AAPS PharmSciTech **2006; 7 (1) Article 26 (http://www.aapspharmscitech.org).**

Solubility Prediction in Octanol: A Technical Note

Submitted: July 21, 2005; Accepted: December 29, 2005; Published: March 24, 2006

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KEYWORDS: octanol solubility, activity coefficient, solubility parameter.

SUMMARY

The purpose of this work was to derive an equation for the rapid estimation of octanol solubilities of organic compounds. Solubilities ranging over 4 orders of magnitude were predicted with an average absolute error of 0.39 logarithmic units using melting point alone. The greatest error in prediction occurred for strongly bonded compounds.

INTRODUCTION

The octanol solubility of environmental and pharmaceutically relevant compounds plays an important role in determining their partitioning and absorption behavior. The accurate prediction of octanol solubility will allow for better modeling and understanding the fate of environmental and pharmaceutically prevalent compounds. Quantitative structure-property relationship (QSPR) schemes for the prediction of the octanol solubility may be attempted; however, their applications are limited to specific classes of compounds.[1] To date, no simple method has been established for the prediction of the octanol solubility and a more general approach is needed.

According to Liu et al, the solubility of a solid solute is not only dependent on the activity coefficient of the solute in the solvent but also on its crystallinity.[2] The mole fraction solubility of a solute in octanol (X_{oct}) can be described by

$$log\ X_{oct} = -\frac{\Delta H_m(T_m - T)}{2.3 \cdot R \cdot T \cdot T_m} - log\ \gamma_{oct} \qquad (1)$$

ΔH_m and R denote the enthalpy of melting and ideal gas constant. T_m and T denote the melting point and reference temperature in Kelvin. It should be noted that Equation 1 assumes the heat capacity change on melting is negligible. The first part of the equation accounts for the crystal contribution to solubility and γ_{oct} represents the activity coefficient of the solute in octanol. In the case of liquid solutes, there is no crystallinity and the above equation is simplified to

$$log\ X^L_{oct} = -\ log\ \gamma_{oct} \qquad (2)$$

in which the solubility of a liquid solute is limited only by the activity coefficient of the solute in octanol.

The Scatchard-Hildebrand equation can be used for the estimation of the activity coefficient of a solute in octanol. This equation assumes mixing is random, interaction forces are additive, interaction is between the centers of molecules, and the constant pressure change of volume on mixing is zero.[3] While these assumptions are generally useful, they are not applicable to strongly hydrogen-bonded compounds such as water. Using octanol, a weakly hydrogen-bonded liquid, the Scatchard-Hildebrand activity coefficient of the solute is

$$log\ \gamma_{oct} = \frac{V_2\ \varphi^2_{oct}(\delta_{oct} - \delta_2)^2}{2.3 \cdot R \cdot T} \qquad (3)$$

where V_2 and δ_2 are the molar volume and solubility parameters of the solute, respectively, and δ_{oct} and φ_{oct} are the solubility parameter and volume fraction of octanol, respectively. Although this equation is intended for nonpolar solutes, numerous variations that account for hydrogen bonding are available. However, as a first approximation, the use of this equation for polar solutes in octanol is reasonable. Combining Equations 2 and 3 leads to Equation 4:

$$log\ X^L_{oct} = -\frac{V_2\ \varphi^2_{oct}(\delta_{oct} - \delta_2)^2}{2.3 \cdot R \cdot T} \qquad (4)$$

In order to estimate the solubility of liquid solutes in octanol, the following generalization is made. Complete miscibility of liquid solutes in octanol is given a mole fraction solubility value of 0.5 (X^L_{oct}). The upper critical solution temperature of 2 liquids (X_1 and X_2) occurs when $X_1 = X_2 = 0.5$.[4] This assumption was used by Hildebrand et al in the determination of the upper critical solution temperature.[4]

