Water Solubilities of Polynuclear Aromatic and Heteroaromatic Compounds

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The water solubilities of several polynuclear aromatic and heteroaromatic hydrocarbons have been compiled and reviewed for consistency through correlations with parameters such as surface area, molecular volume, and boiling point. The carbocycles and oxygen and sulfur heterocycles were governed by the same correlative equations, thereby indicating that these heteroatoms entered into only a limited degree of hydrogen bonding. Equations representing the nitrogen heterocycles differed from their carbocyclic counterparts by an approximately constant amount, suggesting that while the solubilizing effect of the nitrogen heteroatom may be large, it tends to remain constant within a similar series of compounds.

Key words: boiling point; correlations; molecular volume; polynuclear hydrocarbons; surface area; water solubility.

1. Introduction

With the projected increased use of coal derived energy sources, the health and environmental impact of compounds associated with coal will receive progressively greater attention. Some of these compounds such as the polynuclear aromatic hydrocarbons are potent mutagens or carcinogens,[1] and reliable data on the physical properties of these compounds must be available for meaningful health and environmental assessment to be made. Possibly the most important property from this viewpoint is water solubility, since apart from its importance in its own right, several other parameters such as lipophilicity, adsorption, and bioconcentration can be related to it.[2-4] We have compiled and reviewed values for several polynuclear compounds, tested them against available models, and reduced them to a set of validated data.

2. Data Selection

Selection of compounds was based on the following criteria: presence of more than one ring, the absence of all except alkyl substituents and the restriction of heteroatoms to C,H,N,O, and S. An extensive literature search yielded the data presented in Table 1. For some compounds such as naphthalene where a large number of values were found, the search was stopped after 10 to 12 similar values had been acquired.

Evaluation of the data was made in two stages. In the first step, results for a given compound were screened for internal consistency, and this assessment was made as objectively as possible. Initially, the possibility of a more critical evaluation based on weighting the data according to the appropriateness of analytical methodology used, experience of the investigators, etc., was considered, but a workable weighting scheme could not be devised. For example, much of the data reported by Davis *et al.*[15] as early as 1942 was obtained by nephelometry, an indirect method for measuring solubility, and it might seem reasonable to weight these values somewhat more lightly than recent data obtained with more refined techniques. However, with the exception of picene, the data of Davis *et al.*[15] were found to be of remarkably high quality, whereas in several cases, comparable data acquired later were suspect.

In general, where a large number of measurements were available, outliers were identified as such if they deviated from the mean by more than two standard deviations. On occasion, where only a few measurements were reported, the screening was, by necessity, much more subjective. For example, of the three values reported for diphenylmethane, the lower value (20 μmol L^{-1}), while appreciably different from the other two (83.9 and 87.1 μmol L^{-1}), is nevertheless within the two standard deviation criterion of acceptability. However, the value was rejected on the grounds that it was obtained with the use of practical grade material, and it was therefore likely to be relatively inaccurate. The screened

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Table 1. Water Solubilities of Polycyclic Compounds

Compound	T(°C)[a]	Solubility (μmol L^{-1})	Ref.
Acenaphthene	25	25.5	5
Acenaphthene	25	47.8	6
Acenaphthene	25	25.2	7
Acenaphthene	25	15.7	8
Acenaphthene	25	39.8	9
Acenaphthene	25	22	10
Acridine	24	215	11
Acridine	20	300	12
Anthracene	25	0.239	13
Anthracene	25	0.23	14
Anthracene	25	0.42	7
Anthracene	25	0.41	5
Anthracene	27	0.42	15
Anthracene	20	0.5	16
Anthracene	25	0.447	17
Anthracene	22	0.3	18
Anthracene	20	0.224	19
Anthracene	25	0.416	20
Anthracene	25	0.438	21
Anthracene-9-10-dimethyl	25	0.27	5
Anthracene-2-methyl	25	0.22	5
Anthracene-2-methyl	25	0.0971	22
Anthracene-9-methyl	25	1.36	5
Benz(a)anthracene	24	0.19[b]	23
Benz(a)anthracene	25	0.041	22
Benz(a)anthracene	25	0.061	5
Benz(a)anthracene	27	0.048	15
Benz(a)anthracene	25	0.0431	17
Benz(a)anthracene-12-butyl	27	0.03	15
Benz(a)anthracene-4-5-dimethylene	25	0.0106	15
Benz(a)anthracene-7-12-dimethyl	24	0.21	23
Benz(a)anthracene-7-12-dimethyl	27	0.17	15
Benz(a)anthracene-7-12-dimethyl	25	0.24	5
Benz(a)anthracene-7-ethyl	27	0.16	24
Benz(a)anthracene-1-methyl	27	0.23	15
Benz(a)anthracene-7-methyl	24	0.045	23
Benz(a)anthracene-12-methyl	27	0.27	15
Benz(a)anthracene-12-methyl	24	0.15	23
Benzimidazole	20	17000	12
Benzimidazole-2-methyl	20	11000	12
Benzo(b)fluoranthene	25	0.0060	25
Benzo(j)fluoranthene	25	0.0099	25
Benzo(k)fluoranthene	25	0.003	25
Benzo(a)fluorene	25	0.21	5
Benzo(b)fluorene	25	0.0093	5
Benzo(ghi)perylene	25	0.003	25
Benzo(ghi)perylene	25	0.00094	5
Benzo(a)pyrene	25	0.0063	13

