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Molecular Connectivity Index Based Aqueous Solubility Prediction Model

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Correlations for estimation of the aqueous solubility (log Sw) of organic compounds are proposed. The MCI based models proposed are predictive and require only zeroth- and first-order connectivity indices in the calculations. The calculated results of the models for different data sets are comparable to those from the existing models. Because the new models do not require any experimental physico-chemical properties in the calculation, they can be used in cases where it is too dangerous, costly, time consuming or impossible to measure the physico-chemical properties. Furthermore, the obtained equations can be easily applied in computer-aided molecular design for its simplicity and linear formula.

Key Words: Molecular connectivity index, Aqueous solubility, QSPR model, Computer aided molecular design, Molecular modeling.

INTRODUCTION

Computer-aided molecular designs become more and more important due to the need to develop new chemical and pharmaceutical products quickly and more inexpensively in recent years. Property models provide the relationship between the molecular structure and the property value and play a critical role in CAMD. The property models used in CAMD require not only the high predictive accuracy but also the simple and easy-calculating of the correlation. In this article, a model of prediction of aqueous solubility of organic chemicals based on molecular connectivity indices is proposed that possesses the above two criteria.

Aqueous solubility is a particularly important physico-chemical property of organic chemicals that plays a significant role in various physical and biological processes, especially in drug transport and environment impact. Comparing with the time-consuming experimental procedures to determine aqueous solubility directly, reliable computational methods to predict aqueous solubility are more welcome in today's research[1–3].

There are a large number of successful prediction methods, which can be divided into two main groups. The first approach is to build model from more easily measured physico-chemical properties[4–9], such as melting point, boiling point, molar volume, log P, etc. The other method is based on the information

from the molecules of organic chemicals which can be further divided into two classes: one is group contributions method[5, 10, 11] and the other is QSPR approach[12–28]. In order to develop models which can be used in CAMD, only simple QSPR approaches can be selected for they do not need to know which group is present in advance. Molecular connectivity index is chosen to build a simple model with high accuracy in this work.

Theoretical background

The molecular connectivity indices which were proposed 30 years ago have been successfully used in the correlation of various physio-chemical properties of organic substances[29]. In the previous works, correlations of aqueous solubility using molecular connectivity and other descriptors have been studied[13, 20] and the possibility of molecular connectivity indices in modelling aqueous solubility has been demonstrated. In this study, we use different indices compared to the already existing models to correlate the aqueous solubility and obtain the simpler model with the same or higher accuracy. Since molecular connectivity indices can be calculated directly from the molecular structure, the molecular connectivity index based aqueous solubility models are predictive and can be effectively used in computer-aided molecular design[30].

The general expression for the mth-order simple and valence connectivity index can be expressed as follows:

$$ {}^{m}\chi_k^p = \sum_{j=1}^{n_m} \prod_{i=1}^{m+1} (\delta_i^p)_j^{-0.5} \qquad (1) $$

where m is the order of the connectivity index. In this work, both zeroth- and first-order connectivity indices are employed as structural descriptors; k denotes a contiguous path type of fragment, which is divided into paths (P), clusters (C), path/clusters (PC) and chains (cycles)(CH); in this work, it does not involve the clusters (C) and the path/clusters (PC); p denotes connectivity index, simple or valence or other types; nm is the number of the relevant paths.

