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Using artificial neural networks for prediction of organic acid partition coefficients

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Aqueous/organic phase partition coefficients of organic acids were predicted using an artificial neural network (ANN) algorithm taking benzoic acid derivatives as examples. The partition coefficients were determined by extraction of the acids from aqueous salt solutions with hydrophilic solvents (Bu^{n}OH, Bu^{i}OH, and Bu^{t}OH). Using the ANN approach makes it possible to obtain quantitative information on the values of the title parameters.

Key words: partition coefficient, artificial neural networks, extraction, electrochemical analysis of non-aqueous concentrates.

Based on the available concepts of solutions, it is impossible to make *a priori* estimates of extracting activities of organic solvents with respect to aromatic acids. Because of this, prediction of partition coefficients of the organic compounds extracted with hydrophilic solvents becomes particularly topical. In order to solve the problem, it is appropriate to use a specific type of mathematical models, namely, artificial neural networks (ANNs), which represent a combination of nonlinear and nonparametric methods of data processing.[1—6]

In this work we studied the following benzoic acid derivatives: 2-amino- (**1**), 3-amino- (**2**), 4-amino- (**3**), 2-bromo- (**4**), 3-bromo- (**5**), 2,3-dibromo- (**6**), 3,4-dibromo- (**7**), 2-iodo- (**8**), 3-iodo- (**9**), 4-iodo- (**10**), 2,4-diiodo- (**11**), 2,3,5-triiodo- (**12**), 2,3,6-triiodo- (**13**), 2-chloro- (**14**), 4-chloro- (**15**), 2,4-dichloro- (**16**), 2,3,6-trichloro- (**17**), and 5-bromo-2-hydroxybenzoic acid (**18**). Extracting agents used were Me_2CO, Pr^{n}OH, Pr^{i}OH, Bu^{n}OH, Bu^{i}OH, Bu^{t}OH, methyl ethyl ketone (MEK), and ethyl acetate (EA).

Selected physicochemical characteristics of acids **1—18** are listed in Table 1.

Table 1. Selected physicochemical parameters of the acids under study[7—9]

Acid	M	pK_a	M.p. /°C
1	137.15	4.95	146.5
2	137.15	4.74	179.5
3	137.15	4.85	186.5
4	201.20	2.86	150
5	201.20	3.81	175
6	279.93	3.36	149.5
7	279.93	3.49	233.5
8	248.02	2.86	162
9	248.02	3.54	263
10	248.02	3.82	260
11	373.92	2.58	—
12	499.82	2.35	—
13	499.82	2.27	274
14	156.57	2.94	139
15	156.57	3.98	235
16	191.01	2.29	191
17	225.45	1.08	125
18	217.05	2.96	174

Experimental

All samples of the benzoic acid derivatives and extracting agents used in this work were of "chemically pure" grade. The aqueous-phase/extracting-agent-phase acid partition coefficients were determined by potentiometric and conductometric titration.

Extraction. To obtain comparable partition coefficients (D), the acids were extracted under identical conditions (20 °C, acidification with H_2SO_4 to pH ~2, aqueous-phase/organic-phase equilibrium volume ratio $r = 10 : 1$). The hydrophilic solvent phases were separated using Li_2SO_4 as a salting out agent whose concentration was preliminarily optimized in order to provide the maximum values of partition coefficients for each extraction system.

Electrochemical analysis of non-aqueous extracts. The systems for extraction of benzoic acid derivatives from aqueous solutions are recommended for extraction-titrimetric determination of acids with potentiometric and conductometric indication of the stoichiometry point. Titrimetric analysis of non-aqueous concentrates reduces the duration of analysis and improves its accuracy (re-extraction stage is absent). Acid-base titration of weak organic acids is carried out in alcohol

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and ketone solutions, the accuracy of measurements being of the order of ~1%.[10] KOH or NaOH solutions are used as titrants.

The acid content (m/mg) in aqueous solutions analyzed was calculated by the following expression:

$$m = 0.01C \cdot V \cdot \mathrm{M} \cdot R,$$

where C is the titrant concentration (in mol L^{-1}), V is the titrant volume (in mL) consumed for titration, M is the molar weight of the acid equivalent (in g mol^{-1}), and R is the degree of acid extraction at single extraction (in %).

