

# Molecular Connectivity I: Relationship to Nonspecific Local Anesthesia

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**Abstract** □ A very significant linear correlation was found between a recently proposed connectivity index and molecular polarizability, cavity surface areas calculated for water solubility of alcohols and hydrocarbons, and biological potencies of nonspecific local anesthetics. The simplicity of calculation of the index from the connectivity in the molecular skeleton, together with the very significant correlation, indicates its practical value.

**Keyphrases** □ Molecular connectivity—correlation with polarizability, cavity surface areas, and biological potencies, hydrocarbons, alcohols, nonspecific local anesthetics □ Polarizability—correlation with molecular connectivity, hydrocarbons, alcohols, nonspecific local anesthetics □ Cavity surface area—correlation with molecular connectivity, hydrocarbons, alcohols, nonspecific local anesthetics □ Anesthetics, nonspecific local—correlation between molecular connectivity and polarization, cavity surface areas, and biological potencies

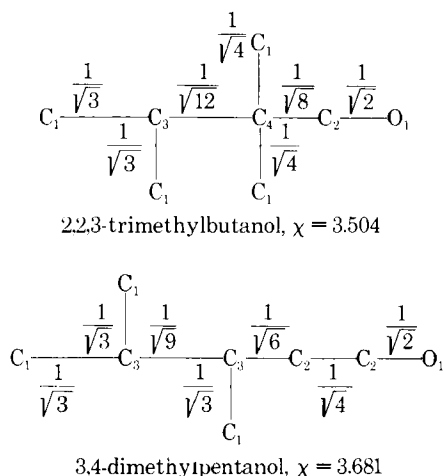
Recent studies in these laboratories on fundamental aspects of drug-receptor interactions have considered, as part of the total energy, the long-range forces of dispersion and polarization (1-4). These forces are predicted to be dominant in interaction phenomena involving molecules with nonpolar to moderately dipolar structures. The predicted energies of interaction involving these forces between model compounds, simulating all or parts of the drug and receptor molecules, were shown to relate to the quantitative biological response of several series of compounds (1-4).

A fundamental property governing the dispersion and polarization energies of interaction is the polarizability of atoms in a molecule (5). The polarizability of bonds between these atoms is derived from this property (6). Close relationships have indeed been found directly between calculated bond and molecular polarizabilities and the extent of a biological re-

sponse (1, 7).

The atomic polarizability relates to the volume of the atom; hence, the total molecular polarizability should bear a relationship to some topological property of a molecule (8). In a recent study, Randić (9) devised an index relating to a topological property of a hydrocarbon: the degree of branching or connectivity in the molecule. He showed that this index has a linear relationship to certain physical properties in a series of molecules, including boiling points, the Kovats constant, and empirical parameters dealing with vapor pressure in the Antoine equation.

It is possible that this simply derived index may be fundamental to a topological property governing physical and, in turn, biological properties, which in some areas may be influenced by molecular volume or surface. The purpose of this study was to test the relationship between this index and a biological property relating to polarizability; a very significant correlation was found. Subsequent papers in this series will show that a very close relationship exists with other molecular properties such as water solubility of organic compounds, partition coefficients, molar refractivity, parachor, and physicochemical and thermodynamic properties of the linear free energy type.



