

## Aqueous Solubility Analysis of Polycyclic Aromatics and Halobenzenes: Influence of Solubility parameter and Molar Volume

D. SATYANARAYANA\*, R. NARAYANA CHARYULU,  
B.G. NAGAVI† and P. GUNDU RAO‡  
*N.G.S.M. Institute of Pharmaceutical Sciences  
Derlakatte, Mangalore-574 160, India*

The aqueous solubility data of non-electrolytes, polycyclic aromatic compounds and halobenzenes are analysed in terms of different physico-chemical properties of the solutes. Solubility parameter and molar volume are estimated using Fedors fragmental constants, while melting point is readily available in the literature. These properties are implicated in the prediction of aqueous solubility and regression equations were obtained. Though the approach is empirical, it permits the estimation of aqueous solubility of untested solutes.

### INTRODUCTION

The aqueous solubility of drugs has attracted the attention of chemists because of its importance in design of dosage forms, absorption, toxicity, pollution and disposal of effluents. Water solubility ( $S_w$ ) and related parameters of organic non-electrolytes are well correlated by the combination of molecular volume ( $V$ ) and a selection of solvatochromic parameters.<sup>1-4</sup> They proposed the equation:

$$\log S_w = a_1 + a_2V + a_3\pi^* + a_4\beta + a_5 (\text{mp}-25) \quad (1)$$

where  $\pi^*$  and  $\beta$  are solvatochromic parameters, mp is the melting point ( $^{\circ}\text{C}$ ) and terms  $a_1$  to  $a_5$  are constants. The  $\pi^*$  term is a measure of dipolarity/polarizability and the  $\beta$  parameter reflects the hydrogen bond basicity. The partition coefficients (PCs) were correlated with the aqueous solubility of crystalline solids and liquid solutes.<sup>5,6</sup> A wide variety of organic compounds (nearly 1400 compounds) were analysed obtaining better correlation. They proposed the theoretical equation.<sup>7</sup>

$$\log S_w = c_1 \log K_{ow} + c_2 (\text{mp}-25) + c_3 \quad (2)$$

where  $K_{ow}$  is the octanol-water partition coefficient (PC) of the solute. They proposed the coefficients  $c_1 = -1$ ;  $c_2 = -0.01$  and  $c_3 = 0.8$  from thermodynamic considerations. One of the advantages of selecting the PC for developing regression equations are the ease with which it can be calculated from the fragmental constant  $f$  developed by Nys and Rekker.<sup>8</sup>

† J.S.S. College of Pharmacy, Mysore-570 015 (Karnataka), India.

‡ Divi's Laboratories Ltd., Divi Towers, Ameerpet, Hyderabad-500 016, India.

In this paper, we reported the usefulness of solubility parameter  $\delta_2$  and molar volume  $V_2$  in predicting the aqueous solubility. The subscript 2 indicates the solute. Both these values can be calculated by using only the Fedors fragmental constants for the compounds.<sup>9</sup> The inclusion of melting point term in the calculations improved the results considerably. Polycyclic aromatics and halobenzenes of environmental interest were chosen for the current analysis, as these were studied earlier for structural correlations.<sup>2,3,5</sup>

## EXPERIMENTAL

The molar volume and solubility parameters of the compounds were calculated using the software developed by us. The aqueous solubility, partition coefficients and melting points for the compounds included in this work have been extracted from earlier reports.<sup>5</sup> Partition coefficient data was used for comparing with the presently proposed analysis. The mp's of liquids were taken as 25°C. This assumption is reasonable because for liquids the term (mp-25) will become zero in the equations. Solubility is expressed in moles/L. Multiple regression analysis of the data was performed using Lotus 1-2-3 (3.0) package on a PC/AT. Fisher F ratio was calculated using standard statistical procedure.<sup>10</sup> All other statistical parameters are directly given by the Lotus package.

## RESULTS AND DISCUSSION

The solubility parameter  $\delta$  is an intrinsic physico-chemical property of a substance. Though  $\delta$  is known as cohesive energy density, it is also useful in understanding solute-solvent interactions and the behaviour of solutions. Some efforts were made to use  $\delta$  as an indicator to explain the aqueous behaviour of non-electrolytes, although the final result was expressed in terms of PC.<sup>11</sup> Appropriate thermodynamic treatment (theoretical) gave an expression which contains five independent variables. These variables were incorporated to get a regression equation. Since their thermodynamic treatment yielded five variables, in the present study we have chosen an empirical approach to use fewer variables. Moreover, such an empirical approach provides insight to review the thermodynamic equations once again.