Data sets and methods

Two data sets of solubility were adopted to testify that molecular connectivity index based aqueous solubility with only zeroth- and first-order connectivity indices as input parameters can be obtained with satisfying results. The first data set is completely taken from Eduardo's research on solubility of chlorinated hydrocarbons[14], the other data set is taken from Kuhne's research on group contribution methods to estimate water solubility of organic chemicals[10]. Both zeroth- and first-order connectivity indices are first calculated using the vertex adjacency matrix. The detailed equations for the simple and valence molecular connectivity indices for zeroth and first order are shown in eqns. 2–5:

$$ {}^{0}\chi = \sum_{i=1}^{n} \frac{1}{\sqrt{\delta_i}} \qquad (2) $$

$$^{0}\chi^{v} = \sum_{i=1}^{n} \frac{1}{\sqrt{\delta_i^v}} \quad (3)$$

$$^{1}\chi^{v} = \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \frac{1}{\sqrt{\delta_i \delta_j}} \quad (4)$$

$$^{1}\chi^{v} = \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \frac{1}{\sqrt{\delta_i^v \delta_j^v}} \quad (5)$$

The simple connectivity index (δ) which is defined as the number of non-H atoms to which a given non-H atom is bonded and the valence connectivity index (δ^v) which is defined as the eqn. (6) used in this study are summarized in Table-1.

$$\delta^v = \frac{Z^v - N_h}{Z - Z^v - 1} \quad (6)$$

TABLE-1
CONNECTIVITY INDEX (δ AND δ^v) VALUES OF GROUPS USED IN THIS WORK

Group	δ	δ^v	Group	δ	δ^v
—CH_3	1	1	=CH_2	1	2
—CH_2—	2	2	=CH—	2	3
>CH—	3	3	=C<	3	4
>C<	4	4	—Cl	1	7/9

An example of the computation of connectivity indices is given in Fig. 1 and the code of the program for calculation of the molecular connectivity indices and the results on the two data sets are available upon request.

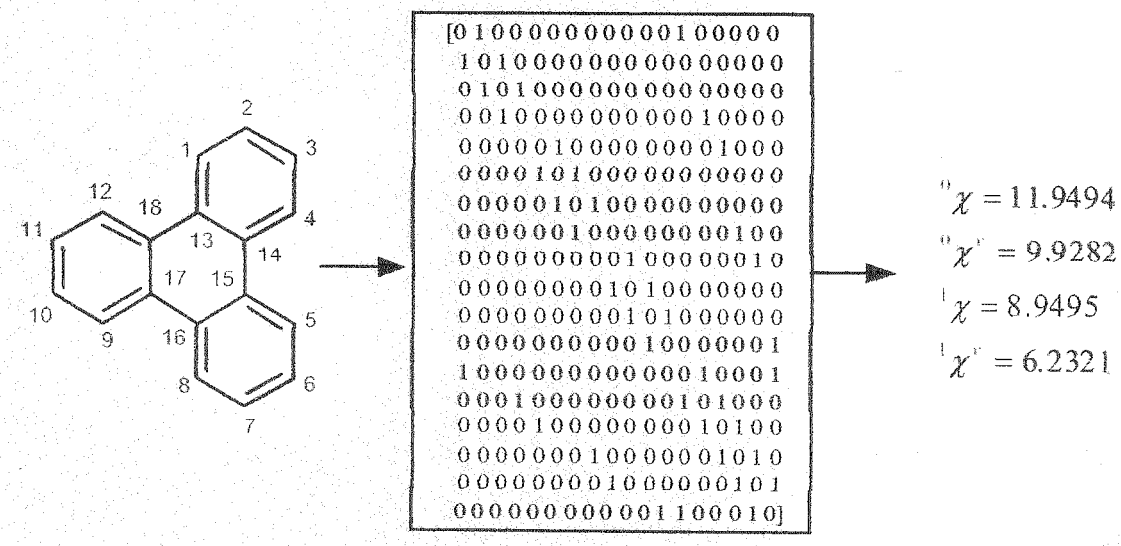

Fig. 1. Computation of connectivity indices of triphenylene (CAS No. 217-59-4)