Table 1. Water Solubilities of Polycyclic Compounds (cont.)

Compound	T(°C)[a]	Solubility (μmol L^{-1})	Ref.
Benzo(a)pyrene	20	0.0472	26
Benzo(a)pyrene	25	0.015	5
Benzo(a)pyrene	22	0.0048	27
Benzo(a)pyrene	27	0.016	24
Benzo(a)pyrene	20	0.024	16
Benzo(a)pyrene	25	0.019	28
Benzo(a)pyrene	22	0.009	18
Benzo(a)pyrene	20	0.003	29
Benzo(e)pyrene	25	0.029	28
Benzo(e)pyrene	23	0.0201	14
Benzo(a)pyrene-6-methyl	25	0.003	15
Benzo(f)quinoline	25	425	27
Benzo(f)quinoline	25	453	30
Benzo(b)thiophene	20	970	27
Benzoxazole	20	70000	12
Bibenzyl	25	24	31
Biphenyl	25	45	5
Biphenyl	25	46	7
Biphenyl	25	48.5	32
Biphenyl	24	55	23
Biphenyl	25	38.6	31
Biphenyl	21	45	33
Biphenyl	25	39.1	6
Biphenyl	25	48	10
2-2'-Biquinoline	24	3.98	11
Carbazole	20	10	12
Carbazole	20	6.17	27
Carbazole	25	5.43	20
Cholanthrene	25	0.014	15
Cholanthrene-3-methyl	25	0.0056	15
Cholanthrene-3-methyl	25	0.011	5
Chrysene	27	0.0066	15
Chrysene	25	0.0088	5
Chrysene	24	0.075[b]	23
Chrysene	20	3.4[b]	16
Chrysene	25	0.0276	17
Chrysene	25	0.0079	22
Chrysene-5-6-dimethyl	27	0.098	15
Chrysene-5-methyl	27	0.26	15
Chrysene-6-methyl	27	0.27	15
Coronene	25	0.00047	5
Coronene	20	0.0486[b]	34
Dibenz(ah)acridine	25	0.57	30
Dibenz(ah)anthracene	25	0.0018	15
Dibenz(ah)anthracene	25	0.00215	17
Dibenz(aj)anthracene	25	0.043	15
Dibenzo(cg)carbazole-7H	22	0.24	27
Dibenzo(ai)carbazole-13H	24	0.0389	11
Dibenzofuran	25	59.6	6

Table 1. Water Solubilities of Polycyclic Compounds (cont.)

