Wavelet Neural Network and Its Application to the Inclusion of *β*-Cyclodextrin with Benzene Derivatives

Lei Liu and Qing-Xiang Guo*

Department of Chemistry, University of Science and Technology of China, Hefei, 230026,
People's Republic of China

A wavelet neural network (WNN) was constituted and applied to the inclusion complexation of *β*-cyclodextrin with mono- and 1,4-disubstituted benzenes. The association constant (K_a) values have been calculated by the WNN from substituent molar refraction (R_m), hydrophobic constant (π), and Hammett constant (σ) of the guest compounds as input parameters. The excellent prediction results with a correlation coefficient of 0.992 and standard deviation of 0.089 suggested that *β*-CD inclusion complexation is mainly driven by van der Waals force, hydrophobic interaction, and electronic effects.

INTRODUCTION

α-, *β*-, and *γ*-cyclodextrin (CD) are cyclic oligomers of six, seven, and eight D-glucose units. They can form inclusion complexes with a variety of guest molecules through a process called molecular recognition. This property enables CD to be applied to many important areas, such as analytical chemistry, pharmaceutical science, catalysis, and separation technology.[1] CD inclusion complexes are also the most valuable models for understanding noncovalent bonding interactions in aqueous solution and mimicking the enzyme−substrate interaction.[2] Great efforts have been devoted to the driving forces of CD inclusion complexation. Up to date, several driving forces have been postulated in the host−guest interaction: (1) van der Waals forces; (2) hydrophobic interactions; (3) hydrogen bonding; (4) release of distortional energy of CD by binding guest; and (5) extrusion of "high energy water" from the cavity of CD upon inclusion complex formation. However, there still remains no clear agreement on the mechanism for the CD inclusion complexation.[3a]

Recently, quantitative studies on the CD inclusion complexation have attracted much attention with the purposes of both understanding the roles of different driving forces and theoretically predicting the association constants (K_a) of CD complexes. Methods including quantum and molecular mechanics computation[4] and linear regression[5] as well as artificial neural networks (ANN)[6] have been used. Many studies have demonstrated that there exists quantitative relation between CD association constants and the substituent properties such as volume, hydrophobicity, and electronic properties of the guest molecules. Although some reliable prediction models have been established for α-CD complexes,[3b,5] little work has been performed on *β*-CD complexation systems. A linear model for the *β*-CD binding with 1,4-disubstituted benzenes has been reported, but the correlation coefficient of only 0.723 could be reached for a rather small sample of 16 complexes.[5a] In our previous work, a multiple linear regression model and a stepwise regression analysis model for the binding of *β*-CD with 24 monosubstituted benzenes were established with correlation coefficients of 0.91[7] and 0.94,[8] respectively. Our approach was also well applied to the *β*-CD·1-substituted naphthalene system.[9] However, to obtain a better model for prediction, some nonlinear analysis method is needed because of the advent of nonlinear mechanisms in the process caused by the interactions of the different driving forces.

It is well known that the artificial neural network is a high performance nonlinear analysis tool, which is capable of covering more relations between the input/output data than classical regression analysis without prior knowledge of the relationship between variables involved in the system.[10] Although great interests have recently been devoted to the application of ANN to different domains of chemistry, potential applications of ANN in supramolecular chemistry still require further exploration. Recently, we have reported the prediction of the driving forces for α-CD complexation with benzene derivatives by the BP networks.[6] In this study, a novel wavelet neural network (WNN) was employed in the inclusion complexation of *β*-CD with mono- and 1,4-disubstituted benzenes, and an excellent driving force prediction was achieved.
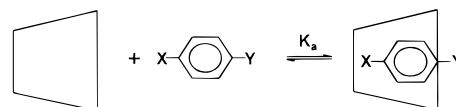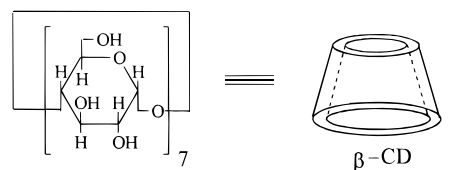
THEORY

1. Wavelet Neural Network. Wavelet theory, a novel field which interests not only mathematicians but also scientists studying acoustics, fluid mechanics, and chemistry, involves representing general signals in terms of simpler, fixed building blocks of constant shape but at different scales and positions. Unlike Fourier transformation, the wavelet transformation has dual localization both in frequency and in time, which makes it an excellent nonlinear analysis tool.[11]
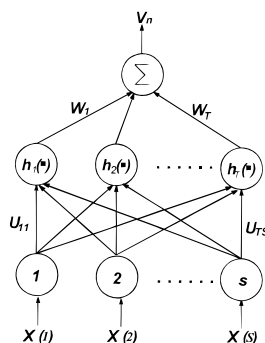
Figure 1. The architecture of the wavelet neural network.