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Therefore, assuming that complete miscibility corresponds to a mole fraction solute solubility of 0.5, the volume fraction of octanol (Φ_{oct}) must also be 0.5. For complete miscibility (ie, $X_2 \geq 0.5$) and a reference temperature of 298 K, Equation 4 becomes

$$log\ (0.5) = -\frac{V_2 \cdot (0.5)^2\ (21.1 - \delta_2)^2}{5709} \qquad (5)$$

where 21.1 $(J/cm^3)^{0.5}$ is the solubility parameter of octanol. This equation is further simplified to

$$82.9 \geq \sqrt{V_2} \cdot |21.1 - \delta_2| \qquad (6)$$

Thus, from the molar volume of a liquid solute its range of complete miscibility with octanol can be obtained. For liquid solutes having solubility parameters outside the calculated range, phase separation will occur upon mixing with octanol. Table 1 depicts several hypothetical liquid molar volumes along with their corresponding ranges of complete miscibility with octanol obtained from Equation 6. As the molar volumes increase in Table 1, the range of complete miscibility decreases.

If a liquid solute has a molar volume near that of octanol (ie, 158 cm^3/mol), Equation 6 is simplified to

$$6.60 \geq |21.1 - \delta_2| \qquad (7)$$

This leads to a solubility parameter range of 15 to 28 $(J/cm^3)^{0.5}$ for liquid solutes that are completely miscible with octanol at 298 K.

Interestingly, the solubility parameters of most common environmental and pharmaceutical compounds fall within this range of complete miscibility with octanol.

Table 1. Liquid Molar Volumes and Corresponding Ranges of Complete Miscibility With Octanol

Liquid Molar Volume (cm^3/mol)	Range of Complete Miscibility $(J/cm^3)^{0.5}$
50	9.4 - 32.8
100	12.8 - 29.4
200	15.2 - 27.0
300	16.3 - 25.9
400	17.0 - 25.2
500	17.4 - 24.8

Since the molarity of pure dry octanol is 6.33 mol/L, a mole-fraction solubility of 0.50 corresponds to a molar solubility of 3.17 mol/L. Coincidentally, the logarithm of 3.17 is 0.50. Thus, if a liquid solute has a solubility parameter value in the above range of complete miscibility, the solubility in octanol (S^L_{oct}) can be approximated on a molar scale by

$$log\ S^L_{oct} = 0.5 \qquad (8)$$

The first part of Equation 1 accounts for the ideal crystalline solubility (X_i), which is a measure of the crystal contribution to solubility in an ideal solution. The ideal crystalline

Table 2. Miscibility Data of 32 Common Organic Liquid Solutes in Octanol*

Liquid Solute	Molar Volume (cm^3/mol)	Solubility Parameter $(J/cm^3)^{0.5}$	Miscibility	
			Obs	Pred
Butane	101	14.7	Y	Y
Hexane	130	14.9	Y	Y
Acetonitrile	52	15.2	Y	Y
Octane	162	15.6	Y	Y
Ether	105	15.7	Y	Y
Hexadecane	131	15.7	Y	Y
Cyclohexane	108	16.8	Y	Y
p-Xylene	123	17.3	Y	Y
Isopropyl Myristate	319	17.5	Y	Y
Carbon tetrachloride	96	17.8	Y	Y
Toluene	106	18.2	Y	Y
Ethyl acetate	99	18.2	Y	Y
Benzene	89	18.6	Y	Y
Chloroform	81	18.7	Y	Y
Acetone	73	20.1	Y	Y
Methylene chloride	65	20.2	Y	Y
Acetic acid	58	21.4	Y	Y
Nitrobenzene	102	22.3	Y	Y
PEG 600	350	22.5	Y	Y
Butanol	91	23.1	Y	Y
PEG 400	525	23.1	Y	Y
Benzyl alcohol	104	23.8	Y	Y
Propanol	75	24.6	Y	Y
PEG 200	175	26.1	Y	Y
DMSO	73	26.6	Y	Y
Ethanol	58	26.6	Y	Y
Methanol	40	29.7	Y	Y
Propylene glycol	74	30.7	Y	Y
Ethylene glycol	56	32.7	Y	Y
Glycerin	73	36.1	N	N
Formamide	40	36.7	N	N
Water	18	48.0	N	N

*Obs indicates observed miscibility data; Pred, predicted miscibility data; PEG, polyethylene glycol; and DMSO, dimethyl sulfoxide.