Compound	T(°C)	Solubility (μmol L^{-1})	Ref.
Dibenzofuran	25	18.5	20
Dibenzothiophene	28	6.03	27
Dibenzothiophene	24	7.99	11
Dibenzothiophene	25	2.88	20
Diphenylether	25	106	6
Diphenylmethane	24	20[b]	23
Diphenylmethane	25	83.9	31
Diphenylmethane	25	87.1	9
Fluoranthene	25	1.02	22
Fluoranthene	27	1.19	15
Fluoranthene	25	1.3	5
Fluoranthene	24	0.59[b]	23
Fluoranthene	25	1.32	17
Fluoranthene	20	1.19	34
Fluorene	25	10.15	22
Fluorene	25	11.9	5
Fluorene	25	11.4	7
Fluorene	25	27.9[b]	20
Indan	25	924.5	5
Indazole	20	7000	12
Indole	20	16000	12
Indole-3-methyl	20	3800	12
Indeno(123cd)pyrene	25	0.00069	25
Isoquinoline	20	35000	12
Isoquinoline-3-methyl	20	6430	35
Naphthacene	20	0.0158[b]	34
Naphthacene	25	0.0025	5
Naphthacene	27	0.0044	15
Naphthacene	25	0.0066	17
Naphthalene	25	247.5	36
Naphthalene	25	248	5
Naphthalene	25	244	7
Naphthalene	25	236	14
Naphthalene	25	269	32
Naphthalene	20	195[b]	12
Naphthalene	25	246	31
Naphthalene	25	97.5[b]	17
Naphthalene	20	175[b]	35
Naphthalene	20	300[b]	19
Naphthalene	25	261.1	37
Naphthalene	25	243	10
Naphthalene-1-3-dimethyl	25	51	5
Naphthalene-1-4-dimethyl	25	73.1	5
Naphthalene-1-5-dimethyl	25	21.7	5
Naphthalene-1-5-dimethyl	25	18	10
Naphthalene-2-3-dimethyl	25	13	10
Naphthalene-2-3-dimethyl	25	19	5
Naphthalene-2-6-dimethyl	25	8.3	10

Table 1. Water Solubilities of Polycyclic Compounds (cont.)

Compound	T(°C)[a]	Solubility (μmol L^{-1})	Ref.
Naphthalene-2-5-dimethyl	25	13	5
Naphthalene-1-ethyl	25	68.6	5
Naphthalene-1-ethyl	25	64	14
Naphthalene-2-ethyl	25	51	10
Naphthalene-1-methyl	25	181	10
Naphthalene-1-methyl	25	201	5
Naphthalene-1-methyl	25	211	14
Naphthalene-1-methyl	20	120	35
Naphthalene-1-methyl	21	210	33
Naphthalene-2-methyl	25	179	5
Naphthalene-2-methyl	25	172	10
Naphthalene-1-4-5-trimethyl	25	12	5
Perylene	25	0.002	5
Perylene	20	0.00042	34
Phenanthrene	25	6	10
Phenanthrene	25	5.629	22
Phenanthrene	27	9.27	24
Phenanthrene	25	7.25	5
Phenanthrene	25	6.63	7
Phenanthrene	25	6.46	14
Phenanthrene	25	5.58	31
Phenanthrene	20	15[b]	16
Phenanthrene	25	9.0	17
Phenanthrene	25	9.0	15
Phenanthrene-1-methyl	25	1.4	22
Phenanthrene-4-5-methylene	27	5.8	15
Picene	25	0.0090	15
Picene	20	0.0155	34
Pyrene	25	0.653	22
Pyrene	25	0.668	5
Pyrene	25	0.733	7
Pyrene	27	0.817	15
Pyrene	25	0.64	8
Pyrene	24	0.16[b]	23
Pyrene	20	1.0[b]	16
Pyrene	25	0.77	17
Pyrene	22	0.8	18
Pyrene	20	0.52[b]	19
Pyrene	25	0.64	14
Quinoline	20	52000	12
Quinoline	20	47000	35
Quinoxaline	50	5120000	12
Triphenylene	25	0.029[b]	36
Triphenylene	25	0.19	5
Triphenylene	27	0.17	15
Triphenylene	25	0.188	17

