

Molecular Connectivity III: Relationship to Partition Coefficients

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Abstract □ The molecular connectivity index is shown to be linearly related to the octanol-water partition coefficients of a variety of monofunctional chemical classes including esters, alcohols, ketones, ethers, carboxylic acids, amines, and hydrocarbons. A modification of the connectivity index, taking into account the valency or degree of unsaturation of an atom, merges the data for all compounds except hydrocarbons. The connectivity index is also shown to be useful for correlating biological activity. These studies indicate that partition coefficients represent empirical quantities having intermediate significance between biological data and the more fundamental property of molecular connectivity.

Keyphrases □ Molecular connectivity—relationship to octanol-water partition coefficients of various chemical classes □ Partition coefficients—octanol-water, relationship to molecular connectivity of various chemical classes

Parts I and II showed the relationship of molecular connectivity, given by χ , to polarizability, cavity surface area, local anesthetic action (1), water solubilities, and boiling points (2). The connectivity index appears to be a topological index in that the calculation is fundamentally dependent on the way constituent atoms of a molecule are attached to one another. Seemingly encoded in the connectivity index, which results from a simple mathematical operation (1), is the molecular structure of a chemical species. It might be expected that any physicochemical or biological property that is a function of the topological structure of a molecule, in this case its connectedness, is going to be related in some fashion to the connectivity index. Having shown the high correlation of a linear relationship between water solubilities and the connectivity index (2), it seems logical to examine the relationship of the connectivity index to partition coefficients.

The work of Hansch *et al.* (3, 4) and Nys and Reker (5) on the partition coefficients of various compounds in an octanol-water system provided partition data ($\log P$) for comparison. From their work were selected $\log P$ values for 45 hydrocarbons, 24 esters, nine carboxylic acids, 49 alcohols, 28 amines, 16

Table I—1-Octanol-Water Partition Coefficients ($\log P$) and Molecular Connectivity Index (χ)

Compound	χ^a	$\log P^b$	Predicted $\log P^c$
Methanol	1.000	-0.66	-0.57
Ethanol	1.414	-0.32	-0.17
Propanol	1.914	0.34	0.31
Butanol	2.414	0.88	0.80
Pentanol	2.914	1.40	1.28
Hexanol	3.414	2.03	1.76
Heptanol	3.914	2.34	2.25
Octanol	4.414	2.84	2.73
Nonanol	4.914	3.15	3.21
2-Propanol	1.732	0.14	0.14
2-Methyl-1-propanol	2.270	0.61	0.66
2-Methyl-2-propanol	2.000	0.37	0.40