Table 3. Predicted Molar Solubilities Obtained With Equation 12 for 123 Reported Octanol Solubilities*

Compound	MP (°C)	Exp log S_{oct}	Est log S_{oct}	Abs Error
1,2,3,5-Tetrachlorobenzene	55	0.15	0.21	0.06
1,2,3-Trichlorobenzene	53	0.09	0.22	0.13
1,2,3-Trichlorobenzene	53	0.18	0.22	0.04
1,2,4,5-Tetrabromobenzene	182	–1.32	–1.07	0.25
1,2,4,5-Tetrachlorobenzene	139	–1.08	–0.64	0.44
1,2,4,5-Tetrachlorobenzene	139	–0.92	–0.64	0.28
1,2,4-Tribromobenzene	43	–0.15	0.32	0.47
1,3,5-Tribromobenzene	124	–0.90	–0.49	0.41
1,3,5-Trichlorobenzene	65	–0.16	0.10	0.26
1,4-Dibromobenzene	87	–0.30	–0.12	0.18
1,4-Dichlorobenzene	53	0.11	0.22	0.11
1,4-Dichlorobenzene	53	0.25	0.22	0.03
1,4-Dichlorobenzene	53	0.20	0.22	0.02
1-Methylfluorene	85	–0.56	–0.10	0.46
2,3,4-Trichloronitrobenzene	56	–0.29	0.20	0.49
2,3,5,6-Tetrachloronitrobenzene	100	–0.68	–0.25	0.43
2,3-Benzanthracene	341	–2.28	–2.66	0.38
2,3-Benzofluorene	208	–1.75	–1.33	0.42
2,4,6-Trichlorophenol	70	0.22	0.06	0.17
2,4-Dichlorophenol	45	0.36	0.30	0.06
2-Methyl-4-nitroimidazole	252	–1.77	–1.77	0.00
3,4-Dichloronitrobenzene	41	–0.08	0.34	0.42
Acenaphthene	94	–0.59	–0.19	0.40
Acetanilide	114	–0.12	–0.39	0.27
Acetylsalicyclic acid	135	–0.69	–0.60	0.09
Anthracene	216	–1.91	–1.41	0.50
Anthracene	216	–1.78	–1.41	0.37
Antipyrene	111	–0.19	–0.36	0.17
Atrazine	175	–1.32	–1.00	0.32
Barbital	190	–0.92	–1.15	0.23
Benzil	95	–0.89	–0.20	0.69
Benzo[a]pyrene	179	–1.60	–1.04	0.56
Benzoic acid	122	–0.95	–0.47	0.48
Benzoic acid	122	–0.06	–0.47	0.41
beta-Carotene	180	–0.75	–1.05	0.30
Bibenzyl	52	–0.35	0.23	0.58
Biphenyl	69	–0.13	0.06	0.19
Butyl p-aminobenzoate	58	0.13	0.17	0.04
Butyl p-hydroxybenzoate	69	0.34	0.06	0.28
Caffeine	238	–1.72	–1.63	0.09
Chrysene	258	–2.60	–1.83	0.77
Chrysene	258	–2.51	–1.83	0.68
Coronene	438	–3.41	–3.63	0.22
Cortisone	222	–1.97	–1.47	0.50
Decachlorobiphenyl	306	–2.77	–2.31	0.46
Deoxycorticosterone	142	–0.71	–0.67	0.04
Dibenz[a,h]anthracene	270	–3.03	–1.95	1.08
Dibenzofuran	82	–0.27	–0.07	0.20
Dieldrin	175	–0.97	–1.00	0.03
Dimetridazole	140	–1.11	–0.65	0.46
Diphenylamine	52	0.03	0.23	0.20
Diphenylethane	25	–0.66	0.50	1.16
Diuron	159	–1.14	–0.84	0.31
Endrin	200	–0.94	–1.25	0.31
Ethyl p-aminobenzoate	89	–0.31	–0.14	0.17
Ethyl p-hydroxybenzoate	116	0.04	–0.41	0.45

