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Modeling the electrophoretic mobility of analytes in binary solvent electrolyte systems in capillary electrophoresis using an artificial neural network

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Received October 26, 2004, accepted November 1, 2004

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Pharmazie 60: 656–660 (2005)

An artificial neural network (ANN) methodology was used to model the electrophoretic mobility of basic analytes in binary solvent electrolyte systems. The electrophoretic mobilities in pure solvent electrolytes, and the volume fractions of the solvents in mixtures were used as input. The electrophoretic mobilities in mixed solvent buffers were employed as the output of the network. The optimized topology of the network was 3-3-1. 32 experimental mobility data sets collected from the literature were employed to test the correlation ability and prediction capability of the proposed method. The mean percentage deviation (MPD) between the experimental and calculated values was used as an accuracy criterion. The MPDs obtained for different numerical analyses varied between 0.21% and 13.74%. The results were also compared with similar calculated mobilities which were derived from the best multiple linear model from the literature. From these results it was found that the ANN methodology is superior to the multiple linear model.

1. Introduction

Capillary electrophoresis (CE) continues to develop as an important separation technique (Altria and Elder 2004; Feng et al. 2004; Perez-Ruiz et al. 2003; Pico et al. 2003), which can offer many advantages over conventional separation techniques in chemical and pharmaceutical analyses including good resolution and high separation efficiency. The selectivity efficiency and resolution of CE methods can be altered and possibly improved using mixed solvent electrolyte systems (Sarmini and Kenndler 1997). A number of mathematical models based on the multiple linear regression (MLR) technique have previously been proposed which calculate the electrophoretic mobility of analytes in mixed solvent electrolyte systems. In a recent paper (Jouyban et al. 2003a), the available models have been reviewed and compared. It should be noted that absolute prediction of the solvent effects on the electrophoretic mobility of analytes is generally difficult due to complex and non-linear relationships between mobility and solvent composition. However, it has been shown earlier (Jouyban-Gh et al. 2000) that it is possible to predict the electrophoretic mobility at other solvent compositions in the solvent mixtures using a minimum number of experimental data.

Various equations based on the MLR method have been presented to calculate the electrophoretic mobility of analytes in binary solvent electrolyte systems. These equations have been reviewed and compared for both correlation ability and their prediction capability (Jouyban et al. 2003a). The most accurate model was the combined nearly ideal binary solvent/Redlich-Kister equation (CNIBS/R-K). The CNIBS/R-K model (Jouyban-Gh et al. 2000) is:

$$\ln \mu_m = f_1 \ln \mu_1 + f_2 \ln \mu_2 + f_1 f_2 \sum_{i=0}^{2} K_i (f_1 - f_2)^i \qquad (1)$$

where μ is the electrophoretic mobility, f is the volume fraction of the solvents in the mixture, subscripts 1, 2 and m denote solvents 1, 2 and mixed solvent electrolyte systems, respectively and K_i is the model constants. The basic model was presented for modeling of solubility of solutes in mixed solvents by Acree (1992) and its applications were extended to represent different physicochemical properties in mixed solvent systems by our group, therefore it was called Jouyban-Acree model (Jouyban et al. 2004). The accuracy of Eq. (1) was evaluated using acidic analytes in water-methanol mixtures (Jouyban-Gh et al. 2000) and basic analytes in water-methanol, water-ethanol and methanol-ethanol mixtures (Jouyban et al. 2003b). This model is capable of predicting the electrophoretic mobility of set of analytes in given binary solvent electrolyte systems within an acceptable error range (Jouyban et al. 2003c). The model is also able to correlate the effects of the solvent composition and temperature on the electrophoretic mobility of analytes using a single equation (Jouyban-Gh 2001).

Artificial neural networks (ANN's) are mathematical methods that simulate a phenomenon based on a model adopted from biological neural networks. ANNs consist of multiple layers of arranged nodes where each node in one layer is connected with another node in the next layer. The strength of a connection between two nodes is termed the weight. The theory of ANN has been reviewed by

Zupan and Gasteiger (1999) and the method has been employed in analytical areas such as CE for quantification of overlapping peaks (Bocaz-Beneventi et al. 2002) and modeling of peak shapes (Farkova et al. 1999). The multiple layer networks usually consist of three layers, which are the input, hidden and output layers. The first practical step in using ANNs is to define the nodes for input and output layers. The number of nodes in the hidden layer, learning rate, momentum, and the number of epochs are adjustable parameters, which should be optimized in the second step. In step three, the network is trained by experimental data and in the final step the network is used for prediction of unmeasured data.