Solubility parameters of compounds can be estimated by the additive atomic and group contributions for the energy of vaporization and molar volume.<sup>9</sup> We have used here Fedors constants because these are precise and obtained after extensive analysis of earlier methods.<sup>12,13</sup>

### Predictions on polycyclic aromatic compounds

Table 1 includes the data required for the regression analysis. Solubility parameter and molar volume were obtained by computation. Correlations were attempted between the aqueous solubility and solubility parameter  $\delta_2$ . The regression equation

$$\log S_w = -1.7655 \delta_2 + 13.5696 \quad (3)$$
$$n = 32; \quad s = 0.8898; \quad R^2 = 0.7286;$$

$$F = 80.50; F(1, 30, 0.01) = 7.56$$

TABLE-1  
SOLUBILITY ESTIMATES FOR SOME POLYCYCLIC HYDROCARBONS

S. No	Name	mp <sup>a</sup> °C	$\delta_2^b$ H	$\delta_2^b$ cc/ mole	log PC <sup>a</sup>	log S <sub>w</sub>		Per cent <sup>d</sup> error
						Obs <sup>a</sup>	Estim <sup>c</sup>	
1.	Indan	25	9.89	116.7	3.57	-3.03	-3.02	0.43
2.	Naphthalene (9.94)	80	10.42	118.0	3.35	-3.61	-3.87	-7.27
3.	1-Methylnaphthalene (10.37)	25	10.25	132.5	3.86	-3.70	-3.71	-0.27
4	2-Methylnaphthalene	35	10.25	132.5	3.86	-3.75	-3.80	-1.36
5.	1,3-Dimethylnaphthalene	25	10.12	147.0	4.38	-4.29	-4.07	-5.08
6.	1,4-Dimethylnaphthalene	25	10.12	147.0	4.38	-4.14	-4.07	1.64
7.	1,5-Dimethylnaphthalene	81	10.12	147.0	4.38	-4.68	-4.58	2.10
8.	2,3-Dimethylnaphthalene	102	10.12	147.0	4.38	-4.72	-4.77	-1.11
9.	2,6-Dimethylnaphthalene	108	10.12	147.0	4.38	-4.89	-4.82	1.27
10.	1-Ethyl-naphthalene	25	10.08	148.6	4.39	-4.16	-4.06	2.24
11.	1,4,5-Trimethylnaphthalene	25	10.01	161.5	4.90	-4.92	-4.45	9.64
12.	Diphenyl	71	10.34	142.8	4.03	-4.34	-4.49	-3.56
13.	Acenaphthene	96	10.96	128.2	4.03	-4.59	-4.64	-1.29
14.	Fluorene	116	11.04	136.9	4.47	-4.92	-5.14	-4.52
15.	Phenanthrene	101	11.11	145.6	4.63	-5.15	-5.31	-3.13
16.	Anthracene	216	11.11	145.6	4.63	-6.38	-6.35	0.34
17.	2-Methylanthracene	209	10.92	160.1	5.15	-6.69	-6.62	1.04
18.	9-Methylanthracene	82	10.92	160.1	5.15	-5.87	-5.46	6.91
19.	9,10-Dimethylanthracene	182	10.76	174.6	5.67	-6.57	-6.71	-2.25
20.	Pyrene	156	11.80	148.4	5.22	-6.18	-6.30	-2.06
21.	Fluoranthene	111	11.80	148.4	5.22	-5.90	-5.89	0.03
22.	1,2-Benzofluorene	187	11.53	164.5	5.75	-6.68	-6.91	-3.54
23.	2,3-Benzofluorene	209	11.53	164.5	5.75	-7.27	-7.11	-2.10
24.	Chrysene	255	11.56	173.2	5.01	-8.06	-7.81	3.10
25.	Triphenylene	199	11.56	173.2	5.45	-6.73	-7.30	-8.58
26.	Naphthacene	357	11.56	173.2	5.91	-8.69	-8.74	-0.63
27.	1,2-Benzanthracene	160	11.56	173.2	5.91	-7.21	-6.95	3.56
28.	9-10-Dimethyl-1,2-benzanthracene	122	11.21	202.2	6.95	-6.63	-7.27	-9.75
29.	Perylene	277	12.12	176.0	6.50	-8.80	-7.89	-10.30
30.	3,4-Benzopyrene	175	12.12	176.0	6.50	-7.82	-7.50	-3.99
31.	3-Methylcholanthrene	178	11.65	197.9	7.11	-7.97	-7.91	0.65
32.	Benzo(ghi)perylene	277	12.64	178.8	7.10	-9.02	-8.83	2.09

