

Prediction of Solvent Effects on Rate Constant of [2+2] Cycloaddition Reaction of Diethyl Azodicarboxylate with Ethyl Vinyl Ether Using Artificial Neural Networks

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Artificial neural networks (ANNs), for a first time, were successfully developed for the modeling and prediction of solvent effects on rate constant of [2+2] cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether in various solvents with diverse chemical structures using quantitative structure-activity relationship. The most positive charge of hydrogen atom (q^+), dipole moment (μ), the Hildebrand solubility parameter (δ_H^2) and total charges in molecule (q_t) are inputs and output of ANN is $\log k_2$. For evaluation of the predictive power of the generated ANN, the optimized network with 68 various solvents as training set was used to predict $\log k_2$ of the reaction in 16 solvents in the prediction set. The results obtained using ANN was compared with the experimental values as well as with those obtained using multi-parameter linear regression (MLR) model and showed superiority of the ANN model over the regression model. Mean square error (MSE) of 0.0806 for the prediction set by MLR model should be compared with the value of 0.0275 for ANN model. These improvements are due to the fact that the reaction rate constant shows non-linear correlations with the descriptors.

Key Words : Artificial neural networks, Solvent effects, Reaction kinetics, Quantitative structure-activity relationship, Multi-parameter linear regression

Introduction

Solvent effects play a key role in many chemical and physical processes in solutions, therefore it has been of the highest interest to develop quantitative structure-activity relationships (QSARs) which reflect intermolecular interactions in dense media.¹⁻³ To obtain a significant correlation, it is crucial that appropriate descriptors be employed, whether they are empirical or theoretical.²⁻⁹ The linear solvation energy relationship (LSER) descriptors based on linear free energy relationship (LFER) are demonstrated to be successful in correlating a wide range of chemical and physical properties involving solute-solvent interactions as well as biological activities of compounds.³ A major step forward in applying LSER to solute-solvent interactions was the work of Kamlet and Taft.¹⁰⁻¹³ The original LSER descriptors (also called the solvatochromic descriptors) were derived from UV-Vis spectral shifts of indicator dyes.¹ Thus their ability to make a priori predictions have been somewhat limited because of their empirical origin. Based on the LSER philosophy, a set of theoretical parameters for correlating a wide variety of properties has been developed.¹³⁻¹⁹ These theoretical linear solvation energy relationship (TLSER) descriptors are summarized in Table 1. In Table 1, V_m is molecular volume of solvent that can be replaced by Hildebrand solubility parameter (δ_H^2); the values of δ_H^2 are easily available in literature for most solvents.⁸ The polarizability term (π) is obtained by dividing the polarizability volume by the

molecular volume to produce a unitless, size independent quantity, which indicates the ease with which the electron cloud may be moved or polarized. Dipole moment (μ) and total charges in molecule (q_t) terms demonstrate dipole-dipole interactions. The hydrogen-bond donating ability is divided into two components: ϵ_A (the energy difference between the ϵ_{HOMO} of water and ϵ_{LUMO} of solvent) and q^+ (the most positive charge of a hydrogen atom) of solvent molecule. Analogously, the hydrogen-bond accepting ability is divided into two components: ϵ_B (the energy difference between the ϵ_{LUMO} of water and ϵ_{HOMO} of solvent) and q^- (the most negative atomic charge) of solvent.

Various methods for constructing QSAR models have been used including multi-parameter linear regression (MLR), principal component analysis (PCA) and partial least-squares regression (PLS). In addition, artificial neural networks (ANNs) have become popular due to their success where complex non-linear relationships exist amongst data.²⁰ ANNs are biologically inspired computer programs designed to simulate the way in which the human brain processes information.^{21,22} ANNs gather their knowledge by detecting the patterns and relationships in data and learned (or trained) through experience, not from programming. Moreover, ANNs may consider not only particular molecular characteristics, but also interrelations and interdependences between mutually influencing molecular descriptors. The wide applicability of ANNs stems from their flexibility and ability to model non-linear systems without prior knowledge

