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A Method for Calculation of the Aqueous Solubility of Organic Compounds by Using New Fragment Solubility Constants[1)]

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For the calculation of the aqueous solubility of organic compounds, we defined new fragment solubility constants (f_s) which were empirically determined on the basis of compiled data from the literature. First, 6 fundamental f_s values were determined from data on 46 liquid alliphatic hydrocarbons. These f_s values were fixed, and data on 249 liquid aliphatic compounds with diverse functional groups were employed to optimize another 19 f_s values of the groups. Then, 15 f_s values of aromatic compounds were calculated based on the solubility data on 58 aromatic liquids and the aliphatic f_s values.

It has been shown that there is a linear relationship between the logarithms of the aqueous solubilities of organic liquids and the octanol–water partition constants (log P), and that the water solubilities can be calculated by using the correlation equation and log P values. The present paper is concerned with a method to calculate the aqueous solubilities of organic liquids simply, directly and more accurately on the basis of f_s values. Furthermore, the calculation of the water solubilities of organic solids was attempted with a correction based on the melting points, in addition to using the f_s values.

Keywords——aqueous solubility; fragment solubility constant; organic liquid; organic solid

The aqueous solubility of drugs is one of the most important factors in determining a specific administration form and/or method. It is well known that many drugs showing good activity when administered parenterally are either weakly active or totally inactive when given orally. In most cases, poor oral activity results from the inability of the administered drug to reach its site of action in an amount sufficient to elicit a response. This is generally due to one or more of the following reasons: insufficient release of the drug from its formulation; weak transport capability of the drug across the gastrointestinal membrane; poor stability of the drug in the gastrointestinal tract and wall, and/or the liver.[2)]

The gastrointestinal absorption of most drugs depends on passive transport, and the combined effects of aqueous solubility and partition coefficients on absorption are considered to be most important. On the basis of the available data, drugs having logarithms of octanol–water partition coefficients log $P \geqq 2$ and aqueous solubilities more than 10 μg/ml are supposed to be well absorbed.[2)] Needless to say, kinetic factors such as transport rate and dissolution rate are very important, in addition to the above thermodynamic factors, for estimating the absorption. However, here we would like to concentrate on a method for calculation of the aqueous solubility.

Past work relating to solubility calculations can be grouped into two categories. One is a theoretical approach[3)] which is able to deal with regular solutions of a liquid in a liquid system and ideal solutions of a solid in a liquid. Since regular solutions are defined to have no chemical interaction, no association and no dipole interaction, and ideal solutions to have no change in total volume or total energy compared with those before mixing, it is difficult to apply such equations to aqueous solutions of organic compounds. The theoretical method is far from being applicable to calculation of the water solubility of organic compounds. The other approach is an empirical one which is based on various correlation equations between the determined solubilities and other physical constants such as log P values, melting points, molar volumes, molar surface areas and so on.

Hansch and coworkers found correlation equations between log P values and the aqueous solubilities of organic liquids.[4] The largest set among those they obtained is described by Eq. 1, where S is the molar concentration of each compound at 25 °C in water, n is the number of data, r is the correlation coefficient and s is the standard deviation from the regression. Yalkowsky *et al.* improved the correlation by employing log P values based on hydrophobic fragment constants to get Eq.2.[2,5]

$$\log 1/S = 1.34 \log P - 0.98 \qquad (1)$$
$$n = 156, \quad r = 0.935, \quad s = 0.472$$

$$\log 1/S = 1.07 \log P - 0.67 \qquad (2)$$
$$n = 156, \quad r = 0.954, \quad s = 0.334$$

On the other hand, several reports in recent years have demonstrated the efficacy of molar volume or surface area as a molecular descriptor in correlating and predicting aqueous solubility.[6-10] Moriguchi and coworkers devised a method for calculation of log P values on the basis of a linear combination of van der Waals volumes (V_W) and the hydrophilic correction terms (V_H)[6] or of solvent accessible surface areas (S_A) and the hydrophilic correction terms (S_H).[7] They applied the method to the calculation of the aqueous solubility of organic liquids to obtain Eqs. 3 and 4, where the same compounds as those in Eqs. 1 and 2 were used. Since in regular solution theory the heat of solution of each element is described to be proportional to molar volume or molar surface area, the employment of a V_W and S_A term might be reasonable. However, the values of V_H or S_H are the differences between the values of V_W or S_A and log P values, respectively, and are therefore dependent on the log P or hydrophobic substituent constants (π).

$$\log 1/S = 3.73\, V_W - 4.10\, V_H - 0.72 \qquad (3)$$
$$n = 156, \quad r = 0.960, \quad s = 0.37$$

$$\log 1/S = 2.23\, S_A - 1.31\, S_H - 1.80 \qquad (4)$$
$$n = 156, \quad r = 0.981, \quad s = 0.26$$

It is well known that log P has an additive-constitutive property with respect to organic molecules.[11] On the other hand, parameters for a bond contribution and a group contribution correlated with the intrinsic hydrophilicity of organic compounds (log γ values) have been determined.[12] Although there is an earlier study concerned with fragment solubility constants, the method seems to be rather complicated, does not always give good results and is restricted to hydrocarbons and halogenohydrocarbons.[13,14] In this study we define new fragment solubility constants (f_s) satisfying an addition rule and present the solubility of each compound as the sum of the constituting f_s values as shown in Eq. 5.

$$\log 1/S = \sum f_s \qquad (5)$$

Results and Discussion

Calculation of Aliphatic Fragment Solubility Constants from the Aqueous Solubilities of Aliphatic Organic Liquids

Among aliphatic liquids, 46 hydrocarbons (No. 1—46 in Table I) were employed to

TABLE I. Aqueous Solubilities and Fragments of Organic Liquids

No.	Compounds	Fragment	log 1/S[c)]		Δ log 1/S	Ref.[e)]
			Obsd.	Calcd.[d)]		
1	1-Pentyne	C: 3, H: 8, C≡C: 1	1.64	1.88	0.24	1, 27, 45
2	1-Hexyne	C: 4, H: 10, C≡C: 1	2.36	2.49	0.13	1, 27
3	1-Heptyne	C: 5, H: 12, C≡C: 1	3.01	3.10	0.09	1, 27
4	1-Octyne	C: 6, H: 14, C≡C: 1	3.66	3.71	0.05	1, 27, 45
5	1-Nonyne	C: 7, H: 16, C≡C: 1	4.24	4.32	0.08	1, 27, 45
6	1,8-Nonadiyne	C: 5, H: 12, C≡C: 2	2.98	2.91	−0.07	1
7	1,6-Heptadiyne	C: 3, H: 8, C≡C: 2	1.75	1.69	−0.06	1
8	1-Pentene	C: 3, H: 10, C=C: 1	2.67	2.72	0.05	1
9	2-Pentene	C: 3, H: 10, C=C: 1	2.54	2.72	0.18	1, 27, 45
10	1-Hexene	C: 4, H: 12, C=C: 1	3.23	3.33	0.10	1, 27, 45
11	2-Heptene	C: 5, H: 14, C=C: 1	3.82	3.94	0.12	1, 27, 45
12	1-Octene	C: 6, H: 16, C=C: 1	4.62	4.55	−0.07	1, 27, 45
13	4-Methyl-1-pentene	C: 4, H: 12, C=C: 1, Brnc: 1	3.24	3.23	−0.01	1, 27, 45
14	1,6-Heptadiene	C: 3, H: 12, C=C: 2	3.34	3.37	0.03	1, 27
15	1,5-Hexadiene	C: 2, H: 10, C=C: 2	2.69	2.76	0.07	1, 27, 45
16	1,4-Pentadiene	C: 1, H: 8, C=C: 2	2.08	2.15	0.07	1
17	Cyclopentene	C: 3, H: 8, C=C: 1, ring: 1	2.10	2.08	−0.02	1, 27, 45
18	Cyclohexene	C: 4, H: 10, C=C: 1, ring: 1	2.58	2.69	0.11	1
19	Cycloheptene	C: 5, H: 12, C=C: 1, ring: 1	3.16	3.30	0.14	1, 27
20	2-Methyl-1-butene	C: 3, H: 10, C=C: 1, Brnc: 1	2.73	2.62	−0.11	27
21	2-Methyl-1-pentene	C: 4, H: 12, C=C: 1, Brnc: 1	3.03	3.23	0.20	27
22	2-Methyl-1,3-butadiene	C: 1, H: 8, C=C: 2, Brnc: 1	2.03	2.05	0.02	27, 45
23	1-Methylcyclohexene	C: 5, H: 12, C=C: 1, Brnc: 1, ring: 1	3.27	3.20	−0.07	27, 45
24	1,4-Cyclohexadiene	C: 2, H: 8, C=C: 2, ring: 1	2.06	2.12	0.06	27
25	4-Vinylcyclohexene	C: 4, H: 12, C=C: 2, Brnc: 1, ring: 1	3.34	3.24	−0.10	27
26	Cycloheptatriene	C: 1, H: 8, C=C: 3, ring: 1	2.17	2.16	−0.01	27
27	2-Methyl-2-butene	C: 3, H: 10, C=C: 1, Brnc: 1	2.56	2.62	0.06	45
28	2,3-Dimethyl-1,3-butadiene	C: 2, H: 10, C=C: 2, Brnc: 2	2.40	2.56	0.16	45
29	*n*-Pentane	C: 5, H: 12	3.27	3.29	0.02	1, 27, 45
30	2-Methylbutane	C: 5, H: 12, Brnc: 1	3.18	3.19	0.01	1, 27, 44
31	2-Methylpentane	C: 6, H: 14, Brnc: 1	3.79	3.80	0.01	1, 44, 45
32	3-Methylpentane	C: 6, H: 14, Brnc: 1	3.83	3.80	−0.03	1, 27, 44
33	*n*-Hexane	C: 6, H: 14	3.96	3.90	−0.06	1, 27, 45
34	*n*-Heptane	C: 7, H: 16	4.53	4.51	−0.02	1, 27, 45
35	2,4-Dimethylpentane	C: 7, H: 16, Brnc: 2	4.39	4.31	−0.08	1, 27, 44
36	*n*-Octane	C: 8, H: 18	5.24	5.12	−0.12	1, 27, 45
37	Cyclopentane	C: 5, H: 10, ring: 1	2.65	2.65	0.00	1, 27, 44
38	Cyclohexane	C: 6, H: 12, ring: 1	3.18	3.26	0.08	1, 27, 44
39	Methylcyclopentane	C: 6, H: 12, Brnc: 1, ring: 1	3.30	3.16	−0.14	1, 27, 44
40	Cycloheptane	C: 7, H: 14, ring: 1	3.51	3.87	0.36	1, 27
41	Methylcyclohexane	C: 7, H: 14, Brnc: 1, ring: 1	3.85	3.77	−0.08	1, 27, 44
42	Cyclooctane	C: 8, H: 16, ring: 1	4.15	4.48	0.33	1, 27, 44
43	1,2-Dimethylcyclohexane	C: 8, H: 16, Brnc: 2, ring: 1	4.27	4.28	0.01	1, 27, 44
44	2,2-Dimethylbutane	C: 6, H: 14, Brnc: 2	3.67	3.70	0.03	27, 44, 45
45	2,2,4-Trimethylpentane	C: 8, H: 18, Brnc: 3	4.67	4.82	0.15	27, 44, 45
46	2,2,5-Trimethylhexane	C: 9, H: 20, Brnc: 3	5.05	5.43	0.38	27, 44
47[a)]	2,2-Dimethylpentane	C: 7, H: 16, Brnc: 2	3.67	4.31	0.64	1
48	1-Butanol	C: 4, H: 9, p-OH: 1	−0.03	−0.09	−0.06	1, 6
49	2-Methyl-1-propanol	C: 4, H: 9, Brnc: 1, p-OH: 1	−0.10	−0.19	−0.09	1
50	2-Butanol	C: 4, H: 9, Brnc: 1, s-OH: 1	−0.29	−0.36	−0.07	1
51	1-Pentanol	C: 5, H: 11, p-OH: 1	0.59	0.52	−0.07	1, 6