Recently, wavelet neural networks (WNN) have been proposed based on the theories of feed-forward neural networks and wavelet decompositions.[12] Although several theoretical studies have proven the exciting superiority of WNN over conventional BP neural network,[12] very little has been reported on the applications of WNN, especially in chemistry.[13] The structure of WNN employed in this study is shown in Figure 1. The computer program was written in Borland C^{++} 3.1 and run on an 80586 personal computer; the back-propagation algorithm[14] was used in the network training process, which is summarized as follows:

(1) Initializing dilation parameter a_t, translation parameter b_t, and node connection weights $u_{ti}w_t$ to some random values.

(2) Inputting data $X_n(i)$ and corresponding output values V_n^T, where superscript T represents the target output state.

(3) Propagating the initial signal forward through the network using

$$V_n = \sum_{t=1}^{T} w_t h\left(\frac{\sum_{i=1}^{S} u_{ti}x_n(i) - b_t}{a_t}\right)$$

where h is taken as a Morlet wavelet

$$h(t) = \cos(1.75t) \exp\left(-\frac{t^2}{2}\right)$$

(4) Calculating the variation of every parameter in the network, defined as

$$\delta_{w_t} = \frac{\partial E}{\partial w_t} = -\sum_{n=1}^{N}(v_n^T - v_n)h\left(\frac{\sum_{i=1}^{S} u_{ti}x_n(i) - b_t}{a_t}\right)$$

$$\delta_{a_t} = \frac{\partial E}{\partial a_t} = -\sum_{n=1}^{N}(v_n^T - v_n)w_t\frac{\partial}{\partial a_t}$$

$$\delta_{b_t} = \frac{\partial E}{\partial b_t} = -\sum_{n=1}^{N}(v_n^T - v_n)w_t\frac{\partial h}{\partial b_t}$$

$$\delta_{u_{ti}} = \frac{\partial E}{\partial u_{ti}} = -\sum_{n=1}^{N}(v_n^T - v_n)w_t\frac{\partial h}{\partial x_n'}x_n(i)$$

where $x_n' = \sum_{i=1}^{S} u_{ti}x_n(i)$ and $t_n' = (x_n' - b_t)/a_t$ for convenience,

$$\frac{\partial h}{\partial x_n'} = -\cos(1.75t_n') \exp\left(-\frac{t_n'^2}{2}\right)\frac{t_n'}{a_t} - $$

$$1.75 \sin(1.75t_n') \exp\left(-\frac{t_n'^2}{2}\right)\frac{1}{a_t}$$

$$\frac{\partial h}{\partial a_t} = \cos(1.75t_n') \exp\left(-\frac{t_n'^2}{2}\right)\frac{t_n'^2}{a_t} + $$

$$1.75 \sin(1.75t_n') \exp\left(-\frac{t_n'^2}{2}\right)\frac{t_n'}{a_t}$$

$$\frac{\partial h}{\partial b_t} = \cos(1.75t_n') \exp\left(-\frac{t_n'^2}{2}\right)\frac{t_n'}{a_t} + $$

$$1.75 \sin(1.75t_n') \exp\left(-\frac{t_n'^2}{2}\right)\frac{1}{a_t}$$

and the objective function E is taken as

$$E = \frac{1}{2}\sum_{n=1}^{N}(v_n^T - v_n)^2$$

(5) Using

$$\Delta w_t^{new} = -\eta\frac{\partial E}{\partial w_t^{old}} + \alpha\Delta w_t^{old} \quad \Delta u_{ti}^{new} = -\eta\frac{\partial E}{\partial u_{ti}^{old}} + \alpha\Delta u_{ti}^{old}$$

$$\Delta a_t^{new} = -\eta\frac{\partial E}{\partial a_t^{old}} + \alpha\Delta a_t^{old} \quad \Delta b_t^{new} = -\eta\frac{\partial E}{\partial b_t^{old}} + \alpha\Delta b_t^{old}$$

updating a_t, b_t, w_t, u_{ti} to

$$u_{ti}^{new} = u_{ti}^{old} + \Delta u_{ti}^{old} \quad a_t^{new} = a_t^{old} + \Delta a_t^{old}$$

$$b_t^{new} = b_t^{old} + \Delta b_t^{old} \quad w_t^{new} = w_t^{old} + \Delta w_t^{old}$$

where η is the learning rate and α the momentum.