The electromotive force was measured with a high-resistance ionomer I-130 and 0.01 M KOH solution in EtOH as titrant. Adding each portion of titrant (0.02—0.05 mL) was followed by obtaining ionomer readings (in mV) and the mixture was kept until a constant signal amplitude. Titration was performed until a constant potential.

Non-aqueous potentiometric titration of acids is usually carried out with a glass pH-electrode as indicator electrode. This permits highly accurate measurements in dipolar aprotic media.[10,11] The time taken to establish a constant glass electrode potential is of the order of a few seconds. However, degradation of the electrode surface in the case of prolonged operation in non-aqueous solutions leads to an increase in the electrode response time.

Conductometric analysis was carried out with a 2BM-509 bridge (Tesla, Czech Republic) in a conventional cell with two Pt-electrodes (surface area of 1 cm^2 each) separated by a distance of 1 cm. The concentrate was five-fold diluted with an extracting agent (in this case the content of the salting out agent in the extract was minimum and did not preclude the determination of the acid) and separated into two equal portions. One of them was titrated with a KOH solution in EtOH, while the other was titrated with a $\mathrm{CuCl_2}$ solution in EtOH.

Results and Discussion

Analysis of the published data[12—21] showed that at present the most appropriate approach to prediction, with sufficient accuracy, of most of practically important characteristics of compounds of different nature involves the use of ANNs. This makes it possible to carry out "smart processing" of experimental data and to establish *a priori* unknown correlations between the empirical and structural parameters on the one hand and the predicted molecular characteristics on the other hand.[12]

The partition coefficients of acids **1—18** in the systems with hydrophilic extracting agents were predicted using a feed-forward back-propagation ANN.[1—6]

Training of an ANN with a training set is reduced to minimization of the difference (H) between the output signals produced by the network and the signals to be obtained.[3] Correctness of the operation of the ANN was assessed by "tuning" the "trainable" parameters of neurons of the network in such a way that the response, Y', of the network to a certain input vector be the best approximation to the desired response Y. In other words, for a training set including N elements, a minimum of the total estimating function was reached

$$H = \sum_{i=1}^{N} \left| Y_i - Y_i' \right| \to \min. \qquad (1)$$

Artificial neural networks were trained using the least squares method (LSM) with a bias of α, which made it possible to accelerate the network learning.

The LSM estimate with the bias α has the form:

$$H = \sum_i P\left(\frac{Y_i - Y_i'}{\alpha}\right), \qquad (2)$$

where $P(\Delta) = \begin{cases} (|\Delta| - 1)^2, & \text{if } |\Delta| \geq 1 \\ 0, & \text{if } |\Delta| < 1. \end{cases}$

This type of estimates allows optimization to be stopped after reaching the preset accuracy.[6]

After training, the ANN topology was optimized by excluding the least significant input signals and elements. Simplification of the ANN included a decrease in the number of: neuron layers, neurons in each layer, input parameters, as well as minimization of the number of signals per neuron and a decrease in the number of synapses connecting neurons.

Since at present there is no theoretically substantiated procedure for choosing an optimum ANN topology, the network topology was empirically determined in each case by training with different sets of input data.

The error of training using the error back-propagation algorithm depends on the network topology, learning rate, and number of iterations.[2] The ANN size corresponding to the smallest error for the training and test sets was considered optimum. In this connection the neural network was trained using three types of input parameters. These were:

1. Characteristics of the acids under study, that is, ionization constant in water ($\mathrm{p}K_\mathrm{a}$), melting point, molecular weight, character, number, and positions of substituents in the benzene ring. The melting points were chosen because of the fact that the reference data on the solubility of benzoic acid derivatives were obtained at different temperatures.

2. Solvent characteristics. We chose the empirical parameters that characterize[11] the following contributions.

a) The contribution of non-specific interaction:

— Kirkwood—Born polarity parameter $f(\varepsilon)$, which is proportional to the $(\varepsilon - 1)/(2\varepsilon - 1)$ ratio, where ε is the dielectric constant of the solvent;

— Lorenz—Lorentz polarizability parameter $f(n) = (n^2 - 1)/(2n^2 - 1)$, where n is the refractive index of the solvent.

b) The contribution of specific interaction:

Table 2. Normalized values of the input parameters for neural network training

Acid	M	pK_a	M.p.	Position of substituent in benzene ring					Substituent				
				2	3	4	5	6	Cl	Br	I	OH	NH_2
1	−1	1	−0.722	1	−1	−1	−1	−1	−1	−1	−1	−1	1
2	−1	0.891	−0.298	−1	1	−1	−1	−1	−1	−1	−1	−1	1
3	−1	0.948	−0.166	−1	−1	1	−1	−1	−1	−1	−1	−1	1
4	−0.647	−0.080	−0.669	1	−1	−1	−1	−1	−1	1	−1	−1	−1
5	−0.647	0.411	−0.338	−1	1	−1	−1	−1	−1	1	−1	−1	−1
6	−0.212	0.178	0	1	1	−1	−1	−1	−1	1	−1	−1	−1
7	−0.212	0.245	0	−1	1	1	−1	−1	−1	1	−1	−1	−1
8	−0.388	−0.080	−0.351	1	−1	−1	−1	−1	−1	−1	1	−1	−1
9	−0.388	0.271	−0.179	−1	1	−1	−1	−1	−1	−1	1	−1	−1
10	−0.388	0.416	0.788	−1	−1	1	−1	−1	−1	−1	1	−1	−1
11	0.306	−0.225	0	1	−1	1	−1	−1	−1	−1	1	−1	−1
12	1	−0.344	0	1	1	−1	1	−1	−1	−1	1	−1	−1
13	1	−0.385	0.974	1	1	−1	−1	1	−1	−1	1	−1	−1
14	−0.895	−0.039	−0.815	1	−1	−1	−1	−1	1	−1	−1	−1	−1
15	−0.895	−0.499	−0.457	−1	−1	1	−1	−1	1	−1	−1	−1	−1
16	−0.702	−0.375	−0.536	1	−1	1	−1	−1	1	−1	−1	−1	−1
17	−0.509	−1	−1	1	1	−1	−1	1	1	−1	−1	−1	−1
18	−0.468	−0.028	−0.340	1	−1	−1	1	−1	−1	1	1	−1	−1

— cohesive energy density δ (in $kJ^{1/2}\ m^{3/2}$), which is related to the work necessary to break all types of intermolecular interactions the solvent is involved in.

c) An additive parameter:

— Dimroth—Reichardt normalized polarity parameter E_t, which describes both specific and non-specific acid—solvent interactions (the parameter related to the absorption spectrum of betaine dye in various solvents).

3. Properties of the acids and solvents under study.

Since often the weights of ANN synapses should belong to a certain range of values, it is impossible to use actual values of the input signals and obtain corresponding output signals (network response) in the desired range of values.[3] Therefore, all the input parameters were normalized using expression (3) in the [−1, 1] range and each component of the input data vector was replaced by corresponding normalized quantity,

$$x_i' = \frac{x_i - \left(x_i^{\max} + x_i^{\min}\right)/2}{\left(x_i^{\max} - x_i^{\min}\right)/2}, \qquad (3)$$

where x'_i is the normalized value of the input parameter, x_i is the component of the input vector, and $x_i^{\max}$ and $x_i^{\min}$ are respectively the maximum and minimum values of the component calculated for the whole training set. This relation was also used to normalize the output vector components.

The normalized input parameters of the ANN trained on the properties of the acids under study are listed in Table 2.

It was established that the partition coefficients can be correctly predicted using 10 out of 13 parameters (three parameters, M, pK_a, and melting point, were excluded as being insignificant and having no effect on the accuracy of prediction). The results of training of the neural network are listed in Table 3, from which it follows that the

Table 3. Results of training of the neural network using the partition coefficients of acids **1—18** in the $Bu^nOH—Li_2SO_4—H_2O$ system as examples

Acid	Normalized values			Actual values		
	Given	Prediction	Error*	Given	Prediction	Error (%)
1	−0.154	−0.1558	0.0018	450	449	0.2
2	−1	−1.0016	0.0016	86	85	1.2
3	−0.972	−0.9703	−0.0017	98	97	1.0
4	−0.069	−0.0671	−0.0019	487	487	0
5	−0.124	−0.1231	0.0009	463	463	0
6	0.101	0.1027	−0.0017	560	560	0
7	0.071	0.0695	0.0015	547	546	0.2
8	−0.229	−0.2305	0.0015	418	417	0.2
9	−0.247	−0.2489	0.0019	410	409	0.2
10	−0.264	−0.2620	−0.0020	403	403	0
11	−0.108	−0.1099	0.0019	470	469	0.2
12	0.108	0.1098	−0.0018	563	563	0
13	0.143	0.1448	−0.0018	578	579	0.2
14	0.036	0.0342	0.0018	532	531	0.2
15	−0.161	−0.1628	0.0018	447	446	0.2
16	0.391	0.3929	−0.0019	685	685	0
17	1	0.9981	0.0019	947	946	0.1
18	−0.917	−0.9188	0.0018	123	121	1.6

* Here and in Tables 4 and 6, this is the difference between the actual and predicted values.