TABLE I. (continued)

No.	Compounds	Fragment	log 1/S[c)]		Δ log 1/S	Ref.[e)]
			Obsd.	Calcd.[d)]		
52	3-Methyl-1-butanol	C: 5, H: 11, Brnc: 1, p-OH: 1	0.51	0.42	−0.09	1, 7, 28
53	2-Methyl-1-butanol	C: 5, H: 11, Brnc: 1, p-OH: 1	0.46	0.42	−0.04	1, 7
54	2-Pentanol	C: 5, H: 11, Brnc: 1, s-OH: 1	0.28	0.25	−0.03	1, 7
55	3-Pentanol	C: 5, H: 11, Brnc: 1, s-OH: 1	0.21	0.25	0.04	1, 7
56	3-Methyl-2-butanol	C: 5, H: 11, Brnc: 2, s-OH: 1	0.18	0.15	−0.03	1, 7
57	2-Methyl-2-butanol	C: 5, H: 11, Brnc: 2, t-OH: 1	−0.15	−0.20	−0.05	1, 7
58	1-Hexanol	C: 6, H: 13, p-OH: 1	1.21	1.13	−0.08	1, 6, 45
59	2-Hexanol	C: 6, H: 13, Brnc: 1, s-OH: 1	0.87	0.86	−0.01	1, 8
60	3-Hexanol	C: 6, H: 13, Brnc: 1, s-OH: 1	0.80	0.86	0.06	1, 8, 45
61	3-Methyl-3-pentanol	C: 6, H: 13, Brnc: 2, t-OH: 1	0.36	0.41	0.05	1, 8
62	2-Methyl-2-pentanol	C: 6, H: 13, Brnc: 2, t-OH: 1	0.49	0.41	−0.08	1, 45
63	2-Methyl-3-pentanol	C: 6, H: 13, Brnc: 2, s-OH: 1	0.70	0.76	0.06	1, 8, 45
64	3-Methyl-2-pentanol	C: 6, H: 13, Brnc: 2, s-OH: 1	0.71	0.76	0.05	1, 8
65	4-Methyl-2-pentanol	C: 6, H: 13, Brnc: 2, s-OH: 1	0.79	0.76	−0.03	1, 8, 45
66	2,3-Dimethyl-2-butanol	C: 6, H: 13, Brnc: 3, t-OH: 1	0.37	0.31	−0.06	1, 8
67	3,3-Dimethyl-1-butanol	C: 6, H: 13, Brnc: 2, p-OH: 1	1.13	0.93	−0.20	1
68	3,3-Dimethyl-2-butanol	C: 6, H: 13, Brnc: 3, s-OH: 1	0.61	0.66	0.05	1, 8
69	1-Heptanol	C: 7, H: 15, p-OH: 1	1.81	1.74	−0.07	1, 6
70	2-Methyl-2-hexanol	C: 7, H: 15, Brnc: 2, t-OH: 1	1.07	1.02	−0.05	1, 9
71	3-Methyl-3-hexanol	C: 7, H: 15, Brnc: 2, t-OH: 1	0.98	1.02	0.04	1, 9
72	3-Ethyl-3-pentanol	C: 7, H: 15, Brnc: 2, t-OH: 1	0.83	1.02	0.19	1, 9
73	2,3-Dimethyl-2-pentanol	C: 7, H: 15, Brnc: 3, t-OH: 1	0.87	0.92	0.05	1, 9
74	2,3-Dimethyl-3-pentanol	C: 7, H: 15, Brnc: 3, t-OH: 1	0.84	0.92	0.08	1, 9
75	2,4-Dimethyl-2-pentanol	C: 7, H: 15, Brnc: 3, t-OH: 1	0.93	0.92	−0.01	1, 9
76	2,4-Dimethyl-3-pentanol	C: 7, H: 15, Brnc: 3, s-OH: 1	1.22	1.27	0.05	1, 9
77	2,2-Dimethyl-3-pentanol	C: 7, H: 15, Brnc: 3, s-OH: 1	1.15	1.27	0.12	1, 9
78	1-Octanol	C: 8, H: 17, p-OH: 1	2.35	2.35	0.00	1, 6
79	2,2,3-Trimethyl-3-pentanol	C: 8, H: 17, Brnc: 4, t-OH: 1	1.27	1.43	0.16	1, 10, 28
80	Cyclohexanol	C: 6, H: 11, Brnc: 1, ring: 1 s-OH: 1	0.42	0.22	−0.20	1
81	4-Penten-1-ol	C: 3, H: 9, C=C: 1, p-OH: 1	0.15	−0.05	−0.20	1, 11
82	3-Penten-2-ol	C: 3, H: 9, C=C: 1, Brnc: 1 s-OH: 1	−0.06	−0.32	−0.26	1
83	1-Penten-3-ol	C: 3, H: 9, C=C: 1, Brnc: 1, s-OH: 1	−0.02	−0.32	−0.30	1, 11
84	2-Hexen-4-ol	C: 4, H: 11, C=C: 1, Brnc: 1, s-OH: 1	0.40	0.29	−0.11	1, 11
85	2-Methyl-4-penten-3-ol	C: 4, H: 11, C=C: 1, Brnc: 2, s-OH: 1	0.50	0.19	−0.31	1, 11
86	2,2-Dimethyl-1-butanol	C: 6, H: 13, Brnc: 2, p-OH: 1	1.04	0.93	−0.11	28
87	2,3,3-Trimethyl-2-butanol	C: 7, H: 15, Brnc: 4, t-OH: 1	0.71	0.82	0.11	9
88	1-Nonanol	C: 9, H: 19, p-OH: 1	3.01	2.96	−0.05	17, 28
89	1-Decanol	C: 10, H: 21, p-OH: 1	3.63	3.57	−0.06	17
90	2-Methyl-1-pentanol	C: 6, H: 13, Brnc: 1, p-OH: 1	1.11	1.03	−0.08	28
91	4-Methyl-1-pentanol	C: 6, H: 13, Brnc: 1, p-OH: 1	1.14	1.03	−0.11	28
92	2-Ethyl-1-butanol	C: 6, H: 13, Brnc: 1, p-OH: 1	1.17	1.03	−0.14	28
93	2,2-Dimethyl-1-pentanol	C: 7, H: 15, Brnc: 2, p-OH: 1	1.52	1.54	0.02	28
94	2,4-Dimethyl-1-pentanol	C: 7, H: 15, Brnc: 2, p-OH: 1	1.60	1.54	−0.06	28
95	4,4-Dimethyl-1-pentanol	C: 7, H: 15, Brnc: 2, p-OH: 1	1.55	1.54	−0.01	28
96	2-Heptanol	C: 7, H: 15, Brnc: 1, s-OH: 1	1.55	1.47	−0.08	28
97	3-Heptanol	C: 7, H: 15, Brnc: 1, s-OH: 1	1.44	1.47	0.03	28
98	4-Heptanol	C: 7, H: 15, Brnc: 1, s-OH: 1	1.40	1.47	0.07	28
99	5-Methyl-2-hexanol	C: 7, H: 15, Brnc: 2, s-OH: 1	1.38	1.37	−0.01	28

Table I. (continued)

No.	Compounds	Fragment	log 1/S[c]		Δ log 1/S	Ref.[e]
			Obsd.	Calcd.[d]		
100	2-Methyl-3-hexanol	C: 7, H: 15, Brnc: 2, s-OH: 1	1.32	1.37	0.05	28
101	2-Ethyl-1-hexanol	C: 8, H: 17, Brnc: 1, p-OH: 1	2.11	2.25	0.14	28
102	2-Octanol	C: 8, H: 17, Brnc: 1, s-OH: 1	2.09	2.08	−0.01	28
103	2-Methyl-2-heptanol	C: 8, H: 17, Brnc: 2, t-OH: 1	1.72	1.63	−0.09	28
104	3-Methyl-3-heptanol	C: 8, H: 17, Brnc: 2, t-OH: 1	1.60	1.63	0.03	28
105	7-Methyl-1-octanol	C: 9, H: 19, Brnc: 1, p-OH: 1	2.49	2.86	0.37	28
106	2,2-Diethyl-1-pentanol	C: 9, H: 19, Brnc: 2, p-OH: 1	2.42	2.76	0.34	28
107	2-Nonanol	C: 9, H: 19, Brnc: 1, s-OH: 1	2.74	2.69	−0.05	28
108	3-Nonanol	C: 9, H: 19, Brnc: 1, s-OH: 1	2.66	2.69	0.03	28
109	4-Nonanol	C: 9, H: 19, Brnc: 1, s-OH: 1	2.59	2.69	0.10	28
110	5-Nonanol	C: 9, H: 19, Brnc: 1, s-OH: 1	2.49	2.69	0.20	28
111	2,6-Dimethyl-4-heptanol	C: 9, H: 19, Brnc: 3, s-OH: 1	2.51	2.49	−0.02	28
112	3,5-Dimethyl-4-heptanol	C: 9, H: 19, Brnc: 3, s-OH: 1	2.51	2.49	−0.02	28
113	2-Undecanol	C: 11, H: 23, Brnc: 1, s-OH: 1	2.94	3.91	0.97	28
114	1-Dodecanol	C: 12, H: 25, p-OH: 1	4.80	4.79	−0.01	28
115	1-Hexen-3-ol	C: 4, H: 11, C=C: 1, Brnc: 1, s-OH: 1	0.59	0.29	−0.30	1
116	2,3-Dimethyl-1-butanol	C: 6, H: 13, Brnc: 2, p-OH: 1	0.37	0.93	0.56	45
117	Ethanethiol	C: 2, H: 5, SH: 1	0.60	0.60	0.00	45
118	2-Butanone	C: 3, H: 8, C=O: 1	−0.68	−0.36	0.32	1, 12
119	2-Pentanone	C: 4, H: 10, C=O: 1	0.17	0.25	0.08	1, 12
120	3-Pentanone	C: 4, H: 10, C=O: 1	0.23	0.25	0.02	1, 12
121	3-Methyl-2-butanone	C: 4, H: 10, Brnc: 1, C=O: 1	0.12	0.15	0.03	1, 12
122	2-Hexanone	C: 5, H: 12, C=O: 1	0.78	0.86	0.08	1
123	3-Hexanone	C: 5, H: 12, C=O: 1	0.83	0.86	0.03	1, 12
124	3-Methyl-2-pentanone	C: 5, H: 12, Brnc: 1, C=O: 1	0.67	0.76	0.09	1, 12
125	4-Methyl-2-pentanone	C: 5, H: 12, Brnc: 1, C=O: 1	0.71	0.76	0.05	1, 12
126	4-Methyl-3-pentanone	C: 5, H: 12, Brnc: 1, C=O: 1	0.81	0.76	−0.05	1, 12
127	2-Heptanone	C: 6, H: 14, C=O: 1	1.42	1.47	0.05	1, 12
128	4-Heptanone	C: 6, H: 14, C=O: 1	1.44	1.47	0.03	1
129	2,4-Dimethyl-3-pentanone	C: 6, H: 14, Brnc: 2, C=O: 1	1.30	1.27	−0.03	1, 12
130	5-Nonanone	C: 8, H: 18, C=O: 1	2.58	2.69	0.11	1
131	3,3-Dimethyl-2-butanone	C: 5, H: 12, Brnc: 2, C=O: 1	0.71	0.66	−0.05	12
132	Propionaldehyde	C: 2, H: 5, CHO: 1	−0.52	−0.48	0.04	25
133	Butyraldehyde	C: 3, H: 7, CHO: 1	0.29	0.13	−0.16	25
134	Ethyl formate	C: 2, H: 6, CO_2: 1	−0.08	−0.44	−0.36	1, 45
135	*n*-Propyl formate	C: 3, H: 8, CO_2: 1	0.49	0.17	−0.32	1
136	Isopropyl formate	C: 3, H: 8, Brnc: 1, CO_2: 1	0.63	0.07	−0.56	45
137	Isobutyl formate	C: 4, H: 10, Brnc: 1, CO_2: 1	1.00	0.68	−0.32	45
138	Isoamyl formate	C: 5, H: 12, Brnc: 1, CO_2: 1	1.52	1.29	−0.23	45
139	Methyl acetate	C: 2, H: 6, CO_2: 1	−0.52	−0.44	0.08	1, 5
140	Ethyl acetate	C: 3, H: 8, CO_2: 1	0.04	0.17	0.13	1, 13
141	*n*-Propyl acetate	C: 4, H: 10, CO_2: 1	0.73	0.78	0.05	1, 5
142	Isopropyl acetate	C: 4, H: 10, Brnc: 1, CO_2: 1	0.52	0.68	0.16	1, 5
143	*n*-Butyl acetate	C: 5, H: 12, CO_2: 1	1.37	1.39	0.02	45
144	Isobutyl acetate	C: 5, H: 12, Brnc: 1, CO_2: 1	1.24	1.29	0.05	1, 5
145	Amyl acetate	C: 6, H: 14, CO_2: 1	1.86	2.00	0.14	45
146	Isoamyl acetate	C: 6, H: 14, Brnc: 1, CO_2: 1	1.91	1.90	−0.01	45
147	Hexyl acetate	C: 7, H: 16, CO_2: 1	2.05	2.61	0.56	45
148	Methyl propionate	C: 3, H: 8, CO_2: 1	0.09	0.17	0.08	1
149	Ethyl propionate	C: 4, H: 10, CO_2: 1	0.64	0.78	0.14	45
150	*n*-Propyl propionate	C: 5, H: 12, CO_2: 1	1.34	1.39	0.05	45
151	Isopropyl propionate	C: 5, H: 12, Brnc: 1, CO_2: 1	1.29	1.29	0.00	45

