

# Molecular Connectivity VII: Specific Treatment of Heteroatoms

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**Abstract** □ The molecular connectivity index,  $\chi$ , initially designed for hydrocarbons, has been formally extended to molecules containing heteroatoms. The  $\delta$  value of the heteroatom is modified to take account of its number of attached hydrogen atoms,  $\delta_i^v = Z^v - h_i$ . These values were successfully tested on boiling points and molar refractions. A table of  $\delta^v$  values is presented for nitrogen, oxygen, fluorine, chlorine, bromine, and iodine in various bonding situations.

**Keyphrases** □ Molecular connectivity—heteroatomic molecules, correlated with boiling points and molar refractions □ Heteroatomic molecules—molecular connectivity indexes calculated, correlated with boiling points and molar refractions □ Boiling points—heteroatomic molecules, correlated with molecular connectivity indexes □ Molar refractions—heteroatomic molecules, correlated with molecular connectivity indexes

In earlier studies using the molecular connectivity index,  $\chi$ , to describe structural features, the heteroatoms oxygen and nitrogen were considered to contribute equally with carbon (1-7). This designation inevitably led to redundant values of  $\chi$  for isomers such as 2-methyl-1-propanol and 2-methyl-2-propanol. An initial approach to the resolution of these redundancies was used in an alcohol solubility study (2). A second regression variable was introduced simply as the contribution to total  $\chi$  from the C—OH bond. This bond value varies in primary, secondary, and tertiary alcohols. Redundancies are destroyed, and there is a 16% decrease in the standard error for the log of the solubility. A 33% decrease in the boiling-point standard error is also observed for this empirical approach.

In a second empirical approach, the total degree of branching,  $\Delta\chi$ , in the heteroatom-containing molecule is partitioned. The branching attributed to functional group position,  $\Delta\chi^F$ , is separated from that due to carbon skeleton branching,  $\Delta\chi^S$ . In a study of the heat of atomization of 20 saturated noncyclic alcohols, the standard error was reduced 40% when these quantities were introduced into the regression (3).

These approaches are now considered to be an interim or first-order solution to a more basic problem of calculating the molecular connectivity contribution of any atom other than carbon.

## METHOD

An alternative approach to heteroatom calculation has a basis in earlier considerations of unsaturated molecules (4). That study used the valence connectedness of the atom as a  $\delta$  value for carbon atoms in a double bond. Thus, the central carbon of propene has a  $\delta$  of 3, the central carbon of 2-methylpropene has a  $\delta$  of 4, and both carbons of ethene have a  $\delta$  of 2. Use of these values gives rise to a  $\chi$  for the molecule designated as a valence  $\chi$  or  $\chi^v$ . Benzene would thus have a  $\chi^v$  of 2.000 [not modifying for the cyclic nature of the molecule (1)].

There are several ways that this  $\delta$  value can be understood within the framework of the connectivity theory already developed (1-7). It can be derived from the total number of bonds emanating from the atom, counting the  $\pi$  electron bonds as well as the  $\sigma$  bonds.

Another derivation for the  $\delta$  value is its equivalence to the number of valence electrons,  $Z^v$ , minus the number of hydrogen atoms,  $h$ , bonded to the atom under consideration,  $Z^v - h$ .

Table I—Valence Delta ( $\delta^v$ ) Values for Heteroatoms

Group	$\delta^v$	Group	$\delta^v$
NH <sub>2</sub>	3	OH	5
NH	4	O	6
N	5	C=O	6
C≡N	5	Furan O	6
C=NH	4	O=NO	6
Pyridine N	5	H <sub>2</sub> O	4
Nitro N	6	H <sub>3</sub> O <sup>+</sup>	3
NH <sub>3</sub>	2	F <sup>-</sup>	(-) <sup>20</sup>
NH <sub>4</sub> <sup>+</sup>	1	Cl	0.690
>N< <sup>+</sup>	6	Br	0.254
=NH <sub>2</sub> <sup>+</sup>	3	I	0.085

Both derivations give identical values for simple unsaturated systems, but the second derivation has more wide ranging applications, especially as an approach to parameterizing the connectivity of heteroatoms.