Table I—Continued

Compound	χ^a	$\log P^b$	Predicted $\log P^c$
3-Methyl-1-butanol	2.563	1.14	0.94
2-Methylbutanol	2.807	1.14	1.17
1-Methylbutanol	2.770	1.14	1.14
3-Pentanol	2.807	1.14	1.17
3-Methyl-2-butanol	2.642	0.91	1.14
2-Methyl-2-butanol	2.561	0.89	0.94
2,2-Dimethyl-1-propanol	3.270	1.36	0.94
2-Hexanol	3.270	1.61	1.62
3-Hexanol	3.307	1.61	1.66
3-Methyl-3-pentanol	3.121	1.39	1.48
2-Methyl-2-pentanol	3.061	1.39	1.42
2-Methyl-3-pentanol	3.180	1.41	1.54
3-Methyl-2-pentanol	3.180	1.41	1.54
4-Methyl-2-pentanol	3.125	1.41	1.48
2,3-Dimethyl-2-butanol	2.944	1.17	1.31
3,3-Dimethyl-1-butanol	3.061	1.86	1.42
3,3-Dimethyl-2-butanol	2.944	1.19	1.31
2-Methyl-2-hexanol	3.561	1.87	1.90
3-Methyl-3-hexanol	3.620	1.87	1.96
3-Ethyl-3-pentanol	3.680	1.87	2.02
2,3-Dimethyl-2-pentanol	3.480	1.67	1.83
2,3-Dimethyl-3-pentanol	3.505	1.67	1.85
2,4-Dimethyl-2-pentanol	3.417	1.67	1.77
2,4-Dimethyl-3-pentanol	3.387	1.71	1.74
2,2-Dimethyl-3-pentanol	3.481	1.69	1.83
2,2,3-Trimethyl-3-pentanol	3.811	1.99	2.15
Cyclohexanol	2.893	1.23	1.26
4-Penten-1-ol	2.520	1.04	0.90
3-Penten-2-ol	2.398	0.81	0.78
1-Penten-3-ol	2.433	0.81	0.82
1-Hexen-3-ol	2.933	1.31	1.30
2-Hexen-4-ol	2.935	1.31	1.30
2-Methyl-4-penten-3-ol	2.806	1.11	1.18
Benzyl alcohol	2.471	1.10	0.85
2-Phenylethanol	2.971	1.36	1.34
3-Phenyl-1-propanol	3.471	1.88	1.82
Diphenylcarbinol	3.975	2.67	2.30
Diethyl ether	2.414	1.03	1.02
Methyl butyl ether	2.914	1.53	1.50
Methyl <i>sec</i> -butyl ether	2.770	1.33	1.36
Methyl isobutyl ether	2.801	1.33	1.40
Methyl <i>tert</i> -butyl ether	2.561	1.06	1.16
Ethyl propyl ether	2.914	1.53	1.50
Ethyl isopropyl ether	2.770	1.33	1.36
Dipropyl ether	3.414	2.03	1.99
Propyl isopropyl ether	3.270	1.83	1.85
Methyl propyl ether	2.414	1.03	1.02
Methyl isopropyl ether	2.270	0.83	0.88
Ethyl cyclopropyl ether	2.432	1.24	1.04
Ethyl formate	2.023	0.23	0.30
Propyl formate	2.523	0.73	0.80
Methyl acetate	1.914	0.23	0.19
Ethyl acetate	2.414	0.73	0.69
Propyl acetate	2.914	1.23	1.19
Isopropyl acetate	2.770	1.03	1.05
Butyl acetate	3.414	1.73	1.69
<i>sec</i> -Butyl acetate	3.270	1.53	1.54
Methyl propionate	2.475	0.73	0.75
Methyl butyrate	2.975	1.23	1.25
Ethyl hexanoate	4.475	2.73	2.74
Ethyl heptanoate	4.975	3.23	3.24
Ethyl octanoate	5.475	3.73	3.74
Ethyl nonanoate	5.975	4.23	4.24
Ethyl decanoate	6.475	4.73	4.74
Ethyl propionate	2.975	1.23	1.25
Ethyl butyrate	3.475	1.73	1.75
Ethyl isobutyrate	3.358	1.53	1.63

