and ±1.6% for the tiodazosin assay or ±1.8 and ±1.6% for the levulinic acid assay.

Accuracy of the assays was determined by recoveries of individual tiodazosin additions to spiked placebo formulation equivalent to 1, 2, 5, 10, and 20 mg of tiodazosin per tablet. Recoveries for the five spiked samples ranged from 95.7 to 99.3% with a mean recovery of 96.7% (s = ±1.8%), calculated from the regression line generated from the linearity study. The spiking of levulinic acid over the concentration range from 0.5 to 1.5 mg per tablet into a placebo matrix produced recovery results, calculated using the regression line generated in the absence of the placebo, of 87.5% at the 0.5-mg level, 95.6% at the 5-mg level, and 99.6% at the 15-mg level.

The forced degradation of 1-mg tiodazosin tablets under conditions of heat (100° for 20 hr), light (~15 W at 300 nm for 1 week), acid (1 N HCl for 20 hr), and base (1 N NaOH for 20 hr) was performed to test the specificity of the tiodazosin assay method. Absorbance ratios were calculated from chromatograms generated at 220, 254, or 340 nm from both undegraded and degraded samples. No apparent interference was observed from any of the degraded samples, and the relative standard deviations of the 254/220-nm and 254/340-nm absorbance ratios was ±1.2 and ±0.7%, respectively. For the levulinic acid assay, no apparent interferences were observed for degraded samples, where the degradation conditions were adjusted to produce a maximum acid degradation of 10%.

Specificity of the tiodazosin method was also demonstrated by the resolution of the principal known decomposition product, 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (II), from the active drug under the assay conditions. A chromatographic tracing of a mixture of I and II is shown in Fig. 3. The results of typical tablet blend analyses gave mean recoveries of 103% for tiodazosin and 99.7% for levulinic acid based on the label claims for a nominal 10 mg of tiodazosin per tablet level. In summary, the reverse-phase HPLC methods described in this paper provide simple, rapid, and quantitative methods for the determination of tiodazosin and levulinic acid from the tablet matrix.

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General Definition of Valence Delta-Values for Molecular Connectivity

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Abstract □ The molecular connectivity valence delta-values have been defined in terms of the count of nonhydrogen valence electrons on a valence-state atom as screened from the nucleus by the core electrons. The core is defined as the nonvalence electrons minus 1. This general definition expresses the valence delta-values for second and third quantum level atoms and halogens. Valence delta-values have been derived for higher oxidation states of sulfur and phosphorus. The internal consistency of these delta-values is tested by their ability to closely correlate molar refraction values with $^1\chi^v$. It is found that a second variable, the count of the number of α hydrogen atoms, greatly increases the quality of the correlation. Some biological SAR applications reveal the general utility of these findings.

Keyphrases □ Molecular connectivity—valence delta-values, definition, applications to structure–activity relationships, comparison with molecular refractivity □ Structure–activity relationships—applications of molecular connectivity valence delta-values, comparison with molecular refractivity □ Molecular refractivity—comparison with molecular connectivity valence delta-values, structure–activity relationships

A major advance in the general applicability of molecular connectivity arose from the introduction of valence molecular connectivity indexes by Kier and Hall (1, 2). This innovation made it possible to encode information about heteroatoms and unsaturated features and to correlate this with the relative differences in properties among such molecules. The subsequent use of valence molecular connectivity has been summarized (3).

BACKGROUND

Early Estimates of δ^v—In the initial description of the valence connectivity delta a bonded atom was described by a count of the valence electrons other than those bonding hydrogen (1). This value, designated δ_i^v for atom i was incorporated into the valence connectivity index, $^1\chi^v$, using the same algorithm as for the simple connectivity index, $^1\chi^v = \Sigma(\delta_i^v\delta_j^v)^{-1/2}$. The structural information encoded in the simple δ, a count of σ bonds (electrons) other than those bonding hydrogen, and the δ^v-value was evident from an inspection of a matrix of the two values (3). The sum of the delta-values ($\delta^v + \delta$) for a hybrid atom relates closely to estimates of the hybrid atom volume. It was also shown that the difference between the delta-values ($\delta^v - \delta$) for a hybrid atom is a count of π and lone-pair electrons, referred to as "exterjacent" to describe their relationship to internuclear axes. A count of exterjacent electrons on an atom in its hybrid state, within a quantum level, bears a close relationship to the Mulliken–Jaffe electronegativity (3).