Using the expression  $\delta^v = Z^v - h$ , the valence  $\delta^v$  values for oxygen and nitrogen in several variations of bonding can be calculated (Table I). Ammonia and water are unique limiting cases of the  $Z^v - h$  expression. The nitro group nitrogen has a  $\delta^v = 6$ , since it can be considered to be derived from a nitroso group ( $\delta_{N^v} = 5$ ) by appending another connection, namely an oxygen atom bonded to the nitrogen atom. The nitrogen atom of a tetraalkylammonium ion can, by the same argument, be assigned a  $\delta^v$  of 6.

**Boiling Point and Solubility**—The validity of these values can be tested by determining their ability to destroy redundant  $\chi$  values in a series of molecules and to improve a correlation with a physical property. The first test of the influence of the  $\chi^v$  term is with a series of aliphatic alcohols (Table II). When using the standard connectivity  $\chi$ , the regression equation and statistics for the boiling points are:

$$\begin{aligned} \text{boiling point} &= 38.79 (\pm 1.61)\chi + 11.26 (\pm 5.85) \\ r &= 0.963 \quad s = 8.39^\circ \quad n = 48 \end{aligned} \quad (\text{Eq. 1})$$

If the  $\chi^v$  value is introduced, the relationship improves to:

$$\begin{aligned} \text{boiling point} &= 196.58 (\pm 11.34)\chi - 157.6 (\pm 11.31)\chi^v \\ &\quad - 41.24 (\pm 4.56) \\ r &= 0.993 \quad s = 3.68^\circ \quad n = 48 \end{aligned} \quad (\text{Eq. 2})$$

The use of the second term,  $\chi^v$ , leads to over a twofold improvement in the standard deviation of the mean. This equation leads to a prediction of the boiling point to within 2.5%.

For this same list of alcohols, the log molar solubility is related to  $\chi$  by:

$$\begin{aligned} \log S &= -2.61 (\pm 0.086)\chi + 6.52 (\pm 0.31) \\ r &= 0.976 \quad s = 0.447 \quad n = 48 \end{aligned} \quad (\text{Eq. 3})$$

When using the  $\chi^v$  term, the multiple regression equation is:

$$\begin{aligned} \log S &= 9.27 (\pm 0.98)\chi + 6.64 (\pm 0.97)\chi^v + 8.73 (\pm 0.39) \\ r &= 0.988 \quad s = 0.317 \quad n = 48 \end{aligned} \quad (\text{Eq. 4})$$

The predicted values are shown in Table II.

Again, the improvement in the relationship is noteworthy upon the introduction of the  $\chi^v$  term. The major effect is the influence of  $\chi^v$  in destroying the seven pairs of redundant  $\chi$  values in the list. Furthermore, the  $\chi^v$  term reorders these redundancies in the correct order relative to the boiling point and log solubility.

The value of the  $\chi^v$  term is dramatically illustrated in the case of the boiling points of several glycols (Table III):

$$\begin{aligned} \text{boiling point} &= 20.71 (\pm 24.28)\chi + 159.38 (\pm 67.23) \\ r &= 0.307 \quad s = 34.0^\circ \quad n = 9 \end{aligned} \quad (\text{Eq. 5})$$

and:

**Table II—Boiling Points and Solubilities of Saturated Alcohols**

Compound	Boiling Point		Log Solubility	
	Obs. <sup>a</sup>	Calc.	Obs. <sup>b</sup>	Calc.
1-Butanol	117.7°	114.56°	0.005	-0.191
2-Methylpropanol	107.9°	108.74°	0.022	0.195
2-Butanol	99.5°	97.40°	0.065	0.673
1-Pentanol	137.8°	134.27°	-1.347	-1.511
3-Methylbutanol	131.2°	128.25°	-1.167	-1.115
2-Methylbutanol	128.7°	129.74°	-1.058	-1.214
2-Pentanol	119.0°	116.91°	-0.634	-0.636
3-Pentanol	115.3°	118.39°	-0.486	-0.736
3-Methyl-2-butanol	111.5°	111.76°	-0.404	-0.294
2-Methyl-2-butanol	102.0°	102.33°	0.338	0.180
1-Hexanol	157.0°	153.58°	-2.790	-2.812
2-Hexanol	139.9°	136.42°	-1.995	-1.947
3-Hexanol	135.4°	137.90°	-1.832	-2.046
3-Methyl-3-pentanol	122.4°	124.23°	-0.830	-1.289
2-Methyl-2-pentanol	121.4°	121.85°	-1.117	-1.129
2-Methyl-3-pentanol	126.5°	132.75°	-1.609	-1.704
3-Methyl-2-pentanol	134.2°	132.75°	-1.639	-1.704
2,3-Dimethyl-2-butanol	118.6°	117.08°	-0.850	-0.813
3,3-Dimethyl-1-butanol	143.0°	139.81°	-2.590	-1.887
3,3-Dimethyl-2-butanol	120.0°	123.86°	-1.410	-1.099
4-Methyl-1-pentanol	151.8°	147.77°	-2.282	-2.425
4-Methyl-2-pentanol	131.7°	130.61°	-1.814	-1.560
2-Ethylbutanol	146.5°	150.73°	-2.787	-2.624
1-Heptanol	176.3°	173.09°	-4.166	-4.122
2-Methyl-2-hexanol	142.5°	141.36°	-2.473	-2.440
3-Methyl-3-hexanol	142.4°	143.74°	-2.263	-2.600
3-Ethyl-3-pentanol	142.5°	146.12°	-1.917	-2.759
2,3-Dimethyl-2-pentanol	139.7°	130.99°	-2.002	-1.924
2,3-Dimethyl-3-pentanol	139.0°	138.97°	-1.937	-2.284
2,4-Dimethyl-2-pentanol	133.0°	135.54°	-2.145	-2.053
2,4-Dimethyl-3-pentanol	138.8°	147.47°	-2.800	-2.689
2,2-Dimethyl-3-pentanol	136.0°	144.85°	-2.643	-2.509
3-Heptanol	156.8°	157.42°	-3.194	-3.357
4-Heptanol	155.0°	157.42°	-3.196	-3.357
1-Octanol	195.2°	192.61°	-5.401	-5.433
2,2,3-Trimethyl-3-pentanol	152.5°	151.11°	-2.931	-3.095
2-Octanol	179.8°	175.45°	-4.755	-4.568
2-Ethylhexanol	184.6°	189.76°	-5.005	-5.245
1-Nonanol	213.1°	212.12°	-6.907	-6.743
2-Nonanol	198.5°	194.96°	-6.319	-5.878
3-Nonanol	194.7°	196.44°	-6.119	-5.978
4-Nonanol	193.0°	196.44°	-5.952	-5.978
5-Nonanol	195.1°	196.44°	-5.744	-5.978
2,6-Dimethyl-3-heptanol	178.0°	174.40°	-5.776	-4.785
3,5-Dimethyl-4-heptanol	187.0°	189.45°	-5.298	-5.509
1,1-Diethylpentanol	192.0°	185.14°	-5.572	-5.381
7-Methyloctanol	206.0°	206.30°	-5.744	-6.357
3,5,5-Trimethylhexanol	193.0°	194.1°	-5.769	-5.531