RESULTS AND DISCUSSION

Case study 1

In the first case study, by fitting the experimental data of the 50 chlorinated hydrocarbons as shown in Table-2, the following general correlation which can be called MCI model was obtained in this work:

$$\log Sw = 1.3668 - 0.0236\ {}^{0}\chi - 1.251\ {}^{0}\chi^{v} - 1.3164\ {}^{1}\chi + 2.6483\ {}^{1}\chi^{v} \quad (7)$$

$$R^2 = 0.9550, F = 238.52.$$

The results calculated with equation (7) are listed in Table-2. To compare the accuracy (AAE for short) of the proposed model, the average absolute error is also calculated. The AAE for the MCI model of data set 1 is 0.396. This value is similar to 0.317 for the XY-CPSA model, indicating that the MCI model has comparable accuracy to the existing XY-CPSA model. The comparison of the experimental *vs.* calculated aqueous solubilities for the two models are shown in Figs. 2 and 3.

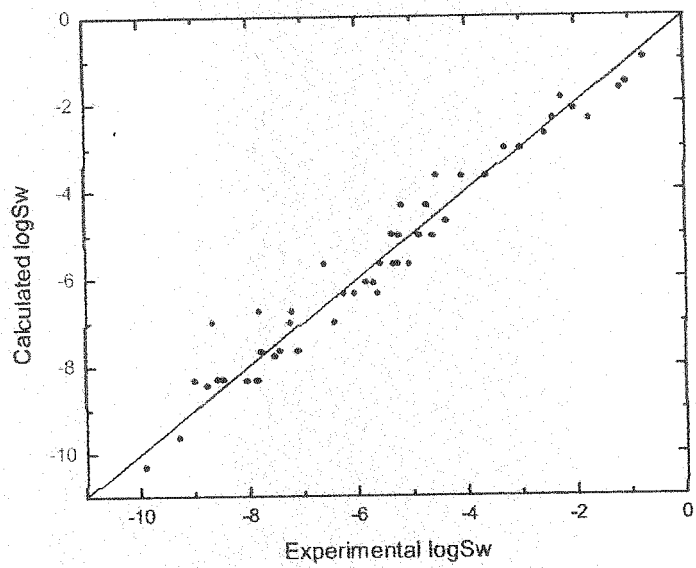

Fig. 2. Calculated values *vs.* experimental values of log Sw for the MCI model of data set 1

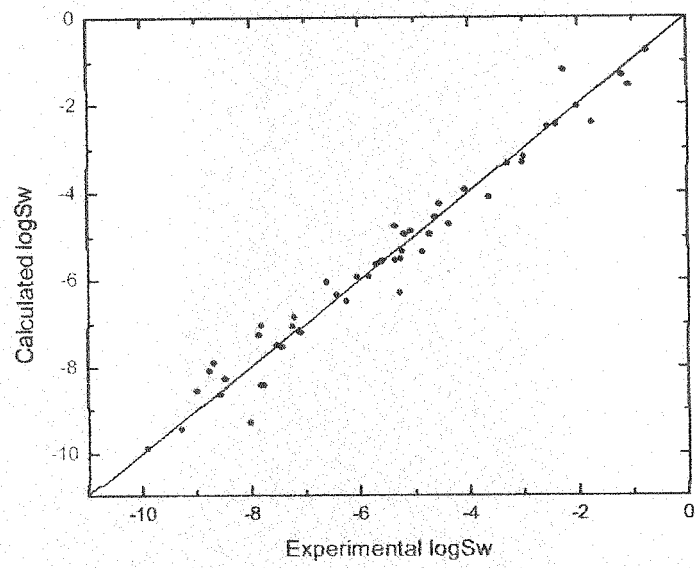

Fig. 3. Calculated values *vs.* experimental values of log Sw for the XY-CPSA model of data set 2