<sup>a</sup> Ref. 5<sup>b</sup> Calculated by Fedors constants, Ref. 9<sup>c</sup> Using eqn (5).<sup>d</sup>  $\frac{\text{observed solubility} - \text{Estimated solubility}}{\text{observed solubility}} \times 100$ 

The correlation coefficient is fairly high (0.7286). As the sign of the coefficient of  $\delta_2$  is negative, the higher the solubility parameter of the solute, the lower its

aqueous solubility would be. In other words, the greater the cohesive energy density of the solute, the lower the aqueous solubility. The solubility parameters of naphthalene (two fused 6-membered rings) and perylene (five fused 6-membered rings) are equal to 10.42 and 12.12 H, respectively. The extended conjugation and delocalised  $\pi$  cloud makes the perylene to exhibit greater cohesive forces of interaction. At the same time, the same delocalised  $\pi$  cloud is expected to offer a site for adhesive interaction with water and thus is expected to increase the aqueous solubility. The aqueous solubilities ( $\log S_w$ ) of naphthalene and perylene, however, are  $-3.61$  and  $-8.80$ , respectively. This is contrary to the expectation. Thus, probably molecular size also influences the aqueous solubility.

Solubility phenomena can be understood as follows<sup>14</sup>. Creating a sufficient cavity in the solvent environment that can accommodate a solute molecule and, finally, placing the molecule in the cavity. In other words, the molar volume of the solute will also determine the requisite space that should be created. The advantage of using molar volume is that it can also be calculated by the fragmental constants by the same procedure.<sup>9</sup> The molar volume,  $V_2$ , is added to the solubility parameter and correlations were obtained. The equation is

$$\log S_w = -1.186 \delta_2 - 0.0405 V_2 + 13.494 \quad (4)$$

$$n = 32; \quad s = 0.5669; \quad r^2 = 0.8935$$

$$F = 121.65; \quad F(2, 29, 0.01) = 5.42$$

There is considerable improvement in  $r^2$  value *i.e.*, 16 per cent (*cf.* Eq. (3)). The sign of the coefficient of molar volume term is negative, indicating that the higher the molar volume, lower the aqueous solubility. Molar volume when considered alone, the correlations are satisfactory ( $r^2 = 0.6707$ ). The low value of correlation coefficient is understandable because error might have been additive for every increase in the number of fused rings in polycyclic aromatic hydrocarbons. However, there is still scope to improve the correlation.

Solubility of a compound is also governed by the entropy of mixing, *i.e.*, entropy of fusion ( $S_f$ ) and melting point. The entropy of fusion is considered to be constant (13.5 eu) for rigid molecules like polycyclic aromatic compounds.<sup>5</sup> Thus mp becomes the only variable. Using an entropy of fusion approximation, and following an elegant line of reasoning, Yalkowsky and Valvani<sup>5</sup> have shown that the solubilities of "supercooled liquids" can be estimated from aqueous solubilities by adding 0.01 (mp-25) to  $\log S_w$ , the term in parentheses being zero for compounds melting below 20°C. Therefore, it was considered worthwhile to incorporate melting point parameter into Eq. (4). The equation thus becomes

$$\log S_w = -0.0091 (\text{mp}-25) - 0.596 \delta_2 - 0.0303 V_2 + 6.4136 \quad (5)$$

$$n = 32; \quad s = 0.2555; \quad r^2 = 0.9791$$

$$F = 450.24; \quad F(2, 29, 0.01) = 5.42$$

There is a considerable improvement in the correlations *i.e.*, 9 per cent. It is interesting that the coefficient of (mp-25), obtained in Eq. (5), agrees remarkably

well with Yalkowsky and Valvani's estimate of 0.01, which was obtained from theoretical consideration.<sup>5</sup> This fact gives the *prima facie* evidence about the usefulness of Eq. (5).