There are different approaches towards training an ANN model (Zupan and Gasteiger 1999) and the most frequent one is the back-propagation (BP) technique (Svozil et al. 1997), which is often used in chemical and pharmaceutical applications. In a BP feed-forward network, a sigmoidal transfer function is used in the hidden layer and a sigmoidal and/or linear transfer function is usually employed in the output layer. In the network system proposed in this work, it was found that the sigmoid transfer function in the hidden layer and output layer gave the best performance.

The output from the j-th node with sigmoidal transfer function is:

$$\mathrm{Out_j} = \frac{1}{1 - \mathrm{e}^{-\mathrm{Net_j}}} \tag{2}$$

where $\mathrm{Net_j}$ is:

$$\mathrm{Net_j} = \sum_{i=1}^{p} \mathrm{Inp_i}\, \mathrm{W_{ij}} + \mathrm{Bias_j} \tag{3}$$

where $\mathrm{Inp_i}$ is the input to j-th node from a previous layer with p nodes and $\mathrm{W_{ij}}$ is the respective weight. The $\mathrm{Bias_j}$ is a node where its input value is equal to 1. The purpose of training such a network is to establish the numerical values of these weights. To assess the success of the process, the mean square error (MSE) is often used as a criterion for finalizing the learning process which can be calculated according to Eq. (4):

$$\mathrm{MSE} = \frac{1}{\mathrm{P} \times \mathrm{M}} \sum_{p=1}^{P} \sum_{m=1}^{M} (\mathrm{O_{pm}} - \mathrm{T_{pm}})^2 \tag{4}$$

where M is the number of neurons in the output layer and P is the number of samples. O and T are the output and target values, respectively.

In developing a CE separation method, an organic modifier may often be added to the aqueous (or non-aqueous) electrolytes in order to alter the selectivity. The most common approach when optimizing the electrolyte solvent composition is the trial and error method, but this is time-consuming and costly. However, by using designed methods, it is possible to collect only a minimum number of experimental data for a set of analytes and then predict the best solvent composition for the separation. To find the best model, the correlation ability of the models is tested using a large amount of experimental data. As a general rule, the most accurate model in this set of analysis is capable of providing the most accurate predictions.

ANN methodology can be used in data modeling/prediction studies and they have been employed for modeling of mobility data in CE (Li et al. 2002; Jalali-Heravi and Garkani-Nejad 2001, 2002; Agatonovic-Kustrin et al. 1999), for modeling of retention behavior in HPLC (Jalali-Heravi and Fatemi 1998), and also optimization of the conditions for other separation techniques (Jalali-Heravi and Parastar 2000). However ANNs have not been used in CE to model the electrophoretic mobility data in mixed solvent electrolyte systems. In this work, the accuracy of the proposed ANN was evaluated using 32 experimental data sets generated and reported by our group (Jouyban et al. 2001a, 2001b, 2001c, 2002, 2003b, 2003c, 2003d). The ANN model is also compared with that of the best MLR method.

2. Investigations, results and discussion

2.1. Mobility of an analyte in a binary mixture

All literature electrophoretic mobility data in each binary solvent system was fitted to the ANN and MLR models and then the back-calculated mobilities were used to calculate the error terms. Table 1 shows the MPD and OMPD values for correlative analysis using ANN and MLR models. The minimum and maximum MPDs for the ANN method were 0.21% and 1.65%. The values for MLR were worse and were 0.40 and 10.21%. The OMPDs and their standard deviations for ANN and MLR methods were $0.63 \pm 0.29\%$ and $2.20 \pm 2.21\%$ and the OMPD difference between two methods was significant (paired t-test, $p < 0.0005$), which shows that the ANN model was capable of providing a more accurate correlation than MLR. The IPD distribution for the evaluated methods is shown in Fig. 1, these values sorted in three subgroups, i.e. $\leq 2\%$ (less than experimental RSD values), 2–5% (acceptable error range) and $>5\%$ (unacceptable error range). ANN was proven to be superior to MLR. ANN gave a lower minimum MPD, maximum MPD, and OMPD values and also a relative frequency of 94, 6 and 0% for three IPD subgroups.