TABLE-2
CALCULATED RESULTS OF THE MOLAR AQUEOUS SOLUBILITY FOR 50 CHLORINATED HYDROCARBONS

No.	CAS No.	Chlorinated hydrocarbons	log Sw		
			exp	MCI	XY-CPSA
1.	75-09-2	Dichloromethane	–0.74	–0.97	–0.77
2.	67-66-3	Trichloromethane	–1.19	–1.69	–1.32
3.	56-23-5	Tetrachloromethane	–2.26	–1.89	–1.20
4.	79-34-5	1,1,2,2-Tetrachloroethane	–1.76	–2.38	–2.42
5.	540-59-0	1,2-Dichloroethene	–1.07	–1.52	–1.54
6.	79-01-6	Trichloroethene	–2.04	–2.15	–2.05
7.	127-18-4	Tetrachloroethene	–2.57	–2.71	–2.51
		Benzene:			
8.	108-90-7	Monochloro	–2.42	–2.37	–2.46
9.	541-73-1	1,3-Dichloro	–3.04	–3.02	–3.31
10.	95-50-1	1,2-Dichloro	–3.02	–3.03	–3.17
11.	106-46-7	1,4-Dichloro	–3.31	–3.02	–3.33
12.	120-82-1	12,4-Trichloro	–3.64	–3.68	–4.11
13.	87-61-6	1,2,3-Trichloro	–4.08	–3.69	–3.94
14.	108-70-3	1,3,5-Trichloro	–4.55	–3.67	–4.26
15.	634-66-2	1,2,3,4-Tetrachloro	–4.38	–4.70	–4.72
16.	95-94-3	1,2,4,5-Tetrachloro	–5.19	–4.34	–4.94
17.	634-90-2	1,2,3,5-Tetrachloro	–4.73	–4.34	–4.94
18.	608-93-5	Pentachloro	–5.37	–5.00	–5.56
		Dibenzo-p-dioxin:			
19.	39227-53-7	1-Chloro	–5.72	–6.10	–5.66
20.	39227-54-8	2-Chloro	–5.86	–6.09	–5.92
21.	29446-15-9	2,3-Dichloro	–7.23	–6.75	–6.83
22.	33857-26-0	2,7-Dichloro	–7.83	–6.74	–7.02
23.	39227-58-2	1,2,4-Trichloro	–7.53	–7.77	–7.50
24.	30746-58-8	1,2,3,4-Tetrachloro	–8.77	–8.43	–8.08
		Biphenyl:			
25.	12051-60-7	2-Chloro	–4.63	–5.03	–4.55
26.	2051-61-8	3-Chloro	–4.88	–5.02	–5.38
27.	2051-62-9	4-Chloro	–5.25	–5.02	–5.35
28.	2050-68-2	4,4′-Dichloro	–6.63	–5.68	–6.05
29.	34883-39-1	2,5-Dichloro	–5.27	–5.68	–5.52

No.	CAS No.	Chlorinated hydrocarbons	log Sw		
			exp	MCI	XY-CPSA
30.	33284-50-3	2,4-Dichloro	–5.29	–5.68	–6.28
31.	33146-45-1	2,6-Dichloro	–5.07	–5.69	–4.86
32.	2050-68-2	2,4′-Dichloro	–5.60	–5.68	–5.57
33.	13029-08-8	2,2′-Dichloro	–5.36	–5.69	–4.76
34.	37680-65-2	2,2′,5-Trichloro	–5.65	–6.34	–5.60
35.	35693-92-6	2,4,6-Trichloro	–6.07	–6.34	–5.93
36.	15862-07-4	2,4,5-Trichloro	–6.27	–6.34	–6.47
37.	32598-13-3	3,3′,4,4′-Tetrachloro	–8.68	–6.99	–7.90
38.	35693-99-3	2,2′,5,5′-Tetrachloro	–6.44	–6.99	–6.33
39.	33284-53-6	2,3,4,5-Tetrachloro	–7.26	–7.00	–7.04
40.	18259-05-7	2,3,4,5,6-Pentachloro	–7.78	–7.67	–8.40
41.	37680-73-2	2,2′,4,5,5′-Pentachloro	–7.44	–7.65	–7.53
42.	55312-69-1	2,2′,3,4,5-Pentachloro	–7.10	–7.66	–7.21
43.	74472-44-9	2,3,3′,4′,5,6-Hexachloro	–7.83	–8.31	–8.40
44.	55215-18-4	2,2′,3,3′,4,5-Hexachloro	–8.04	–8.32	–9.30
45.	33979-03-2	2,2′,4,4′,6,6′-Hexachloro	–8.48	–8.30	–8.26
46.	35065-27-1	2,2′,4,4′,5,5′-Hexachloro	–8.57	–8.30	–8.61
47.	38411-22-2	2,2′,3,3′,6,6′-Hexachloro	–7.86	–8.32	–7.27
48.	38380-07-3	2,2′,3,3′,4,4′-Hexachloro	–9.00	–8.32	–8.53
49.	2136-99-4	2,2′,3,3′,5,5′,6,6′-Octachloro	–9.30	–9.63	–9.45
50.	40186-72-9	2,2′,3,3′,4,4′,5,5′,6-Nonachloro	–9.93	–10.30	–9.88