<sup>a</sup>Boiling points are in degrees centigrade, and the logarithms of the solubility (expressed as molality) were taken from the following sources and references cited therein: G. L. Amidon, S. H. Yalkowski, and S. J. Leung, *J. Pharm. Sci.*, **63**, 1858(1974), and "Handbook of Chemistry and Physics," 51st ed., Chemical Rubber Co., Cleveland, Ohio, 1971.

$$\text{boiling point} = 249.64 (\pm 10.04)\chi - 222.1 (\pm 9.38)\chi^v - 29.11 (\pm 10.92)$$

$$r = 0.995 \quad s = 3.78^\circ \quad n = 9 \quad (\text{Eq. 6})$$

The use of  $\chi^v$  with the  $\chi$  term lowers the  $s$  value almost 10-fold.

The use of the  $\chi^v$  terms in the case of primary and secondary amines (Table IV) also significantly improves the correlation of connectivity indexes with the boiling points. For a series of primary amines, the equations and statistics are:

$$\text{boiling point} = 50.93 (\pm 1.00)\chi - 49.17 (\pm 3.30)$$

$$r = 0.996 \quad s = 4.59^\circ \quad n = 21 \quad (\text{Eq. 7})$$

and:

$$\text{boiling point} = 154.09 (\pm 17.20)\chi - 103.5 (\pm 17.84)\chi^v - 75.92 (\pm 5.03)$$

$$r = 0.999 \quad s = 2.79^\circ \quad n = 21 \quad (\text{Eq. 8})$$

For secondary amines, the relationships are:

**Table III—Boiling Points of Polyols**

	Boiling Point		Connectivity Index	
	Obs. <sup>a</sup>	Calc.	$\chi$	$\chi^v$
2-Methyl-2,4-pentanediol	196.0°	197.3°	3.417	2.821
Ethanediol	197.8°	197.3°	1.914	1.132
1,3-Butanediol	207.5°	204.8°	2.770	2.060
1,3-Propanediol	214.7°	211.0°	2.414	1.632
1,2-Propanediol	187.4°	191.1°	2.270	1.560
2,3-Butanediol	181.7°	185.6°	2.643	2.004
1,4-Butanediol	230.0°	224.8°	2.914	2.132
1,5-Pentanediol	238°	238.5°	3.414	2.632
Glycerol	290°	292.7°	2.808	1.707

<sup>a</sup>Boiling points were taken from the "Handbook of Tables for Organic Compound Identification," 3rd ed., CRC Press, Cleveland, Ohio, 1967.

$$\text{boiling point} = 48.50 (\pm 1.15)\chi - 58.55 (\pm 4.07)$$

$$r = 0.997 \quad s = 4.28^\circ \quad n = 13 \quad (\text{Eq. 9})$$

and:

$$\text{boiling point} = 171.40 (\pm 21.84)\chi - 120.07 (\pm 21.45)\chi^v - 102.4 (\pm 8.07)$$

$$r = 0.999 \quad s = 2.20^\circ \quad n = 13 \quad (\text{Eq. 10})$$

The primary and secondary amines must apparently be considered separately with the framework of the present development of connectivity indexes. The intermolecular forces between primary amines differ enough from intermolecular forces between secondary amines,