Table I—Continued

Compound	χ^a	Log P^b	Predicted Log P^c
Pentyl acetate	3.914	2.23	2.19
Butyl pentanoate	4.975	3.23	3.24
Benzyl acetate	3.616	1.96	1.74
Methyl 3-phenylpropionate	4.032	2.32	2.30
Methyl 2-phenylacetate	3.532	1.83	1.80
Methyl 4-phenylbutyrate	4.532	2.77	2.80
Acetic acid	1.354	-0.17	-0.15
Propionic acid	1.915	0.25	0.37
Butyric acid	2.415	0.79	0.83
Hexanoic acid	3.415	1.88	1.76
Decanoic acid	5.915	4.09	4.07
2-Phenylacetic acid	2.971	1.41	1.34
3-Phenylpropionic acid	3.471	1.84	1.81
4-Phenylbutyric acid	3.971	2.42	2.27
2,2-Diphenylacetic acid	5.041	3.05	3.26
Methylamine	1.000	-0.57	-0.54
Ethylamine	1.414	-0.13	-0.13
Propylamine	1.914	0.48	0.36
Butylamine	2.414	0.75	0.84
Pentylamine	2.914	1.49	1.33
Hexylamine	3.414	1.98	1.82
Heptylamine	3.914	2.57	2.31
Isobutylamine	2.270	0.73	0.70
sec-Butylamine	2.270	0.74	0.70
2-Aminooctane	4.307	2.82	2.69
Cyclohexylamine	2.893	1.49	1.31
Isopropylamine	1.732	0.26	0.18
Methylethylamine	1.914	0.15	0.36
Dipropylamine	3.414	1.67	1.82
Triethylamine	3.346	1.44	1.76
Dibutylamine	4.414	2.68	2.80
Diethylamine	2.414	0.57	0.84
Propylbutylamine	3.914	2.12	2.31
Methylbutylamine	2.914	1.33	1.33
Piperidine	2.500	0.85	0.93
Ethylisopropylamine	2.770	0.93	1.19
Propyl-sec-butylamine	3.807	1.91	2.20
Propylisobutylamine	3.769	2.07	1.77
Trimethylamine	1.732	0.27	0.18
Dimethylbutylamine	3.270	1.70	1.68
Dimethylbenzylamine	3.327	1.98	1.74
Benzylamine	2.471	1.09	0.90
Phenethylamine	2.971	1.41	1.39
Acetone	1.354	-0.21	-0.28
2-Butanone	1.915	0.29	0.27
2-Pentanone	2.414	0.79	0.76
3-Pentanone	2.475	0.79	0.82
3-Methyl-2-butanone	2.298	0.59	0.64
2-Hexanone	2.914	1.29	1.25
3-Hexanone	2.975	1.29	1.31
3-Methyl-2-pentanone	2.835	1.09	1.17
4-Methyl-2-pentanone	2.770	1.09	1.11
2-Methyl-3-pentanone	2.859	1.09	1.20
2-Heptanone	3.414	1.79	1.74
3-Heptanone	3.475	1.79	1.80
2,4-Dimethyl-3-pentanone	3.240	1.39	1.57
5-Nonanone	4.475	2.79	2.78
2-Nonanone	4.414	2.79	2.72
Acetophenone	3.014	1.58	1.35
Pentane	2.414	2.50	2.54
2-Methylbutane	2.270	2.30	2.41
2-Methylpentane	2.770	2.80	2.85
3-Methylpentane	2.807	2.80	2.88
Hexane	2.914	3.00	2.98
Heptane	3.414	3.50	3.42
2,4-Dimethylpentane	3.125	3.10	3.17
Octane	3.914	4.00	3.89
Cyclopentane	2.000	2.05	2.17
Cyclohexane	2.500	2.46	2.62
Methylcyclopentane	2.398	2.35	2.52
Cycloheptane	3.000	2.87	3.06
Methylcyclohexane	2.893	2.76	2.96
Cyclooctane	3.500	3.28	3.50
1,2-Dimethylcyclohexane	3.304	3.06	3.33
1-Pentyne	1.850	1.98	2.04
1-Hexyne	2.350	2.48	2.48

Table I—Continued

Compound	χ^a	Log P^b	Predicted Log P^c
1-Heptyne	2.850	2.98	2.93
1-Octyne	3.350	3.48	3.37
1-Nonyne	3.850	3.98	3.81
1,8-Nonadiyne	3.286	3.46	3.31
1,6-Heptadiyne	2.284	2.46	2.42
1-Pentene	2.023	2.20	2.20
2-Pentene	2.025	2.20	2.20
1-Hexene	2.523	2.70	2.64
2-Heptene	3.025	3.20	3.08
1-Octene	3.523	3.70	3.52
4-Methyl-1-pentene	2.379	2.50	2.51
1,6-Heptadiene	2.633	2.90	2.73
1,5-Hexadiene	2.133	2.40	2.29
1,4-Pentadiene	1.633	1.90	1.85
Cyclopentene	1.649	1.75	1.86
Cyclohexene	2.149	2.16	2.31
Cycloheptene	2.649	2.57	2.75
Toluene	2.410	2.73	2.54
Ethylbenzene	2.906	3.15	2.98
Isopropylbenzene	3.199	3.66	3.23
Propylbenzene	3.411	3.68	3.42
Diphenylmethane	4.528	4.14	4.41
1,2-Diphenylethane	5.028	4.79	4.85
Biphenyl	4.071	4.04	4.01
p-Xylene	2.821	3.25	2.90
Benzene	1.999	2.13	2.17
Naphthalene	3.403	3.37	3.42
Phenanthrene	4.814	4.46	4.66

^aThe connectivity index was calculated using valency modification described in text. ^bPartition coefficients in a 1-octanol-water system were taken from Refs. 3, 5, and 7 and references cited therein. ^cCalculated log P values were derived from the equations developed for each functional group series compiled in Table II.