In the earliest consideration of heteroatoms (1), the δ^v-values for second quantum level atoms were verified by relating the calculated $^1\chi^v$ values to molar refraction (MR) data for substituted benzenes (4). The correlation was good, however the experimental value of fluorobenzene presented a problem. The fact that it has a value of 0.4 less than benzene led to the rejection of the logical $\delta_F^v = 7$ and to the derivation of an empirical value of −20. Thus the $(\delta_i^v\delta_F^v)^{-1/2}$ would have a negative value. This subtraction of the modest value of this term in the calculation of $^1\chi^v$ permitted a fairly accurate reproduction of the effect of fluorine in molecules as far as certain physical property values. Using the same approach, empirical values were derived for the other halogens (1) and sulfur (2). These are shown in Table I, column 1.

The Quantum Level Effect on δ^v—Following these initial empirical assignments of higher level atom δ^v-values, a fundamental significance for these numbers was sought. This led to the realization that the empirical δ^v-values for Cl, Br, I, and S were close to the numbers derived by a general expression:

$$\delta^v = \frac{Z^v - h}{Z - Z^v} \qquad \text{(Eq. 1)}$$

where h is the count of hydrogen atoms, Z^v is the count of valence electrons, and Z is the count of all electrons (5). The value $Z - Z^v$ is the count of all nonvalence electrons on the atom; thus, it constitutes information on the principal quantum number of the atom. The denominator in Eq. 1 may be viewed as simulating a radial dimension or a valence orbital screening factor associated with the particular quantum level. Indeed this influence on the valence electrons has been approximated by the use

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Table I—δ^v-Values for Third Quantum Level Atoms and Halogens

Atom	δ^{va}	δ^{vb}	δ^c
F	−20		7
Cl	0.690	0.70	0.78
Br	0.250	0.25	0.26
I	0.085	0.15	0.16
—S—	0.944	0.60	0.67
	—	—	0.56
—SO—	—	—	1.33
—SO_2—	—	—	2.67
—S—S—	—	—	0.89
	—	—	2.22

[a] Data from Refs. 1 and 2. [b] Data calculated using Eq. 1 of Ref. 5. [c] Calculated using Eq. 2.

(6) of the atomic radius (r), the use (7) of r^2, or the use (8, 9) of the square of the quantum number (N^2) in estimating orbital electronegativity or boundary potentials. The values derived from the use of Eq. 1 are listed in Table I, column 2.

Equation 1 now may be viewed as an attempt to simultaneously model two characteristics of valence orbitals: the distance from the nucleus and their boundary potential or electronegativity. The value of $^1\chi^v$ derived from these delta-values contains information related to both of these properties. Recent applications of this information to molecular volume (10), orbital electronegativity (3), and molecular polarity (11) have been published.

THEORETICAL

General Equation for δ^v—The generality of Eq. 1 within the third quantum level is evident; however, it does not correctly describe the previously established δ^v-values for second quantum level atoms. The value $Z - Z^v = 2$ is not correct in Eq. 1 for these atoms. The denominator term $Z - Z^v - 1$ reproduces the δ^v-values for C, N, and O in their various valence states. This is equivalent to counting (or weighting) the pair of $1s^2$ electrons of oxygen as one. To make this count of screening electrons equivalent for both the second and third quantum levels, a general expression for δ^v is necessary:

$$\delta^v = \frac{Z^v - h}{Z - Z^v - 1} \qquad \text{(Eq. 2)}$$

This count of screening electrons, $(Z - Z^v - 1)$, can be explained in two ways. First, there can be invoked an assumption of a difference in the screening contributions of the $1s^2$ electrons relative to the contributions of 2s and 2p electrons. This is a notion embodied in Slater's rules for the same structural characteristic (12). A second explanation arises from the fact that hydrogen atoms are suppressed in formulating δ^v. Thus, the hydrogen electron structure may be viewed as the zero-value reference structure in the count of screening electrons. From this basis, oxygen would have a count of one screening electron while sulfur would have a count of nine electrons. The values of δ^v using Eq. 2 differ very little from those derived from Eq. 1 (Table I, column 3).

The Special Case of Fluorine—The estimation of electronegativity from $\delta^v - \delta$, or a count of exterjacent electrons (3), for the second quantum level leads to the relationship:

$$\epsilon_M(\text{eV}) = 2.05(\delta^v - \delta) + 6.99 \qquad \text{(Eq. 3)}$$

The assumption that fluorine is sp^3 hybridized results in $\delta^v = 7$ and $\delta^v - \delta = 6$. From Eq. 3, this electronic structure predicts an electronegativity for fluorine in its bonding state of 19.3 eV. Hinze and Jaffe report an electronegativity of only 12.18 eV using $s^2p^2p^2p$ as the bonding state of the atom (13). Considerable work confirms the assumption that bound fluorine has little or no sp^3 character. Recalculating $\delta^v - \delta$ for fluorine from the unhybridized structure gives a value of 4 which, from Eq. 3, predicts an electronegativity of 15.2 eV. To reproduce the Mulliken–Jaffe fluorine electronegativity of 12.18 eV would require fluorine to have a δ^v-value of 3.5, corresponding to a fractional hybridization of the valence electrons.