Table 1. The theoretical descriptors used in MLR and ANN models^a

Symbol	Name	Definition	Units
V_m	Molecular volume	Molecular volume	\AA^3
π_i	Polarizability index	Polarizability/ V_m	none
ϵ_A	Covalent HB acidity	$0.3-0.01 (E_l-E_{hw})$	heV
q+	Electrostatic HB acidity	Maximum (+) charge on an H atom	acu
ϵ_B	Covalent HB basicity	$0.3-0.01 (E_{hw}-E_h)$	heV
q-	Electrostatic HB basicity	Maximum (-) charge on an atom	acu
q _t	Total charge	Total charge on molecule	acu
μ	Dipole moment	Dipole moment	D

^aHeV = hecto-electron volt (1 heV = 100 eV = 9.6485×10^3 kJmol⁻¹); acu = atomic charge unit; D = debye; HB = hydrogen bond; E_l = LUMO energy; E_h = HOMO energy; E_{hw} and E_{hw} refer to the LUMO and HOMO energy of water, respectively.

**Scheme 1**

of an empirical model. Neural networks do not need on explicit formulation of the mathematical or physical relationships of the handled problem. These give ANNs an advantage over traditional fitting methods for some chemical application. For these reasons in recent years, ANNs have been used to a wide variety of chemical problems such as simulation of mass spectra, ion interaction chromatography, aqueous solubility and partition coefficient, simulation of nuclear magnetic resonance spectra, prediction of bioconcentration factor and prediction of various physicochemical properties of compounds.²³⁻³⁵

Modeling of solvent effects is one of the most useful methods to obtain information about the mechanism of organic reactions. Detailed kinetic studies on cycloaddition reactions have been restricted to [2+4] and [2+3] cycloaddition reactions. Therefore, we have studied solvent effects on [2+2] cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether in various solvents using solvatochromic descriptors (Scheme 1).⁵ Because of their empirical origin of solvatochromic descriptors of solvents, their ability to make a priori predictions have been somewhat limited.³⁶

The main aim of the present work is to develop a QSAR model based on theoretical descriptors using ANNs for modeling and prediction, for a first time, solvent effects on the rate constant of [2+2] cycloaddition reaction in various solvents with diverse chemical structures. In the first step, a MLR model was constructed. Then for inspection of non-linear interactions/relations between different parameters of solvents in the model, an ANN model was generated for the prediction of the reaction rate constant and the results were compared with the experimental values.

Theory

A detailed description of theory behind neural networks has been adequately described by different researchers.^{21,22}

There are many types of neural networks designed by now and new ones are invented every week, but the behavior of a neural network is determined by transfer functions of its neurons, by learning rule, and by the architecture itself. An ANN is formed from artificial neuron or processing elements (PE), connected with coefficients (weights), which constitute the neural structure and are organized in layers. The first layer is termed the input layer, and the last layer is the output layer. The layers of neurons between the input and output layers are called hidden layers. The number of neurons in the input and output layers are defined by systems properties. The number of neurons in the hidden layer could be considered as an adjustable parameter, which should be optimized. The input layer receives the experimental or theoretical information and the output layer produces the calculated values of dependent variables. ANNs allow one to estimate relationships between input variables and one or several output dependent variables. The use of ANNs consists of two steps: "training" and "prediction". In the training phase the optimum structure, weight coefficients and biases are searched for. These parameters are found from a training data set. After the training phase, the trained network can be used to predict (calculate) the outputs from a set of inputs. There are many types of network architectures, but the type that has been most useful for QSAR/QSPR studies is the multilayer feedforward network with back-propagation (BP) learning rule.²² Information from inputs is fed forward through the network to optimize the weights between neurons. The ANN reads the input and target values in the training data set and changes the values of the weighted links to reduce the difference between the calculated output and target values. The error between output and target values is minimized across many training cycles until network reaches specified level of accuracy. If a network is left to train for too long, however, it will overtrain and will lose the ability to generalize.³³

Experimental Section

Data set. Recently, we have studied solvent effects on rate constant of [2+2] cycloaddition reaction of diethyl azodicarboxylate with ethyl vinyl ether.⁵ In the present work, the

values of $\log k_2$ in 84 various solvents calculated from correlation equation of $\log k_2$ versus dipolarity-polarizability and hydrogen-bond donor acidity of media. The theoretical descriptors have been calculated by optimizing geometries of the solvents by *ab initio* method (at the RHF/6-31G* level of the theory).³⁶ All of the calculation have been accomplished using the Gaussian 98 package.³⁷ The data set was randomly divided into two groups: a training set and a prediction set consisting of 68 and 16 molecules, respectively. The prediction set is a good representative of the training set. The training set was used for the model generation and the prediction set was used for the evaluation of generated model.