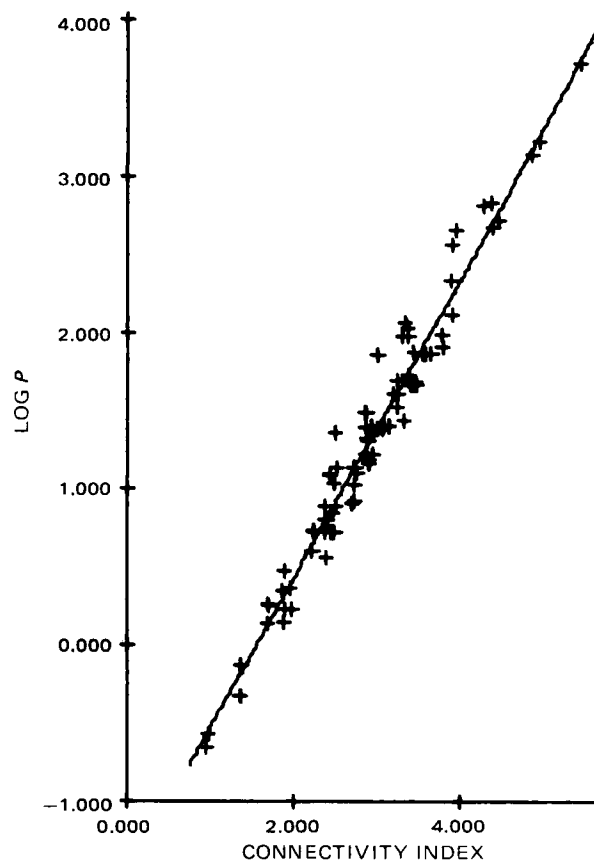


Figure 1—Computer-drawn plot of the logarithm of the partition coefficient versus the molecular connectivity index for 24 esters, nine carboxylic acids, 49 alcohols, 28 amines, 16 ketones, and 12 ethers with the corresponding regression line.

Table II—Summary of Regression Equations, Correlation Coefficients, and Standard Deviations

Class of Compounds	<i>n</i>	Slope	Intercept	<i>r</i>	<i>s</i>
Carboxylic acids	9	0.927 ± 0.03	-1.41 ± 0.11	0.996	0.122
Esters	24	0.996 ± 0.01	-1.71 ± 0.04	0.999	0.060
Ethers	12	0.964 ± 0.07	-1.30 ± 0.19	0.976	0.080
Alcohols	49	0.966 ± 0.03	-1.53 ± 0.09	0.997	0.151
Amines	28	0.977 ± 0.04	-1.51 ± 0.12	0.979	0.179
Ketones	16	0.982 ± 0.03	-1.16 ± 0.09	0.993	0.094
Hydrocarbons	45	0.884 ± 0.03	0.406 ± 0.09	0.975	0.160
All compounds except hydrocarbons	138	0.950 ± 0.01	-1.48 ± 0.04	0.986	0.152

ketones, and 12 ethers (Table I). In addition to the functional group differences, each series provides compounds with structural diversity, *i.e.*, branched, straight-chain, cyclic, unsaturated, and aromatic hydrocarbon skeletons. This selection provides sufficient breadth of structure to demonstrate that a linear relationship between log *P* and the connectivity index is more than simply fortuitous.

EXPERIMENTAL

The molecular connectivity (χ) was calculated in the usual manner (1, 2). The molecular skeleton was drawn and each carbon atom in the skeleton was assigned a number, 1, 2, 3, or 4, corresponding to the number of nonhydrogen atoms connected to the carbon atom. The isosteric relationship of $-\text{CH}_3$, $-\text{OH}$, and $-\text{NH}_2$ was utilized so hydroxyl and amino functionalities were assigned the number 1, an ether oxygen was assigned the number 2, and the nitrogen atom of substituted amines, $\text{RNH}-$ and $\text{R}_2\text{N}-$, were assigned connectivities of 2 and 3, respectively. Initially, the valency of atoms was ignored so that, for example, a carbonyl oxygen was assigned a connectivity of 1 and unsaturated carbon atoms, $\text{RHC}=\text{}$, were given connectivity numbers based solely on the number of nonhydrogen attachments.