Table 3. Continued

Compound	MP (°C)	Exp log S_{oct}	Est log S_{oct}	Abs Error
Fenchlorphos	35	–0.16	0.40	0.56
Fenuron	134	–0.77	–0.59	0.19
Fenuron	134	–0.77	–0.59	0.19
Fluoranthene	108	–0.76	–0.33	0.43
Fluorene	112	–0.62	–0.37	0.25
Fluorodifen	94	–1.52	–0.19	1.33
Flurbiprofen	111	–0.20	–0.36	0.16
Gentisic acid	205	–0.13	–1.30	1.17
Heptachlor	95	–0.63	–0.20	0.43
Hexachlorobenzene	230	–1.86	–1.55	0.31
Hexachlorobenzene	230	–1.82	–1.55	0.27
Hexachloroethane	187	–0.28	–1.12	0.84
Hexamethylbenzene	164	–0.89	–0.89	0.00
Ibuprofen	76	0.18	–0.01	0.19
Ipronidazole	61	–0.06	0.14	0.20
Isazophos	25	0.50	0.50	0.00
Ketoprofen	94	–0.26	–0.19	0.07
Ketoprofen	94	–0.10	–0.19	0.09
Lindane	113	–0.74	–0.38	0.36
m-Bromobenzoic acid	157	–0.07	–0.82	0.75
Metalaxyl	72	–0.33	0.03	0.36
Methyl p-aminobenzoate	114	–0.53	–0.39	0.14
Methyl p-hydroxybenzoate	131	–0.08	–0.56	0.48
Methyltestosterone	163	–0.45	–0.88	0.43
Metolachlor	25	0.47	0.50	0.03
Metoxuron	127	–1.06	–0.52	0.55
Metronidazole	160	–1.53	–0.85	0.68
Mirex	485	–0.51	–4.10	3.59
Monuron	172	–1.04	–0.97	0.07
Naphthalene	80	–0.36	–0.05	0.31
Naphthalene	80	–0.15	–0.05	0.10
Naproxen	153	–0.89	–0.78	0.11
o,p′-DDT	75	–0.49	0.01	0.50
o-Bromobenzoic acid	146	–0.12	–0.71	0.59
p,p-DDT	109	–0.98	–0.34	0.65
p,p-DDT	109	–0.79	–0.34	0.46
p-Aminobenzoic acid	189	–0.80	–1.14	0.34
p-Aminobenzoic acid	189	–1.68	–1.14	0.54
p-Bromobenzoic acid	252	–1.11	–1.77	0.66
PCB-15	149	–0.89	–0.74	0.15
PCB-29	76	–0.75	–0.01	0.74
PCB-3	78	–0.22	–0.03	0.19
PCB-52	87	–0.63	–0.12	0.52
PCB-61	91	–0.85	–0.16	0.70
Pentachlorobenzene	86	–0.63	–0.11	0.52
Pentachlorobenzene	86	–0.56	–0.11	0.45
Pentachlorophenol	174	–0.11	–0.99	0.88
Perlyene	277	–2.52	–2.02	0.50
Phenacetin	135	–0.84	–0.60	0.24
Phenanthracene	99	–0.53	–0.24	0.29
Phenanthracene	99	–0.45	–0.24	0.21
Phenobarbital	176	–1.09	–1.01	0.08
Phenol	41	0.94	0.34	0.60
Prednisolone	240	–1.62	–1.65	0.03
Profluralin	32	–0.20	0.43	0.63