Linear correlations. Multi-parameter linear regression model was developed for prediction of solvent effects on the reaction rate constant by various descriptors. The method of stepwise multi-parameter linear regression was used to select the most important theoretical descriptors and to calculate the coefficients relating theoretical descriptors to the $\log k_2$ of the reaction. The multi-parameter linear model was generated using spss/pc software package.

Neural network generation. The specification of a typical neural network model requires the choice of the type of inputs, the number of hidden layers, the number of neurons in each hidden layer and the connection structure between the inputs and the output layers. Three-layer network with sigmoidal transfer function for neurons was designed. The initial weights were randomly selected between 0 and 1. Before training, the input and output values were normalized between 0.1 and 0.9. The number of input nodes in the neural networks was equal to the number of theoretical descriptors in the MLR model and the number of nodes in hidden layer was optimized. The optimizations of the weights and biases were carried out according to Levenberg-Marquardt algorithms for back-propagation of error, which, although requiring far more extensive computer memory, is significantly faster than other algorithms based on gradient descent.³⁸ For evaluation of the prediction power of the network, the trained ANN was used to predict $\log k_2$ of the reaction in 16 various solvents included in the prediction set. The performances of training and prediction of ANN are evaluated by individual percentage deviation (IPD) and mean square error (MSE), which are defined as follows:

$$IPD = 100 \times \left(\frac{P_i^{\text{exp}} - P_i^{\text{cal}}}{P_i^{\text{exp}}} \right) \quad (1)$$

$$MSE = \frac{1}{N} \sum_{i=1}^N (P_i^{\text{exp}} - P_i^{\text{cal}})^2 \quad (2)$$

where P_i^{exp} and P_i^{cal} are experimental and calculated values of $\log k_2$ with MLR and ANN models and N denotes number of data points.

The processing of the data was carried on Intel Pentium III processor, 800 MHz PC with 256 Mb of RAM in windows

XP environment using Matlab 6.5.³⁹ The neural networks were implemented using Neural Network Toolbox Ver. 4.0 for Matlab.⁴⁰

Results and Discussion

Multi-parameter linear correlation of $\log k_2$ of the reaction vs. the eight descriptors for 68 solvents in the training set gives equation (3).

$$\log k_2 = 6.126(\pm 0.157) + 0.774(\pm 0.272) \delta_{\text{H}}^2 + 4.312(\pm 0.434) q^+ + 0.129(\pm 0.034) \mu - 0.0578(\pm 0.027) q_{\text{t}} \quad (3)$$

$$(n = 68, r = 0.898, s.e = 0.2941, F_{4,63} = 65.92) \\ \beta_{\delta_{\text{H}}^2} = 0.222, \beta_{q^+} = 0.667, \beta_{\mu} = 0.253, \beta_{q_{\text{t}}} = -0.126$$

Effects of q^+ , μ and δ_{H}^2 on the reaction rate are higher than that of the q_{t} , because standardized coefficients of q^+ , μ and δ_{H}^2 are higher than that of the q_{t} . It is clear that rate of the reaction increases with increasing q^+ , δ_{H}^2 and μ . Because polarity of the activated complex is higher than that of the reactants of the reaction,⁵ therefore, hydrogen-bonding and dipole-dipole interactions between the activated complex and molecules of solvent are higher than that of the reactants. For this reason, the reaction rate increases with increasing solvent electrostatic acidity and dipole moment. The results are comparable with correlation of $\log k_2$ with empirical descriptors of solvents, because the second-order rate constant of the reaction increases with increasing dipolarity/polarizability and hydrogen-bonding acidity of the medium. Therefore, the increase in the rate constant was attributed to a major interaction of polar media with the activated complex relative to the reactants.