To test the prediction capability of the models, five data points with almost constant volume fraction intervals (i.e. $f_1 = 0$, 0.3, 0.5, 0.7 and 1) from each binary data set were used to train the models. The mobility at other solvent compositions was then predicted. The MPD for predictive analysis for ANN and MLR is listed in columns 7 and 8 of Table 1. The MPD for ANN varied between 0.70 to 3.64% and the corresponding range for MLR was 0.65 to 14.00%. The OMPDs and the standard deviations for ANN and MLR were $1.97 \pm 0.65\%$ and $3.41 \pm 3.24\%$, respectively and the difference between the OMPDs was

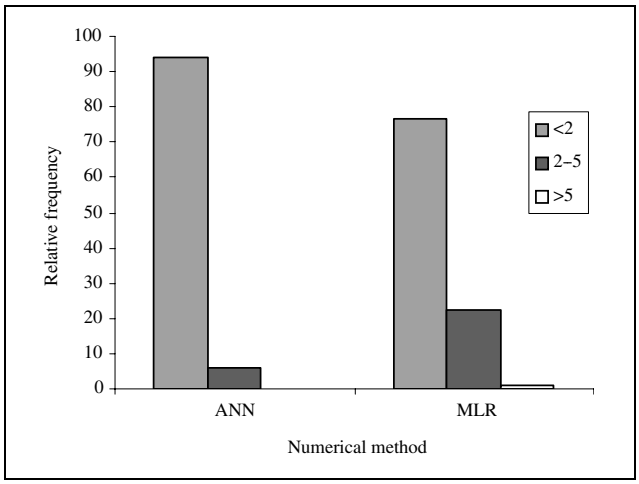

Fig. 1: Individual percentage deviation (IPD) for correlative analysis using ANN and MLR methods

Table 1: Detail of the experimental data and the mean percentage differences (MPD) for different numerical analyses

No.	Analyte	Solvent system	N[a]	MPD[b] MLR	MPD[b] ANN	MPD[c] MLR	MPD[c] ANN	MPD[d] MLR	MPD[d] ANN	Reference
1	Labetalol	Water-methanol	13	2.03	0.40	2.80	1.98	6.14	7.26	Jouyban et al. (2003b)
2	Alprenolol	Water-methanol	13	1.98	0.83	2.72	2.52	10.08	5.47	Jouyban et al. (2003d)
3	Atenolol	Water-methanol	13	1.58	0.43	2.15	1.93	1.45	1.04	Jouyban et al. (2003b)
4	Practolol	Water-methanol	13	1.18	0.24	1.55	1.14	1.37	1.19	Jouyban et al. (2002)
5	Timolol	Water-methanol	13	1.55	0.43	1.89	2.16	3.22	3.23	Jouyban et al. (2002)
6	Propranolol	Water-methanol	13	2.98	1.65	4.32	3.64	3.19	5.76	Jouyban et al. (2002)
7	Labetalol	Water-ethanol	11	10.21	0.34	14.00	2.16	18.52	10.79	Jouyban et al. (2003b)
8	Alprenolol	Water-ethanol	10	5.11	0.63	8.23	2.77	7.71	3.86	Jouyban et al. (2003d)
9	Atenolol	Water-ethanol	10	4.27	0.65	7.08	2.59	9.95	2.23	Jouyban et al. (2003b)
10	Practolol	Water-ethanol	10	4.51	0.53	7.51	2.27	10.78	3.88	Jouyban et al. (2002)
11	Timolol	Water-ethanol	10	6.50	0.35	9.85	1.39	9.28	4.35	Jouyban et al. (2002)
12	Propranolol	Water-ethanol	10	6.08	0.62	9.38	2.65	9.21	5.66	Jouyban et al. (2002)
13	Labetalol	Methanol-ethanol	13	0.82	0.97	1.20	1.39	6.35	4.33	Jouyban et al. (2003b)
14	Alprenolol	Methanol-ethanol	13	1.02	0.64	1.45	1.94	1.29	1.37	Jouyban et al. (2003d)
15	Atenolol	Methanol-ethanol	13	0.95	1.12	1.43	1.77	4.53	6.10	Jouyban et al. (2003b)
16	Practolol	Methanol-ethanol	13	0.86	0.83	1.13	1.19	4.10	3.01	Jouyban et al. (2002)
17	Timolol	Methanol-ethanol	13	1.21	0.60	1.66	1.79	3.84	4.85	Jouyban et al. (2002)
18	Propranolol	Methanol-ethanol	13	1.13	0.71	1.78	1.77	2.11	2.79	Jouyban et al. (2002)
19	Propranolol	Water-methanol	13	1.15	0.71	2.11	2.08	1.20	1.33	Jouyban et al. (2001b)
20	Timolol	Water-methanol	12	1.18	0.73	2.72	2.16	2.00	1.87	Jouyban et al. (2001b)
21	Atenolol	Water-methanol	12	1.35	0.76	2.77	2.66	1.40	1.54	Jouyban et al. (2003c)
22	Alprenolol	Water-methanol	13	1.06	0.56	1.80	2.10	1.93	2.70	Jouyban et al. (2003c)
23	Acebutalol	Water-methanol	13	1.12	0.84	1.73	2.16	1.44	1.62	Jouyban et al. (2001b)
24	Labetalol	Water-methanol	12	1.22	0.79	1.95	1.50	3.78	2.22	Jouyban et al. (2003c)
25	Metoprolol	Water-methanol	13	1.15	0.84	1.95	1.93	1.50	1.61	Jouyban et al. (2003c)
26	Nadolol	Water-methanol	11	0.75	0.21	1.44	1.44	1.71	1.46	Jouyban et al. (2001c)
27	Oxprenolol	Water-methanol	11	0.77	0.49	1.51	1.65	3.07	3.00	Jouyban et al. (2001c)
28	Pindolol	Water-methanol	11	0.50	0.33	1.01	1.16	0.98	1.81	Jouyban et al. (2001c)
29	Monomethyl-amine	Water-methanol	11	0.40	0.29	0.65	0.70	10.32	10.46	Jouyban et al. (2001a)
30	Dimethyl-amine	Water-methanol	11	0.58	0.56	1.05	0.99	4.37	8.04	Jouyban et al. (2001a)
31	Diethylamine	Water-methanol	11	4.08	0.75	6.39	3.34	16.28	13.74	Jouyban et al. (2001a)
32	Triethylamine	Water-methanol	11	1.16	0.26	1.86	2.12	3.12	13.52	Jouyban et al. (2001a)
			OMPD S.D.	2.20 ± 2.21[e]	0.63 ± 0.29[e]	3.41 ± 3.24[f]	1.97 ± 0.65[f]	5.19 ± 4.51[g]	4.44 ± 3.52[g]	