Table 3. Continued

Compound	MP (°C)	Exp log S_{oct}	Est log S_{oct}	Abs Error
Progesterone	131	–0.71	–0.56	0.15
Propyl p-hydroxybenzoate	96	0.36	–0.21	0.57
p-Toluic acid	180	–0.32	–1.05	0.73
Pyrene	156	–0.95	–0.81	0.14
Pyrene	156	–0.90	–0.81	0.09
Salicylic acid	158	0.15	–0.83	0.98
Terbutyrne	105	–0.27	–0.30	0.03
Testosterone	155	–0.49	–0.80	0.31
Theophylline	272	–1.99	–1.97	0.02
trans-Stilbene	125	–1.10	–0.50	0.60
Triazolam	224	–2.05	–1.49	0.56
Triphenylene	199	–1.77	–1.24	0.53

*MP indicates melting point (in Celsius); Exp, logarithm of the experimental molar octanol solubility; Est, logarithm of the estimated molar octanol solubility; and Abs, absolute; o,p′-DDT, 1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethane; p,p-DDT, Dichlorodiphenyltrichloroethane; PCB, Polychlorobiphenyl.

solubility is also called the crystal-liquid solubility ratio and is given by

$$log\ X_i = -\frac{\Delta H_m (T_m - T)}{2.3 \cdot R \cdot T \cdot T_m} \tag{9}$$

Equation 9 is further simplified by use of Walden's rule.[5] Walden's rule states that the entropy of melting ($\Delta S_m = \Delta H_m / T_m$) for coal tar derivatives (which are primarily rigid organic compounds) can be approximated by a constant value of 56.5 J/mol·K.[5] If the experimental temperature of interest is 298 K, Equation 9 is simplified to

$$\begin{aligned} log\ X_i &= -\frac{56.5 \cdot (T_m - 298)}{5709} \\ &= -0.01 \cdot (MP - 25) \end{aligned} \tag{10}$$

where MP denotes the melting point of a compound in Celsius and 25°C represents the experimental temperature of interest. Thus, MP − 25 is used in place of $T_m - 298$, since melting point data are normally reported in Celsius.

The solubility of a crystalline solute in octanol can be determined from the product of the solubility it would have if it were a liquid and its ideal crystalline solubility. This expression is given by

$$S^C_{oct} = S^L_{oct} \cdot X_i \tag{11}$$

where (S^C_{oct}) is the molar solubility of a crystalline solute in octanol. Taking the logarithm of both sides and substituting Equations 8 and 10 into the above equation leads to

$$log\ S^C_{oct} = 0.5 - 0.01 \cdot (MP - 25) \tag{12}$$

Thus, for crystalline solutes having solubility parameters in the range of 15 to 28 $(J/cm^3)^{0.5}$, the molar octanol solubility can be predicted by the melting point alone. It should be noted that the term in the parentheses cannot be less than zero. Therefore, for all compounds that melt below ambient temperature, the melting point is set to 25°C.

DATA COLLECTION

The miscibility of 32 common organic liquids with octanol was determined by mixing equal volumes and visually evaluating for phase separation over a 3-day period. All liquid solutes were of high purity (>98%) and used as received without further modification or purification from the following companies: Sigma-Aldrich, St Louis, MO; Burdick and Jackson, Morristown, NJ; and AAPER Alcohol and Chemical Co, Shelbyville, KY.

The reported octanol solubilities of 123 compounds were taken from the literature.[6-16] The melting points ranged from below room temperature to 485°C and included environmentally prevalent compounds such as polycyclic aromatic