Case study 2

To testify the validation of the MCI based aqueous solubility prediction model, we correlate much more substance log Sw data. In the second case study, the first 100 organic chemicals are taken from literature without intently selection. The correlation equation obtained this time is:

$$\log Sw = 0.6075 - 1.7809\ {}^{0}\chi - 1.5912\ {}^{0}\chi^{v} - 1.5702\ {}^{1}\chi + 2.5691\ {}^{1}\chi^{v} \quad (8)$$

$$R^2 = 0.9202, F = 273.73$$

The results calculated with eqn. 7 are listed in Table-3. The AAE for the MCI model of data set 2 is 0.401. This value is much lower than 0.73 for model[13] of literature which correlates 120 chemicals using different indices and is much lower than the GSE model[7] (0.64) and Klopmans methods[11] (0.71) respectively. The calculated and experimental values of log Sw are compared in Table-3 and the scatter plot is shown in Fig. 4.

TABLE-3
CALCULATED RESULTS OF THE MOLAR AQUEOUS SOLUBILITY FOR 100 COMPOUNDS

No.	CAS No.	Compounds	log Sw_exp	log Sw_cal
1.	109-66-0	Pentane	–3.18	–2.58
2.	287-92-3	Cyclopentane	–2.64	–2.56
3.	110-54-3	Hexane	–3.84	–3.22
4.	107-83-5	2-Methylpentane	–3.74	–3.10
5.	96-14-0	3-Methylpentane	–3.68	–3.14
6.	75-83-2	2,2-Dimethylbutane	–3.55	–2.94
7.	110-82-7	Cyclohexane	–3.10	–3.19
8.	96-37-7	Methylcyclopentane	–3.30	–3.12
9.	142-82-5	Heptane	–4.53	–3.85
10.	108-08-7	2,4-Dimethylpentane	–4.26	–3.63
11.	108-87-2	Methylcyclohexane	–3.85	–3.75
12.	111-65-9	Octane	–5.24	–4.48
13.	540-84-1	2,2,4-Trimethylpentane	–4.74	–4.09
14.	6876-23-9	1,2-dimethylcyclohexane	–4.30	–4.33
15.	109-67-1	1-Pentene	–2.68	–2.25
16.	109-68-2	*trans*-2-Pentene	–2.54	–2.00
17.	142-29-0	Cyclopentene	–2.10	–2.07
18.	592-41-6	1-Hexene	–3.23	–2.89
19.	691-37-2	4-Methyl-l-pentene	–3.24	–2.77
20.	110-83-8	Cyclohexene	–2.59	–2.71
21.	14686-13-6	*trans*-2-Heptene	–3.82	–3.27
22.	591-49-1	Methylcyclohexene	–3.27	–3.20
23.	111-66-0	1-Octene	–4.44	–4.15
24.	124-11-8	1-Nonene	–5.05	–4.79
25.	591-93-5	1,4-Pentadiene	–2.09	–1.92
26.	592-42-7	1,5-Hexadiene	–2.68	–2.56
27.	78-79-5	2-Methyl-1,3-butadiene	–2.03	–1.88
28.	627-19-0	1-Pentyne	–1.64	–2.14
29.	693-02-7	1-Hexyne	–2.36	–2.77
30.	628-71-7	1-Heptyne	–3.01	–3.40
31.	629-05-0	1-Octyne	–3.66	–4.04
32.	3452-09-3	1-Nonyne	–4.24	–4.67
33.	71-43-2	Benzene	–1.64	–1.86
34.	108-88-3	Toluene	–2.21	–2.38
35.	95-47-6	*o*-Xylene	–2.80	–2.89
36.	100-41-4	Ethyl benzene	–2.77	–3.11