**Table IV—Boiling Points of Primary and Secondary Aliphatic Amines**

Compound	Boiling Point		Residual
	Obs. <sup>a</sup>	Calc.	
<b>Primary Amines</b>			
<i>n</i> -Propylamine	49.0°	51.91°	-2.91
2-Aminopropane	33.0°	37.00°	-4.00
2-Amino-2-methylpropane	46.0°	47.15°	-1.15
2-Aminobutane	63.0°	64.23°	-1.23
2-Methylpropylamine	69.0°	69.93°	-0.93
<i>n</i> -Butylamine	77.0°	77.21°	-0.21
2-Amino-2-methylbutane	78.0°	75.66°	2.35
2-Aminopentane	92.0°	89.54°	2.45
3-Methylbutylamine	96.0°	95.23°	0.77
2-Methylbutylamine	96.0°	97.16°	-1.16
<i>n</i> -Pentylamine	104.0°	102.52°	1.47
4-Methylpentylamine	125.0°	120.54°	4.45
<i>n</i> -Hexylamine	130.0°	127.83°	2.17
3-Methylpentylamine	114.0°	114.85°	-0.85
4-Aminoheptane	139.0°	142.08°	-2.58
2-Aminoheptane	142.0°	136.44°	5.56
<i>n</i> -Heptylamine	155.0°	153.14°	1.86
<i>n</i> -Octylamine	180.0°	178.45°	1.55
<i>n</i> -Nonylamine	201.0°	203.76°	-2.76
2-Aminoundecane	237.0°	241.40°	-4.40
3-Aminopentane	91.0°	91.47°	-0.47
<b>Secondary Amines</b>			
<i>N</i> -(Methyl)ethylamine	36.0°	37.19°	-1.19
<i>N</i> -Methyl-1-methylethylamine	50.0°	52.09°	-2.09
Diethylamine	56.0°	55.28°	0.72
<i>N</i> -Methyl-1-methylpropylamine	78.5°	79.35°	-0.85
<i>N</i> -(Ethyl)propylamine	80.5°	80.62°	-0.12
Bis(1-methylethyl)amine	84.0°	84.84°	-0.84
<i>N</i> -(Methyl)butylamine	90.5°	87.86°	2.64
<i>N</i> -Methyl-1-methylbutylamine	105.0°	104.69°	0.31
Dipropylamine	109.5°	105.95°	3.55
Bis(2-methylpropyl)amine	139.0°	142.03°	-3.03
Dibutylamine	159.0°	156.62°	2.38
Bis(3-methylbutyl)amine	187.5°	186.66°	0.84
Dipentylamine	205.0°	207.29°	-2.29

<sup>a</sup>Boiling points were taken from the "Handbook of Tables for Organic Compound Identification," 3rd ed., CRC Press, Cleveland, Ohio, 1967.

**Table V—Substituent Parameters for Molar Refraction ( $R_m$ )**

Substituent	Molar Refraction		Connectivity Index <sup>b</sup>	
	Obs. <sup>a</sup>	Calc.	$\chi^c$	$\chi^v$
Methyl	4.7	4.14	0.577	0.500
Ethyl	9.4	9.58	1.115	1.06
Propyl	14.0	14.48	1.615	1.561
1-Methylethyl	14.0	13.30	1.488	1.443
Butyl	18.7	19.37	2.115	2.061
1,1-Dimethylethyl	18.5	16.29	1.789	1.750
Phenyl	24.3	22.84	3.150	2.161
Hydroxyl	1.5	2.17	0.577	0.224
Methoxyl	6.5	6.37	1.115	0.612
Ethoxyl	11.3	11.90	1.615	1.200
Propoxyl	15.9	16.80	2.115	1.700
1-Methylethoxyl	16.0	15.66	1.971	1.595
Butoxyl	20.7	21.69	2.615	2.200
Pentoxyl	25.3	26.59	3.115	2.700
Phenoxyl	26.6	25.25	3.633	2.319
Acetate	11.6	12.22	1.971	1.112
Amino	4.2	2.95	0.577	0.333
Acetamido	14.6	12.87	1.971	1.204
Nitro	6.0	6.83	1.488	0.537
Aldehyde	5.3	5.74	1.115	0.524
Acyl	9.9	9.81	1.488	0.954
Methylcarboxylate	11.4	12.03	2.026	1.066
Ethylcarboxylate	16.2	17.56	5.526	1.654
Amido	8.8	8.30	1.488	0.743
Cyano	5.2	5.85	1.115	0.539
Fluoro <sup>c</sup>	-0.4	—	0.577	-0.124
Chloro <sup>c</sup>	4.8	—	0.577	0.602
Bromo <sup>c</sup>	7.6	—	0.577	0.992
Iodo <sup>c</sup>	12.8	—	0.577	1.719