Yalkowsky and Valvani predicted good correlations between the aqueous solubility and partition coefficients.<sup>5</sup> In the present study, the partition coefficient and mp data from their studies have been used, but regression analysis was done on the Lotus package. The regression equation is

$$\log S_w = -0.011 (\text{mp}-25) - 0.8205 \log \text{PC} - 0.50 \quad (6)$$

$$n = 32; \quad s = 0.3067; \quad r^2 = 0.9688$$

$$F = 450.24; \quad F(2, 29, 0.01) = 5.42$$

The  $r^2$  value in Eq. (6) is high indicating that the partition coefficient has provided good correlations. The reason may be that PCs were estimated from the fragmental constants which were in turn derived from multiple regression analysis of reliable experimental PCs of a large number of compounds.<sup>8</sup> A comparison of Eqs. (5) and (6) indicate that both the equations estimate the aqueous solubility with nearly the same precision.

Eq. (5) was used to back calculate  $\log S_w$ . The results are given in Table-1. The regression equation between observed and estimated solubility is

$$\log S_w (\text{obs}) = 1.0159 \log S_w (\text{est}) + 0.061 \quad (7)$$

$$n = 32; \quad s = 0.2911; \quad r^2 = 0.971$$

A good linear relationship was observed between the estimated and observed solubility (Fig. 1). A scattergram (Fig. 2) was constructed by plotting estimated  $\log S_w$  along the vertical axis and residual along the horizontal axis. The residuals are standardised by dividing each by its standard deviation. The scattering of points is random and the residuals are below 2 SD units. Thus, Eq. (5) can be used to predict the aqueous solubility of polycyclic aromatic compounds.

### Predictions for halobenzenes

Like polycyclic aromatic compounds, halobenzenes are also rigid. They also exhibit hydrophobic interaction. The relevant physico-chemical data for this series is reported in Table-2. The melting point,  $V_2$  and  $\delta_2$  of halobenzenes are considered individually for regression. The  $r^2$  values are 0.7042, 0.9031 and 0.8396, respectively. The solubility parameter alone had given good correlation coefficient.

TABLE-2  
SOLUBILITY ESTIMATES OF SOME HALOBENZENES

S. No.	Name	mp <sup>a</sup> °C	$\delta_2$ <sup>b</sup>	$V_2$ <sup>b</sup> cc/mole	log PC <sup>a</sup>	log $S_w$		Per cent error <sup>c</sup>
						Obs. <sup>a</sup>	Estim. <sup>c</sup>	
1.	Hexachlorobenzene	230	12.02	144.6	6.53	-7.76	-7.70	0.73
2.	Pentachlorobenzene	86	11.74	135.4	5.79	-5.65	-5.70	0.80
3.	1,2,3,4-Tetrachlorobenzene	47	11.41	126.4	5.05	-4.70	-4.70	-0.06
4.	1,2,3,5-Tetrachlorobenzene	54	11.41	126.4	5.05	-4.79	-4.77	0.36
5.	1,2,3,5-Tetrachlorobenzene	140	11.41	126.4	5.05	-5.56	-5.63	-1.23