No.	CAS No.	Compounds	log Sw_exp	log Sw_cal
37.	106-42-3	*p*-Xylene	–2.77	–2.90
38.	108-38-3	*m*-Xylene	–2.82	–2.90
39.	103-65-1	Propyl benzene	–3.37	–3.74
40.	95-63-6	1,2,4-Trimethyl benzene	–3.31	–3.41
41.	108-67-8	1,3,5-Trimethyl benzene	–3.40	–3.42
42.	526-73-8	1,2,3-Trimethyl benzene	–3.20	–3.39
43.	611-14-3	1-Ethyl-2-methyl benzene	–3.21	–3.62
44.	622-96-8	1-Ethyl-4-methyl benzene	–3.11	–3.63
45.	98-82-8	Isopropyl benzene	–3.27	–3.67
46.	496-11-7	Indane	–3.04	–3.69
47.	95-93-2	1,2,4,5-Tetramethyl benzene	–4.59	–3.91
48.	104-51-8	Butyl benzene	–4.06	–4.38
49.	105-05-5	1,4-Diethyl benzene	–3.75	–4.36
50	99-87-6	*p*-Isopropyl toluen e	–3.77	–4.19
51.	98-06-6	*t*-Butyl benzene	–3.66	–4.16
52.	538-93-2	Isobutyl benzene	–4.12	–4.26
53.	135-98-8	2-Butyl benzene	–3.89	–4.34
54.	700-12-9	Pentamethyl benzene	–4.00	–4.41
55.	538-68-1	Pentyl benzene	–4.64	–5.01
56.	2049-95-8	*t*-Amyl benzene	–4.15	–4.86
57.	1077-16-3	Hexyl benzene	–5.21	–5.64
58.	100-42-5	Styrene	–2.82	–2.85
59.	92-52-4	Biphenyl	–4.31	–4.35
60.	101-81-5	Diphenyl methane	–4.08	–4.90
61.	86-73-7	Fluorene	–5.00	–4.90
62.	103-29-7	Bibenzyl	–4.62	–5.54
63.	1730-37-6	1-Methylfluorene	–5.22	–5.41
64.	103-30-0	*t*-Stilbene	–5.80	–5.19
65.	91-20-3	Naphthalene	–3.60	–3.53
66.	91-57-6	2-Methyl naphthalene	–3.77	–4.05
67.	90-12-0	1-Methyl naphthalene	–3.70	–4.04
68.	1127-76-0	1-Ethyl naphthalene	–4.17	–4.77
69.	939-27-5	2-Ethyl naphthalene	–4.29	–4.78
70.	571-61-9	1,5-Dimethyl naphthalene	–4.74	–4.54
71.	581-40-8	2,3-Dimethyl naphthalene	–4.72	–4.55
72.	208-96-8	Acenaphthylene	–3.96	–4.36
73.	575-41-7	1,3-Dimethyl naphthalene	–4.29	–4.55
74.	571-58-4	1,4-Dimethyl naphthalene	–4.14	–4.54
75.	581-42-0	2,6-Dimethyl naphthalene	–4.89	–4.57