The next step in this work was the generation of the artificial neural network. ANN consists of four inputs, the same as the number of descriptors in the MLR model, and one output for $\log k_2$ of the reaction. There are no rigorously theoretical principles for choosing the proper network

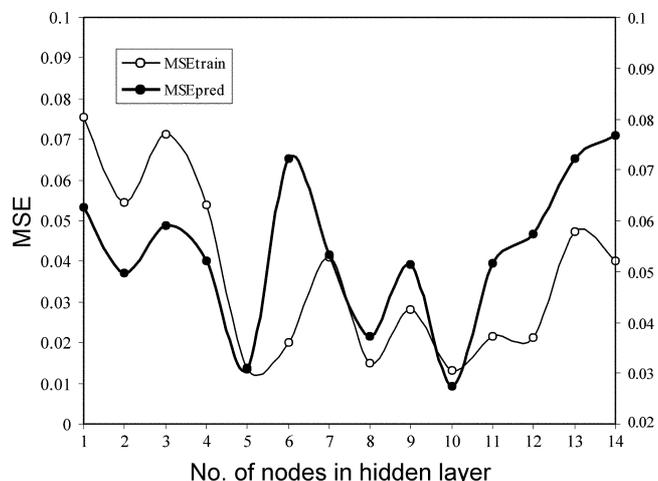


Figure 1. Plot of MSE for training and prediction sets versus the number of neurons in hidden layer.

Table 2. Experimental and calculated values of $-\log k_2$ of the reaction for training and prediction sets by multi-parameter linear regression (MLR) and artificial neural network (ANN) models along with individual percent deviation (IPD)^a

No.	Solvent	$-\log k_2$	MLR	IPD (MLR)	ANN	IPD (ANN)
Training set						
1	Hexane	5.9437	5.5094	-7.306	5.9636	0.335
2	Cyclohexane	5.767	5.4313	-5.821	5.7292	-0.66
3	Benzene	4.9245	5.1313	4.1992	4.9777	1.08
4	Toluene	5.0931	5.0835	-0.188	5.0144	-1.55
5	<i>o</i> -xylene	4.9479	5.183	4.7521	4.9957	0.966
6	<i>p</i> -xylene	5.0443	5.2554	4.1853	5.0472	0.057
7	Cumene	5.1085	5.2526	2.8202	5.0472	-1.2
8	Fluorobenzene	4.7713	4.8747	2.1671	4.9155	3.022
9	Chlorobenzene	4.6749	4.6833	0.1801	4.7076	0.699
10	Bromobenzene	4.5304	4.6738	3.1655	4.6599	2.858
11	<i>o</i> -dichlorobenzene	4.5304	4.485	-1.002	4.6216	2.013
12	1,2,4-trichlorobenzene	4.707	4.5574	-3.178	4.4947	-4.51
13	1,1,1,-trichlorobenzene	5.0604	4.6664	-7.787	5.0887	0.559
14	Chloroform	4.5633	4.4156	-3.238	4.559	-0.09
15	Bromoform	4.7032	4.3777	-6.921	4.6809	-0.47
16	1,1,2,2-tetrachloroethane	4.2413	4.3736	3.1184	4.3867	3.428
17	Methanol	3.4696	3.4384	-0.9	3.4861	0.476
18	Ethanol	3.6091	3.6416	0.8997	3.5951	-0.39
19	2-propanol	3.8356	3.8135	-0.575	3.8936	1.512
20	Butanol	3.8689	3.813	-1.445	3.9318	1.626
21	2-butanol	4.1855	3.8422	-8.201	3.8943	-6.96
22	2-methyl-2-propanol	4.5369	3.9406	-13.14	4.2988	-5.25
23	Pentanol	3.9814	3.8496	-3.312	4.0337	1.314
24	Isopentanol	3.9814	3.899	-2.071	4.1458	4.129
25	Hexanol	4.0358	3.9343	-2.516	4.1572	3.008
26	Octanol	4.0766	4.0382	-0.941	4.1879	2.73
27	Benzyl alcohol	3.3765	3.7494	11.044	3.6151	7.066
28	2-chloroethanol	3.2862	3.7795	15.01	3.3603	2.255
29	Trifluoroethanol	2.5395	3.7	45.7	2.5397	0.008
30	Allyl alcohol	3.7886	3.714	-1.97	3.9239	3.571
31	2-methoxy ethanol	3.6196	3.5121	-2.971	3.5076	-3.09
32	2-cyano ethanol	3.0434	3.3303	9.4276	3.1084	2.136
33	Dipropyl ether	5.3334	5.3048	-0.537	5.386	0.986
34	Dioxane	4.8761	5.2206	7.064	4.989	2.315
35	Tetrahydrofuran	4.8665	4.9358	1.4242	4.8654	-0.02
36	Nitromethane	4.2631	4.2398	-0.546	4.2067	-1.32
37	Nitrobenzene	4.3858	4.1371	-5.67	4.254	-3.01
38	Benzaldehyde	5.0604	4.5173	-10.73	4.746	-6.21
39	2-butanone	4.7217	4.78	1.2339	4.8213	2.109
40	Acetophenone	4.4117	4.5581	3.3187	4.5094	2.215
41	Diethyl amine	5.1641	4.5893	-11.13	5.1604	-0.07
42	Triethyl amine	5.6225	5.3909	-4.12	5.5833	-0.7
43	Benzyl amine	4.2176	4.3483	3.0982	4.2478	0.716
44	Piperidine	4.964	4.5135	-9.076	4.984	0.403
45	Tributyl amine	5.6706	5.5798	-1.601	5.6813	0.189
46	Aniline	3.6787	4.1596	13.073	3.7513	1.974
47	N-methyl aniline	4.2187	4.2708	1.2338	4.2471	0.673
48	2-chloroaniline	4.0938	3.991	-2.51	3.9522	-3.46
49	Pyridine	4.3698	4.6911	7.3527	4.5695	4.57
50	2-methyl pyridine	4.6107	4.8434	5.0467	4.6476	0.8
51	2,4-dimethyl pyridine	4.4501	4.9013	10.14	4.7016	5.652
52	2-bromo pyridine	4.1931	4.3628	4.0469	4.257	1.524
53	Morpholine	4.1839	4.3409	3.7518	4.2253	0.99
54	Pyrrolidine	4.9229	4.4614	-9.375	5.0131	1.832
55	N,N-dimethyl acetamide	4.4019	4.5153	2.5753	4.4187	0.382
56	Formamide	3.2429	2.8301	-12.73	3.2685	0.789
57	N,N-dimethyl formamide	4.4295	4.4789	1.115	4.5882	3.583