[a] Temperature of measurement in °C

[b] Outlier

Table 2. Averaged Water Solubilities of Polycyclic Compounds

Compound	Melting[a] Point (°C)	Boiling[a] Point (°C)	Solubility (μmol L^{-1})	Percent[b] Standard Deviation	n[c]	Surface Area ($Å^2$)	Molecular Volume ($Å^3$)
Acenaphthene	93	279	29	37	6	180.8	148.8
Acridine	110	346	260	17	2	197.3	165.4
Anthracene	216	340	0.37	26	11	202.2	170.3
Anthracene-9-10-dimethyl	183	Sub[d]	0.27		1	230.1	199.5
Anthracene-2-methyl	205	Sub[d]	0.16	39	2	224.0	186.2
Anthracene-9-methyl	80	345	1.4		1	216.1	184.9
Benz(a)anthracene	158	435	0.048	16	4	244.3	212.9
Benz(a)anthracene-12-butyl	97		0.03		1	326.2	276.3
Benz(a)anthracene-4-5-dimethylene	234		0.011		1	269.3	234.8
Benz(a)anthracene-7-12-dimethyl	122		0.21	14	3	267.3	239.4
Benz(a)anthracene-7-ethyl	113		0.16		1	280.8	243.7
Benz(a)anthracene-1-methyl	139		0.23		1	257.9	225.8
Benz(a)anthracene-7-methyl	141		0.045		1	258.3	227.5
Benz(a)anthracene-12-methyl	138		0.21	29	2	253.3	224.8
Benzimidazole	171	>360	17000		1	140.2	109.2
Benzimidazole-2-methyl	177		11000		1	163.2	125.5
Benzo(b)fluoranthene	168		0.0060		1	260.8	230.3
Benzo(j)fluoranthene	166		0.0099		1	259.7	230.3
Benzo(k)fluoranthene	217	480	0.003		1	265.0	231.1
Benzo(a)fluorene	188	413	0.21		1	240.3	203.8
Benzo(b)fluorene	210		0.0093		1	240.3	203.8
Benzo(ghi)perylene	278	>500	0.0020	52	2	266.9	244.3
Benzo(a)pyrene	179	495	0.016	80	9	255.6	228.6
Benzo(e)pyrene	178		0.025	18	2	251.5	227.8
Benzo(a)pyrene-6-methyl	216		0.003		1	269.6	243.2
Benzo(f)quinoline	94	350	439	3	2	192.9	164.6
Benzo(b)thiophene	32	221	970		1	146.9	118.1
Benzoxazole	31	183	70000		1	134.2	104.8
Bibenzyl	52	285	24		1	237.0	188.0
Biphenyl	71	256	46	11	8	189.6	155.1
2-2'-Biquinoline	195		4.0		1	271.2	231.3
Carbazole	248	355	7.2	28	3	188.7	156.0
Cholanthrene	173	472	0.014		1	269.2	234.8
Cholanthrene-3-methyl	179	382[e]	0.0083	33	2	291.0	250.7
Chrysene	252	448	0.013	68	4	240.2	212.1
Chrysene-5-6-dimethyl	128	435	0.098		1	267.8	239.5
Chrysene-5-methyl	118		0.26		1	253.7	225.0
Chrysene-6-methyl	161		0.27		1	259.3	227.7
Coronene	>360	525	0.00047		1	282.4	260.8
Dibenz(ah)acridine	228		0.57		1	284.5	251.3

Table 2. Averaged Water Solubilities of Polycyclic Compounds (cont.)

Compound	Melting[a] Point (°C)	Boiling[a] Point (°C)	Solubility (μmol L^{-1})	Percent[b] Standard Deviation	n[c]	Surface Area ($Å^2$)	Molecular Volume ($Å^3$)
Dibenz(ah)anthracene	267	524	0.0020	9	2	286.5	255.4
Dibenz(aj)anthracene	197		0.043		1	286.5	255.4
Dibenzo(cg)carbazole-7H	157		0.24		1	267.0	237.5
Dibenzo(ai)carbazole(13H)	220		0.039		1	279.1	242.6
Dibenzofuran	82	287	39	53	2	183.8	152.4
Dibenzothiophene	100	332	5.6	37	3	193.6	163.4
Diphenylether	28	259	106		1	202.1	162.4
Diphenylmethane	L[g]	265	86	19	2	214.2	171.7
Fluoranthene	110	375	1.2	9	5	218.6	187.7
Fluorene	114	298	11	7	3	194.0	160.4
Indan	L[g]	178	920		1	156.7	121.6
Indazole	148	268	7000[f]		1	134.4	105.2
Indole	53	254	16000		1	140.6	110.0
Indole-3-methyl	98	266	3800		1	163.5	126.2
Indeno(123cd)pyrene	163		0.00069[e]		1	276.3	246.8
Isoquinoline	27	243	35000		1	150.5	122.0
Isoquinoline-3-methyl	68	246	6400		1	172.7	137.9
Naphthacene	357	Sub[d]	0.0045	37	3	248.5	213.7
Naphthalene	81	218	249	4	8	155.8	126.9
Naphthalene-1-3-dimethyl	L[g]	263	51		1	196.8	158.5
Naphthalene-1-4-dimethyl	L[g]	268	73		1	194.1	158.2
Naphthalene-1-5-dimethyl	82	265	20	9	2	194.1	158.2
Naphthalene-2-3-dimethyl	103	268	16	19	2	196.2	158.3
Naphthalene-2-6-dimethyl	109	262	11	22	2	199.5	158.7
Naphthalene-1-ethyl	L[g]	259	66	3	2	192.3	158.6
Naphthalene-2-ethyl	L[g]	251	51		1	199.9	158.9
Naphthalene-1-methyl	L[g]	245	180	18	5	174.9	142.6
Naphthalene-2-methyl	L[g]	241	180	2	2	177.7	142.8
Naphthalene-1-4-5-trimethyl	L[g]		12		1	204.4	170.7
Perylene	278	503	0.0012	65	2	251.5	227.8
Phenanthrene	97	340	7.2	20	9	198.0	169.5
Phenanthrene-1-methyl	119	390	1.4		1	217.1	185.1
Phenanthrene-4-5-methylene	115		5.8		1	204.0	175.6
Picene	366	519	0.012[e]	27	2	282.3	284.6
Pyrene	150	393	0.72	10	8	213.5	186.0
Quinoline	L[g]	238	49000	5	2	150.7	122.0
Quinoxaline	33	230	5120000		1	145.4	117.0
Triphenylene	197	425	0.18	5	3	236.0	211.3