Scheme I—Calculation of connectivity indexes for two isomers of heptanol

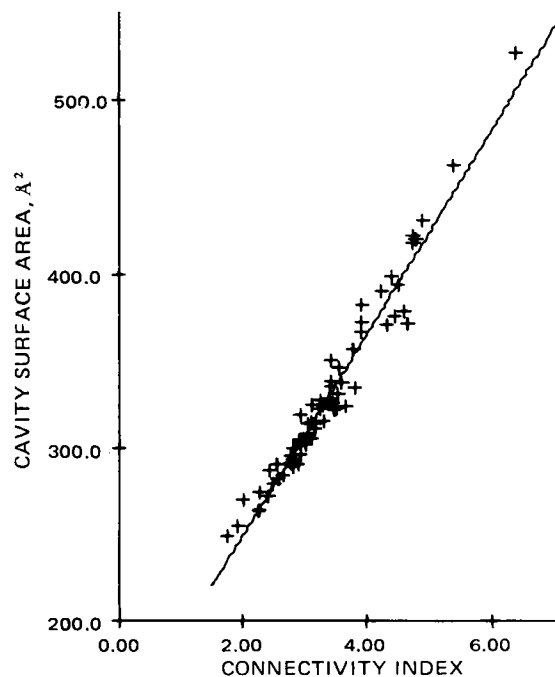


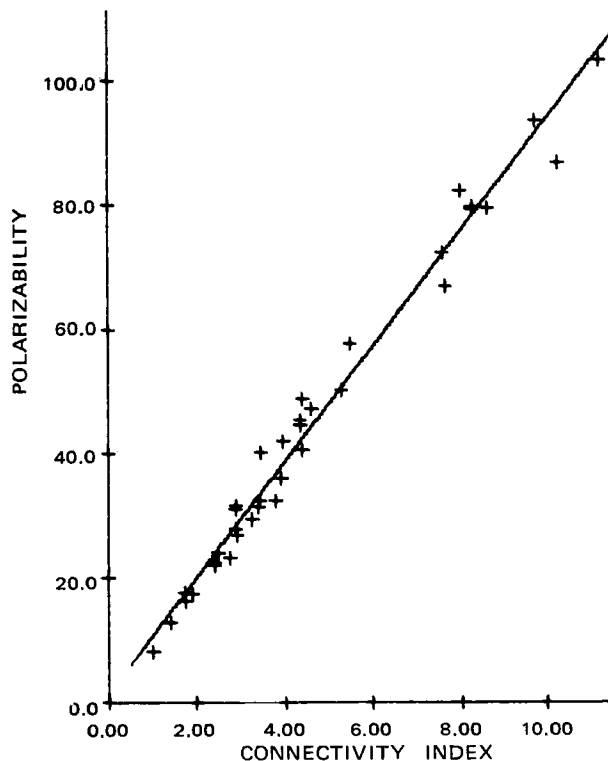
Figure 1—Computer-drawn plot of the cavity surface area versus the connectivity index for 51 aliphatic alcohols and 18 nonaromatic hydrocarbons.

**Table I—Cavity Surface Area (CSA) and Connectivity Index ( $\chi$ )**

Compound	$\chi$	CSA	CSA Predicted
1-Butanol	2.414	272.1	273.8
2-Methyl-1-propanol	2.269	263.8	265.6
2-Butanol	2.269	264.1	265.6
1-Pentanol	2.914	303.9	303.1
3-Methyl-1-butanol	2.769	291.4	294.9
2-Methyl-1-butanol	2.807	289.4	297.2
2-Pentanol	2.769	295.9	294.9
3-Pentanol	2.807	293.5	297.2
3-Methyl-2-butanol	2.641	284.3	287.2
2-Methyl-2-butanol	2.561	282.5	282.5
1-Hexanol	3.414	335.7	332.4
2-Hexanol	3.270	327.7	324.2
3-Hexanol	3.307	325.3	326.5
3-Methyl-3-pentanol	3.122	305.8	315.4
2-Methyl-2-pentanol	3.061	314.3	311.9
2-Methyl-3-pentanol	3.179	314.3	318.9
3-Methyl-2-pentanol	3.179	311.3	318.9
2,3-Dimethyl-2-butanol	2.943	301.2	304.8
3,3-Dimethyl-1-butanol	3.061	307.5	311.9
3,3-Dimethyl-2-butanol	2.943	296.7	304.8
4-Methyl-1-pentanol	3.269	323.0	324.2
4-Methyl-2-pentanol	3.124	314.9	315.4
2-Ethyl-1-butanol	3.346	308.6	311.9
Cyclohexanol	2.893	290.5	301.9
1-Heptanol	3.914	367.5	361.7
2-Methyl-2-hexanol	3.561	346.1	341.2
3-Methyl-3-hexanol	3.622	337.7	344.7
3-Ethyl-3-pentanol	3.683	324.4	348.2
2,3-Dimethyl-2-pentanol	3.481	323.8	336.5
2,3-Dimethyl-3-pentanol	3.504	321.8	337.6
2,4-Dimethyl-2-pentanol	3.416	328.6	332.9
2,4-Dimethyl-3-pentanol	3.552	331.7	340.6
2,2-Dimethyl-3-pentanol	3.481	326.1	336.5
3-Heptanol	3.807	357.1	355.8
4-Heptanol	3.807	357.1	355.8
1-Octanol	4.414	399.4	391.0
2,2,3-Trimethyl-3-pentanol	3.811	335.2	355.8
2-Octanol	4.269	391.0	382.8
2-Ethyl-1-hexanol	4.345	371.3	387.5
1-Nonanol	4.914	431.2	420.3
2-Nonanol	4.769	423.2	412.1
3-Nonanol	4.807	420.8	414.4
4-Nonanol	4.807	420.8	414.4
5-Nonanol	4.807	420.8	414.4
2,6-Dimethyl-4-heptanol	4.520	394.0	397.4
3,5-Dimethyl-4-heptanol	4.628	379.3	403.9
2,2-Diethyl-1-pentanol	4.743	372.5	406.8
7-Methyl-1-octanol	4.769	418.7	388.0
3,5,5-Trimethyl-1-hexanol	4.454	376.6	393.3
1-Decanol	5.414	463	449.6
1-Dodecanol	6.414	527	508.2
n-Butane	1.914	255.2	244.7
2-Methylpropane	1.732	249.1	234.0
n-Pentane	2.414	287.0	274.0
2-Methylbutane	2.270	274.6	265.6
3-Methylpentane	2.807	300.1	297.0
Neopentane	2.000	270.1	249.7
2,2-Dimethylbutane	2.561	290.8	282.6
2,4-Dimethylpentane	3.125	324.7	315.7
2,2,4-Trimethylpentane	3.417	338.9	332.8
2,2,5-Trimethylhexane	3.917	373.0	362.1
Cyclohexane	2.500	279.1	279.0
Methylcyclohexane	2.893	304.9	302.1
1-cis-2-Dimethylcyclohexane	3.304	315.5	326.2
Cycloheptane	3.000	301.9	308.3
Cyclooctane	3.500	322.6	337.6
n-Hexane	2.914	319	303.3
n-Heptane	3.414	351	332.6
n-Octane	3.914	383	361.9