Table 4. Prediction of partition coefficients of acids **19—23** in the $Bu^nOH—Li_2SO_4—H_2O$ system using the ANN trained ingnoring normalized M, pK_a and melting point values and with inclusion of these parameters (in parentheses)

Acid	Normalized values			Actual values		
	Given	Prediction	Error	Given	Prediction	Error (%)
19	0.433	0.5921	−0.1591	703	770	9.5
	(0.433)	(0.1834)	(0.2496)	(703)	(595)	(15.4)
20	0.967	1.0369	−0.0699	933	962	3.1
	(0.967)	(0.2827)	(0.6843)	(933)	(639)	(31.5)
21	−0.185	−0.1021	0.0829	437	472	8.0
	(−0.185)	(−0.1047)	(0.0803)	(437)	(471)	(7.8)
22	−0.761	−0.6930	0.0680	189	218	15.3
	(−0.761)	(−0.1270)	(0.6340)	(189)	(461)	(144)
23	−0.057	−0.1030	−0.046	492	472	4.1
	(−0.057)	(−0.0023)	(0.0547)	(492)	(515)	(4.7)

relative error of partition coefficient prediction is at most 2%.

Correctness of operation of the neural network was checked taking a set of partition coefficients of 2,6-dichloro- (**19**), 2,4,5-trichloro- (**20**), 4-bromo- (**21**), 6-bromo-2-hydroxy- (**22**), and 2,5-diiodobenzoic acid (**23**) that were not included in the training set (Table 4).

Data in Table 4 show that the trained neural network can predict the partition coefficients with high accuracy. Large error in the case of acid **22** (15.3%) can be explained by the lack of the input data, because the training set contained only one partition coefficient of the OH-containing acid (compound **18**).

Despite the fact that the ANN was trained ignoring the molecular weights, ionization constants, and melting temperatures, these parameters to some extent affect the *D* values. In this connection we designed yet another ANN using an analogous algorithm and used only the normalized M, pK_a, and melting point values as input signals. The results of test evaluation of this network are also listed in Table 4. Analysis of the results obtained shows that this ANN can not be used for reliable prediction of benzoic acid partition coefficients. Large error is due to the small size and low informativity of the input data array and by the lack of the melting point values for certain acids. Thus, it is impossible to estimate the efficiency of extraction using only the physicochemical characteristics of the acids under study (M, pK_a, and melting points). One should take into account specific features of the molecular structures of benzoic acid derivatives.

In order to predict a relation between the partition coefficients of benzoic acid derivatives and the extracting agent characteristics, we designed a new ANN. It was trained on the normalized values of the physicochemical characteristics and some empirical parameters of organic solvents (extracting agents) as the input parameters.

The training set was constructed for seven extracting agents using 13 parameters (Table 5) taking extraction of acid **15** as an example. The input parameters were normalized using expression (3).

To test the trained neural network, we used Bu^iOH; the corresponding normalized values of the input parameters are listed below.

M (*1*)	B.p. (*2*)	*n* (*3*)	ε (*4*)	μ (*5*)	*d* (*6*)	σ (*7*)
0.068	0.667	0.551	0.638	−1	−0.981	0.476

η (*8*)	*S** (*9*)	*f*(ε) (*10*)	*f*(*n*) (*11*)	δ (*12*)	E_t (*13*)
0.845	−0.956	0.908	0.574	−0.586	0.429

Training was carried out with a preset accuracy of ±0.002. After simplification, we obtained a three-layer, feed-forward back-propagation neural network containing 29 neurons. The number of training cycles was 5814. Assessment of significance of the input parameters (Fig. 1) showed that the results of partition coefficient prediction are mainly affected by the interfacial tension (*7*), extracting agent solubility in water (*9*), and density (*6*).