TABLE I. (continued)

No.	Compounds	Fragment	log 1/*S*[c]		Δ log 1/*S*	Ref.[e]
			Obsd.	Calcd.[d]		
152	Amyl propionate	C: 7, H: 16, CO_2: 1	2.25	2.61	0.36	45
153	Methyl butyrate	C: 4, H: 10, CO_2: 1	0.78	0.78	0.00	1
154	Ethyl butyrate	C: 5, H: 12, CO_2: 1	1.28	1.39	0.11	1
155	*n*-Propyl butyrate	C: 6, H: 14, CO_2: 1	1.91	2.00	0.09	1, 2, 5
156	Ethyl valerate	C: 6, H: 14, CO_2: 1	1.77	2.00	0.23	1, 14
157	Ethyl hexanoate	C: 7, H: 16, CO_2: 1	2.36	2.61	0.25	1, 14
158	Ethyl heptanoate	C: 8, H: 18, CO_2: 1	2.74	3.22	0.48	1, 14, 45
159	Ethyl octanoate	C: 9, H: 20, CO_2: 1	3.39	3.83	0.44	1, 14
160	Ethyl nonanoate	C: 10, H: 22, CO_2: 1	3.80	4.44	0.64	1
161	Ethyl decanoate	C: 11, H: 24, CO_2: 1	4.10	5.05	0.95	1
162	Ethyl succinate	C: 6, H: 14, CO_2: 2	0.96	0.10	−0.86	14
163	Ethyl glutamate	C: 7, H: 16, CO_2: 2	1.33	0.71	−0.62	14
164	Ethyl adipate	C: 8, H: 18, CO_2: 2	1.68	1.32	−0.36	4, 14
165	Ethyl pimelate	C: 9, H: 20, CO_2: 2	2.04	1.93	−0.11	14
166	Ethyl suberate	C: 10, H: 22, CO_2: 2	2.53	2.54	0.01	14
167	Ethyl azelate	C: 11, H: 24, CO_2: 2	2.99	3.15	0.16	14
168	Ethyl sebacate	C: 12, H: 26, CO_2: 2	3.51	3.76	0.25	14
169	Diethyl ether	C: 4, H: 10, –O–: 1	0.06	0.17	0.11	1, 15
170	Methyl *n*-butyl ether	C: 5, H: 12, –O–: 1	0.99	0.78	−0.21	1, 15, 25
171	Methyl isobutyl ether	C: 5, H: 12, Brnc: 1, –O–: 1	0.90	0.68	−0.22	1, 15, 25
172	Methyl *sec*-butyl ether	C: 5, H: 12, Brnc: 1, –O–: 1	0.73	0.68	−0.05	1, 15, 25
173	Methyl *tert*-butyl ether	C: 5, H: 12, Brnc: 2, –O–: 1	0.21	0.58	0.37	1, 15, 25
174	Ethyl *n*-propyl ether	C: 5, H: 12, –O–: 1	0.67	0.78	0.11	1, 15, 25
175	Ethyl isopropyl ether	C: 5, H: 12, Brnc: 1, –O–: 1	0.55	0.68	0.13	1, 25
176	*n*-Propyl ether	C: 6, H: 14, –O–: 1	1.32	1.39	0.07	1
177	Propyl isopropyl ether	C: 6, H: 14, Brnc: 1, –O–: 1	1.34	1.29	−0.05	1
178	Diisopropyl ether	C: 6, H: 14, Brnc: 2, –O–: 1	1.70	1.19	−0.51	45
179	Methyl *n*-propyl ether	C: 4, H: 10, –O–: 1	0.37	0.17	−0.20	1
180	Methyl isopropyl ether	C: 4, H: 10, Brnc: 1, –O–: 1	0.03	0.07	0.04	1
181	Cyclopropyl ethyl ether	C: 5, H: 10, ring: 1, –O–: 1	0.64	0.14	−0.50	1, 26
182	Diallyl ether	C: 2, H: 10, C=C: 2, –O–: 1	0.02	0.25	0.23	15
183	α-Methyl tetramethyleneoxide	C: 5, H: 10, Brnc: 1, –O–: 1, ring: 1	−0.31	0.04	0.35	25
184	β-Methyl tetramethyleneoxide	C: 5, H: 10, Brnc: 1, –O–: 1, ring: 1	−0.09	0.04	0.13	25
185	Pentamethyleneoxide	C: 5, H: 10, ring: 1, –O–: 1	−0.05	0.14	0.19	25
186	Tetrahydrofuran	C: 4, H: 8, ring: 1, –O–: 1	−0.62	−0.47	0.15	26
187	*n*-Butyl ether	C: 8, H: 18, –O–: 1	2.77	2.61	−0.16	57
188	Dimethyl sulfide	C: 2, H: 6, –S–: 1	0.45	0.77	0.32	45
189	Diethyl sulfide	C: 4, H: 10, –S–: 1	1.45	1.99	0.54	45
190	1,1,2,2-Tetrachlorodifluoroethane	C: 2, Brnc: 4, F: 2, Cl: 4, 3-hal: 2	3.19	2.80	−0.39	45
191	1,1,2-Trichlorotrifluoroethane	C: 2, Brnc: 4, F: 3, Cl: 3, 3-hal: 2	3.04	2.75	−0.29	45, 58
192	1-Chloropropane	C: 3, H: 7, Cl: 1	1.53	1.83	0.30	1, 5
193	1-Chlorobutane	C: 4, H: 9, Cl: 1	2.14	2.44	0.30	1, 5, 45
194	2-Methyl-1-chloropropane	C: 4, H: 9, Brnc: 1, Cl: 1	2.00	2.34	0.34	1, 5
195	1,3-Dichloropropane	C: 3, H: 6, Cl: 2	1.61	1.59	−0.02	1
196	Chloroform	C: 1, H: 1, Brnc: 1, Cl: 3, 3-hal: 1	0.92	1.67	0.75	1
197	$(ClCH_2CH_2)_2S$	C: 4, H: 8, –S–: 1, Cl: 2	2.37	1.51	−0.86	1
198	2-Chloropropane	C: 3, H: 7, Brnc: 1, Cl: 1	1.36	1.73	0.37	1, 5

Table I. (continued)