Table 2. Continued

No.	Solvent	$-\log k_2$	MLR	IPD (MLR)	ANN	IPD (ANN)
58	Methyl formate	4.8837	4.8675	-0.331	4.7245	-3.26
59	Ethyl formate	4.7873	4.8717	1.7622	4.5871	-4.18
60	Methyl ethanoate	4.9801	4.9098	-1.413	4.7627	-4.37
61	Propyl ethanoate	4.9158	4.9988	1.689	4.8635	-1.06
62	Methyl benzoate	4.5625	4.7183	3.415	4.4611	-2.22
63	Ethyl benzoate	4.6749	4.817	3.0386	4.6302	-0.96
64	Ethyl trichloroacetate	4.8676	4.8758	0.1689	4.8852	0.362
65	Diethyl sulfate	4.7713	4.7767	0.1132	4.7768	0.115
66	Sulfolane	4.3216	4.1193	-4.681	4.3464	0.574
67	Diethyl sulfide	5.0604	5.1065	0.9108	5.0137	-0.92
68	Anhydride acetic	4.5464	4.5985	1.1451	4.5733	0.592
Prediction set						
69	Octane	5.7509	5.5679	-3.183	5.9356	3.212
70	<i>m</i> -xylene	5.0122	5.19157	3.5787	5.0208	0.172
71	<i>m</i> -dichlorobenzene	4.7231	4.567	-3.305	4.5863	-2.9
72	Propanol	3.6904	3.7436	1.4418	3.6915	0.03
73	Isobutanol	4.0494	3.8347	-5.302	4.025	-0.6
74	Cyclohexanol	4.146	3.8884	-6.213	3.8149	-7.99
75	Diethyl ether	5.3816	5.2054	-3.274	5.3482	-0.62
76	Cyclohexanone	4.6749	4.7634	1.8939	4.7005	0.548
77	Butyl amine	5.2011	4.4884	-13.7	4.8296	-7.14
78	N,N-dimethyl aniline	4.5464	5.1067	12.323	4.7692	4.901
79	2-cyano pyridine	3.8398	3.9817	3.6955	3.9847	3.774
80	Pyrrole	3.603	3.8617	7.1796	3.6765	2.04
81	N,N-diethyl formamide	4.4822	4.6388	3.4932	4.6357	3.425
82	Ethyl ethanoate	4.7122	4.964	5.3432	4.8683	3.313
83	Dimethyl sulfate	4.6428	4.6064	-0.785	4.5923	-1.09
84	Dimethyl sulfoxide	4.0768	4.2956	5.3672	4.1805	2.544