The molecular weight (*1*), boiling temperature (*2*), refractive index (*3*), viscosity (*8*), and the Lorenz—Lorentz polarizability parameter (*11*) were not used for prediction.

Table 5. Normalized values of the input parameters used for training the neural network taking extraction of acid **15** as an example

Extr-agent	M (*1*)	B.p. (*2*)	*n* (*3*)	ε (*4*)	μ (*5*)	*d* (*6*)	σ (*7*)	η (*8*)	*S* (*9*)	*f*(ε) (*10*)	*f*(*n*) (*11*)	δ (*12*)	E_t (*13*)
Pr^nOH	−0.865	0.300	0.322	0.937	−0.981	−0.963	0.713	−0.139	1	1	0.348	−0.224	1
Pr^iOH	−0.865	−0.167	−0.077	0.689	−0.907	1	−0.008	−0.263	1	0.920	−0.049	1	0.667
Bu^nOH	0.068	1	1	0.581	−1	−0.916	1	−0.001	−1	0.883	1	−0.453	0.921
Bu^tOH	0.068	−0.200	0.431	−0.113	−0.869	−1	−0.275	1	1	0.502	0.461	−0.858	−0.079
Me_2CO	−1	−1	−1	1	1	−0.993	−0.209	−1	1	0.286	−1	−0.614	−0.349
MEK	−0.066	−0.267	−0.032	0.717	1	−0.963	−1	−0.986	−0.593	0.932	0.007	−0.797	−0.492
EA	1	−0.367	−0.337	−1	−0.663	−0.639	0.729	−0.954	−0.896	−1	−0.305	−1	−1

Note. Notations: μ is the dipole moment, *d* is density, σ is the surface tension of solvent, η is the dynamic viscosity, *S* is the solubility in water, and δ is the cohesive energy density.

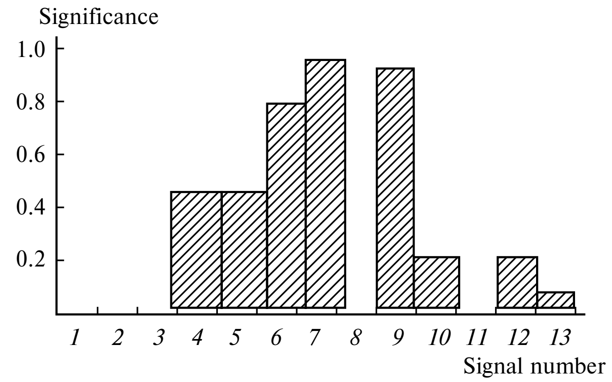

Fig. 1. Significance of the ANN input parameters (signal numbering scheme corresponds to that listed in Table 5).

Table 6. Training of neural network taking extraction of acid **15** from aqueous salt solutions as an example

Extr-agent	Normalized values			Actual values		
	Given	Prediction	Error	Given	Prediction	Error (%)
Pr^nOH	−0.426	−0.4242	−0.0018	198	198	0
Pr^iOH	−0.509	−0.5108	0.0018	181	181	0
Bu^nOH	0.807	0.8076	−0.0006	447	447	0
Bu^tOH	−0.317	−0.3189	0.0019	220	220	0
Me_2CO	−1	−0.9992	−0.0008	82	82	0
MEK	−0.351	−0.3491	−0.0019	213	213	0
EA	1	1.0011	−0.0011	486	486	0

The results of training (Table 6) show that the network designed is capable of predicting the partition coefficients of acid **15** almost faultlessly.

The trained neural network was tested using the normalized characteristics of Bu^iOH (see above). The experimentally determined partition coefficient of acid **15** in the $Bu^iOH—Li_2SO_4—H_2O$ system is 143 (*cf.* 129 for the predicted value). Thus, the relative error of prediction is 9.8%.

The results obtained showed that reliable prediction of numerical values of partition coefficients requires construction of a mathematical model that simultaneously includes the physicochemical characteristics of the benzoic acid derivatives and extracting agents.

Here, the input parameters of the neural network were the most significant pre-established parameters of the acids and extracting agents. The artificial neural network was designed using a known algorithm taking extraction of iodobenzoic acids with butyl alcohols as examples.

The normalized input parameters for six iodobenzoic acids and three extracting agents are listed in Table 7.