S. No.	Name	mp <sup>a</sup> °C	$\delta_2^b$	V <sub>2</sub> <sup>b</sup> cc/mole	log PC <sup>a</sup>	log S <sub>w</sub>		Per cent error <sup>c</sup>
						Obs. <sup>a</sup>	Estim. <sup>c</sup>	
6.	1,2,4,5-Tetrabromobenzene	182	11.38	150.4	6.01	-6.98	-6.98	-0.00
7.	1,2,3-Tribromobenzene	87	11.04	135.4	4.98	—	-5.19	—
8.	1,2,4-Tribromobenzene	44	11.04	135.4	4.98	-4.50	-4.76	-5.70
9.	1,3,5-Tribromobenzene	122	11.04	135.4	4.98	-5.60	-5.53	1.20
10.	1,2,3-Trichlorobenzene	53	11.02	117.4	4.27	-3.76	-4.11	-9.41
11.	1,2,4-Trichlorobenzene	25	11.02	117.4	4.27	-3.72	-3.84	-3.10
12.	1,3,5-Trichlorobenzene	63	11.02	117.4	4.27	-4.44	-4.21	5.11
13.	1,2,3-Triiodobenzene	116	11.52	139.9	5.86	—	-6.01	—
14.	1,2,4-Triiodobenzene	91	11.52	139.9	5.85	—	-5.76	—
15.	1,3,5-Triiodobenzene	184	11.52	139.9	5.85	—	-6.69	—
16.	1,2-Dibromobenzene	25	10.61	120.4	4.07	-3.50	-3.65	-4.28
17.	1,3-Dibromobenzene	25	10.61	120.4	4.07	-3.38	-3.65	-8.09
18.	1,4-Dibromobenzene	87	10.61	120.4	4.07	-4.07	-4.27	-4.82
19.	1,2-Dichlorobenzene	25	10.54	108.4	3.59	-3.20	-3.12	-2.52
20.	1,3-Dichlorobenzene	25	10.54	108.4	3.59	-3.09	-3.12	-0.95
21.	1,4-Dichlorobenzene	53	10.54	108.4	3.59	-3.20	-3.40	-6.18
22.	1,2-Difluorobenzene	25	9.79	96.4	2.59	-2.00	-2.08	-4.14
23.	1,3-Difluorobenzene	25	9.79	96.4	2.58	-2.00	-2.08	-4.14
24.	1,4-Difluorobenzene	25	9.79	96.4	2.58	-1.97	-2.08	-5.72
25.	1,2-Diiodobenzene	27	10.99	123.4	4.65	-4.24	-4.07	3.96
26.	1,3-Diiodobenzene	40	10.99	123.4	4.64	-4.57	-4.20	2.04
27.	1,4-Diiodobenzene	132	10.99	123.4	4.64	-5.25	-5.12	2.54
28.	Bromobenzene	25	10.02	103.4	3.07	-2.64	-2.61	1.04
29.	Chlorobenzene	25	9.95	99.4	2.83	-2.35	-2.32	1.22
30.	Fluorobenzene	25	9.50	93.4	2.33	-1.79	-1.75	2.38
31.	Iodobenzene	25	10.27	106.9	3.36	-2.95	-2.86	3.10
32.	Benzene	25	9.19	90.4	2.13	-1.64	-1.40	14.81
33.	2-Bromochlorobenzene	25	10.58	114.4	3.83	-3.19	-3.39	-6.21
34.	3-Bromochlorobenzene	25	10.58	114.4	3.83	-3.21	-3.39	-5.55
35.	4-Bromochlorobenzene	68	10.80	114.4	3.83	-3.63	-3.82	-5.12
36.	2-Bromoiodobenzene	25	10.80	121.9	4.36	—	-3.85	—
37.	3-Bromoiodobenzene	25	10.80	121.9	4.36	—	-3.85	—
38.	4-Bromoiodobenzene	25	10.80	121.9	4.36	-4.56	-4.52	0.93
39.	2-Chloroiodobenzene	25	10.78	115.9	4.12	-3.54	-3.60	-1.60
40.	3-Chloroiodobenzene	25	10.78	115.9	4.12	-3.55	-3.60	-1.32
41.	4-Chloroiodobenzene	57	10.78	115.9	4.12	-4.03	-3.92	-2.85

<sup>a</sup> Ref. 5.<sup>b</sup> Calculated by Fedors constants, Ref. 9<sup>c</sup> Using Eq. (11).<sup>d</sup>  $\frac{\text{Observed solubility} - \text{Estimated solubility}}{\text{observed solubility}} \times 100$