(6) Returning to step 2 and repeating for another round of training. This process is continued until the network output satisfies the error criteria.

2. Parameters.[15] Molecular refraction is defined as

$$R_m = [(n^2 - 1)/(n^2 + 2)]\cdot MW/d$$

where n, MW, and d represent the refractivity, molecular weight, and density of the compound, respectively. In this work the substituent molar refraction was used, in which MW is replaced by the weight of the substituent.

Substituent hydrophobic constant π_x is defined as

$$\pi_x = \log P_X - \log P_H$$

where P_X and P_H are the partition coefficients of substituted compound (RX) and the parent compound (RH), such as PhX and PhH, in 1-octanol/water.

Hammett σ constant, the electronic effect of substituent (X) relative to that of hydrogen, may be obtained by a comparison of ΔG for dissociation constants of substituted benzoic acid (K_X) with that of the parent compound, benzoic

Table 1. ln K_a Values Calculated by the WNN and the Experimental Data for the Inclusion Complexation of β-CD with Mono- and 1,4-Disubstituted Benzenes

no.	X	Y	ln K_a (obs)	ref	ln K_a (WNN)	R_{mX}	π_X	σ_X	R_{mY}	π_Y	σ_Y
1	H	H	5.13	17	5.13	0.34	0.00	0.00	0.34	0.00	0.00
2[a]	CH$_3$	H	5.37	7	5.40	5.07	0.56	−0.17	0.34	0.00	0.00
3	Et	H	5.96	7	5.96	9.77	1.02	−0.15	0.34	0.00	0.00
4	CCH	H	5.44	7	5.42	8.52	0.40	0.23	0.34	0.00	0.00
5	OH	H	4.55	7	4.46	5.05	−0.67	−0.37	0.34	0.00	0.00
6[a]	OCH$_3$	H	5.34	7	5.29	9.44	−0.02	−0.32	0.34	0.00	0.00
7	OEt	H	5.73	7	5.67	13.86	0.44	−0.24	0.34	0.00	0.00
8	CH$_2$OH	H	4.96	7	4.86	9.31	−1.03	0.08	0.34	0.00	0.00
9[a]	CH$_2$Cl	H	5.63	7	5.58	14.11	0.17	0.18	0.34	0.00	0.00
10	CHO	H	5.01	7	5.16	8.78	−0.65	0.22	0.34	0.00	0.00
11	COMe	H	5.23	7	5.19	13.00	−0.55	0.50	0.34	0.00	0.00
12[a]	CO$_2$Me	H	5.76	7	5.58	16.42	−0.01	0.39	0.34	0.00	0.00
13	CO$_2$Et	H	6.29	7	6.38	20.59	0.45	0.45	0.34	0.00	0.00
14	CN	H	5.14	7	5.09	7.79	−0.57	0.66	0.34	0.00	0.00
15[a]	NHCH$_3$	H	4.87	7	4.67	9.96	−0.36	−0.84	0.34	0.00	0.00
16	NHEt	H	5.38	7	5.42	14.69	0.13	−0.61	0.34	0.00	0.00
17	N(CH$_3$)$_2$	H	5.44	7	5.36	14.48	0.18	−0.83	0.34	0.00	0.00
18	NHCOMe	H	5.06	7	5.04	15.04	−0.97	0.00	0.34	0.00	0.00
19	NO$_2$	H	5.63	7	5.68	12.29	−0.28	0.78	0.34	0.00	0.00
20	F	H	4.51	7	4.55	5.17	0.14	0.06	0.34	0.00	0.00
21[a]	Br	H	5.76	7	5.89	17.25	0.86	0.27	0.34	0.00	0.00
22	I	H	6.74	7	6.69	24.38	1.12	0.30	0.34	0.00	0.00
23	NH$_2$	H	3.91	18	3.96	5.25	−1.23	−0.66	0.34	0.00	0.00
24	CH$_3$	CH$_3$	5.48	19	5.48	5.07	0.56	−0.17	5.07	0.56	−0.17
25[a]	Br	Br	6.85	20	6.87	17.25	0.86	0.27	17.25	0.86	0.27
26	I	I	7.31	20	7.28	24.38	1.12	0.30	24.38	1.12	0.30
27	CH$_2$OH	OH	4.98	21	4.97	9.31	−1.03	0.08	5.05	−0.67	−0.37
28	Et	OH	6.20	21	6.20	9.77	1.02	−0.15	5.05	−0.67	−0.37
29	NO$_2$	OH	5.50	22	5.34	12.29	−0.28	0.78	5.05	−0.67	−0.37
30	COOH	OH	5.06	22	5.22	13.07	−0.28	0.45	5.05	−0.67	−0.37
31	NO$_2$	NH$_2$	5.72	22	5.74	12.29	−0.28	0.78	5.25	−1.23	−0.66
32	I	OH	6.86	23	6.90	24.38	1.12	0.30	5.05	−0.67	−0.37
33	CH$_3$CO	OH	5.02	24	5.04	13.00	−0.55	0.50	5.05	−0.67	−0.37
34	Br	OH	6.10	24	6.05	17.25	0.86	0.27	5.05	−0.67	−0.37
35	CH$_3$O	OH	5.09	24	5.09	9.44	−0.02	−0.32	5.05	−0.67	−0.37
36	OH	OH	4.73	25	4.77	5.05	−0.67	−0.37	5.05	−0.67	−0.37
37[a]	Cl	OH	6.02	25	6.32	9.83	0.71	0.30	5.05	−0.67	−0.37
38	CH$_3$	OH	5.52	25	5.50	5.07	0.56	−0.17	5.05	−0.67	−0.37
39	COOH	NO$_2$	5.39	25	5.38	13.07	−0.28	0.45	12.29	−0.28	0.78
40	Cl	NO$_2$	4.95	26	4.96	9.83	0.71	0.30	12.29	−0.28	0.78