<sup>a</sup>Data were taken from Ref. 8. <sup>b</sup>Connectivity index was calculated only for the substituent as if attached to the phenyl ring. <sup>c</sup>No  $R_m$  values are shown as calculated for the halogens because the observed  $R_m$  values were used to calculate the  $\delta^v$  value for the halogens.

in the bulk phase, to give rise to a different boiling point for comparable connectivity indexes. Thus, diethylamine and butylamine have similar  $\chi^v$  values (2.121 and 2.115), but the boiling points differ by 21°. The difference is probably due to differing electron densities in the lone-pair electron orbitals and the different number of amino hydrogen atoms capable of hydrogen bonding. These effects are not encoded in the connectivity indexes at the present level of development. Therefore, it is necessary to consider classes of amines when relating boiling point with molecular connectivity indexes. This question will be discussed in a subsequent paper.

**Table VI—Boiling Points of Alkyl Halides**

Compound	Boiling Point			Connectivity Index	
	Obs.	Calc.	Residual	$\chi^c$	$\chi^v$
Ethyl chloride	13.0°	17.9°	-4.9	1.414	1.558
Ethyl bromide	38.0°	38.9°	-0.9	1.414	2.110
Ethyl iodide	72.0°	77.8°	-5.8	1.414	3.132
Propyl chloride	46.5°	46.9°	-0.4	1.914	2.058
Propyl bromide	71.0°	67.9°	3.1	1.914	2.610
Propyl iodide	102.5°	106.8°	-4.3	1.914	3.632
1-Methylethyl chloride	36.5°	35.4°	1.1	1.732	1.850
1-Methylethyl bromide	60.0°	54.5°	7.5	1.732	2.300
1-Methylethyl iodide	90.0°	84.3°	5.7	1.732	3.135
1-Methylpropyl chloride	69.0°	67.5°	1.5	2.270	2.414
1-Methylpropyl bromide	91.0°	88.6°	2.4	2.270	2.966
1-Methylpropyl iodide	120.0°	127.5°	-7.5	2.270	3.988
1,1-Dimethylethyl chloride	51.0°	50.3°	0.7	2.000	2.102
1,1-Dimethylethyl bromide	72.5°	65.1°	7.4	2.000	2.492
1,1-Dimethylethyl iodide	98.0°	92.7°	5.3	2.000	3.215
Butyl chloride	78.0°	75.9°	2.1	2.414	2.558
Butyl bromide	101.0°	96.9°	4.1	2.414	3.110
Butyl iodide	130.0°	135.8°	-5.8	2.414	4.132
1-Methylbutyl chloride	97.0°	95.5°	1.5	2.770	2.888
1-Methylbutyl bromide	117.0°	112.7°	4.3	2.770	3.338
1-Methylbutyl iodide	142.0°	144.5°	-2.5	2.770	4.173
Propyl fluoride	2.5°	8.5°	-6.0	1.914	1.049
Butyl fluoride	32.5°	37.5°	-5.0	2.414	1.549
Pentyl fluoride	62.8°	66.5°	-3.7	2.914	2.049

**Molar Refraction**—If these or similar intermolecular effects are minimal in influencing a physical property, it may be possible to relate the connectivity of various molecules, containing different heteroatoms, with that property. This approach appears to be possible with molar refraction (Table V). A comparison of  $\chi$  and  $\chi^v$  values with molar refraction provides a severe test of the  $\chi^v$  values because they must recreate connectivity properties of carbon, nitrogen, and oxygen in a self-consistent manner.