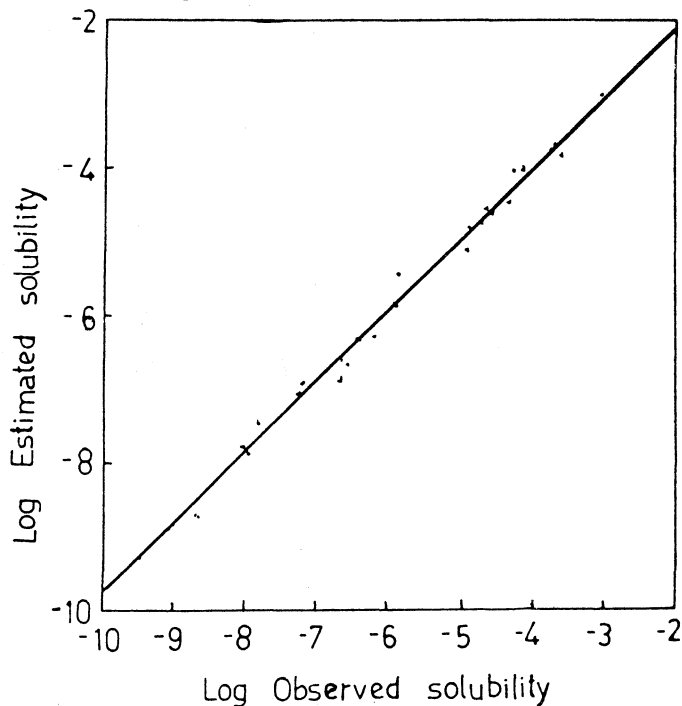


Fig. 1 Relationship between estimated and observed log molar aqueous solubility of polycyclic aromatic hydrocarbons (Eq. (7)).

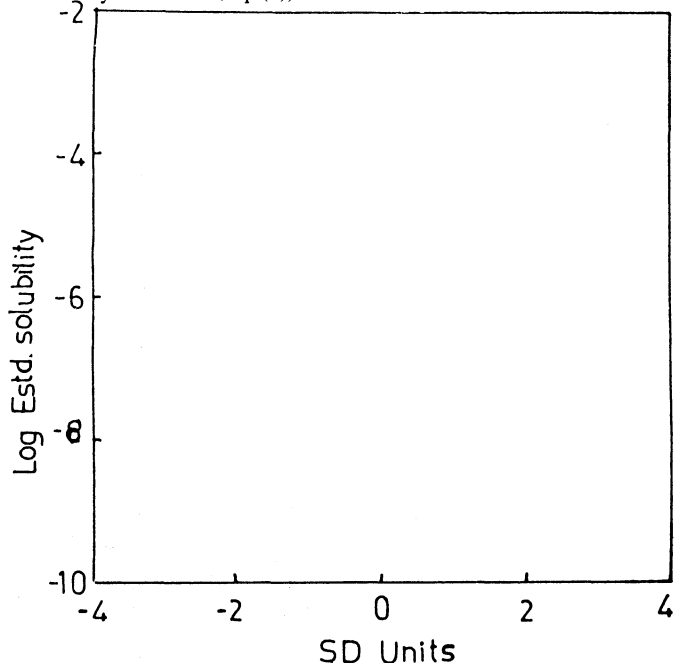


Fig. 2 Plot of residuals (scattergram) obtained from Eq. (5) for aqueous solubility prediction of polycyclic aromatic hydrocarbons. Standardised residuals are expressed in standard deviation (SD) units.

### Two parameter approach

When any two of the above parameters are selected, the equations are:

mp +  $V_2$ :

$$\log S_w = -0.00957 \text{ mp} - 0.07102 V_2 + 4.955 \quad (8)$$

$$n = 35; \quad s = 0.2834; \quad r^2 = 0.9615$$

mp +  $\delta_2$ :

$$\log S_w = -0.01238 \text{ mp} - 1.4483 \delta_2 + 12.3015 \quad (9)$$

$$n = 35; \quad s = 0.2966; \quad r^2 = 0.9579$$

$V_2$  +  $\delta_2$ :

$$\log S_w = -0.6399 \delta_2 - 0.0688 V_2 + 11.0084 \quad (10)$$

$$n = 35; \quad s = 0.4186; \quad r^2 = 0.9160$$

Eqs. (8) and (9) indicate that mp had contributed to the same extent to the other parameter,  $\delta_2$  or  $V_2$ . A similar observation was made while analysing polycyclic aromatic compounds. There is still to improve the correlations.

### Three parameter approach

$$\log S_w = -0.00995 (\text{mp}-25) - 0.7442 \delta_2 - 0.03986 V_2 + 9.0455 \quad (11)$$

$$n = 35; \quad s = 0.2128; \quad r^2 = 0.979$$

$$F = 481.73 \quad F(3, 31, 0.01) = 4.46$$

The result was improved by 2 per cent (0.979 in Eq. 11). The coefficient of (mp-25) is 0.00995 (Eq. 11), *i.e.*, *ca.* 0.01, which agrees with the value proposed by Yalkowski and Valvani.<sup>5</sup> A similar agreement was also observed in polycyclic aromatic compounds (Eq. 5). The sign of the  $\delta_2$  coefficient is negative, and it is in contrast to the concept of 'like dissolves like'. In fact, according to the regular solutions theory, the higher the  $\delta_2$  value of the solute, the greater should be the aqueous solubility. When (mp-25) and log PC are used for correlations, Eq. (12) is obtained.