No.	Compounds	Fragment	$\log 1/S$ [c]		$\Delta \log 1/S$	Ref.[e]
			Obsd.	Calcd.[d]		
199	1,2-Dichloroethane	C: 2, H: 4, Cl: 2	1.04	0.98	−0.06	3
200	Dichloromethane	C: 1, H: 2, Cl: 2, 2-hal: 1	0.63	1.04	0.41	45
201	Tetrachloromethane	C: 1, Brnc: 2, Cl: 4, 4-hal: 1	2.28	2.29	0.01	3
202	1-Chloro-2-bromoethane	C: 2, H: 4, Cl: 1, Br: 1	1.32	1.15	−0.17	4, 45
203	1,1-Dichloroethane	C: 2, H: 4, Brnc: 1, Cl: 2, 2-hal: 1	1.29	1.55	0.26	16, 45
204	1,1,1-Trichloroethane	C: 2, H: 3, Brnc: 2, Cl: 3, 3-hal: 1	2.01	2.18	0.17	45
205	1,1,2-Trichloroethane	C: 2, H: 3, Brnc: 1, Cl: 3, 2-hal: 1	1.46	1.31	−0.15	45
206	1,1,2,2-Tetrachloroethane	C: 2, H: 2, Brnc: 2, Cl: 4, 2-hal: 2	1.76	1.64	−0.12	45
207	Pentachloroethane	C: 2, H: 1, Brnc: 3, Cl: 5, 2-hal: 1, 3-hal: 1	2.61	2.27	−0.34	45
208	1,2-Dichloropropane	C: 3, H: 6, Brnc: 1, Cl: 2	1.61	1.49	−0.12	16, 45
209	1,1-Dichlorobutane	C: 4, H: 8, Brnc: 1, Cl: 2, 2-hal: 1	2.40	2.77	0.37	45
210	1-Chloropentane	C: 5, H: 11, Cl: 1	2.73	3.05	0.32	45
211	2-Chloropentane	C: 5, H: 11, Brnc: 1, Cl: 1	2.63	2.95	0.32	45
212	3-Chloropentane	C: 5, H: 11, Brnc: 1, Cl: 1	2.63	2.95	0.32	45
213	Dibromomethane	C: 1, H: 2, Br: 2, 2-hal: 1	1.18	1.38	0.20	45
214	Bromoethane	C: 2, H: 5, Br: 1	1.06	1.39	0.33	1, 5, 26
215	1,1,2,2-Tetrabromoethane	C: 2, H: 2, Brnc: 2, Br: 4, 2-hal: 2	2.73	2.32	−0.41	4, 58
216	1-Bromopropane	C: 3, H: 7, Br: 1	1.73	2.00	0.27	1, 3, 5
217	2-Bromopropane	C: 3, H: 7, Brnc: 1, Br: 1	1.63	1.90	0.27	1, 5
218	1,2-Dibromopropane	C: 3, H: 6, Brnc: 1, Br: 2	2.14	1.83	−0.31	45
219	1-Bromobutane	C: 4, H: 9, Br: 1	2.37	2.61	0.24	1
220	2-Methyl-1-bromopropane	C: 4, H: 9, Brnc: 1, Br: 1	2.43	2.51	0.08	1, 5, 58
221	3-Methyl-1-bromobutane	C: 5, H: 11, Brnc: 1, Br: 1	2.89	3.12	0.23	1, 5
222	1,3-Dibromopropane	C: 3, H: 6, Br: 2	2.08	1.93	−0.15	1, 4, 45
223	Bromoform	C: 1, H: 1, Brnc: 1, Br: 3, 3-hal: 1	1.90	2.18	0.28	2, 3
224	1,2-Dibromoethane	C: 2, H: 4, Br: 2	1.64	1.32	−0.32	3
225	Iodomethane	C: 1, H: 3, I: 1	1.00	1.13	0.13	1, 45
226	Iodoethane	C: 2, H: 5, I: 1	1.60	1.74	0.14	1, 5, 26
227	1-Iodopropane	C: 3, H: 7, I: 1	2.29	2.35	0.06	1, 5
228	2-Iodopropane	C: 3, H: 7, Brnc: 1, I: 1	2.09	2.25	0.16	45
229	1-Iodobutane	C: 4, H: 9, I: 1	2.96	2.96	0.00	1, 5
230	Diiodomethane	C: 1, H: 2, I: 2, 2-hal: 1	2.34	2.08	−0.26	1
231	3-Chloropropene	C: 1, H: 5, C=C: 1, Cl: 1	1.28	1.26	−0.02	45
232	Bromochloromethane	C: 1, H: 2, Cl: 1, Br: 1, 2-hal: 1	1.16	1.21	0.05	58
233	Nitroethane	C: 2, H: 5, NO_2: 1	0.24	0.24	0.00	45
234	1-Nitropropane	C: 3, H: 7, NO_2: 1	0.81	0.85	0.04	45
235	2-Nitropropane	C: 3, H: 7, Brnc: 1, NO_2: 1	0.73	0.75	0.02	45
236	Nitromethane	C: 1, H: 3, NO_2: 1	−0.19	−0.37	−0.18	59
237	1-Nitrobutane	C: 4, H: 9, NO_2: 1	1.35	1.46	0.11	59
238	Propionitrile	C: 2, H: 5, CN: 1	−0.28	0.05	0.33	1
239	Acrylonitrile	H: 3, C=C: 1, CN: 1	−0.18	−0.52	−0.34	57
240	Hexachlorobutadiene	C=C: 2, Brnc: 4, 2-hal: 2, d-Cl: 6	4.91	4.16	−0.75	32

TABLE I. (continued)

No.	Compounds	Fragment	log $1/S$[c] Obsd.	log $1/S$[c] Calcd.[d]	Δ log $1/S$	Ref.[e]
241	Tetrachloroethylene	C=C: 1, Brnc: 2, 2-hal: 2, d-Cl: 4	2.53	3.15	0.62	32
242	Trichloroethylene	H: 1, C=C: 1, Brnc: 1, 2-hal: 1, d-Cl: 3	1.95	2.30	0.35	32
243	*cis*-1,2-Dichloroethylene	H: 2, C=C: 1, d-Cl: 2	1.10	1.45	0.35	45
244	*trans*-1,2-Dichloroethylene	H: 2, C=C: 1, d-Cl: 2	1.19	1.45	0.26	45
245	α-Terpineol	C: 8, H: 17, C=C: 1, Brnc: 4, ring: 1, t-OH: 1	1.89	1.44	−0.45	2
246	Menthone	C: 9, H: 18, Brnc: 3, ring: 1, C=O: 1	2.35	2.36	0.01	2
247	Carvone	C: 5, H: 14, C=C: 2, Brnc: 3, ring: 1, C=O: 1	2.06	1.22	−0.84	2
248	Heptaldehyde	C: 6, H: 13, CHO: 1	1.96	1.96	0.00	2
249	Isobutyraldehyde	C: 3, H: 7, Brnc: 1, CHO: 1	−0.10	0.03	0.13	2
250	2-Bromo-2-chloro-1,1,1-trifluoroethane	C: 2, H: 1, Brnc: 3, F: 3, Cl: 1, Br: 1, 2-hal: 1, 3-hal: 1	1.70	2.29	0.59	58
251[a]	Ethyl malonate	C: 5, H: 12, CO_2: 2	0.89	−0.51	−1.40	14
252[a]	Divinyl ether	H: 6, C=C: 2, –O–: 1	0.96	−0.97	−1.93	26
253[a]	Cyclopropyl vinyl ether	C: 3, H: 8, C=C: 1, ring: 1, –O–: 1	1.10	−0.43	−1.53	26
254[a]	1,1-Diethoxyethane	C: 6, H: 14, Brnc: 1, –O–: 2	0.33	−1.22	−1.55	45
255[a]	1,2-Diethoxyethane	C: 6, H: 14, –O–: 2	0.15	−1.12	−1.27	45
256	Benzene	H: 6, Ph: 1	1.64	1.80	0.16	1, 18, 27
257	Toluene	C: 1, H: 8, Ph: 1	2.29	2.41	0.12	1, 5, 44
258	Ethylbenzene	C: 2, H: 10, Ph: 1	2.88	3.02	0.14	1, 44
259	*n*-Propylbenzene	C: 3, H: 12, Ph: 1	3.30	3.63	0.33	1, 5, 44
260	Benzyl alcohol	H: 5, Ph: 1, CH_2OH: 1[b]	0.45	0.45	0.00	1
261	Fluorobenzene	H: 5, Ph: 1, F: 1[b]	1.79	1.89	0.10	28, 58
262	Chlorobenzene	H: 5, Ph: 1, Cl: 1[b]	2.36	2.54	0.18	1, 3
263	Bromobenzene	H: 5, Ph: 1, Br: 1[b]	2.55	2.57	0.02	1, 3
264	Nitrobenzene	H: 5, Ph: 1, NO_2: 1[b]	1.78	1.64	−0.14	1, 3
265	1,2,4-Trimethylbenzene	C: 3, H: 12, Ph: 1	3.32	3.63	0.31	1, 27, 44
266	1,2-Dimethylbenzene	C: 2, H: 10, Ph: 1	2.78	3.02	0.24	1, 44, 45
267	Isopropylbenzene	C: 3, H: 12, Brnc: 1, Ph: 1	3.38	3.53	0.15	1, 27, 44
268	3-Nitrotoluene	C: 1, H: 7, Ph: 1, NO_2: 1[b]	2.44	2.25	−0.19	1, 4
269	1,2-Dichlorobenzene	H: 4, Ph: 1, Cl: 2[b]	3.01	3.28	0.27	1, 45, 58
270	1,3-Dichlorobenzene	H: 4, Ph: 1, Cl: 2[b]	3.08	3.28	0.20	1, 45, 58
271	Ethyl benzoate	C: 2, H: 10, Ph: 1, CO_2: 1[b]	2.28	2.21	−0.07	1
272	Aniline	H: 5, Ph: 1, NH_2: 1[b]	0.41	0.41	0.00	1
273	2-Nitroanisole	C: 1, H: 7, Ph: 1, NO_2: 1,[b] –O–: 1[b]	1.95	2.33	0.38	4
274	2-Nitrotoluene	C: 1, H: 7, Ph: 1, NO_2: 1[b]	2.32	2.25	−0.07	4, 45
275	Iodobenzene	H: 5, Ph: 1, I: 1[b]	2.77	2.79	0.02	4
276	1,3-Dimethylbenzene	C: 2, H: 10, Ph: 1	2.73	3.02	0.29	18
277	1,4-Dimethylbenzene	C: 2, H: 10, Ph: 1	2.73	3.02	0.29	18, 45
278	Indan	C: 3, H: 10, ring: 1, Ph: 1	3.03	2.99	−0.04	28, 54
279	1-Methylnaphthalene	C: 1, H: 10, Ph: 1.67	3.70	3.37	−0.33	28, 56
280	1,3-Dimethylnaphthalene	C: 2, H: 12, Ph: 1.67	4.29	3.98	−0.31	28, 54, 56
281	1,4-Dimethylnaphthalene	C: 2, H: 12, Ph: 1.67	4.14	3.98	−0.16	28, 54, 56
282	1-Ethylnaphthalene	C: 2, H: 12, Ph: 1.67	4.16	3.98	−0.18	28, 54, 56
283	1,4,5-Trimethylnaphthalene	C: 3, H: 14, Ph: 1.67	4.92	4.59	−0.33	28
284	1,2,4-Trichlorobenzene	H: 3, Ph: 1, Cl: 3[b]	3.72	4.02	0.30	28
285	1,2-Dibromobenzene	H: 4, Ph: 1, Br: 2[b]	3.50	3.34	−0.16	28

TABLE I. (continued)

No.	Compounds	Fragment	log 1/S[c] Obsd.	Calcd.[d]	Δ log 1/S	Ref.[e]
286	1,3-Dibromobenzene	H: 4, Ph: 1, Br: 2[b]	3.38	3.34	−0.04	28
287	1,2-Difluorobenzene	H: 4, Ph: 1, F: 2[b]	2.00	1.98	−0.02	28
288	1,3-Difluorobenzene	H: 4, Ph: 1, F: 2[b]	2.00	1.98	−0.02	28
289	1,4-Difluorobenzene	H: 4, Ph: 1, F: 2[b]	1.97	1.98	0.01	28
290	2-Bromochlorobenzene	H: 4, Ph: 1, Cl: 1,[b] Br: 1[b]	3.19	3.31	0.12	28
291	3-Bromochlorobenzene	H: 4, Ph: 1, Cl: 1,[b] Br: 1[b]	3.21	3.31	0.10	28
292	2-Chloroiodobenzene	H: 4, Ph: 1, Cl: 1,[b] I: 1[b]	3.54	3.53	−0.01	28
293	3-Chloroiodobenzene	H: 4, Ph: 1, Cl: 1,[b] I: 1[b]	3.55	3.53	−0.02	28
294	*p*-Cymene	C: 4, H: 14, Brnc: 1, Ph: 1	3.76	4.14	0.38	32
295	Styrene	H: 8, C=C: 1, Ph: 1	2.81	2.45	−0.36	32
296	2-Chlorophenol	H: 4, Ph: 1, Cl: 1,[b] OH: 1[b]	1.05	0.92	−0.13	32
297	*n*-Butylbenzene	C: 4, H: 14, Ph: 1	3.94	4.24	0.30	45
298	*sec*-Butylbenzene	C: 4, H: 14, Brnc: 1, Ph: 1	3.67	4.14	0.47	45
299	*tert*-Butylbenzene	C: 4, H: 14, Brnc: 2, Ph: 1	3.60	4.04	0.44	45
300	*tert*-Amylbenzene	C: 5, H: 16, Brnc: 2, Ph: 1	4.15	4.65	0.50	45
301	Thiophenol	H: 5, Ph: 1, SH: 1[b]	2.12	2.12	0.00	45
302	Thioanisole	C: 1, H: 8, Ph: 1, –S–: 1[b]	2.39	2.39	0.00	45
303	Anisole	C: 1, H: 8, Ph: 1, –O–: 1[b]	2.88	2.49	−0.39	45
304	1-Bromo-2-ethylbenzene	C: 2, H: 9, Ph: 1, Br: 1[b]	3.67	3.79	0.12	45
305	Benzaldehyde	H: 5, Ph: 1, CHO: 1[b]	1.21	1.21	0.00	45
306	Acetophenone	C: 1, H: 8, Ph: 1, C=O: 1[b]	1.34	1.34	0.00	45
307	Methyl benzoate	C: 1, H: 8, Ph: 1, CO_2: 1[b]	1.53	1.60	0.07	45
308	2-Ethylnaphthalene	C: 2, H: 12, Ph: 1.67	4.29	3.98	−0.31	52
309	2,4-Dichlorobiphenyl	H: 8, Ph: 2, Cl: 2[b]	5.20	4.84	−0.36	53
310	2,5-Dichlorobiphenyl	H: 8, Ph: 2, Cl: 2[b]	5.59	4.84	−0.75	53
311	α,α,α-Trifluorotoluene	C: 1, H: 5, Brnc: 2, F: 3, 3-hal: 1, Ph: 1	2.51	2.98	0.47	58
312	α-Chlorotoluene	C: 1, H: 7, Cl: 1, Ph: 1	2.43	2.17	−0.26	58
313	*m*-Cresol	C: 1, H: 7, Ph: 1, OH: 1[b]	0.66	0.79	0.13	2
314[a]	3-Chlorobiphenyl	H: 9, Ph: 2, Cl: 1[b]	5.16	4.10	−1.06	53