[a] From Reference [38] and manufacturer's specifications.

[b] Standard deviation expressed as a percentage of the mean. Where only two values were available the average deviation from the mean was used.

[c] Number of acceptable measurements from Table 1.

[d] Sublimes

[e] Outlier

[f] Value could not be validated.

[g] Liquid

data from Table 1 were averaged, and the results are listed along with associated physical parameters in Table 2.

3. Correlation of Solubility with Other Parameters

In the second stage of data evaluation, equations that relate solubility to various physical parameters were used. The solubility of a crystalline hydrophobic solute can be expressed as in Eq. (1), where x is the mole fraction solubility, ΔS_f is the entropy of fusion, T_m is the melting point in °C, and γ_w is the activity coefficient of the compound in water. For liquids, where the entropy term does not apply, T_m is assigned a value of 25. Equation (1),

$$\log x = -\frac{\Delta S_f}{1364}(T_m - 25) - \log \gamma_w, \quad (1)$$

is more conveniently represented by Eq. (2) where S is the solubility in units of μmol L^{-1}, X is any parameter that represents $\log \gamma_w$, and a,b, and c are constants.

$$\log S = a + bT_m + cX. \quad (2)$$

For rigid molecules, ΔS_f approximates 13.5 cal K^{-1} mol^{-1},[39] and the coefficient b should therefore equal -0.01.

Several parameters have been used to represent X in Eq. (2), and these have included both experimental and calculated properties. Examples of the former are molar volume,[40–42] the octanol:water partition coefficient ,[6,39,43–45] boiling point[33] and chromatographic retention indices.[46] Of the calculated parameters that have been used, surface area and molecular volume[47–50] have been the most widely applied. For evaluation of our compiled solubility data, we have selected surface area (A), molecular volume (V), and boiling point T_b.

3.1. Surface Area and Molecular Volume

For the surface area and volume calculations, each atom of a molecule was represented by a sphere centered at the equilibrium position of the nucleus. The radius of the sphere was that of the van der Waal's radius of the atom. The van der Waal surface was defined as the surface of the intersection of all the spheres in the molecule. The area of this surface and the volume contained by it were calculated by numerical integration using an algorithm and program described by Pearlman.[47] The calculated molecular volume is not to be confused with molar volume which is experimentally derived. The input to this program consists essentially of the Cartesian coordinates and van der Waal's radius of each atom in the molecule. The atomic coordinates were chosen to be those of the preferred molecular conformation, and the van der Waal's radii used for hydrogen, aromatic carbon, aliphatic carbon, nitrogen, and oxygen were 1.2, 1.7, 1.6, 1.5, and 1.4 Å, respectively. An effective solvent radius, which is occasionally included in calculations of this type, was not used in this study.

With the exception of the nitrogen and oxygen heterocycles, indenopyrene and picene, the solubilities of all the components in Table 2 were well represented by Eq. (3) and the relationship is illustrated in Fig. 1.