[a] Used in the prediction set.

acid (K_H).

$$\sigma_X = \Delta G_X - \Delta G_H = \log K_X - \log K_H$$

3. Orientation of the Guest Compound in the Complex. The determination of the orientation of the guest molecule in CD cavity is a rather complicated and controversial problem not only theoretically[5] but also experimentally.[16] In our present study, the orientation of the benzene derivatives was postulated as following:

1. For monosubstituted benzene, since the substituent groups are generally far larger than hydrogen, which in consequence fit more snugly in β-CD cavity *via* van der Waals forces, the substituent groups are proposed to stay in CD cavity.[7]

2. For para-substituted phenol and para-substituted aniline, the OH and NH$_2$ are readily proposed to stay outside since OH and NH$_2$ are highly hydrophilic.

3. For *p*-nitrobenzoic acid, the carboxyl group was proposed to stay in CD cavity, since the volume of the COOH is larger than that of NO$_2$.

4. For *p*-chloronitrobenzene, the nitro group was proposed to stay outside the β-CD cavity, because Cl is more hydrophobic than NO$_2$.

In this paper, the substituent X is located in the β-CD cavity and the substituent Y outside the cavity. Despite the empirical nature of the above postulations, the excellent prediction of the WNN gives further confidence on them.

CALCULATION

The association constants (ln K_a) and the corresponding substituent constants R_m, π, and σ of 32 benzene derivatives were used to train the network. After the network training, to examine the network eight other association constants were predicted. Different 6-*n*-1 WNNs (*n* = 1−10) were also respectively trained. It was found that the WNNs with both very few and too many hidden nodes have difficulties in quickly generalizing the model. In this study, the topological structure capable of the best performance and hence selected was found to be 6-6-1. Several independent networks of the 6-6-1 structure were also trained respectively in order to avoid the possible chance effects.[14b] However, since no significant difference in the network predictions between them was observed in our study, we here only list the predictions of one network in Table 1, with its optimized weights summarized in Table 2.