Brnc, branch; p-OH, primary alcohol; s-OH, secondary alcohol; t-OH, tertiary alcohol. *a*) These were not used in the optimization calculation in the correlation. *b*) These are aromatic substituents (Table IV). *c*) *S* is the molar concentration. *d*) Calculated values for compounds were obtained by using the constants in Tables II—IV. *e*) References are: 1) C. Hansch, J. E. Quinlan and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968). 2) A. Seidell, "Solubilities of Organic Compounds," Vol. 2, 3rd ed., D. Van Nostrand Co., New York, 1941. 3) P. M. Gross and J. H. Saylor, *J. Am. Chem. Soc.*, **53**, 1744 (1931). 4) P. M. Gross, J. H. Saylor and A. Gorman, *J. Am. Chem. Soc.*, **55**, 650 (1933). 5) H. Fuhner, *Ber.*, **57**, 510 (1942). 6) J. A. V. Butler, D. W. Thompson and W. H. Maclennan, *J. Chem. Soc.*, **1933**, 674. 7) P. M. Ginnings and R. Baum, *J. Am. Chem. Soc.*, **59**, 1111 (1937). 8) P. M. Ginnings and R. Webb, *J. Am. Chem. Soc.*, **60**, 1388 (1938). 9) P. M. Ginnings and M. Hauser, *J. Am. Chem. Soc.*, **60**, 2581 (1938). 10) P. M. Ginnings and D. Coltrane, *J. Am. Chem. Soc.*, **61**, 525 (1939). 11) P. M. Ginnings, E. Herring and D. Coltrane, *J. Am. Chem. Soc.*, **61**, 807 (1939). 12) P. M. Ginnings, D. Plonk and E. Carter, *J. Am. Chem. Soc.*, **62**, 1923 (1940). 13) A. P. Altshuller and H. E. Everson, *J. Am. Chem. Soc.*, **75**, 1727 (1953). 14) H. Sobotka and J. Kahn, *J. Am. Chem. Soc.*, **53**, 2935 (1931). 15) G. M. Bennett and W. G. Phillip, *J. Chem. Soc.*, **1928**, 1930. 16) P. Gross, *J. Am. Chem. Soc.*, **51**, 2362 (1929). 17) K. Kinoshita, H. Ishikawa and K. Shinoda, *Bull. Chem. Soc. Jpn.*, **31**, 1081 (1958). 18) R. L. Bohon and W. F. Claussen, *J. Am. Chem. Soc.*, **73**, 1571 (1951). 19) D. S. Goodman, *J. Am. Chem. Soc.*, **80**, 3887 (1958). 20) E. M. Arnett, W. B. Kover and J. V. Carter, *J. Am. Chem. Soc.*, **91**, 4028 (1969). 21) R. Smiss and C. Tanford, *Proc. Nat. Acad. Sci. U.S.A.*, **70**, 289 (1973). 22) W. F. Claussen and M. F. Polglase, *J. Am. Chem. Soc.*, **74**, 4817 (1952). 23) T. J. Morrison and F. Billett, *J. Chem. Soc.*, **1952**, 3819. 24) C. V. Than, *Ber.*, **36**, 1408 (1901). 25) S. R. Palit, *J. Phys. Chem.*, **51**, 837 (1947). 26) I. Fischer and L. Ehrenberg, *Acta Chem. Scand.*, **2**, 669 (1948). 27) C. McAuliffe, *J. Phys. Chem.*, **70**, 1267 (1966). 28) S. H. Yalkowsky and S. C. Valvani, *J. Pharm. Sci.*, **69**, 912 (1980). 29) S. H. Yalkowsky, G. L. Flynn and T. G. Slunick, *J. Pharm. Sci.*, **61**, 852 (1972). 30) E. Martin, S. H. Yalkowsky and J. E. Wells, *J. Pharm. Sci.*, **68**, 565 (1979). 31) A. Martin, J. Newburger and A. Adjei, *J. Pharm. Sci.*, **69**, 487 (1980). 32) S. H. Yalkowsky and S. C. Valvani, *Environ. Sci. Technol.*, **14**, 1227 (1980). 33) S. H. Yalkowsky, *J. Pharm. Sci.*, **70**, 971 (1981). 34) C. T. Chiou, D. W. Schmedding and J. H. Block, *J. Pharm. Sci.*, **70**, 1176 (1981). 35) S. H. Yalkowsky and S. C. Valvani, *J. Pharm. Sci.*, **70**, 1177 (1981). 36) S. H. Yalkowsky, S. C. Valvani and T. J. Roseman, *J. Pharm. Sci.*, **72**, 866 (1983). 37) M. H. Abraham, *J. Am. Chem. Soc.*, **104**, 2087 (1982). 38) M. J. Kamlet, R. Doherty, R. W. Taft and M. H. Abraham, *J. Am. Chem. Soc.*, **105**, 6741 (1983). 39) M. H. Abraham, M. J. Kamlet, R. W. Taft and P. K. Weathersby, *J. Am. Chem. Soc.*, **105**, 6797 (1983). 40) M. J. Kamlet, R. M. Doherty, R. W. Taft, M. H. Abraham and W. J. Koros, *J. Am. Chem. Soc.*, **106**, 1205 (1984). 41) M. Mashima, R. R. McIver, Jr. and R. W. Taft, *J. Am. Chem. Soc.*, **106**, 2717 (1984). 42) M. J. Kamlet, M. H. Abraham, R. M. Doherty and R. W. Taft, *J. Am. Chem. Soc.*, **106**, 464 (1984). 43) R. B. Hermann, *J. Phys. Chem.*, **75**, 363 (1971). 44) R. B. Hermann, *J. Phys. Chem.*, **76**, 2754 (1972). 45) J. Hine and P. K. Mookerjee, *J. Org. Chem.*, **40**, 292 (1975). 46) C.

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TABLE II. Fundamental Fragment Solubility Constants Derived from Aliphatic Liquid Hydrocarbons

Fragment[a)]	f_s	$n^{b)}$
C	0.37	46
H	0.12	46
C≡C	−0.19	7
C=C	0.41	21
Brnc	−0.10	18
Ring	−0.40	14

a) C, sp^3 carbon; H, hydrogen attached to carbon atom; Brnc, branch. *b)* Number of compounds used for the determination of f_s.

determine fundamental fragment solubility constants, that is, f_s values for C, H, C≡C, C=C, branch and ring listed in Table II, by the least-squares method based on Eq. 5. Although the values for branch and ring are in fact correction constants, here we would like to treat them as identical to the other fragments. It is reasonable for the f_s values for C, H and C=C to be positive and those for C≡C, branch and ring to be negative compared with hydrophobic fragment constants.[11)] One compound (No. 47) was not used in the optimization or in the following correlation, because the observed solubility compared with those of the congeners is so small that the datum seems to be of poor quality. The correlation of the log 1/*S* values (computed from the observed solubilities) with the calculated $\sum f_s$ is shown in Eq. 6, where the figures in parentheses are the 95% confidence intervals.

$$\log 1/S = 0.986\ (\pm 0.041) \sum f_s - 0.006\ (\pm 0.141) \qquad (6)$$

$$n = 46,\ r = 0.991,\ s = 0.122$$

The equation produces excellent results from a statistical point of view. The standard deviation shows that the aqueous solubilities of the compounds correlated are calculated in the range of 1.32 times (antilog of 0.122) on average. More than 98% of the variance in the data ($r^2 > 0.98$) can be accounted for by this equation.

These 6 f_s values were fixed to determine the 19 f_s values in Table III using all aliphatic liquids (No. 1—250 in Table I) for which aqueous solubilities have been found. The f_s value of a branch is defined for all atoms except hydrogens at this stage, although it has been determined using only hydrocarbons as shown in Table II. Here the constant of a branch is assumed to be the correction term of molar volume or surface area generated and is not presumed to accout for other effects such as electronic or polar effects, which are separately defined in other fragments. The fragment constants of alcohols are calculated independently for a primary, a secondary and a tertiary alcohol, whose values decreased with the multiplicity of branching in the carbon atom attached to the alcohol function. This seems reasonable because the negative inductive effects increase with the multiplicity, outweighing the compensating effect of the branching index in hydrocarbons. The large negative values for alcohols, ketones, aldehydes, esters, ethers, CN and NO_2 functions might be considered to be useful for designing more soluble compounds with these functions. The difference between the value for Cl on a

TABLE III. Fragment Solubility Constants of Various Functions Derived from Aliphatic Liquids

Fragment[a]	f_s	n[b]
p-OH	−2.65	24
s-OH	−2.82	30
t-OH	−3.17	15
SH	−0.74	1
C=O (ketones)	−2.43	16
CHO	−1.82	4
CO_2 (esters)	−1.90	35
–O– (ethers)	−2.51	19
–S– (thioethers)	−0.69	3
F	−0.17	3
Cl	−0.12	26
Br	0.05	15
I	0.40	6
2-Hal	0.67	14
3-Hal	1.64	7
4-Hal	2.60	1
CN	−1.29	2
NO_2	−1.10	5
d-Cl	0.40	5

a) p-OH, primary alcohol; s-OH, secondary alcohol; t-OH, tertiary alcohol; F, Cl, Br, I, halogens attached to sp^3 carbons; 2-hal, 3-hal, 4-hal, di-, tri-, tetrahalogens attached to a carbon respectively. d-Cl, chlorine on a carbon–carbon double bond. *b*) Number of compounds used for the determination of f_s.