$$\log S_w = -0.00863 (\text{mp}-25) - 1.0256 \log \text{PC} + 0.584 \quad (12)$$

$$n = 35; \quad S = 0.1880; \quad r^2 = 0.9831; \quad F = 925.18; \quad F(2, 32, 0.01) = 5.34$$

Comparison of Eqs. (11) and (12) indicates that both the equations estimate the aqueous solubility with nearly same precision. Interestingly, the contribution of mp to partition coefficient is also nearly same.

The regression Eqs. (11) was used to estimate aqueous solubility. Good linear relationship was observed between the experimental and estimated values (Fig. 3). Random distribution of errors was observed in the scattergram (Fig. 4).

Thus, the results involving the three-parameter approach are gratifying. Though solubility parameter indicates cohesive energy density, it is a useful parameter to predict the aqueous solubility of these series of compounds.



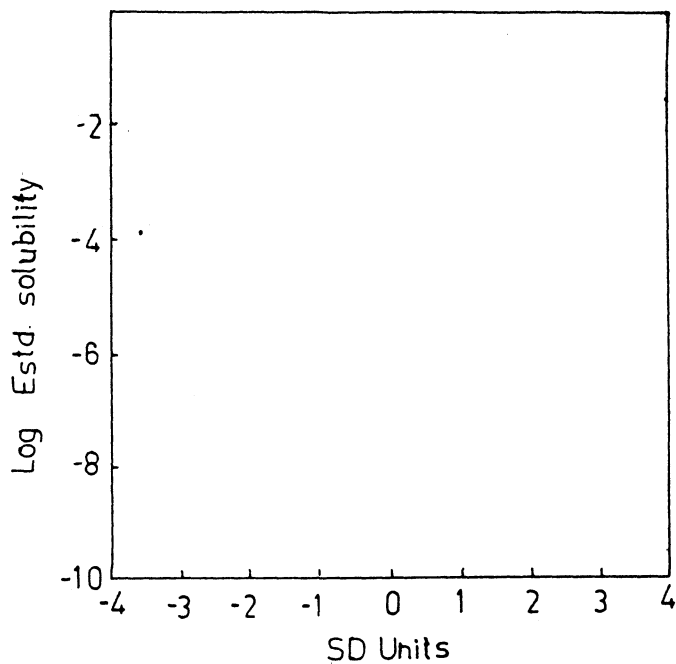


Fig. 3. Relationship between estimated and observed aqueous solubility for halobenzenes. Estimated values are obtained from Eq. (11).

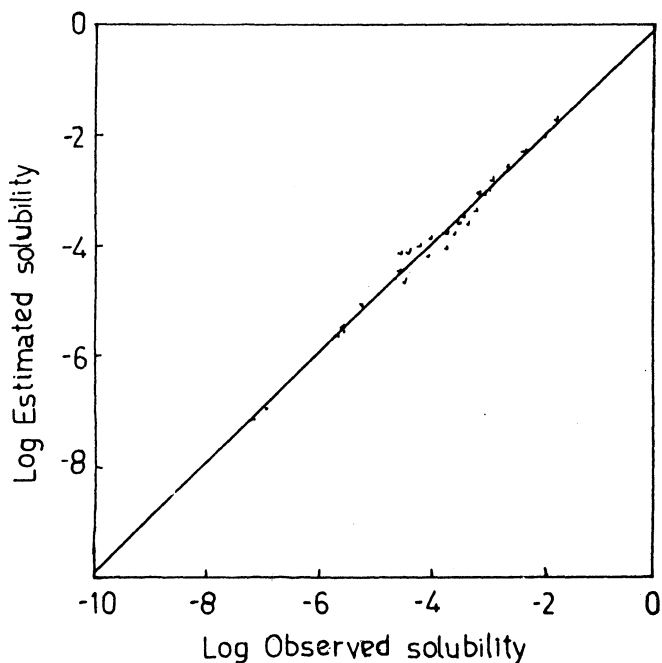


Fig. 4. Scatterogram obtained from Eq. (11) for aqueous solubility predictions of halobenzenes.

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