[a] N is the number of data points in each set
[b] All data points in each binary set were used to train the models and MPD values were computed using back-calculated mobilities
[c] Five data points with nearly constant f1 intervals from each binary set were used to train the models and mobility at other solvent compositions were predicted. The number of data points for this analysis was N-5
[d] All data points for different drugs in a given binary mixtures (except one data set) were used as training set and then mobility of the excluded data set predicted using trained model. As an example, the electrophoretic data of sets 2–6 was used as training set and the mobility of labetalol in water-methanol mixtures were predicted and then MPD value was computed. The number of data points for this analysis is N-2
[e] OMPD difference between MLR and ANN is statistically significant (paired t-test, $p < 0.0005$)
[f] OMPD difference between MLR and ANN is statistically significant (paired t-test, $p < 0.01$)
[g] OMPD difference between MLR and ANN is not statistically significant (paired t-test, $p > 0.23$)

Table 2: Correlation ability of MLR and ANN methods for the mobility of a given analyte in different binary solvent systems

Method Drug	Set numbers in Table 1	N	Maximum IPD[a]	MPD[a]	S.D. % of MPD[a]
MLR:					
Labetalol	1, 7, 13	37	61.46	22.17	19.69
Alprenolol	2, 8, 14	36	61.24	20.60	18.52
Atenolol	3, 9, 15	36	41.45	15.44	13.77
Practolol	4, 10, 16	36	41.98	15.70	13.69
Timolol	5, 11, 17	36	54.23	19.49	17.13
Propranolol	6, 12, 18	36	59.01	16.77	15.48
			OMPD	18.36	
ANN:					
Labetalol	1, 7, 13	37	2.81	1.02	0.68
Alprenolol	2, 8, 14	36	8.79	2.97	2.33
Atenolol	3, 9, 15	36	6.23	1.96	1.47
Practolol	4, 10, 16	36	4.17	0.88	0.83
Timolol	5, 11, 17	36	8.39	2.02	1.98
Propranolol	6, 12, 18	36	9.41	1.67	1.77
			OMPD	1.75	

[a] All data points for different drugs in binary mixtures were used to train the models, and the back-calculated mobilities were employed to compute IPD, MPD and OMPD values