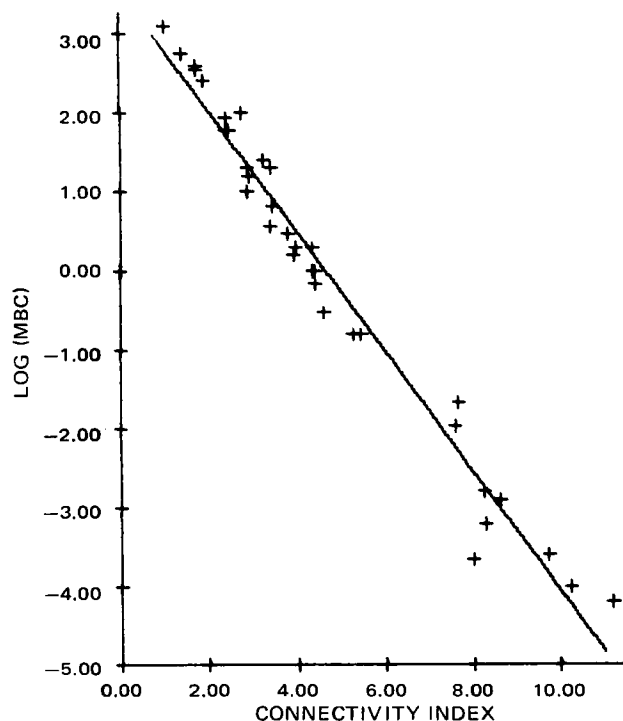
**EXPERIMENTAL**

**Calculation of Connectivity Index**—The index is derived from the numerical extent of branching or connectivity in the molecular skeleton. The first row atoms of a molecule are dealt with in an identical manner. The hydrogen atoms are suppressed. The degree of bond saturation is ignored in this study but will be considered later.



**Figure 2**—Computer-drawn plot of the molecular polarizability versus the connectivity index for 36 compounds used in a nonspecific anesthesia study.

The structure is drawn out in skeletal form. Each atom is assigned a number corresponding to the number of atoms attached, i.e., 1, 2, 3, or 4 in the case of a carbon atom. Hydrogen atoms are not included in the count. A number is derived for each bond by calculating the product of the numbers associated with the two



**Figure 3**—Computer-drawn plot of the log of the minimum blocking concentration versus the connectivity index for 36 compounds used in a nonspecific anesthesia study.

Table II—Polarizability ( $\alpha$ ), Minimum Blocking Concentration (MBC), and Connectivity Index ( $\chi$ ) of Local Anesthetics