Table 2. Optimized Weights of the Wavelet Neural Network

hidden node	1	2	3	4	5	6
U_1	−2.888 110	5.162 836	−5.036 614	−0.968 686	4.218 651	5.185 442
U_2	−8.561 712	2.137 373	5.826 611	−0.866 055	−8.232 189	−9.754 425
U_3	−1.997 538	3.611 767	−4.680 911	−1.887 442	−4.597 124	−5.876 666
U_4	−0.036 586	6.326 932	−1.889 969	1.083 224	1.734 114	2.649 754
U_5	4.643 066	−1.190 588	−2.418 538	−0.319 131	4.381 264	6.686 687
U_6	0.401 329	1.016 571	−1.272 372	−0.149 267	2.841 160	2.372 448
a	−54.446 556	−32.699 768	−23.379 061	145.266 556	41.205 219	35.503 597
b	1.398 565	−0.273 823	−6.062 471	0.716 122	−8.888 271	0.956 005
w	−2.276 946	−1.837 876	4.742 377	6.615 698	7.015 137	−8.035 176
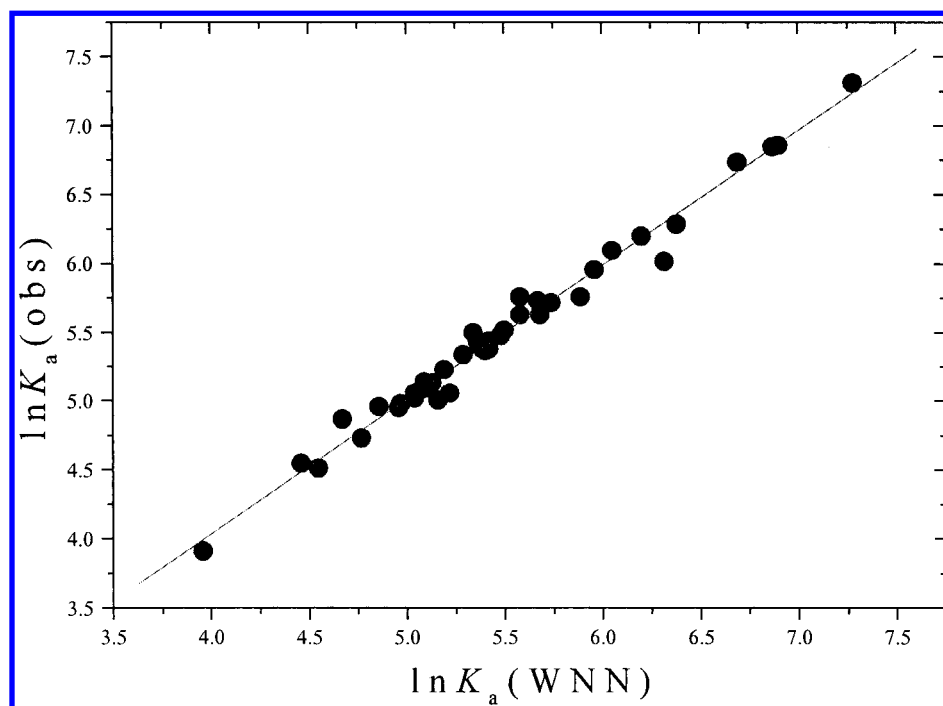
Figure 2. Plot of ln K_a (obs) versus ln K_a(WNN) for the inclusion complexation of β-CD with benzene derivatives.

From Table 1 it can be seen that the ln K_a (WNN) values predicted by WNN from the substituent R_m, π and σ constants are very close to those determined experimentally. Plotting ln K_a observed against those predicted by WNN gives a straight line (Figure 2), which fits the following equation:

$$\ln K_a(\text{obs}) = 0.976 \ln K_a(\text{WNN}) + 0.134 \qquad (1)$$

$$n = 40, \quad r = 0.992, \quad \text{sd} = 0.089$$

Although the calculation sample in our study is somewhat small, due to the limited experimental data in the literature, the performance of the wavelet neural network demonstrates that WNN is a promising novel nonlinear analysis tool.

DISCUSSION

1. WNN versus BP Neural Networks. It is worthy to note that WNNs replace the Sigmoid transfer function in conventional BP neural networks with scalar wavelets. However, this replacement results in nontrivial improvement due to the desirable properties of wavelet transformation. Theoretical studies as well as simulation results have confirmed the superiority of WNN.[12] Herein, in order to compare the performance of WNN with BP neural network based on the real physical model in our study, a BP network of 6-6-1 structure was also implemented.[27] This BP network yields predictions for the same sample with a correlation coefficient of 0.981. It is obvious that WNN can offer a better estimation due to the desirable properties of wavelet transformation. This result is in agreement with previous studies.[12,13] It is therefore hopeful that the novel wavelet neural network could be a good alternative of the BP network, which has already been heavily used in chemistry.