The matter is further complicated by the awareness that in calculating electronegativities, Hinze and Jaffe (13) used ground-state ionization potentials and electron affinities; thus, the actual promotion process may not be faithfully reproduced by their model in the case of fluorine. A comparison of other electronegativity scales suggests that the value of 19 eV is not unreasonable in the Mulliken–Jaffe scale. Fully aware of these complications, we adopt at this time, the nonempirical value of 7 for δ^v_F.

Third Quantum Level Atom Deltas—Applying Eq. 3 to third-level atoms, chlorine, sulfur, and phosphorus atoms have values of 0.78, 0.67, and 0.55, respectively, for δ^v (when there are no bonded hydrogens). These are listed in column 3 of Table I.

The higher oxidation states of sulfur and phosphorus present a new

Table II—Molecules for MR Calculation

Subset	Number in Subset
Alkyl fluorides	9
Alkyl chlorides	9
Alkyl bromides	9
Alkyl iodides	6
Alkanols	6
Dialkyl ethers	6
Alkylamines	6
Alkylnitriles	6
Alkylthiols	8
Dialkyl sulfides	9
Alkylphosphines	10
Dialkyl sulfites	4
Dialkyl sulfates	3
Dialkyl disulfides	5
Trialkyl phosphates	5
Total	101

Table III—Binding of Phenyl Glycosides

para-Substituent	−Log M_{50}[a]	$^1\chi^v$
OH	2.32	0.224
CH_3O	2.40	0.612
C_2H_5O	2.46	1.200
C_4H_9O	2.59	2.200
CH_3	2.29	0.500
C_2H_5	2.46	1.061
C_3H_7	2.51	1.561
sec-Bu	2.58	1.981
tert-Bu	2.63	1.750
H	2.23	0.000
F	2.26	0.189
Cl	2.36	0.566
Br	2.38	0.981
I	2.44	1.250
—$COCH_3$	2.50	0.954
—COC_2H_5	2.56	1.515
CN	2.35	0.474
NO_2	2.34	0.589
NH_2	2.25	0.289

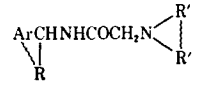
[a] Data taken from Ref. 17.

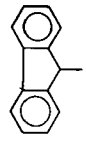
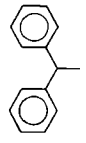
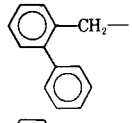
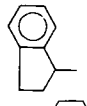
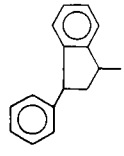
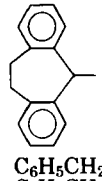
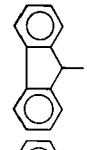
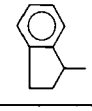
Table IV—Physicochemical Data for 7-R-4-Hydroxyquinoline-3-Carboxylic Acids and Relationships of Cell Inhibition Potency and χ

R	MDH pI_{50}[a]	$^1\chi^v$	MR[b]
Cl	2.44	0.586	0.603
F	1.98	0.189	0.092
$COCH_3$	3.04	0.954	1.118
$N(CH_3)_2$	3.32	1.118	1.555
$OCH_2C_6H_5$	4.49	2.757	3.174
$OCH_2C_6H_3$-3,4-Cl_2	5.32	3.717	4.174
NO_2	2.72	0.589	0.736
$CONH_2$	3.13	0.743	0.981
COOH	2.97	0.678	0.605
SO_2CH_3	3.18	1.419	1.349
OH	3.31	0.224	0.285
SO_2NH_2	3.02	1.161	1.228
SO_3^-	2.67	1.058	0.971

[a] Data taken from Ref. 18. [b] Data taken from Hansch *et al.*, *J. Med. Chem.*, **16**, 1207 (1973).