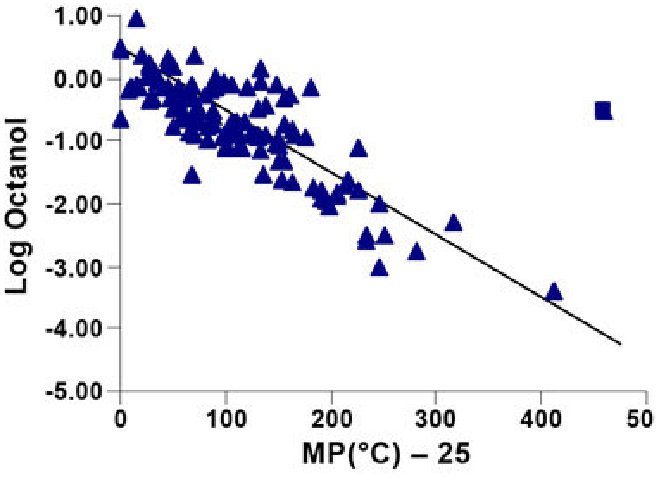

Figure 1. Dependence of octanol solubility on melting points.

Table 4. Octanol Solubilities Estimated From Using 56.5 J/mol·K and Experimental Entropies of Melting*

Compound	MP (°C)	Exp logS$_{oct}$	Est logS$_{oct}$†	ΔS$_{m}$‡	Est logS$_{oct}$§	Abs Error‖	Abs Error¶
1,2,3,5-Tetrachlorobenzene	55	0.15	0.21	58.7	0.20	0.06	0.05
1,2,3-Trichlorobenzene	53	0.09	0.22	62.7	0.20	0.13	0.11
1,2,3-Trichlorobenzene	53	0.18	0.22	62.7	0.20	0.04	0.02
1,2,4,5-Tetrabromobenzene	182	–1.32	–1.07	62.3	–1.21	0.25	0.11
1,2,4,5-Tetrachlorobenzene	139	–1.08	–0.64	57.2	–0.64	0.44	0.44
1,2,4,5-Tetrachlorobenzene	139	–0.92	–0.64	57.2	–0.64	0.28	0.28
1,3,5-Trichlorobenzene	65	–0.16	0.10	54.1	0.12	0.26	0.28
1,4-Dibromobenzene	87	–0.30	–0.12	55.7	–0.11	0.18	0.19
1,4-Dichlorobenzene	53	0.11	0.22	55.7	0.23	0.11	0.12
1,4-Dichlorobenzene	53	0.25	0.22	55.7	0.23	0.03	0.02
1,4-Dichlorobenzene	53	0.20	0.22	55.7	0.23	0.02	0.03
2,3-Benzofluorene	208	–1.75	–1.33	47.8	–1.03	0.42	0.72
2,4-Dichlorophenol	45	0.36	0.30	63.2	0.28	0.06	0.08
Acenaphthene	94	–0.59	–0.19	42.4	–0.01	0.40	0.58
Acetylsalicyclic acid	135	–0.69	–0.60	56.4	–0.59	0.09	0.10
Anthracene	216	–1.91	–1.41	60.1	–1.51	0.50	0.40
Anthracene	216	–1.78	–1.41	60.1	–1.51	0.37	0.27
Barbital	190	–0.92	–1.15	54.0	–1.06	0.23	0.14
Benzil	95	–0.89	–0.20	64.5	–0.29	0.69	0.60
Benzo[a]Pyrene	179	–1.60	–1.04	59.9	–1.12	0.56	0.48
Benzoic acid	122	–0.95	–0.47	45.5	–0.27	0.48	0.68
Benzoic acid	122	–0.06	–0.47	45.5	–0.27	0.41	0.21
Biphenyl	69	–0.13	0.06	54.6	0.08	0.19	0.21
Butyl p-Aminobenzoate	58	0.13	0.17	61.8	0.14	0.04	0.01
Caffeine	238	–1.72	–1.63	47.6	–1.28	0.09	0.44
Chrysene	258	–2.60	–1.83	55.3	–1.76	0.77	0.84
Chrysene	258	–2.51	–1.83	55.3	–1.76	0.68	0.75
Coronene	438	–3.41	–3.63	27.0	–1.45	0.22	1.96
Cortisone	222	–1.97	–1.47	74.5	–2.07	0.50	0.10
Decachlorobiphenyl	306	–2.77	–2.31	68.1	–2.85	0.46	0.08
Deoxycorticosterone	142	–0.71	–0.67	67.6	–0.89	0.04	0.18
Dibenz[a,h]anthracene	270	–3.03	–1.95	57.3	–1.96	1.08	1.07
Dibenzofuran	82	–0.27	–0.07	52.3	–0.02	0.20	0.25
Diphenylamine	52	0.03	0.23	54.8	0.24	0.20	0.21
Ethyl p-Aminobenzoate	89	–0.31	–0.14	61.4	–0.19	0.17	0.12
Fluoranthene	108	–0.76	–0.33	48.9	–0.21	0.43	0.55
Fluorene	112	–0.62	–0.37	50.5	–0.27	0.25	0.35
Fluorodifen	94	–1.52	–0.19	50.6	–0.11	1.33	1.41
Hexachlorobenzene	230	–1.86	–1.55	47.2	–1.20	0.31	0.66
Hexachlorobenzene	230	–1.82	–1.55	47.2	–1.20	0.27	0.62
Hexachloroethane	187	–0.28	–1.12	53.2	–1.01	0.84	0.73
Hexamethylbenzene	164	–0.89	–0.89	51.0	–0.74	0.00	0.15
Methyl p-Aminobenzoate	114	–0.53	–0.39	58.6	–0.41	0.14	0.12
Naphthalene	80	–0.36	–0.05	54.1	–0.02	0.31	0.34
Naphthalene	80	–0.15	–0.05	54.1	–0.02	0.10	0.13
Naproxen	153	–0.89	–0.78	67.0	–1.00	0.11	0.11
o,p′-DDT	75	–0.49	0.01	66.8	–0.08	0.50	0.41
p-Aminobenzoic acid	189	–0.80	–1.14	45.3	–0.80	0.34	0.00
p-Aminobenzoic acid	189	–1.68	–1.14	45.3	–0.80	0.54	0.88
PCB-29	76	–0.75	–0.01	65.2	–0.09	0.74	0.67
PCB-3	78	–0.22	–0.03	38.2	0.15	0.19	0.36
PCB-61	91	–0.85	–0.16	69.3	–0.30	0.70	0.56
Pentachlorobenzene	86	–0.63	–0.11	57.6	–0.12	0.52	0.51
Pentachlorobenzene	86	–0.56	–0.11	57.6	–0.12	0.45	0.44
pentachlorophenol	174	–0.11	–0.99	37.1	–0.47	0.88	0.36