saturated carbon and that on a double bond might be ascribed to the diverse polarization modes, that is, the former exhibiting a partially negative chlorine owing to inductive effects and the latter a delocalized system owing to inductive as well as mesomeric effects. Multihalogens attached to one carbon (dihalo, trihalo and tetrahalo correction terms) cause a great decrease in aqueous solubility, exceeding the compensating effect of the branching index in hydrocarbons. This might be ascribed to the restriction of the polarization resulting from the electronic repulsions between halogen atoms. The f_s values for thiols, aldehydes, sulfides, F, tetrahalo and CN functions are based on less than five compounds, and may be improved by increasing the number of compounds. The correlation of log $1/S$ with $\sum f_s$ is shown in Eq. 7; the correlation coefficient is still very good. The standard deviation shows that the aqueous solubility of the aliphatic liquids correlated (249 compounds) are computed in the range of 1.74 times (antilog of 0.241) on average. Five compounds (No. 251—255 in Table I) were removed from the optimization and the correlation. The much smaller calculated values than the observed values for the vinyl ethers (No. 252 and No. 253) having the electrons of the oxygen delocalized over the vinyl bond with decreasing hydrophilicity and for the malonate (No. 251), the ketal (No. 254) and the 1,2-diethoxyethane (No. 255) having two hydrophilic groups located very close to each other are accounted for through restricted polarization in order to avoid electronic repulsion.

$$\log 1/S = 0.945\ (\pm 0.023) \sum f_s + 0.060\ (\pm 0.050) \qquad (7)$$
$$n = 249,\quad r = 0.981,\quad s = 0.241$$

Calculation of Aromatic Fragment Solubility Constants and Correlation of All Organic Liquids

The above 25 f_s values (in Tables II and III) were fixed to calculate the 15 aromatic fragment solubility constants in Table IV employing 58 aromatic liquids (No. 256—313 in Table I) whose aqueous solubilities were found in the literature. Since all f_s constants except

TABLE IV. Fragment Solubility Constants of Aromatic Liquids

Fragment[a]	f_s	n[b]
Ph	1.08	58
CH_2OH	−1.23	1
F	0.21	4
Cl	0.86	11
Br	0.89	6
I	1.11	3
NO_2	−0.04	4
CO_2 (esters)	−0.81	2
NH_2	−1.27	1
–O– (ethers)	0.08	2
–S– (thioethers)	−0.02	1
OH	−1.50	2
SH	0.44	1
C=O (ketones)	−1.07	1
CHO	−0.47	1

a) Ph shows only carbon atoms excluding substituents as well as hydrogens. Fragments except Ph are aromatic substituents which are directly attached to the benzenoid rings. *b*) Number of compounds used for the determination of f_s.

for Ph, Cl and Br were determined on the basis of too small a number of compounds, they should be refined in the future to improve the values. However the present constants in Table IV seem to be reasonably satisfactory, that is, the negative values of CH_2OH, NO_2, esters, ethers, alcohols, ketones and aldehydes are smaller than the corresponding aliphatic constants just as in the case of the π constants[11] and the values of halogens can be rationalized in the same way as that of Cl on a double bond.

The correlation of the observed log $1/S$ with the calculated $\sum f_s$ of aromatic liquids is shown in Eq. 8. From this, the total organic liquids were correlated to give Eq.9, which gives excellent results from a statistical point of view. The standard deviation shows that the aqueous solubilities of the organic liquids correlated (307 compounds) are calculated in the range of 1.76 times (antilog of 0.245) on average.

$$\log 1/S = 0.993(\pm 0.062)\sum f_s + 0.013(\pm 0.191) \quad (8)$$
$$n=58,\quad r=0.974,\quad s=0.254$$

$$\log 1/S = 0.957(\pm 0.021)\sum f_s + 0.048(\pm 0.049) \quad (9)$$
$$n=307,\quad r=0.982,\quad s=0.245$$

Calculation of Organic Fragment Solubility Constants from the Aqueous Solubilities of Organic Solids

Aqueous solubilities of organic solids, which are related to the heat of fusion as well as the solubility properties of the constituent fragments, are difficult to calculate because of the symmetric characteristics of the molecules, the arrangements and the stabilities of crystals, and various other factors affecting the heat of fusion. There are several papers where melting points are employed as a correction term in estimating the heat of fusion.[2,5,13,14] We also wished to use melting points in place of heat of fusion, which is not always easy to estimate. However, our method is not identical to the others, but is suitable for optimizing the coefficient of the melting point term as well as the fragment solubility constants. The merit of this pragmatic method is the separation of the intrinsic solubility properties of the fragments from the contribution of the heat of fusion. What has bothered us very much in designing more soluble compounds is that the introduction of hydrophilic groups (such as sulfonamides,

TABLE V. Aqueous Solubilities and Fragments of Aliphatic Solids

No.	Compounds	Fragment[a]	$\log 1/S$		$\Delta \log 1/S$	Ref.[b]
			Obsd.	Calcd.		
1	2,2-Dimethyl-1-propanol	C: 5, H: 11, Brnc: 2, MP: 0.27	0.39	0.42	0.03	1, 7
2	Hexachloroethane	C: 2, Brnc: 4, Cl: 6, 3-hal: 2, MP: 1.62	3.67	3.50	−0.17	45
3	Tetrabromomethane	C: 1, Brnc: 2, Br: 4, 4-hal: 1, MP: 0.63	3.14	3.20	0.06	3, 58
4	Methyl carbamate	C: 1, H: 3, MP: 0.27, NH_2CO_2: 1	−0.96	−1.06	−0.10	5
5	Ethyl carbamate	C: 2, H: 5, MP: 0.23, NH_2CO_2: 1	−0.73	−0.47	0.27	5
6	Propyl carbamate	C: 3, H: 7, MP: 0.35, NH_2CO_2: 1	0.13	0.19	0.06	5
7	Isobutyl carbamate	C: 4, H: 9, Brnc: 1, MP: 0.42, NH_2CO_2: 1	0.77	0.73	−0.04	5
8	Isoamyl carbamate	C: 5, H: 11, Brnc: 1, MP: 0.24, NH_2CO_2: 1	1.44	1.27	−0.17	5
9	1-Tetradecanol	C: 14, H: 29, p-OH: 1, MP: 0.13	5.84	6.06	0.22	28
10	1-Pentadecanol	C: 15, H: 31, p-OH: 1, MP: 0.20	6.35	6.69	0.34	28
11	1-Hexadecanol	C: 16, H: 33, p-OH: 1, MP: 0.23	7.00	7.32	0.32	28
12	1-Octadecanol	C: 18, H: 37, p-OH: 1, MP: 0.33	8.40	8.57	0.17	28
13	Triiodomethane	C: 1, H: 1, Brnc: 1, I: 3, 3-hal: 1, MP: 1	3.55	3.60	0.05	58
14	1,2-Diiodoethylene	H: 2, C=C: 1, MP: 0.48, d-I: 2	3.22	3.23	0.01	58
15	Menthol	C: 10, H: 19, Brnc: 4, ring: 1, s-OH: 1, MP: 0.16	2.57	2.42	−0.15	2

a) Fragments are compiled in Tables II, IV and VI. *b)* References are the same as those in Table I.

TABLE VI. Fragment Solubility Constants Derived from Aliphatic Solids

Fragment[a]	f_s	n[b]
MP	0.37	15
NH_2CO_2	−1.89	5
d-I	1.20	1

a) MP, (melting point (°C) − 25)/100; NH_2CO_2, carbamates; d-I, iodine on a carbon–carbon double bond. *b)* Number of compounds used for the determination of f_s.

carboxamides, ketones and even alcohols) into a specific molecule often makes the modified compounds more insoluble. In these examples, markedly higher melting points than those of the original molecules have been observed, without exception.

For the aliphatic solids (15 compounds) shown in Table V, Eq. 5 was applied to optimize the fragment solubility constants of carbamates and iodine on a double bond, and the coefficient of MP, which is derived from the following equation to obtain equiscalar values with other fragment constants (melting point (°C) − 25)/100. Of course, the values of the other fragments were taken from Tables II and III. The new fragment constants are shown in Table VI. The correlation of the aqueous solubilities with $\sum f_s$ was computed to give Eq. 10. Unfortunately, although the equation is excellent, the solubilities of only a rather small number of aliphatic solids were determined. The analysis of aliphatic solids should be extended to cover more compounds in order to obtain more detailed understanding.

$$\log 1/S = 0.969(\pm 0.029)\sum f_s + 0.036(\pm 0.122) \qquad (10)$$

$$n = 15, \quad r = 0.999, \quad s = 0.151$$

TABLE VII. Aqueous Solubilities and Fragments of Aromatic Solids

No.	Compounds	Fragment	log 1/S		Δ log 1/S	Ref.[c]
			Obsd.	Calcd.		
1	4-Nitroaniline	H: 4, Ph: 1, NO$_2$: 1,[b] NH$_2$: 1,[b] MP: 1.24	2.28	2.02	−0.26	3
2	1,3-Dinitrobenzene	H: 4, Ph: 1, NO$_2$: 2,[b] MP: 0.63	2.41	2.38	−0.03	3
3	1,4-Dichlorobenzene	H: 4, Ph: 1, Cl: 2,[b] MP: 0.29	3.28	3.69	0.41	3, 45, 58
4[a]	2-Nitroaniline	H: 4, Ph: 1, NO$_2$: 1,[b] NH$_2$: 1,[b] MP: 0.46	1.97	0.91	−1.06	4
5	3-Nitroaniline	H: 4, Ph: 1, NO$_2$: 1,[b] NH$_2$: 1,[b] MP: 0.87	2.06	1.49	−0.57	4
6	4-Nitroanisole	C: 1, H: 7, Ph: 1, NO$_2$: 1,[b] –O–: 1,[b] MP: 0.29	2.41	2.74	0.33	4
7	4-Nitrotoluene	C: 1, H: 7, Ph: 1, NO$_2$: 1,[b] MP: 0.27	2.49	2.64	0.15	4
8	Biphenyl	H: 10, Ph: 2, MP: 0.44	4.31	3.99	−0.32	18, 53
9	Naphthalene	H: 8, Ph: 1.67, MP: 0.55	3.57	3.55	−0.02	18, 45
10[a]	2-Nitrophenol	H: 4, Ph: 1, NO$_2$: 1,[b] OH: 1,[b] MP: 0.19	1.62	0.29	−1.33	25
11	3-Nitrophenol	H: 4, Ph: 1, NO$_2$: 1,[b] OH: 1,[b] MP: 0.71	0.66	1.04	0.38	25
12	4-Nitrophenol	H: 4, Ph: 1, NO$_2$: 1,[b] OH: 1,[b] MP: 0.87	0.63	1.26	0.63	25
13	2-Methylnaphthalene	C: 1, H: 10, Ph: 1.67, MP: 0.09	3.75	3.50	−0.25	28, 54, 56
14	1,5-Dimethylnaphthalene	C: 2, H: 12, Ph: 1.67, MP: 0.56	4.68	4.78	0.10	28, 54
15	2,3-Dimethylnaphthalene	C: 2, H: 12, Ph: 1.67, MP: 0.77	4.72	5.08	0.36	28, 54, 56
16	2,6-Dimethylnaphthalene	C: 2, H: 12, Ph: 1.67, MP: 0.83	4.89	5.17	0.28	28, 54, 56
17	Acenaphthene	C: 2, H: 10, ring: 1, Ph: 1.67, MP: 0.70	4.59	4.34	−0.25	28, 54, 56
18	Fluorene	C: 1, H: 10, ring: 1, Ph: 2, MP: 0.87	4.92	4.57	−0.35	28, 56
19	Phenanthrene	H: 10, Ph: 2.33, MP: 0.74	5.15	4.77	−0.38	28, 54
20	Anthracene	H: 10, Ph: 2.33, MP: 1.89	6.38	6.42	0.04	28, 54
21	2-Methylanthracene	C: 1, H: 12, Ph: 2.33, MP: 1.79	6.69	6.89	0.20	28, 54, 56
22	9-Methylanthracene	C: 1, H: 12, Ph: 2.33, MP: 0.54	5.87	5.10	−0.77	28, 54, 56
23	9,10-Dimethylanthracene	C: 2, H: 14, Ph: 2.33, MP: 1.57	6.57	7.18	0.61	28, 54, 56
24	Pyrene	H: 10, Ph: 2.67, MP: 1.24	6.18	5.86	−0.32	28, 54, 56
25	Fluoranthene	H: 10, Ph: 2.67, MP: 0.82	5.90	5.26	−0.64	28, 50, 54
26	1,2-Benzofluorene	C: 1, H: 12, ring: 1, Ph: 2.67, MP: 1.62	6.68	6.61	−0.07	28, 54, 56
27	2,3-Benzofluorene	C: 1, H: 12, ring: 1, Ph: 2.67, MP: 1.84	7.27	6.92	−0.35	28
28	Chrysene	H: 12, Ph: 3, MP: 2.25	8.06	7.90	−0.16	28, 54, 56
29	Triphenylene	H: 12, Ph: 3, MP: 1.70	6.73	7.11	0.38	28, 50, 54
30	Naphthacene	H: 12, Ph: 3, MP: 3.32	8.69	9.43	0.74	28, 50, 54
31	1,2-Benzanthracene	H: 12, Ph: 3, MP: 1.32	7.21	6.57	−0.64	28, 54, 56
32	9,10-Dimethyl-1,2-benzanthracene	C: 2, H: 16, Ph: 3, MP: 0.96	6.63	7.27	0.64	28, 54
33	Perylene	H: 12, Ph: 3.33, MP: 2.52	8.80	8.64	−0.16	28, 50, 54