Training was carried out with an accuracy of ±0.002. After simplification and ANN topology optimization, we obtained a three-layer, feed-forward back-propagation neural network containing 22 neurons. The number of training cycles was 7006. The problem posed was solved using all the input parameters, with those including the substituent position in the benzene ring being the most significant (Fig. 2).

Table 7. Normalized input parameters for training the artificial neural network

Acid	Extracting agent	pK_a	Substituent position in benzene ring					ε	*d*	σ	*S*	δ
		(*1*)	2 (*2*)	3 (*3*)	4 (*4*)	5 (*5*)	6 (*6*)	(*7*)	(*8*)	(*9*)	(*10*)	(*11*)
8	Bu^nOH	−0.239	1	−1	−1	−1	−1	0.846	1	1	−1	1
	Bu^iOH	−0.239	1	−1	−1	−1	−1	1	−0.535	0.089	−0.955	0.344
	Bu^tOH	−0.239	1	−1	−1	−1	−1	−1	−1	−1	1	−1
9	Bu^iOH	0.639	−1	1	−1	−1	−1	1	−0.535	0.089	−0.955	0.344
	Bu^tOH	0.639	−1	1	−1	−1	−1	−1	−1	−1	1	−1
10	Bu^nOH	1	1	1	−1	1	−1	0.846	1	1	−1	1
	Bu^iOH	1	1	1	−1	1	−1	1	−0.535	0.089	−0.955	0.344
	Bu^tOH	1	1	1	−1	1	−1	−1	−1	−1	1	−1
11	Bu^nOH	0.600	1	−1	1	−1	−1	0.846	1	1	−1	1
	Bu^tOH	0.600	1	−1	1	−1	−1	−1	−1	−1	1	−1
12	Bu^nOH	−0.897	1	1	−1	1	−1	0.846	1	1	−1	1
	Bu^iOH	−0.897	1	1	−1	1	−1	1	−0.535	0.089	−0.955	0.344
13	Bu^nOH	−1	1	1	−1	−1	1	0.846	1	1	−1	1
	Bu^iOH	−1	1	1	−1	−1	1	1	−0.535	0.089	−0.955	0.344
	Bu^tOH	−1	1	1	−1	−1	1	−1	−1	−1	1	−1
23	Bu^nOH	−0.109	1	−1	−1	1	−1	0.846	1	1	−1	1
	Bu^iOH	−0.109	1	−1	−1	1	−1	1	−0.535	0.089	−0.955	0.344
	Bu^tOH	−0.109	1	−1	−1	1	−1	−1	−1	−1	1	−1

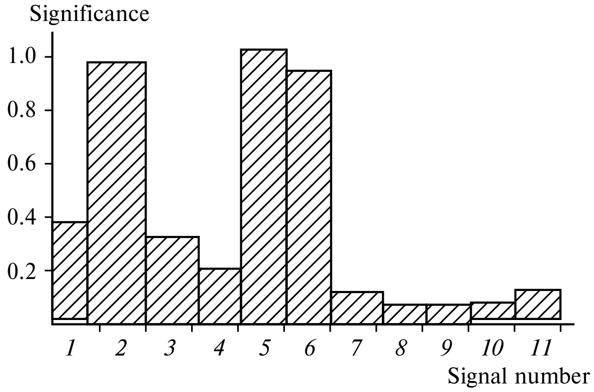

Fig. 2. Significance of the ANN input parameters (signal numbering scheme corresponds to that listed in Table 7).

Table 8. Results of testing the ANN designed

Acid	Extr-agent	Coefficient D				
		normalized		actual		
		Given	Prediction	Given	Prediction	Error (%)
9	Bu^{n}OH	–0.920	–0.8612	410	415	1.2
11	Bu^{i}OH	–0.208	–0.2367	155	152	1.9
12	Bu^{t}OH	0.849	0.8835	300	303	1.0

The results of evaluation of this neural network (Table 8) showed that it can predict the numeral values of iodobenzoic acid partition coefficients with a relative error of at most 2%.

Thus, taking the extraction of iodobenzoic acids from aqueous salt solutions with butyl alcohols as examples, we have shown that the use of the ANN approach allows quantitative information on the partition coefficients to be obtained.

This problem can be solved more accurately provided that the training set includes the physicochemical characteristics of both acids and extracting agents.

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