Table 4. Continued

Compound	MP (°C)	Exp $\log S_{oct}$	Est $\log S_{oct}$†	ΔS_m‡	Est $\log S_{oct}$§	Abs Error‖	Abs Error¶
Phenanthracene	99	–0.53	–0.24	44.8	–0.08	0.29	0.45
Phenanthracene	99	–0.45	–0.24	44.8	–0.08	0.21	0.37
Phenol	41	0.94	0.34	36.7	0.40	0.60	0.54
Prednisolone	240	–1.62	–1.65	75.8	–2.35	0.03	0.73
Progesterone	131	–0.71	–0.56	66.8	–0.74	0.15	0.03
p-Toluic acid	180	–0.32	–1.05	50.2	–0.86	0.73	0.54
Pyrene	156	–0.95	–0.81	43.4	–0.49	0.14	0.46
Pyrene	156	–0.90	–0.81	43.4	–0.49	0.09	0.41
Salicylic acid	158	0.15	–0.83	57.0	–0.83	0.98	0.98
Testosterone	155	–0.49	–0.80	68.8	–1.07	0.31	0.58
Theophylline	272	–1.99	–1.97	51.8	–1.74	0.02	0.25
trans-Stilbene	125	–1.10	–0.50	68.8	–0.71	0.60	0.39
Triphenylene	199	–1.77	–1.24	52.5	–1.10	0.53	0.67

*MP indicates melting point (in Celsius); Exp, logarithm of the experimental molar octanol solubility; Est, logarithm of the estimated molar octanol solubility; and Abs, absolute.