TABLE VII. (continued)

No.	Compounds	Fragment	$\log 1/S$ Obsd.	$\log 1/S$ Calcd.	$\Delta \log 1/S$	Ref.[c]
34	3,4-Benzopyrene	H: 12, Ph: 3.33, MP: 1.50	7.82	7.18	−0.64	28, 54, 56
35	3-Methylcholanthrene	C: 3, H: 16, ring: 1, Ph: 3, MP: 1.54	7.97	8.07	0.10	28, 54
36	Benzo[*g*, *h*, *i*]perylene	H: 12, Ph: 3.67, MP: 2.02	9.02	8.29	−0.73	28, 50, 54
37[a]	Coronene	H: 12, Ph: 4, MP: 4.14	9.33	11.68	2.35	56
38[a]	Hexachlorobenzene	Ph: 1, Cl: 6,[b] MP: 2.02	7.76	9.13	1.37	28
39	Pentachlorobenzene	H: 1, Ph: 1, Cl: 5,[b] MP: 0.57	5.65	6.32	0.66	28
40	1,2,3,4-Tetrachlorobenzene	H: 2, Ph: 1, Cl: 4,[b] MP: 0.21	4.70	5.06	0.36	28
41	1,2,3,5-Tetrachlorobenzene	H: 2, Ph: 1, Cl: 4,[b] MP: 0.25	4.79	5.12	0.33	28
42	1,2,4,5-Tetrachlorobenzene	H: 2, Ph: 1, Cl: 4,[b] MP: 1.13	5.56	6.38	0.82	28
43	1,2,4,5-Tetrabromobenzene	H: 2, Ph: 1, Br: 4,[b] MP: 1.57	6.98	7.13	0.14	28
44	1,2,4-Tribromobenzene	H: 3, Ph: 1, Br: 3,[b] MP: 0.19	4.50	4.38	−0.12	28
45	1,3,5-Tribromobenzene	H: 3, Ph: 1, Br: 3,[b] MP: 0.96	5.60	5.48	−0.12	28
46	1,2,3-Trichlorobenzene	H: 3, Ph: 1, Cl: 3,[b] MP: 0.26	3.76	4.39	0.63	28
47	1,3,5-Trichlorobenzene	H: 3, Ph: 1, Cl: 3,[b] MP: 0.38	4.44	4.56	0.12	28
48	1,4-Dibromobenzene	H: 4, Ph: 1, Br: 2,[b] MP: 0.62	4.07	4.23	0.16	45, 58
49	1,2-Diiodobenzene	H: 4, Ph: 1, I: 2,[b] MP: 0.02	4.24	3.81	−0.43	28
50	1,3-Diiodobenzene	H: 4, Ph: 1, I: 2,[b] MP: 0.15	4.57	3.99	−0.58	28
51	1,4-Diiodobenzene	H: 4, Ph: 1, I: 2,[b] MP: 1.06	5.25	5.30	0.05	28
52	4-Bromochlorobenzene	H: 4, Ph: 1, Cl: 1,[b] Br: 1,[b] MP: 0.41	3.63	3.90	0.27	28
53	4-Chloroiodobenzene	H: 4, Ph: 1, Cl: 1,[b] I: 1,[b] MP: 0.28	4.03	3.93	−0.10	28
54	Methyl *p*-aminobenzoate	C: 1, H: 7, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.87	1.60	1.45	−0.15	28, 29
55	Ethyl *p*-aminobenzoate	C: 2, H: 9, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.63	1.99	1.72	−0.27	28, 29
56	Propyl *p*-aminobenzoate	C: 3, H: 11, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.49	2.33	2.13	−0.20	28, 29
57	Butyl *p*-aminobenzoate	C: 4, H: 13, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.31	2.76	2.48	−0.28	28, 29
58	Pentyl *p*-aminobenzoate	C: 5, H: 15, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.27	3.35	3.04	−0.31	28, 29
59	Hexyl *p*-aminobenzoate	C: 6, H: 17, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.36	3.95	3.77	−0.18	28
60	Heptyl *p*-aminobenzoate	C: 7, H: 19, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.50	4.60	4.59	−0.01	28, 29
61	Octyl *p*-aminobenzoate	C: 8, H: 21, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.46	5.40	5.14	−0.26	28, 29
62	Nonyl *p*-aminobenzoate	C: 9, H: 23, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.44	6.00	5.72	−0.28	28, 29
63	Dodecyl *p*-aminobenzoate	C: 12, H: 29, Ph: 1, CO_2: 1,[b] NH_2: 1,[b] MP: 0.57	7.80	7.74	−0.06	28, 29
64	Methyl *p*-hydroxybenzoate	C: 1, H: 7, Ph: 1, CO_2: 1,[b] OH: 1,[b] MP: 1.01	1.84	1.42	−0.42	28
65	Ethyl *p*-hydroxybenzoate	C: 2, H: 9, Ph: 1, CO_2: 1,[b] OH: 1,[b] MP: 0.91	2.22	1.89	−0.33	28
66	Propyl *p*-hydroxybenzoate	C: 3, H: 11, Ph: 1, CO_2: 1,[b] OH: 1,[b] MP: 0.70	2.59	2.20	−0.39	28
67	Butyl *p*-hydroxybenzoate	C: 4, H: 13, Ph: 1, CO_2: 1,[b] OH: 1,[b] MP: 0.43	2.89	2.42	−0.47	28
68[a]	3,3′-Dichlorobenzidine	H: 6, Ph: 2, Cl: 2,[b] NH_2: 2,[b] MP: 1.07	4.91	3.59	−1.32	32

TABLE VII. (continued)

No.	Compounds	Fragment	$\log 1/S$		$\Delta \log 1/S$	Ref.[c]
			Obsd.	Calcd.		
69[a]	Diphenyl ether	Ph: 2, –O–: 1,[b] MP: 0.03	3.97	2.28	−1.69	32
70[a]	2,4-Dimethylphenol	C: 2, H: 9, Ph: 1, OH: 1,[b] MP: 0.01	3.19	1.41	−1.78	32
71[a]	2-Bromo-1-isopropylbenzene	C: 3, H: 11, Brnc: 1, Ph: 1, Br: 1,[b] MP: 0.81	4.19	5.46	1.27	45, 58
72	4-Bromotoluene	C: 1, H: 7, Ph: 1, Br: 1,[b] MP: 0.01	3.19	3.19	0.00	45, 58
73	Dibenz[*a*, *h*]anthracene	H: 14, Ph: 3.67, MP: 2.44	8.74	9.13	0.39	50
74	Benzo[*e*]pyrene	H: 12, Ph: 3.33, MP: 1.51	7.72	7.20	−0.52	50
75[a]	Benzo[*b*]fluorancene	H: 12, Ph: 3.33, MP: 1.43	8.23	7.08	−1.15	50
76	Benzo[*j*]fluoranthene	H: 12, Ph: 3.33, MP: 1.41	8.00	7.05	−0.95	50
77	Benzo[*k*]fluoranthene	H: 12, Ph: 3.33, MP: 2.27	8.50	8.28	−0.22	50
78	Indeno[1,2,3-*cd*]pyrene	H: 12, Ph: 3.67, MP: 2.51	9.16	8.99	−0.17	50
79[a]	Dibenz[*aj*]anthracene	H: 14, Ph: 3.67, MP: 2.53	7.51	9.26	1.75	50
80	2-Chlorobiphenyl	H: 9, Ph: 2, Cl: 1,[b] MP: 0.09	4.50	4.23	−0.27	53
81	4-Chlorobiphenyl	H: 9, Ph: 2, Cl: 1,[b] MP: 0.53	5.21	4.86	−0.35	53
82	2,2′-Dichlorobiphenyl	H: 8, Ph: 2, Cl: 2,[b] MP: 0.36	5.17	5.35	0.18	53
83	2,4′-Dichlorobiphenyl	H: 8, Ph: 2, Cl: 2,[b] MP: 0.18	5.54	5.10	−0.44	53
84	4,4′-Dichlorobiphenyl	H: 8, Ph: 2, Cl: 2,[b] MP: 1.24	6.56	6.61	0.05	53
85	2,2′,5-Trichlorobiphenyl	H: 7, Ph: 2, Cl: 3,[b] MP: 0.19	6.16	5.85	−0.31	53
86	2′,3,4-Trichlorobiphenyl	H: 7, Ph: 2, Cl: 3,[b] MP: 0.35	6.52	6.08	−0.44	53
87	2,4,4′-Trichlorobiphenyl	H: 7, Ph: 2, Cl: 3,[b] MP: 0.32	6.48	6.04	−0.44	53
88	2,4,5-Trichlorobiphenyl	H: 7, Ph: 2, Cl: 3,[b] MP: 0.53	6.45	6.34	−0.11	53
89	3,4,4′-Trichlorobiphenyl	H: 7, Ph: 2, Cl: 3,[b] MP: 0.63	7.23	6.48	−0.75	53
90	2,2′,3,3′-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 0.96	6.93	7.69	0.76	53
91	2,2′,3,5-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 0.22	6.23	6.63	0.40	53
92	2,2′,4,4′-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 0.16	6.63	6.55	−0.08	53
93	2,2′,5,5′-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 0.62	7.96	7.21	−0.75	53
94[a]	2,3′,4,4′-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 1.03	6.70	7.79	1.09	53
95	2,3,4,5-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 0.67	7.18	7.28	0.10	53
96	2,3′,4′,5-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 0.79	6.85	7.45	0.60	53
97[a]	3,3′,4,4′-Tetrachlorobiphenyl	H: 6, Ph: 2, Cl: 4,[b] MP: 1.55	6.22	8.54	2.32	53
98	2,2′,3,4,5-Pentachlorobiphenyl	H: 5, Ph: 2, Cl: 5,[b] MP: 0.75	7.52	8.13	0.61	53
99	2,2′,3,4,5′-Pentachlorobiphenyl	H: 5, Ph: 2, Cl: 5,[b] MP: 0.87	7.86	8.30	0.44	53
100	2,2′,3-4,6-Pentachlorobiphenyl	H-5, Ph: 2, Cl: 5,[b] MP: 0.75	7.43	8.13	0.70	53
101	2,2′,4,5,5′-Pentachlorobiphenyl	H: 5, Ph: 2, Cl: 5,[b] MP: 0.52	7.50	7.80	0.30	53
102	2,3,4,5,6-Pentachlorobiphenyl	H: 5, Ph: 2, Cl: 5,[b] MP: 0.99	7.68	8.48	0.80	53
103	2,2′,3,3′,4,4′-Hexachlorobiphenyl	H: 4, Ph: 2, Cl: 6,[b] MP: 1.25	8.91	9.59	0.68	53