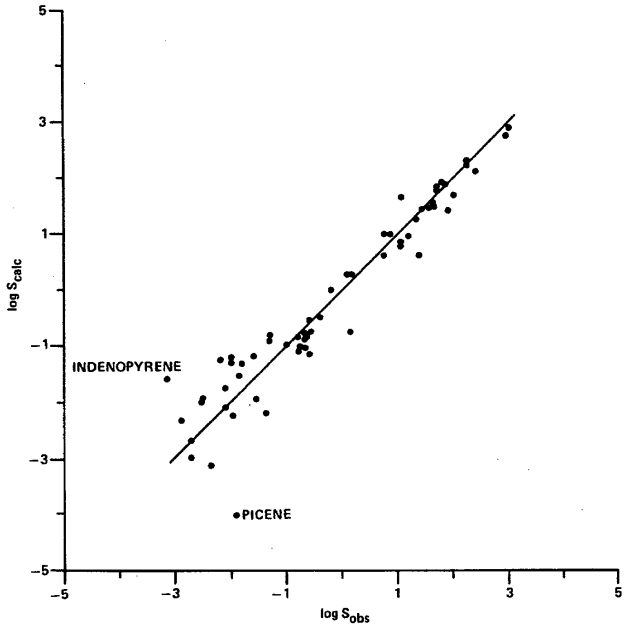

FIG. 1. Comparison of solubilities calculated from Eq. (3) with measured values.

$$\log S = 6.62 - 0.0114T_m - 0.0229A \quad (n = 59,\ r^2 = 0.95). \quad (3)$$

The terms n and r^2 in Eq. (3) and in succeeding equations refer to the sample size and the coefficient of determination, respectively. The solubility–volume relationship is represented by Eq. (4), and for correlative purposes, there appears to be little to choose from between area and volume.

$$\log S = 6.00 - 0.0103T_m - 0.0244V \quad (n = 59,\ r^2 = 0.95). \quad (4)$$

The deviation of picene and indenopyrene from Eqs. (3) and (4) is probably caused by experimental factors rather than by a breakdown of the relationship. The solubility of picene was obtained through nephelometric[15] and spectrophotometric analysis,[34] and the presence of soluble impurities would tend to lead to artificially high values. The deviation of indenopyrene is more serious, since the procedure used to obtain its solubility is relatively new, and considerable effort[22,36] has been spent by the National Bureau of Standards to develop and validate it. The technique consists of pumping water through a column containing glass beads coated with the compound of interest, and analyzing the effluent solution. Measurements are made over a range of flow rates to ensure that saturation has occurred. The method has been validated for a number of compounds, and it has been deemed to be both precise and accurate.[36] On the other hand, the solubility–area correlation applies to numerous hydrophobic compounds,[39,48,50] and indenopyrene does not appear to possess any distinguishing structural features which would cause it to deviate. Examination of the other data in Table 1 obtained by the column technique reveals that in almost all cases, the reported values are lower than

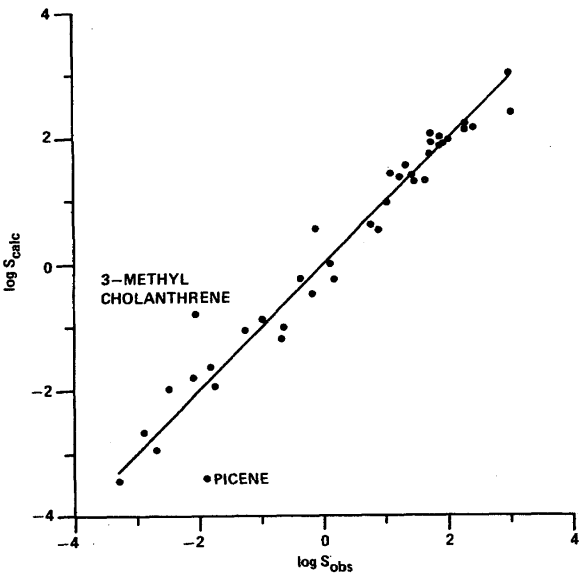

FIG. 2. Comparison of solubilities calculated from Eq. (5) with measured values.

those measured by others or those obtained by calculation. As a case in point, values measured for the benzofluoranthenes differ from their calculated counterparts by a factor of 6. In our view, a lower value obtained by the column method can be allowed only if discrepancies in the application of more traditional methods are clearly and unequivocally identified. This is not the case with indenopyrene, and we are therefore forced to regard the value as suspect.