No.	CAS No.	Compounds	log Sw_exp	log Sw_cal
76.	83-32-9	Acenaphthene	–4.63	–4.71
77.	2131-41-1	1,4,5-Trimethyl naphthalene	–4.92	–5.05
78.	120-12-7	Anthracene	–6.35	–5.20
79.	85-01-8	Phenanthrene	–5.26	–5.19
80.	779-02-2	9-Methyl anthracene	–5.89	–5.69
81.	613-12-7	2-Methyl anthracene	–6.96	–5.71
82.	129-00-0	Pyrene	–6.19	–6.02
83.	781-43-1	9,10-Dimethyl anthracene	–6.57	–6.19
84.	206-44-0	Fluoranthene	–6.00	–6.01
85.	1732-13-4	1,2,3,6,7,8-Hexahydropyrene	–5.96	–7.16
86.	238-84-6	Benzo(a)fluorene	–6.68	–6.56
87.	243-17-4	Benzo(b)fluorene	–8.04	–6.57
88.	92-24-0	Naphthacene	–8.60	–6.86
89.	217-59-4	Triphenylene	–6.74	–6.83
90.	50-32-8	Benzo(e)pyrene	–8.19	–7.67
91.	57-97-6	7,12-Dimethylbenz(a)-anthracene	–7.02	–7.84
92.	192-97-2	Benzo(e)pyrene	–7.80	–7.66
93.	205-99-2	Benzo(b)fluoranthene	–8.23	–7.66
94.	205-82-3	Benzo(j)fluoranthene	–8.00	–7.66
95.	207-08-9	Benzo(k)fluoranthene	–8.49	–7.67
96.	56-49-5	3-Methyl cholanthrene	–7.92	–8.53
97.	53-70-3	1,2,5,6-Dibenzanthracene	–8.66	–8.51
98.	191-07-1	Coronene	–9.33	–9.33
99.	74-88-4	Iodo methane	–1.00	–0.16
100.	75-09-2	Dichloro methane	–0.63	–1.04

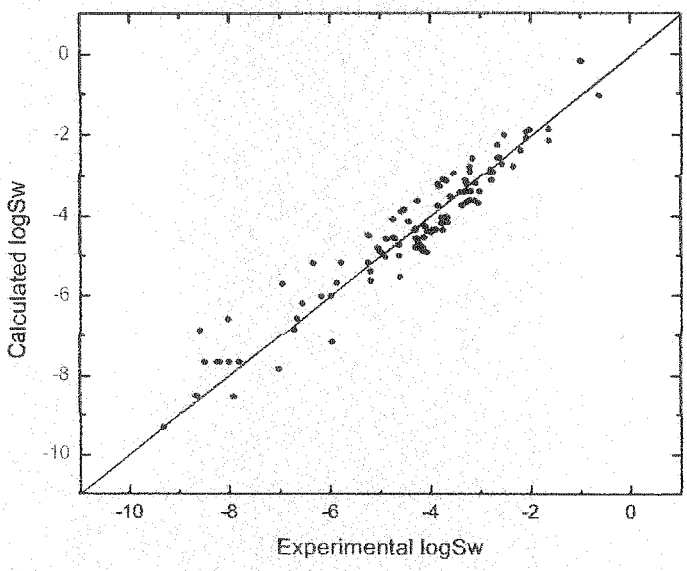

Fig. 4. Calculated values *vs.* experimental values of log Sw for the MCI model

Conclusions: Molecular connectivity index based aqueous solubility prediction models have been developed to predict the aqueous solubility of various organic chemicals. The equations, containing only zeroth- and first-order connectivity indices, predict the solubility with satisfying coefficients. The obtained equations can be easily used in computer-aided molecular design especially in drug design[15, 31] for their accuracy, simplicity and linear formula[30].

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