Twenty-five phenyl substituent group molar refractions, listed by Norrington *et al.* (8), were used. This list includes alkyls, ethers, amines, esters, amides, ketones, an aldehyde, alcohol, and a nitro group. The relationship is:

$$R_m = 2.656 (\pm 0.593)\chi + 7.140 (\pm 0.688)\chi^v - 0.958 (\pm 0.518)$$

$$r = 0.990 \quad s = 1.03 \quad n = 25 \quad (\text{Eq. 11})$$

This successful relationship illustrates the consistency of the oxygen and nitrogen connectivity parameters with the parameters established for the carbon atom. All  $\chi$  and  $\chi^v$  parameters are derived nonempirically from basic considerations of connectivity defined in terms of simple branching and the number of valence electrons not bonding to a hydrogen atom.

With these parameters, we have increased the ability of connectivity indexes to correlate with certain properties such as the boiling point within classes of molecular types. Furthermore, with other properties like molar refraction, these heteroatom parameters permit the correlation of connectivity indexes among mixed molecular types.

Table V includes a number of halogen-containing molecules. It would be highly desirable if these atoms could be considered within the framework of molecular connectivity. A derivation of  $\delta^v$  values based upon the  $\delta^v = Z^v - h$  relationship is not satisfactory. The values would obviously be 7 for each halogen. At this time, it is necessary to develop empirical parameters for the halogens, fitting them to molar refraction data such as those in Table V. These empirical  $\delta^v$  values for halogens are listed in Table I.

A test of the  $\delta^v$  values for the halogens to determine their internal consistency can be made by considering the ability of  $\chi$  and  $\chi^v$  to predict the boiling points of a mixed list of alkyl halides (Table VI). This objective is accomplished quite satisfactorily from the equation:

$$\text{boiling point} = -69.55 (\pm 5.17) + 19.91 (\pm 2.41)\chi + 38.07 (\pm 1.27)\chi^v$$

$$r = 0.992 \quad s = 4.79^\circ \quad n = 24 \quad (\text{Eq. 12})$$

Thus,  $\delta^v$  values empirically derived from molar refraction are useful in correlating the boiling points in a mixed list of alkyl halides.

To test the consistency of the halogen parameters in a larger list with molecules containing oxygen and nitrogen, calculations of molar