Plots of log *P* versus the connectivity index were computed, and families of parallel lines were obtained, each having approximately the same slope but different intercepts. These families of curves appear to be related to the degree of unsaturation inherent in each functional group or in the hydrocarbon skeleton.

Table III—Molecular Connectivity Index (χ) versus Selected Biological Activities^a

Compound	χ^b	V-17 ^c , <i>pC</i> obs.	V-18 ^d , <i>pC</i> obs.	V-19 ^d , <i>pC</i> obs.
Methanol	1.000	-0.14	-0.20	-0.14
Ethanol	1.414	0.28	0.21	0.28
Propanol	1.914	0.79	0.98	0.98
2-Propanol	1.732	0.92	—	—
Butanol	2.414	1.46	1.72	1.67
Pentanol	2.914	1.84	—	—
Hexanol	3.414	2.41	3.17	2.99
Heptanol	3.914	3.02	3.70	3.57
Octanol	4.414	3.62	4.12	3.97
2-Methyl-1-propanol	2.270	1.54	—	—
2-Butanol	2.270	1.16	—	—
2-Methyl-2-propanol	2.000	0.98	—	—
3-Methyl-1-butanol	2.770	1.86	2.18	2.09
2-Methyl-2-butanol	2.561	1.34	—	—
Benzyl alcohol	2.971	2.15 ^e	—	—

^a Biological activities (*pC*, obs.) were obtained from Ref. 9. ^b The connectivity index was calculated using valency modification described in text. ^c Biological activity is barnacle larvae narcosis (10). ^d Biological activity is I_{100} , movement of 2.5-day-old and 12-day-old tadpoles at 18° (11). ^e Not included in the derivation of regression equation.

It is assumed that a π -bond increases the connectivity of a carbon or oxygen atom by one unit, *e.g.*, $\text{CH}_2=$ has connectivity 2, $\text{RHC}=\text{}$ has connectivity 3, $\text{R}_2\text{C}=\text{}$ connectivity 4, $\text{O}=\text{}$ connectivity 2, and $\text{HC}\equiv$ connectivity 3. The valency modification merges the data for all classes of compounds (except the hydrocarbons) onto one line (Fig. 1). Table II summarizes the regression equations, correlation coefficients, and standard deviations for each class of compounds.

This refinement, *i.e.*, the use of valency, is not always necessary. In the linear relationship between the connectivity index and polarizability (1), a correlation coefficient of 0.990 was obtained, taking into account only attachments. The modification does, however, appear to be necessary in correlating the connectivity index to log *P* and solubility (2).

DISCUSSION

The molecular connectivity index, suggested by Randić (6), correlates significantly with a number of physicochemical properties (1, 2). It is now shown to have a high degree of correlation with the partition coefficients (log *P*) of a variety of compounds, encompassing several monofunctional groups and having structural diversity.

The importance of log *P* as a measure of lipophilicity and its use in structure-activity relationships are well known (7-9). It seems obvious that since the connectivity index is linearly related to log *P*, it should correlate in the same fashion as log *P* to biological activity. This hypothesis was tested on several systems where log *P* had been correlated with biological activity (9). Table III summarizes the data. These systems were all linearly related to log *P* and the connectivity index. For these systems, the following relationship and statistics were obtained.