Table V—Local Anesthetic Activity of *N*-[(*N'*,*N'*-Disubstituted-amino)acetyl]arylamines



Ar—CH(R)—	—N(R')R'	$^0\chi^v$	pAD		
			Observed[a]	Calculated	Residual
	$(C_2H_5)_2$	13.22	1.82	1.75	0.06
	$(C_2H_5)_2$	13.38	1.82	1.73	0.08
	$(C_2H_5)_2$	13.43	1.82	1.73	0.08
	$(C_2H_5)_2$	11.33	1.45	1.48	−0.03
	$(C_2H_5)_2$	14.58	1.55	1.43	0.11
	$(C_2H_5)_2$	14.63	1.25	1.41	−0.16
$C_6H_5CH_2$—	$(C_2H_5)_2$	10.25	0.93	0.96	−0.03
$C_6H_5CH_2$—	$(n\text{-}C_3H_7)_2$	12.03	1.75	1.68	0.06
$C_6H_5CH_2$—	$(n\text{-}C_4H_9)_2$	12.95	1.80	1.76	0.03
$C_6H_5CH_2$—		9.53	0.71	0.46	0.24
$C_6H_5CH_2$—		10.21	0.73	0.95	−0.22
$C_6H_5CH_2$—		9.94	0.73	0.76	−0.03
$C_6H_5CH_2$—	$(n\text{-}C_5H_{11})_2$	14.36	1.53	1.51[b]	0.01
	$(n\text{-}C_3H_7)_2$	13.30	1.68	1.74[b]	−0.06
	$(n\text{-}C_3H_7)_2$	12.74	1.89	1.76[b]	0.12

[a] Data taken from Ref. 19. [b] Predicted value.

problem. Vogel has shown that the fragment contributions to the molar refraction made by —S—, —SO—, and —SO_2— are nearly identical at 7.92, 7.98, and 7.84, respectively (14). This suggests that the groups —SO— and —SO_2— may be described by the same δ^v used for —S—. It also indicates that the value of δ_S^S for the sulfur atom in each of these groups would be different than the δ_S^S for a sulfide sulfur atom. One may choose the expedient of adopting $\delta_S^S = 0.67$ for —S—, —SO—, and —SO_2—, which subsumes the presence of the oxygen atom(s). The assumption implies that the volume occupied by each sulfur lone-pair orbital is the same as the volume occupied by each oxygen atom bonded to sulfur in —SO— and —SO_2—. This is what Vogel's molar refraction fragment values reveal. The use of $\delta_S^S = 0.67$ as a group value for all three classes of sulfur compounds accurately reproduces MR data for these molecules.

A more useful alternative is to explicitly consider the oxygens bonded to sulfur in SO and SO_2 and to derive from theory, or to calculate empirically, values of δ_S^S in each oxidation state. From molar refractivities of several sulfites and sulfates, averaged values have been found which are close to:

$$\delta^v(\text{S in SO}) = 2\delta^v(\text{—S—}) = 12/9 = 1.333 \quad \text{(Eq. 4)}$$

$$\delta^v(\text{S in } SO_2) = 4\delta^v(\text{—S—}) = 24/9 = 2.666 \quad \text{(Eq. 5)}$$

The theoretical justification for these values is evident from the relative contribution of each sulfur atom to the volume and the relative polarity of one and two S—O bonds. From molar refractivity values, one can also derive a δ^v-value for each sulfur in the disulfide group. This is close to δ^v(S in—S—S—) = 8/9 = 0.888. Finally, the δ^v for phosphorus in orthophosphates is described by δ^v(P in PO) = $4\delta^v(-\underset{|}{P}-) = 20/9 = 2.222$.

It is generally accepted that these S—O and P—O bonds are semipolar. As a consequence, one could expect an appreciably different (increased) value for the δ^v-value for S and P relative to the values in alkyl analogues, reflecting the increased valence state electronegativity.

DISCUSSION

Test of δ^v-Values—A meaningful way of evaluating the interrelationship of the δ^v-values is to relate the molar refraction (MR) values for a mixed group of molecules to molecular connectivity indices. If the δ^v-values encode structural information in an accurate manner among atoms in the second and third quantum levels, it is to be expected that the first-order valence connectivity index, $^1\chi^v$, should bear a close relationship to this physical property. These values have been tested on a set of single function molecules, embracing the important, covalent bonding atoms in the second and third quantum level. These are classified by heteroatom in Table II. (Specific entries are available on request.) Using the δ^v-values shown in column 3 of Table I, the relationship is found to be:

$$MR = 8.444\,^1\chi^v + 5.360$$
$$r = 0.979, s = 2.39, n = 101, F = 2327 \quad \text{(Eq. 6)}$$

It came to our attention in the course of the study on third quantum level atoms that an additional structural feature is important in influencing the MR-value. This feature is the number of hydrogen atoms α to certain heteroatoms, which cannot be accounted for in the δ^v description of the heteroatoms. It was found in the case of the halides beyond fluorine, sulfides and disulfides, and secondary and tertiary phosphines, that the MR-value is diminished roughly in proportion to the number of α hydrogens. The inclusion of the count of α hydrogens for these atoms makes a marked improvement in the correlation with MR:

$$MR = 9.042\,^1\chi^v - 1.286\alpha H + 4.777$$
$$r = 0.996, s = 1.038, n = 101, F = 6397 \quad \text{(Eq. 7)}$$