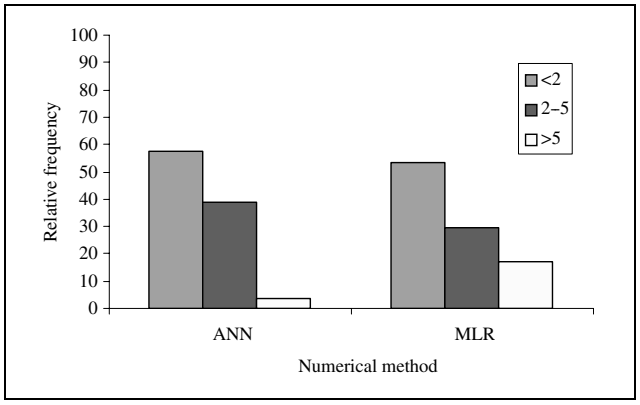

Fig. 2: Individual percentage deviation (IPD) for predictive analysis using ANN and MLR methods

statistically significant (paired t-test, $p < 0.01$). This result showed that the ANN model could provide more accurate predictions when five experimental data points were employed as a training set. The IPD distributions for both methods are shown in Fig. 2. The relative frequency of IPD >5% for the ANN method was 3.6% whereas the corresponding value for MLR was 17.1%.

2.2. Mobility of a beta-blocker in different binary solvent mixtures

It is suggested that the electrophoretic mobility of an analyte in different binary solvent systems could provide useful information for an analyst. It is proposed that the data would be especially useful in method development when the mobility of an analyte in different solvent systems could be electronically calculated. In this case the electrophoretic mobility of an analyte under the same analytical conditions and at the same electrolyte concentrations in different solvent systems was used to compare the ability of the methods considered in this study and back-calculated mobilities were used to compute MPD values. The details of the sets, the number of data points, maximum IPD, MPD and its standard deviation are shown in Table 2. Maximum IPD for ANN and MLR methods were 9.41 and 61.46%, respectively. MPDs obtained were in the range of 0.88 to 2.97% for ANN and 15.44 to 22.17% for MLR and the OMPDs were 1.75 and 18.36%, respectively for ANN and MLR methods. These findings indicated that the ANN method is better able to correlate such mobility data than the MLR method.

2.3. Mobility of a set of analytes in a given binary mixture

In pharmaceutical industry, a large number of chemically/pharmacologically related compounds are synthesized, or extracted from natural sources, to evaluate their biological activities. During this period, the development of an appropriate analytical method to measure these compounds is a priority. If a method was available to calculate the electrophoretic mobility of an analyte under given analytical conditions, this would be useful for the analyst in speeding up the method development. It is suggested that the ANN and MLR methods both possess the capability to generate this information.

All data points for set of analytes in a given binary solvent system under the same analytical conditions but at different solvent compositions were used to train the models. Mobilities were then back-calculated and employed to compute IPD, MPD and OMPD values. The OMPD values for ANN and MLR were 2.51% and 4.61%, respectively (for details see Table 3). In another set of analyses, one of the data sets was excluded during the training process to test the prediction capability of the methods. The mobility of the excluded data set was then predicted using the trained models. The MPD values for the predicted data using ANN and MLR are listed in columns 9 and 10 of Table 1. The MPDs for ANN varied between 1.04–13.74% and for MLR varied from 0.98–16.28%. The OMPD and its standard deviation for ANN and MLR methods was $4.44 \pm 3.52\%$ and $5.19 \pm 4.51\%$, respectively, and there was no significant difference between the OMPDs.

2.4. Conclusions

Artificial neural networks (ANN) were successfully employed to model the electrophoretic mobility of basic analytes in various binary solvent electrolyte systems. Both solute mobilities in pure solvent electrolytes and the volume fractions of the solvents in mixtures were used as input data. The electrophoretic mobilities in mixed solvent buffers were employed as the output of the network. The mean percentage deviation (MPD) between the experimen-

Table 3: Correlation ability of MLR and ANN methods for the mobility of set of analytes (with similar structure, pK_a, molecular weight etc) in a given binary systems