Anesthetic	$\chi$	$\alpha$	Predicted $\alpha$	Log MBC, mM	Predicted Log MBC
Methanol	1.000	8.2	10.9	3.09	2.79
Ethanol	1.414	12.9	14.7	2.75	2.47
Acetone	1.732	16.2	17.7	2.6	2.23
2-Propanol	1.732	17.6	17.7	2.55	2.23
1-Propanol	1.914	17.5	19.3	2.4	2.09
Urethan	2.769	23.2	27.3	2.0	1.44
Ether	2.414	22.5	24.0	1.93	1.71
Butanol	2.414	22.1	24.0	1.78	1.71
Pyridine	2.500	24.1	24.8	1.77	1.65
Hydroquinone	3.288	29.4	32.1	1.4	1.05
Aniline	2.893	31.6	28.4	1.3	1.35
Benzyl alcohol	3.432	32.5	33.4	1.3	0.935
Pentanol	2.914	26.8	28.6	1.2	1.33
Phenol	2.893	27.8	28.4	1.0	1.35
Toluene	2.893	31.1	28.4	1.0	1.35
Benzimidazole	3.466	40.2	33.7	0.81	0.901
Hexanol	3.414	31.4	33.2	0.56	0.949
Nitrobenzene	3.804	32.5	36.8	0.47	0.651
Quinoline	3.966	42.1	38.3	0.3	0.528
8-Hydroxyquinoline	4.376	44.7	42.1	0.3	0.215
Heptanol	3.914	36.0	37.9	0.2	0.567
2-Naphthol	4.359	45.4	42.0	0.0	0.228
Methyl anthranilate	4.423	48.9	42.6	0.0	0.182
Octanol	4.414	40.6	42.5	-0.16	0.186
Thymol	4.608	47.3	44.3	-0.52	0.038
<i>o</i> -Phenanthroline	5.448	57.8	52.1	-0.8	-0.602
Ephedrine	5.253	50.2	50.3	-0.8	-0.453
Procaine	7.668	67.0	72.6	-1.67	-2.29
Lidocaine	7.578	72.5	71.8	-1.96	-2.22
Diphenhydramine	8.270	79.5	78.2	-2.8	-2.75
Tetracaine	8.629	79.7	81.5	-2.9	-3.03
Phenyltoloxamine	8.254	79.9	78.1	-3.2	-2.74
Quinine	9.705	93.8	91.5	-3.6	-3.85
Physostigmine	7.969	82.4	75.4	-3.66	-2.52
Caramiphen	10.224	87.0	96.3	-4.0	-4.24
Dibucaine	11.182	103.6	105.2	-4.2	-4.97

atoms of the bond. The reciprocal of the square root of this number is then computed and becomes the bond value. Finally, the bond values are summed to give a number, called the connectivity index ( $\chi$ ) for the molecule. Two examples of this process are illustrated in Scheme I.

The two molecules, isomers differing only in their branching, yield different connectivity indexes, which are also different from the index for 1-heptanol, 3.914. It appears, then, that the degree of branching is also related to the connectivity index.

Cyclic structures possess one additional bond for each ring relative to the chain isomer. The value of one bond must be subtracted for each ring. For cyclohexane, the summation yields 3.000, from which  $1/\sqrt{2} \times 2$  must be subtracted to yield  $\chi = 2.500$ . Aromatic molecules are treated in the same way in this study. Thus, benzene has  $\chi = 2.500$  while acetanilide has  $\chi = 4.287$ . Molecules that can ionize are considered in their neutral state.

**Correlation of Solvent Cavity Surface Area with Connectivity Index**—In studies of hydrocarbon solubility in water, Hermann (10) developed a method for calculating the surface area inside the idealized solvent cavity required to accommodate the hydrocarbon solute. The calculated cavity surface contains the centers of the water molecules in the first layer around the solute. Since this cavity area has the properties of an envelope of enclosure, and hence depends upon the connectivity of the molecular skeleton, it was felt that it may be related to the connectivity index.

These studies found a highly significant correlation between the calculated cavity surface area (CSA) and the connectivity index for 18 hydrocarbons (branched or straight chain). Cyclohexanol is the only cyclic alcohol included. In computing the connectivity index, the quantity 0.5 is subtracted for each ring in the cyclic compounds; e.g., for methylcyclohexane,  $\chi = 3.393 - 0.500$ .

The regression equation, correlation coefficient, and standard deviation are:

$$\text{CSA} = 133.4 + 58.24\chi \quad (\text{Eq. 1})$$

$$r = 0.978 \quad s = 11.2 \quad n = 69$$

The plot of the cavity surface area *versus* the connectivity index

is shown in Fig. 1, and the supporting data are presented in Table I.

The second paper in this series discusses the relationship between the connectivity index and the water solubility of hydrocarbons and aliphatic alcohols (11), a property whose fundamental relationship to the cavity surface area was explored by Hermann (10).

**Correlation of Molecular Polarizability with Connectivity Index**—The polarizability ( $\alpha$ ) of a molecule may be derived as a sum of atomic refraction constants (7). To explore further how the connectivity index may be related to physical properties of biological importance, the dependence of polarizability on the connectivity index was considered, and a high degree of correlation between these quantities was found.