3.2. Boiling Point

The boiling points listed in Table 2 were either measured at 1 atm (0.1 MPa), or were extrapolated to 1 atm from data reported at lower pressures. With the exception of the nitrogen and oxygen heterocycles, picene, and cholanthrene, the solubility data were governed by Eq. (5), and the correlation is illustrated in Fig. 2. The melting point coefficient in Eq. (5) is lower than

$$\log S = 5.55 - 0.004\,04\ T_m - 0.0137\ T_b \quad (n = 37,\ r^2 = 0.981), \tag{5}$$

that obtained in Eqs. (3) and (4). This is a consequence of a high degree of correlation ($r^2 = 0.89$) between T_m and T_b for these compounds, and thus, a portion of the melting point coefficient is contained in the coefficient for boiling point. Picene, which was an outlier in the area and volume correlations, also deviated from Eq. (5), probably for the same reason. It is likely that the deviation of cholanthrene originates from an incorrect boiling point rather than from an incorrect solubility, since a similar deviation was not obtained with Eqs. (3) and (4).

4. Discussion

Equations (3)–(5) apply to hydrophobic compounds, and heterocycles will be governed by them only if the heteroatom does not enter into significant hydrogen bonding. The thiophenes and furans exemplify this situation, and benzo- and dibenzothiophene and dibenzofuran are well correlated by one or more of Eqs. (3)–(5), as are thiophene ($S = 1.7\times10^4$ μmol L^{-1}, $T_b = 84°$) and furan ($S = 3.2\times10^5$ μmol L^{-1}, $T_b = 32°$). On the other hand, the azoles are expected to participate extensively in hydrogen bonding, and their deviation from Eqs. (3)–(5) is therefore, not surprising. However, if the extent of hydrogen bonding remained constant, then the solubilizing effect of the heteroatom would tend to appear in the intercept a in Eq. (2) and leave the other coefficients essentially unaltered. This is indeed the case with the azoles as illustrated by Eq. (6), and despite the small sample set used, the close correspondence of

$$\log S = 9.21 - 0.0103\ T_m - 0.0303\ A \quad (n = 5,\ r^2 = 0.993), \tag{6}$$

the coefficients for melting point and area between Eq. (3) and Eq. (6) suggests that the latter equation holds promise for more general use. A similar approach to the azines in Table 2 led to the unexpected result shown in Eq. (7) that

$$\log S = 5.20 - 0.024\ T_m \quad (n = 7,\ r^2 = 0.992), \tag{7}$$

solubility was governed by melting point alone. This is a consequence of a fortuitous relationship between melting point and area, and the correlation is expected to breakdown in the presence of a larger data set. If the melting point coefficient is assigned a value of -0.01, then the data for the azines leads to Eq. (8) where the coefficient for the area term is similar to those obtained in Eqs. (3) and (6).

$$\log S = 7.78 - 0.01\ T_m - 0.020\ A \quad (n = 7,\ r^2 = 0.98). \tag{8}$$

Compounds containing two or more heteroatoms would conform to Eqs. (3)–(5) only if the degree of hydrogen bonding per heteroatom was additive. In order to test this hypothesis, we considered the difference in intercept between Eqs. (3) and (8) to be a crude measure of the extent of hydrogen bonding of aza nitrogen. This translates to a factor of 15 in solubility. For the compounds in Table 3 which bear more than one heteroatom, solubilities calculated from Eq. (3) for benzoxazole and Eq. (6) for the remaining compounds were multiplied by 15 to correct for hydrogen bonding of aza nitrogen. Comparison of the resulting values with experimental data in Table 3 shows that with the exception of indazole, agreement is satisfactory in the light of the approximations made. The high calculated value for indazole is understandable since the heteroatoms in indazole are adja-

Table 3. Comparison of calculated and measured solubilities of some heterocycles

	Solubility (μM)	
	Calculated	Measured
Benzimidazole	24,000	17,000
Benzimidazole-2-methyl	4,100	11,000
Benzooxazole	23,000	70,000
Indazole	61,000	7,000

cent to each other, and it is probable that their solubilizing effects are less than additive.

In summary, we have compiled in Table 2 validated data for the solubility of polynuclear aromatics. Outlying values are identified, as are values for which validation was impossible. For the carbocycles, correlations with surface area, molecular volume, or boiling point led to comparable results. For the nitrogen heterocycles, preliminary evidence indicates that the solubilizing effect of the heteroatom may be constant, and in some cases, additive.

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6. References

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