For Study V-17 [narcosis, larvae, barnacle (10)]:

$$pC = -1.167(\pm 0.011) + 1.073(\pm 0.041)\chi \quad (\text{Eq. 1})$$

$$r = 0.991 \quad s = 0.141 \quad n = 15$$

For Study V-18 [I_{100} , movement 2.5-day-old tadpoles, 18° (11)]:

$$pC = -1.541(\pm 0.115) + 1.328(\pm 0.040)\chi \quad (\text{Eq. 2})$$

$$r = 0.997 \quad s = 0.127 \quad n = 8$$

For Study V-19 [I_{100} , movement 12-day-old tadpoles, 18° (11)]:

$$pC = -1.41(\pm 0.088) + 1.294(\pm 0.030)\chi \quad (\text{Eq. 3})$$

$$r = 0.998 \quad s = 0.097 \quad n = 8$$

These results compare very favorably with relationships to log *P* (9). Current studies are extending this exploration of the direct correlation of molecular connectivity to biological activity. The relationship of the connectivity index to other parameters such as Taft's steric parameter, E_s (12), used in structure-activity relationships is also being investigated.

Apparently, the partition coefficient represents an experimental quantity of intermediate significance between biological data and the more fundamental property of molecular connectivity, expressed as χ .

The tremendous utility of the connectivity index lies in the simplicity of its computation; no tables are needed for the calculations. Simply by assigning the degree of connectedness and the valency of an atom in a molecule and by performing a simple arithmetic computation, the connectivity index may be calculated. Simultaneously, the connectivity index appears to be related to the

fundamental notion that molecular structure, or connectedness, plays an important role in physicochemical and, hence, biological properties. The relation of the connectivity index to other constitutive, additive properties is being pursued.

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Size Distribution Effects in Multiparticulate Dissolution

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Abstract □ The evaluation of models for single-particle dissolution, based on multiparticulate dissolution data, is complicated by the distribution effect present when the particles are not truly monodispersed. By using simulated data, it is shown that remarkably good linearity can be obtained with log-normal powders using an incorrect model. It is suggested that particle-size analysis is necessary to enable calculation of the distribution effect and to prevent this type of misinterpretation. The change in particle-size distribution during dissolution is calculated and shows potential for distinguishing between two, but not all three, of the models investigated. Four theoretical rules for multiparticulate dissolution are stated and discussed. The concept of "time scaling" is presented. By using this procedure, it should be possible to reduce considerably computational errors arising from nonlinear dissolution data. It is demonstrated that dissolution profiles can be transformed to a standard form, enabling the distribution effect to be evaluated without interference from rate or particle-size parameters.

Keyphrases □ Dissolution, multiparticulate—size distribution effects, log-normal powders, three single-particle models investigated □ Powders, dissolution—size distribution effects, log-normal distribution profile, three single-particle models investigated □ Particle dissolution—size distribution effects, log-normal powders, three single-particle models investigated

The dissolution profile of a powder is determined by its particle-size distribution and the way the single particles dissolve. Several mathematical models have been presented to describe single-particle dissolution (1–4), but none of these has yet received complete acceptance. Experimental evaluation of the models on the basis of multiparticulate dissolution data is complicated by the distribution effect present when the powder is not truly monodispersed. Such powders are impossible to obtain in most cases (5). Processes such as sieving, precipitation, and grinding

do not yield completely uniform particles. This situation is particularly true for fine powders which are of greatest pharmaceutical importance.

In recent years, there has been increasing interest in evaluating the distribution effect in multiparticulate dissolution (6–9). A previous paper (9) discussed the theory and mathematics of multiparticulate systems in relation to single-particle dissolution and the initial size distribution. The present paper evaluates distribution effects for log-normal powder systems; three single-particle dissolution models from the literature are considered. By using simulated dissolution data and particle-size distributions, the possibility of distinguishing between the models is investigated.

THEORY

Let:

$$w = g(w_0, t) \quad (\text{Eq. 1})$$

and:

$$w_0 = g^{-1}(w, t) \quad (\text{Eq. 2})$$

describe the dissolution equation and inverse dissolution equation, respectively, for a single particle, where w and w_0 are the particle weights at time t and 0, respectively. Further, let $l_0(a_0)$ denote the initial ($t = 0$) particle-size density ("probability") distribution. By assuming that particles are spherical and remain so during dissolution, the particle weight, w , is related to the diameter, a , at any time by $w = \rho\pi a^3/6$, where ρ is the particle density.

By using a technique similar to the one used in a previous paper (9), the following equation can be derived which rigorously describes the particle-size distribution, $l(a)$, at any time if the initial distribution, $l_0(a_0)$, is known together with the particle dissolution function, g :