In Fig. 2 the polarizability is plotted against the connectivity index, and the supporting data are displayed in Table II. The regression equation, correlation coefficient, and standard deviation are:

$$\alpha = 1.60 + 9.26\chi \quad (\text{Eq. 2})$$

$$r = 0.990 \quad s = 3.59 \quad n = 36$$

Because of the high degree of correlation found between the connectivity index and polarizability, the relationship of the connectivity index to nonspecific anesthesia, a property thought to be related to molecular polarizability (7), was examined.

**Correlation between Local Anesthetic Potency and Connectivity Index**—Agin *et al.* (7) compiled and obtained experimentally the minimum blocking concentrations (MBC) of almost 40 molecules on isolated nerve or muscle fiber. They measured the minimum concentration required to excite cells in a standardized set of conditions (Table II). The relationship between the log MBC and the connectivity index is shown in Fig. 3. The regression equation, correlation coefficient, and standard deviation are:

$$\log \text{MBC} = 3.55 - 0.762\chi \quad (\text{Eq. 3})$$

$$r = 0.983 \quad s = 0.390 \quad n = 36$$

Acetanilide and aminopyrine were not included from the Agin *et al.* data, because they made an unexplained correction in the activ-

ity for these molecules. Chloroform was not included because of some uncertainties about the chlorine parameter.

## DISCUSSION

Two observations come boldly into view: the correlations of the connectivity index with cavity surface area, polarizability, and biological activity are very good, suggesting a fundamental significance for the connectivity index; and the connectivity index value for each molecule is very simply derived, almost by inspection, from no more than four numbers (1, 2, 3, and 4) describing connections.

The mathematical derivation of the connectivity index is extremely simple and is based on discrimination of bond types in a molecule according to the number of its nearest neighbors. The physical significance of the connectivity index is more fundamental than may appear. The individual connectivity index values reflect molecular connectivity and present ultimate fragmentation of the molecular skeleton. Any function of a molecule can be represented as a power expansion of bond contributions. At this initial stage, attention was confined to the linear term of such bond additive schemes.

One may look at connectivity index values as distinctive weighting of bond contributions. It is very significant that the weighting is based solely on the valency of vertexes of molecular graphs and, hence, is nonempirical.

It is plausible to expect that the connectivity index relates to such molecular properties as enclosure volume and surface area. The predictive value of this simply computed index is demonstrated to the biological scientist. In subsequent papers, additional correlations will be described.

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# Molecular Connectivity II: Relationship to Water Solubility and Boiling Point

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**Abstract** □ The connectivity index, easily computed by arithmetic and based upon the degree of connectedness at each vertex in the molecular skeleton, is shown to give highly significant correlations with water solubility of branched, cyclic, and straight-chain alcohols and hydrocarbons as well as with boiling points of alcohols. These correlations are superior to those based on well-founded theory relating to solvent cavity surface area. An empirical modification to the connectivity index gave an improved correlation for both solubilities and boiling points.

**Keyphrases** □ Molecular connectivity—correlation with water solubility and boiling point, hydrocarbons, alcohols □ Solubility—correlation with molecular connectivity, hydrocarbons, alcohols □ Boiling point—correlation with molecular connectivity, hydrocarbons, alcohols

It has long been known that branched- and straight-chain organic molecules differ in their properties. For example, branched-chain alcohols and hydrocarbons generally have lower boiling points and higher solubilities than the corresponding straight-chain isomers. However, until the recent suggestion by Randić (1), there was no simply computed quantitative scheme for correlating physicochemical data with such topological characteristics as branching. The earlier ideas of Hosoyea (2) and Smolenski (3)

have not received acceptance as means for correlating properties. The Hosoyea index shows only a qualitative correlation, and the Smolenski additivity function becomes complex to apply.

Since the manner in which organic groups are connected to form a molecule appears to influence molecular properties, the relationship between a connectivity index and various physicochemical and biological properties was studied. Success in correlating the connectivity index ( $\chi$ ) with polarizability and biological activity of certain nonspecific local anesthetics was reported in Part I (4).

The great utility of a simply computed index that could be used to predict physicochemical properties led to the study of the water solubilities of aliphatic alcohols and hydrocarbons. By applying the significant structure theory to the solubilities of these compounds, several studies showed that the log of the solubilities correlates well with the calculated surface area of the cavity required to accommodate the solute in the solvent water (5, 6).

In Part I, a highly significant correlation of the cavity surface area to the connectivity index was shown (4). This paper explores the correlation of the