^a $-\log k_2$ refers to experimental data; the rate of the reaction have been studied spectrophotometrically by monitoring the decrease in diethyl azodicarboxylate absorbance in 405 nm at 30 °C; MLR and ANN refer to multi-parameter linear regression and artificial neural network calculated values of $-\log k_2$, respectively.

architecture, so different structures were tested in order to obtain the optimal number of neurons in hidden layer and training cycle. Three-layer network with a sigmoidal transfer function were designed for ANN. Before training the network, the number of nodes in the hidden layer was optimized. In order to optimize the number of nodes in the hidden layer, several training sessions were conducted with different numbers of hidden nodes (from one to fourteen). The mean squared error of training (MSET) and prediction (MSEP) sets were plotted versus the number of iterations for different number of neurons at the hidden layer and the minimum value of MSEP was recorded as the optimum value. Plot of MSET and MSEP versus the number of nodes in the hidden layer has been shown in Figure 1. It is clear that ten nodes in hidden layer is optimum value. Then an ANN with architecture 4-10-1 was generated using the four descriptions q^+ , δ_H^2 , μ and q_1 appearing in the MLR model as inputs.

It is note worthy that training of the network was stopped when the MSEP started to increases *i.e.* when overtraining begins. The overtraining causes the ANN to loose its prediction power. Therefore, during training of the networks,

it is desirable that iterations are stopped when overtraining begins. To control the overtraining of the network during the

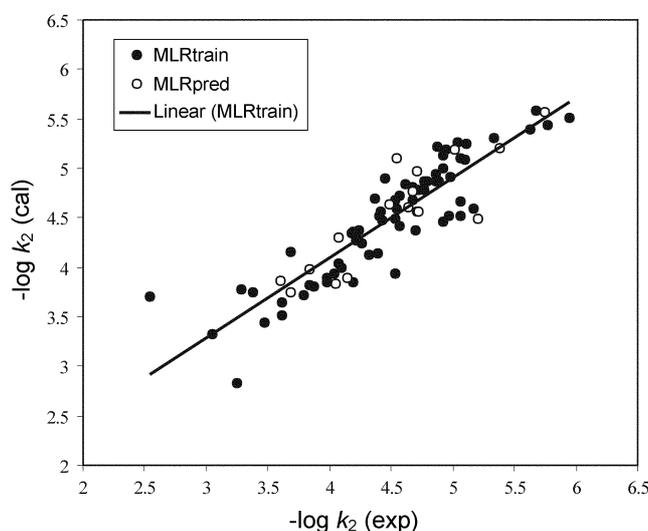
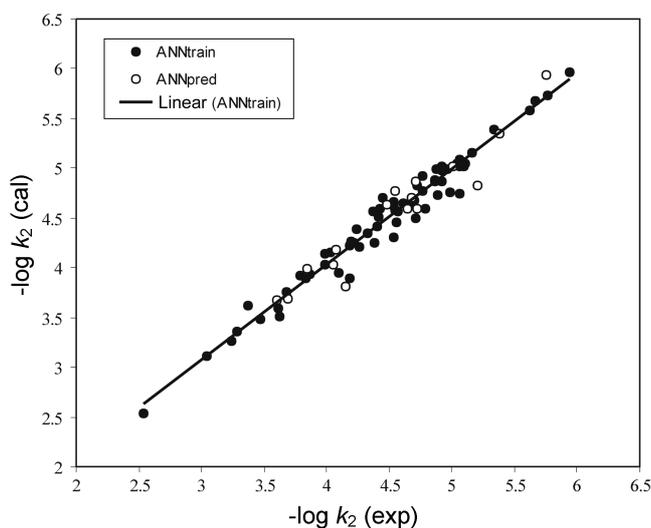


Figure 2. Plot of the calculated values of $-\log k_2$ from MLR model versus the experimental values of it.