Method Solvent system	Set numbers in Table 1	N	Maximum IPD[a]	MPD[a]	S.D. % of MPD[a]
MLR:					
Water-methanol	1–6	78	19.26	3.68	4.86
Water-ethanol	7–12	61	39.10	9.69	9.02
Methanol-ethanol	13–18	78	9.94	3.14	2.70
Water-methanol	19–28	121	6.94	1.78	1.63
Water-methanol	29–32	44	25.88	6.51	6.39
			OMPD	4.61	
ANN:					
Water-methanol	1–6	78	11.88	2.59	2.28
Water-ethanol	7–12	61	22.32	2.13	3.34
Methanol-ethanol	13–18	78	10.27	1.66	1.56
Water-methanol	19–28	121	4.81	1.25	0.98
Water-methanol	29–32	44	18.95	4.94	3.96
			OMPD	2.51	

[a] All data points for different drugs in binary mixtures were used to train the models, and the back-calculated mobilities were employed to compute IPD, MPD and OMPD values

tal and calculated values was used as an accuracy criterion. The MPDs obtained for different numerical analyses varied between 0.21% and 13.74%. The results were also compared with similar calculated mobilities which were derived from the best multiple linear (MLR) model, i.e. Eq. (1), from the literature. The predicted data from the ANN methodology proved more accurate when compared with MLR. ANN calculations are considered simple and straightforward and the required software is available. It is therefore concluded that the use of ANN methodology is an efficient and effective tool for both data modeling and prediction and therefore ANN can be recommended for method optimisation studies in CE.

3. Experimental

Details of experimental mobility data (Jouyban et al. 2001a, 2001b, 2001c, 2002, 2003b, 2003c, 2003d) reported by the authors are shown in Table 1. Data set numbers 1–18 were collected using a 37 cm (30 cm effective length) $\times$ 75 μm I.D. fused silica capillary. The electrolyte was 80 mM sodium acetate buffer containing different concentrations of water, methanol and ethanol. The applied voltage was 25 kV. Temperature was 25 °C and the wavelength was 214 nm. For set numbers 19–28 and 29–32 the analaytical conditions were the same as above. For sets 19–28 buffer concentration was 104 mM sodium acetate buffer and the applied voltage was 20 kV. The corresponding conditions for aliphatic amines (sets numbers 29–32 in Table 1) were sodium acetate (20 mM) + imidazole (10 mM) and 8 kV.

All ANN calculations were carried out using MATLAB 6.1 (MathWorks, Natick) with the mathworks Neural Network Toolbox (MathWorks, Natick). The other calculations and statistical tests were performed using SPSS software (SPSS, Chicago).

The first stage was to train the network, and initially the input and target values were normalized between 0.1 and 0.9. The volume fraction of solvent 1, and the solute electrophoretic mobilities in pure solvents 1 and 2 were used as inputs. The mobilities of the same solutes in mixed solvents were used as outputs. The number of neurons in the hidden layers, values of learning rate, momentum and number of epochs were optimized. Different numbers of neurons in the hidden layer (from 1 to 10) were tested at an arbitrary learning rate and momentum, and 10000 iterations. The number of neurons in the hidden layer which gave the minimum value of MSE was selected as the optimum number. Then, learning rate and momentum were optimized in a similar way. Optimum model values of three neurons in hidden layer, a learning rate of 0.1 and a momentum of 0.8 were selected. To ensure that the global optimum had been reached, and that it was not a local optimum, the algorithm was run from different starting values of initial weights. Each set of starting values resulted in almost the same set of optimum values, confirming that a global optimum had been found.

To evaluate the accuracy of the proposed numerical methods, the experimental mobility values were fitted into the models and back-calculated and/or predicted mobilities were used to calculate the mean percentage differences (MPD) between experimental and calculated μ_m values and considered as an accuracy criterion. MPD was defined as:

$$\mathrm{MPD} = \frac{100}{\mathrm{N}} \sum \left| \frac{\mu^{\mathrm{Cal.}} - \mu^{\mathrm{obs.}}}{\mu^{\mathrm{obs.}}} \right| \qquad (5)$$

where N is the number of experimental data points. The overall MPD (OMPD) is defined as the sum of the MPDs divided by the number of data sets considered in the calculations. The MPD and OMPD give an overall indication of the accuracy of the error and in order to detect the range of individual errors, the individual percentage deviation (IPD) was also calculated by:

$$\mathrm{IPD} = 100 \left| \frac{\mu^{\mathrm{Cal.}} - \mu^{\mathrm{obs.}}}{\mu^{\mathrm{obs.}}} \right| \qquad (6)$$

Acknowledgement: The financial support from Research Affairs of the University of Tabriz is gratefully acknowledged.

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