Table VII—Molar Refraction of Mixed Classes of Compounds

Compound	Molar Refraction		Connectivity Index		Compound	Molar Refraction		Connectivity Index	
	Obs.	Calc.	$\chi^c$	$\chi^v$		Obs.	Calc.	$\chi^c$	$\chi^v$
Butyl methyl ether	27.020	28.519	2.914	2.560	2-Ethyl-1-butanol	31.180	32.163	3.346	2.955
Dibutyl ether	40.987	42.173	4.414	4.121	2-Methyl-2-pentanol	31.210	30.225	3.060	2.784
Dipropyl ether	32.226	33.282	3.414	3.121	2-Methyl-3-pentanol	31.138	31.068	3.180	2.861
Ethyl 1-methylethyl ether	27.678	27.695	2.770	2.504	4-Methyl-2-pentanol	31.351	30.581	3.125	2.806
Ethyl pentyl ether	36.363	37.727	3.914	3.621	2,2-Dimethyl-1-butanol	31.268	30.165	3.121	2.730
1-Methylpropyl ethyl ether	31.560	32.478	3.308	3.042	3-Methyl-3-pentanol	31.182	30.764	3.121	2.844
Butyl 1-methylethyl ether	36.027	36.586	3.770	3.504	2-Methyl-1-hexanol	35.930	36.271	3.808	3.417
1-Methylpropyl methyl ether	31.337	30.585	3.121	2.810	3-Ethyl-3-pentanol	35.821	35.748	3.681	3.405
Butyldimethylamine	33.816	31.689	3.270	2.917	2-Ethyl-1-hexanol	40.625	41.054	4.346	3.955
Methyl-2-methylpropylamine	33.852	34.520	4.201	2.806	2-Methyl-1-propanol	22.103	22.597	2.270	1.879
Dimethylpentylamine	38.281	36.135	3.770	3.417	4-Ethyl-4-heptanol	44.919	44.639	4.681	4.405
Triethylamine	33.793	32.764	3.346	3.070	6-Methyl-1-heptanol	40.736	40.378	4.270	3.879
Trimethylamine	19.594	17.816	1.732	1.341	3-Methyl-3-heptanol	40.446	39.655	4.121	3.844
Tripopylamine	47.783	46.100	4.846	4.570	4-Methyl-4-heptanol	40.439	39.655	4.121	3.844
1-Aminopropane	19.400	19.915	1.914	1.615	1-Octanol	40.637	41.660	4.414	4.023
1-Aminobutane	24.079	24.360	2.414	2.115	1-Chloropropane	20.847	22.231	1.914	2.058
1-Amino-3-methylbutane	28.672	27.523	2.770	2.471	2-Chlorobutane	25.506	25.257	2.270	2.387
1-Aminopentane	28.727	28.805	2.914	2.615	1-Chloro-2-methylpropane	25.359	25.395	2.270	2.414
3-Aminopentane	28.617	28.148	2.808	2.564	2-Chlorobutane	25.440	26.677	2.414	2.558
1-Aminohexane	33.290	33.251	3.414	3.115	3-Chloropentane	30.160	30.040	2.808	2.925
1-Aminoheptane	38.003	37.696	3.914	3.615	2-Bromopropane	23.935	22.877	1.732	2.309
2-Aminoheptane	38.037	36.701	3.770	3.526	1-Bromopropane	23.679	25.176	1.914	2.621
1-Aminononane	47.277	46.586	4.914	4.615	1-Bromo-2-methylpropane	28.537	28.339	2.270	2.977
2-Propanol	17.705	18.189	1.732	1.412	2-Bromobutane	28.651	27.661	2.270	2.847
2-Pentanol	26.680	27.418	2.770	2.450	1-Bromobutane	28.347	29.621	2.414	3.121
3-Pentanol	26.639	28.048	2.914	2.470	3-Bromopentane	33.067	32.444	2.808	3.385
1-Hexanol	31.428	32.769	3.414	3.023	2-Iodobutane	33.939	32.297	2.270	3.733
1-Heptanol	36.093	37.215	3.914	3.523	2-Iodopentane	38.314	36.742	2.770	4.233
3-Methyl-1-butanol	26.904	27.042	2.770	2.379	3-Iodopentane	38.354	37.080	2.808	4.271
2-Methyl-1-butanol	26.697	27.380	2.808	2.417	1-Iodopentane	38.263	39.745	2.914	4.707
2-Methyl-2-butanol	26.721	25.779	2.560	2.284	1-Iodoheptane	42.891	44.190	3.414	5.207
4-Methyl-1-pentanol	31.489	31.487	3.270	2.879					
2-Methyl-1-pentanol	31.164	31.825	3.308	2.917					

refraction were compared with experimentally derived values (Table VII). The consistency of all  $\delta^v$  values appears to be quite good as seen from:

$$R_m = 4.460 + 5.230 (\pm 0.211) \chi^v + 3.661 (\pm 0.227) \chi^c$$

$$r = 0.990 \quad s = 1.022 \quad n = 65 \quad (\text{Eq. 13})$$

### CONCLUSIONS

A set of valence  $\delta$  values were developed for use in calculating the connectivity index,  $\chi$ , for heteroatom-containing molecules. The improvement in the correlations with the boiling point and molar refraction for a wide range of molecules suggests the general applicability of these values.

The use of the number of valence electrons together with the number of attached hydrogen atoms provides a firm relationship between the structural characteristics expressed in the hydrogen-suppressed graph and the properties of molecules (3).

An important advance is made by this development in that drug molecules containing heteroatoms may now be considered with a more sophisticated molecular connectivity treatment. These  $\delta^v$  values are currently being used in biological studies in this laboratory (3, 9).

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