Table 3. Comparison of statistical parameters obtained by MLR and ANN models for correlation of $\log k_2$ values of the reaction with descriptors^a

Model	R_{tot}	R_{train}	R_{pred}	MSE_{tot}	MSE_{train}	MSE_{pred}	F_{tot}	F_{train}	F_{pred}
MLR	0.801	0.898	0.880	0.0803	0.0802	0.0806	330.95	276.22	47.89
ANN	0.980	0.984	0.962	0.0159	0.0132	0.0275	2015.17	2043.16	172.48

^aSubscript train is referring to the training set, pred is referring to the prediction set, tot is referring to total data set, R is the correlation coefficient, F is the statistical F-value.

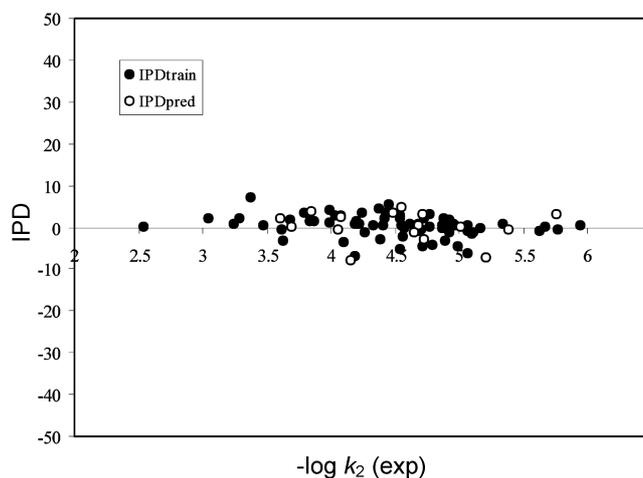
**Figure 3.** Plot of the calculated values of $-\log k_2$ from ANN model versus the experimental values of it.

training procedure, the values of MSET and MSEP were calculated and recorded to monitor the extent of the learning for various iterations. Results obtained showed that after 150 iterations the value of MSEP started to increase and overfitting began. The generated ANN was then trained using the training set for the optimization of the weights and biases. For evaluation of the prediction power of the network, the trained ANN was used to predict $\log k_2$ of the reaction for 16 various solvents included in the prediction set.

The experimental and calculated values of the $\log k_2$ for training and prediction sets along with IPD by the MLR and ANN models are given in Table 2.

Figure 2 and 3 show the plot of the MLR and ANN calculated against experimental values of $\log k_2$ of the reaction. The IPD of the ANN calculated values of $\log k_2$ are plotted against the experimental values of it (Fig. 4). The propagation of errors in both sides of zero indicates that systematic error does not exist in development of the neural network.

Table 3 compares the results obtained using the MLR and ANN models. The correlation coefficients (R), MSE and F-value of these models show the superiority of the ANN over that of the MLR model for prediction of $\log k_2$ of the reaction. The MSE of 0.0802 and 0.0806 for the training and prediction set for MLR model should be compared with the values of 0.0132 and 0.0275 for ANN model with architecture 4-10-1. It can be seen from Table 3 that although the

**Figure 4.** Plot of the IPD (individual percent deviation) for $\log k_2$ values from ANN model versus the experimental values of it.

parameters appearing in the MLR model are used as inputs for the generated ANN, the statistics shows a large improvement. These improvements are due to the fact that the reaction rate constant shows non-linear correlations with the descriptors.

Conclusions

A four-descriptor nonlinear computational neural network model has been developed for prediction of solvent effects on rate constant of [2+2] cycloaddition reaction of diethyl-azodicarboxylate with ethyl vinyl ether in various solvents with diverse chemical structures using quantitative structure-activity relationship. Comparison of the values of MSE for training and prediction sets (and other statistical parameters in Table 3) for MLR and ANN models shows superiority of the ANN model over the regression model. Mean square error (MSE) of 0.0806 for the prediction set by MLR model should be compared with the value of 0.0275 for ANN model. Since the improvement of the results obtained using nonlinear model (ANN) is considerable, it can be concluded that the nonlinear characteristics of solvent effects on the rate constant is serious.

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