†Estimated octanol solubilities using 56.5 J/mol·K as the entropy of melting.

‡Experimental entropies of melting obtained from Jain and Yalkowsky et al.

§Estimated octanol solubilities using experimental entropies of melting.

‖Absolute errors determined from experimental octanol solubilities and those estimated by using 56.5 J/mol·K as the entropy of melting.

¶Absolute errors determined from experimental octanol solubilities and those estimated by using experimental entropies of melting.

hydrocarbons, polychlorinated biphenyls, and polychlorinated benzenes, as well as steroids and nonsteroidal anti-inflammatory drugs. Multiple solubility values obtained for several compounds from various sources were used independently without averaging. The molar volumes and solubility parameters of the liquid solutes were determined by the Bondi group contribution method described by Barton.[17]

RESULTS AND DISCUSSION

Table 2 depicts the observed and predicted miscibility data of 32 common organic liquids with octanol. Predicted miscibility data were obtained by use of Equation 6. It can be seen that complete miscibility occurs with solutes having solubility parameters ranging from 14 to 32 $(\text{J/cm}^3)^{0.5}$. This range includes the range of 15 to 28 $(\text{J/cm}^3)^{0.5}$, which is based on the assumption that a liquid solute has a molar volume near that of octanol.

Glycerin, formamide, and water have solubility parameters outside their calculated ranges of complete miscibility and are thus predicted not to be completely miscible with octanol. This was validated by the presence of 2 phases when equal volumes of these solutes were mixed with octanol.

Table 3 depicts the melting points and the experimental and predicted molar solubilities of 123 compounds reported in literature.[6-16] The predicted values were obtained by use of Equation 12.

Figure 1 represents the relationship between the experimental molar solubilities in octanol and melting point (MP – 25°C). The figure shows that melting point is the primary determinant of octanol solubility. As the melting point increases, a corresponding decrease in octanol solubility occurs. The line in the figure is the theoretical relationship described by Equation 12.

Linear regression analysis was performed with SPSS Version 10.0 (SPSS Inc, Chicago, IL). Regression analysis was based on 149 solubilities, corresponding to 123 reported solubilities and 26 miscible liquid solutes from Table 2 that lie in the theoretical range of complete miscibility. Mirex, the square point in Figure 1 was deemed a statistical outlier and not included in the regression analysis.

Linear regression analysis results in $\log S_{oct}^{C} = 0.378 - 0.0099 \cdot (MP - 25)$, which is in agreement with those of Equation 12. The average absolute error for the predictions for the entire data set was determined to be 0.39 logarithmic units.

The accuracy in predicting octanol solubility will be limited to the availability of reliable experimental data and the compounds having solubility parameters in the range of complete miscibility. The equation also does not account for the self-association of solutes in octanol.

The estimation of octanol solubility with the proposed equation uses Walden's rule for the entropy of melting. A literature search of entropies of melting resulted in 68 experimental entropies of melting taken from the work of Jain et al.[18] For comparison, octanol solubilities were estimated from Equation 12 and from the experimental entropies of melting. These values are presented in Table 4.

The use of experimental entropies of melting resulted in an average absolute error of 0.36 logarithmic units as compared with 0.41, which was obtained by using 56.5 J/mol·K as the entropy of melting. Interestingly, for the compounds in Table 4 the entropies of melting values are close to the value estimated by Walden's rule.

CONCLUSION

A theoretical range of complete miscibility of liquid solutes with octanol was derived from the Scatchard-Hildebrand equation and validated with a group of common organic solvents. Molar octanol solubilities ranging over 4 orders of magnitude were predicted with a nonregression-based equation using melting point as the only molecular descriptor. The use of experimental entropies of melting resulted in only a slight improvement in predicting octanol solubilities for 68 compounds having melting points above ambient temperature. The equation in its current form is unable to account for strongly hydrogen-bonded compounds.

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