The αH term is independent of the $^1\chi^v$ index and describes a structural feature not encoded in $^1\chi^v$ or the values of δ^v used in its calculation. It is further of note that the coefficient of the αH term in Eq. 7 is close to the Vogel estimate of the hydrogen contribution to molar refraction (14). This analysis constitutes a valid test of the δ^v-value internal relationship. The correlation with MR-values leads to a degree of confidence in the δ^v-values, and they are proposed for use at this time.

Biological Applications—This demonstrated ability of $^1\chi^v$ to relate to MR stimulates the test of $^1\chi^v$ in biological studies in which MR has been used in property–activity analyses. There has been some recent interest in MR as a surrogate for molecular structure in structure–activity relationship (SAR) analyses (15). In several of these studies, values of MR for substituent groups have been employed. These have been derived from MR-values of whole molecules by partitioning (14). The absolute values of these substituent contributions may vary depending on the method of calculation, although the correlation of values is usually good. A few examples of χ *versus* activity illustrate the capability of this index.

Binding of Substituted Phenyl Glycosides to Concanavalin A—Loonteins *et al.* (17) have reported a study of glycosides binding to the hemagglutinin, concanavalin. Hansch and Leo have shown that MR of the substituent groups on the phenyl ring of the glycosides correlates well with the binding parameters, M_{50} (16).

$$\log M_{50} = 0.0188\,MR + 2.23$$
$$r = 0.954, s = 0.038, n = 19 \quad \text{(Eq. 8)}$$

A single connectivity index $^1\chi^v$, correlates with log M_{50} almost as well:

$$\log M_{50} = 0.181\,^1\chi^v + 2.246$$
$$r = 0.945, s = 0.041, n = 19 \quad \text{(Eq. 9)}$$

The influence of heteroatoms is directly apparent from Eq. 9 as is molecular size (Table III). A second connectivity index would certainly contain more information about influential structure; however, the quality of the data would probably not be compatible with this further refinement.

Quinoline Carboxylic Acids as Cell Respiration Inhibitors—Shah and Coats (18) have reported on a series of 7-substituted 4-hydroxyquinoline-3-carboxylic acids as cell respiration inhibitors. They reported a correlation of inhibitory potency (pI_{50}) and MR:

$$pI_{50} = 0.70MR + 2.29$$
$$r = 0.935, s = 0.318, n = 19 \quad \text{(Eq. 10)}$$

Using $^1\chi^v$ reveals a relationship:

$$pI_{50} = 0.785\,^1\chi^v + 2.82$$
$$r = 0.916, s = 0.360, n = 19 \quad \text{(Eq. 11)}$$

The results are in Table IV. The role of heteroatoms and group size is clearly encoded in the $^1\chi^v$ index.

Local Anesthetic Activity of Arylamines—In a recent study by Heymans *et al.* (19), a series of arylamines were tested for local anesthetic potency (pAD).

$$pAD = 0.497MR - 0.0028(MR)^2 - 20.02$$
$$r = 0.951, s = 0.16, n = 12 \quad \text{(Eq. 12)}$$

Using $^0\chi^v$ in a quadratic equation, we find a relationship:

$$pAD = 2.99\,^0\chi^v - 0.116(^0\chi^v)^2 - 17.5$$
$$r = 0.964, s = 0.14, n = 12 \quad \text{(Eq. 13)}$$

The equation is of sufficient quality to predict the activity of three additional compounds, as shown by the last three entries in Table V.

CONCLUSION

The interpretation of structural influence on activity from an MR *versus* activity relationship is not direct. In contrast, a connectivity index *versus* activity relationship permits a direct assessment of the important structural features influencing activity. Further, it is possible to make predictions of structures with favorable characteristics from a good χ *versus* activity equation. Finally, the use of molecular connectivity in structural quantitation makes it possible to employ more than one index, all of which have a logical and consistent derivation from structure and which guide the investigator to an interpretation of structure, meeting the objectives of the study.

This study presents new delta-values for the higher oxidation states of sulfur and phosphorus, atoms which occur on occasion in biological studies. These findings have broadened the utility of χ^v indices.

It has been shown that valence molecular connectivity indices, calculated from delta-values derived in a consistent manner, can closely reproduce molecular properties such as molar refraction. This leads to the direct correlation of biological activity with valence connectivity indices rather than attempting to relate them to molar refraction.

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