common moeities (the gadolinium(III) ions) and consider only the ligands. In this way, the complexity of the calculation can be greatly reduced. (2) For the descriptions of the complicated structures in this work, only the quantum-chemical descriptors and topological descriptors were used, and good predictive models were constructed. (3) The results in this paper are useful for other research work, such as the design and syntheses of MRI contrast agents in our laboratory.

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