2. Driving Forces for CD Inclusion Complexation. The above WNN model demonstrates that β-CD inclusion complexation is affected by substituent molar refraction (R_m) of the guest molecules. Since R_m well reflects the volume and polarizability of the substrate, it readily concluded that CD host−guest complexation is affected by van der Waals forces. The van der Waals forces primarily consist of induction and dispersion forces, which depend on molecular volume and polarizability. Many studies have confirmed that van der Waals forces play overwhelming roles in CD inclusion complexation.[28]

Another factor influencing the CD inclusion complexation is hydrophobic interaction,[29] which was included in above WNN model by hydrophobic constant (π). The involvement of hydrophobic interaction in CD inclusion complexation has been disputable for years. However, many authors tend to conclude that hydrophobic interaction plays at least a significant role, if not a dominant role, in CD inclusion

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complexation. Although the hydrophobic interaction partly results from the van der Waals force, it is mainly due to the effects of entropy produced in the water molecules. The substituent with larger π values is more hydrophobic and thus strongly driven into the hydrophobic cavity of α-CD from the water cluster. This process is exothermic by entropic gain.[7]

Since CD is highly polar,[30a] electrostatic force, sometimes also referred as dipole−dipole interaction, can to some extent contribute to the CD inclusion complexation.[30] However, ambiguity exists because this type of interaction is often combined with dipole-induced dipole and dispersion forces. Different authors ranked electrostatic force in CD inclusion complexation extremely differently. The substituent Hammett σ constant in above WNN model well reflects this factor.

Although still other factors may contribute to the CD inclusion mechanism,[3a,31] the successful prediction of above WNN model suggests that van der Waals forces, hydrophobic interaction, and electronic effect comprise the major driving forces.

3. Multilinear Regression versus Neural Network. To be compared with the performance of the WNN, the multilinear regression (MLR) analysis is implemented for the above 40 inclusion complexes with R_m, π, and σ constants as input descriptors. The optimized MLR equation is obtained as follows:

$$\ln K_a = 4.779 + 0.050R_{mX} + 0.539\pi_X + 0.273\sigma_X +$$
$$0.019R_{mY} + 0.349\pi_Y - 0.641\sigma_Y \quad (2)$$

$$r^2 = 0.893, \quad sd = 0.244, \quad n = 40$$

It is notably better than that reported in the literature[5a] in which the effect of the hydrophobic interaction was neglected. Omitting π_X and π_Y from eq 2 could only yield

$$\ln K_a = 4.382 + 0.081R_{mX} + 0.081\sigma_X +$$
$$0.037R_{mY} - 0.332\sigma_Y \quad (3)$$

$$r^2 = 0.638, \quad sd = 0.437, \quad n = 40$$

From eq 2, it can be seen that the larger the R_m and π constants of the substituents, the greater the stability of the inclusion complexes. This indicates that stronger van der Waals forces and hydrophobic interactions favor the molecular recognition process.[7] It is also interesting to notice that differently located substituents play different roles in electronic interactions according to eq 2. The group (X) inside β-CD cavity positively contributes to the binding, while the group (Y) outside CD cavity negatively affects the binding if it possesses more positive σ constant. This agrees with other studies which proposed that the antiparallel arrangement of the polarity of the guest with CD favors the binding.[5a,30]

Although above MLR model offers more insight into the inclusion mechanism, it is obvious that WNN covers more relations than conventional regression and therefore gives much better predictions. Hence, the WNN is more recommendable for the purpose of prediction association constants of CD complexation.

CONCLUSIONS

A novel wavelet neural network was successfully employed to predict the inclusion of β-CD with mono- and 1,4-

disubstituted benzenes from substituent molar refraction R_m, hydrophobic constant π, and Hammett constant σ. The study well supported the postulation that van der Waals forces, hydrophobic interactions, and electronic effects mainly contribute to the β-CD inclusion complexation. The study also demonstrates the desirable properties of the WNN surely deserve further exploration.

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