Table VII. (continued)

No.	Compounds	Fragment	log 1/*S*		Δ log 1/*S*	Ref.[c)]
			Obsd.	Calcd.		
104	2,2′,3,3′,4,5-Hexachlorobiphenyl	H: 4, Ph: 2, Cl: 6,[b)] MP: 0.60	8.63	8.66	0.03	53
105	2,2′,3,3′,5,6-Hexachlorobiphenyl	H: 4, Ph: 2, Cl: 6,[b)] MP: 0.75	8.60	8.87	0.27	53
106	2,2′,4,4′,5,5′-Hexachlorobiphenyl	H: 4, Ph: 2, Cl: 6,[b)] MP: 0.78	8.54	8.92	0.39	53
107	2,2′,4,4′,6,6′-Hexachlorobiphenyl	H: 4, Ph: 2, Cl: 6,[b)] MP: 0.89	8.60	9.07	0.47	53
108[a)]	2,2′,3,4′,5,5′,6-Heptachlorobiphenyl	H: 3, Ph: 2, Cl: 7,[b)] MP: 1.24	8.89	10.31	1.42	53
109[a)]	2,2′,3,3′,4,4′,5,5′-Octachlorobiphenyl	H: 2, Ph: 2, Cl: 8,[b)] MP: 1.34	9.16	11.20	2.04	53
110[a)]	2,2′,3,3′,5,5′,6,6′-Octachlorobiphenyl	H: 2, Ph: 2, Cl: 8,[b)] MP: 1.37	9.83	11.24	1.41	53
111[a)]	2,2′3,3′,4,4′,5,5′,6-Nonachlorobiphenyl	H: 1, Ph: 2, Cl: 9,[b)] MP: 1.81	9.62	12.61	2.99	53
112[a)]	Decachlorobiphenyl	Ph: 2, Cl: 10,[b)] MP: 2.80	10.49	14.76	4.27	53
113	Dichlorodiphenyltrichloroethane	C: 2, H: 9, Cl: 3, 3-hal: 1, Ph: 2, Cl: 2,[b)] MP: 0.83	8.47	8.17	−0.30	58
114[a)]	6-Fluoro-7-methylbenz[*a*]anthracene	C: 1, H: 13, Ph: 3, F: 1,[b)] MP: 0.85	7.72	6.60	−1.12	58
115	5-Fluoro-7-methylbenz[*a*]anthracene	C: 1, H: 13, Ph: 3, F: 1,[b)] MP: 1.17	7.72	7.05	−0.67	58
116	9-Chloro-7-methylbenz[*a*]anthracene	C: 1, H: 13, Ph: 3, Cl: 1,[b)] MP: 1.33	7.44	7.93	0.49	58
117	*m*-Phenylenediamine	H: 4, Ph: 1, NH$_2$: 2,[b)] MP: 0.39	−0.34	−0.42	−0.08	2
118[a)]	*p*-Phenylenediamine	H: 4, Ph: 1, NH$_2$: 2,[b)] MP: 2.20	0.47	2.17	1.70	2
119	*o*-Toluenesulfonamide	C: 1, H: 7, Ph: 1, MP: 1.18, SO$_2$NH$_2$: 1[b)]	2.02	1.90	−0.12	2
120	*m*-Toluenesulfonamide	C: 1, H: 7, Ph: 1, MP: 0.83, SO$_2$NH$_2$: 1[b)]	1.34	1.40	0.06	2
121	*p*-Toluenesulfonamide	C: 1, H: 7, Ph: 1, MP: 1.12, SO$_2$NH$_2$: 1[b)]	1.73	1.81	0.08	2
122	Benzamide	H: 5, Ph: 1, MP: 1.05, CONH$_2$: 1[b)]	1.32	1.32	0.00	2
123[a)]	Thymol	C: 4, H: 13, Brnc: 1, Ph: 1, OH: 1,[b)] MP: 0.24	1.10	2.86	1.76	2
124[a)]	*p*-Acetophenetide	C: 3, H: 12, Ph: 1, –O–: 1,[b)] MP: 1.09, NHC=O: 1[b)]	1.10	2.52	1.42	2
125	*p*-Acetanisidine	C: 2, H: 10, Ph: 1, –O–: 1,[b)] MP: 1.05, NHC=O: 1[b)]	1.04	1.85	0.81	2
126	Acetanilide	C: 1, H: 8, Ph: 1, MP: 0.88, NHC=O: 1[b)]	1.41	0.92	−0.49	2
127	*o*-Nitroacetanilide	C: 1, H: 7, Ph: 1, NO$_2$: 1,[b)] MP: 1.26, NHC=O: 1[b)]	1.91	1.30	−0.61	2
128	*p*-Nitroacetanilide	C: 1, H: 7, Ph: 1, NO$_2$: 1,[b)] MP: 1.89, NHC=O: 1[b)]	1.91	2.20	0.29	2
129	Vanillin	C: 1, H: 6, Ph: 1, –O–: 1,[b)] CHO: 1,[b)] OH: 1,[b)] MP: 0.55	1.18	1.07	−0.11	2
130[a)]	*o*-Toluidine	C: 1, H: 7, Ph: 1, NH$_2$: 1,[b)] MP: 1.75	0.85	3.52	2.67	2

TABLE VII. (continued)

No.	Compounds	Fragment	log $1/S$ Obsd.	log $1/S$ Calcd.	$\Delta \log 1/S$	Ref.[c]
131	Phthalimide	H: 4, Ph: 1, MP: 2.13, Imide: 1[b]	2.39	2.40	0.01	2
132	Phenylthiourea	H: 5, Ph: 1, MP: 1.29, Thiourea: 1[b]	1.86	1.86	0.00	2
133	*p*-Nitrobenzaldehyde	H: 4, Ph: 1, NO_2: 1,[b] CHO: 1,[b] MP: 0.80	1.81	2.19	0.38	2
134	*m*-Nitrobenzaldehyde	H: 4, Ph: 1, NO_2: 1,[b] CHO: 1,[b] MP: 0.32	1.97	1.51	−0.46	2

a) These compounds were not used in the optimization calculation or in the correlation. *b*) These fragments are aromatic substituents (Tables IV and VIII). *c*) References are the same as those in Table I.

TABLE VIII. Fragment Solubility Constants Derived from Aromatic Solids

Fragment[a]	f_s	n[b]
MP	1.43	112
SO_2NH_2	−2.08	3
$CONH_2$	−1.86	1
NHC=O (amides)	−2.75	5
Imide	−2.21	1
Thiourea	−1.66	1

a) Fragments except MP are aromatic substituents. *b*) Number of compounds used for the determination of f_s.

On the other hand, a considerable number of aromatic solids (more than 130 compounds) have known aqueous solubility values, as listed in Table VII. The optimization of 6 f_s values, including the coefficient of MP, was performed by the use of Eq. 5. These f_s values are shown in Table VIII. Large negative values for SO_2NH_2, $CONH_2$, NHCO, imide and thiourea were found. The coefficient of MP was far greater than that in Table VI. Comparing the coefficients to those found in the literature,[2,5,13,14] which are calculated to be 0.95—1.2 on the basis of our MP constants, the coefficient in Table VIII, namely 1.43, might be deemed reasonable. This value indicates that a difference of 100 °C between the melting points of two molecules with identical fragments (such as isomers) makes for a difference in solubilities by a factor of 10. On the other hand, the coefficient in Table VI is so small that it is difficult to understand; this will be checked when we get more solubility data on aliphatic solids.

$$\log 1/S = 0.963(\pm 0.031)\sum f_s + 0.208(\pm 0.175) \qquad (11)$$
$$n = 112, \quad r = 0.986, \quad s = 0.410$$

The correlation of the observed aqueous solubilities of aromatic solids with $\sum f_s$ was computed to give Eq. 11, which is not as good as the other equations (Eqs. 6—10) from a statistical standpoint. However, the correlation coefficient is comparable to the others and the standard deviation is small enough to show that the compounds correlated are calculated in the range of 2.57 times (antilog of 0.410) on average. In fact, 22 compounds showing large differences between observed and calculated values were removed from the optimization and the correlation. Although there are too many compounds to explain here why the differences arise, a few characteristic features may be mentioned. Molecules with a 1,2-disubstituted benzene moiety seem to have intramolecular interactions, and polyhalogenated compounds show restricted polarization because of disturbed electronic effects.

Conclusion

The largest available set of aqueous solubilities of organic molecules has been compiled. New fragment solubility constants have been determined from those of organic solids, as well as organic liquids, by separating the intrinsic solubility properties of the fragments from the term of heat of fusion. The correlation of the observed aqueous solubilities with the calculated values is excellent. In order to confirm this, the same set of organic liquids as calculated by Hansch and others[4-7] to give Eqs. 1—4 was correlated with the sum of fragment solubility constants to give Eq. 12, which is clearly better than the former equations from a statistical point of view. Approximately, 97.8% of the variance in the data (r^2) can be accounted for by this equation.

$$\log 1/S = 0.941\,(\pm 0.022) \sum f_s + 0.047\,(\pm 0.050) \qquad (12)$$
$$n = 156, \quad r = 0.989, \quad s = 0.195$$

The method for calculation of aqueous solubilities of organic compounds in this paper is not theoretical, but empirical, on the basis of additive and constitutive properties of fragment solubility constants. As a matter of fact, the most accurate method for calculation of log P of organic molecules is to add or substract π values from the measured log P values of the most similar compounds.[11] In the state of the art, we believe that the same can be concluded in the calculation of aqueous solubilities, and the fragment solubility method is therefore useful in practice.

The molecular modification of a specific compound to make it more soluble is not always easy, even for experienced organic chemists. This is because the introduction of a hydrophilic group often makes the compound more insoluble as a result of the formation of more stable crystalline structures with higher melting points through intermolecular interactions such as hydrogen bonding, ionic interaction, hydrophobic or desolvation effect and so on. On the other hand, effective design of more soluble molecules would involve disturbing the above interactions, and one of the easiest modifications would be to destroy symmetry elements of a molecule, thus lowering the melting point.

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