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ACKNOWLEDGMENTS AND ADDRESSES

Received March 15, 1976, from the **Drug Research Laboratories, Health Protection Branch, Health and Welfare Canada, Ottawa, Canada K1A OL2,* and the ‡ *Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A OR6.*

Accepted for publication June 17, 1976.

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Structure–Activity Studies Using Valence Molecular Connectivity

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Abstract □ The extension of the molecular connectivity concept to the treatment of heteroatom molecules affords an opportunity to examine structure–activity relationships in a wide variety of molecule series that possess biological activity. Four series are described in this report. The correlations found indicate that molecular connectivity is an extremely useful descriptor of structure in studying drug molecule structure–activity relationships.

Keyphrases □ Molecular connectivity index—related to structure–activity relationships, various types of molecules □ Structure–activity relationships—various types of molecules, related to molecular connectivity index □ Topological indexes—molecular connectivity index, related to structure–activity relationships, various types of molecules

Recently (1, 2), the extension of molecular connectivity to the treatment of heteroatom molecules was described. By considering the valence electrons, whether bonded or nonbonded, an atom connectivity term, δ^v, for multiply bonded carbon atoms or heteroatoms was assigned.

The work presented in this paper tests the ability of δ^v to describe the atomic connectivity in heteroatoms so that the molecular connectivity indexes bear some relationship to structure influencing biological properties.

DISCUSSION

The simple prescription for assigning δ^v is $Z^v - h_i$, where Z^v is the number of valence electrons and h_i is the number of attached hydrogens. For alcohols, ethers, primary amines, and pyridine, the δ^v values for the heteroatoms are 5, 6, 3, and 5, respectively. The δ^v values for heteroatoms are shown in Table I.

Since halogen atoms have an identical number of valence electrons, this prescription yields identical values of δ^v. It is necessary to derive empirical values of δ^v for the halogens by calibrating them to a physical property. The molar refraction was chosen for this assignment (1, 2) (Table I).

Table I—Valence Delta, δ^v, Values for Heteroatoms

Atom	δ^v	Atom	δ^v
—NH_2	3	—OH	5
—NH—	4	—O—	6
	5	—C=O	6
—C≡N	5	Furan O	6
—C=NH	4	O=N—O	6
Pyridine N	5	H_2O	4
Nitro N	6	H_3O+	3
NH_3	2	F	(−)20
NH_4^+	1	Cl	0.690
	6	Br	0.254
=NH_2^+	3	I	0.085

The use of δ^v thus permits the calculation of a valence chi term of the first order, $^1\chi^v$, by the expression:

$$^1\chi^v = \sum (\delta_i^v \delta_j^v)^{-1/2} \qquad \text{(Eq. 1)}$$

The $^1\chi^v$ terms provide a further structural description of heteroatom molecules, eliminating the redundancies found when simple connectivity values are used. The refinement permits the close correlation of chi terms with physical properties such as boiling point, solubility, and molar refraction (1, 2).

Cytochrome Conversion by Phenols—The conversion of cytochrome P-450 to P-420 in the rabbit liver by a series of phenols was reported (3). An analysis of these molecules using $^1\chi^v$ reveals the following relationship to the minimum active concentration (−log *c*), p*C*:

$$pC = 0.816\ (\pm 0.105)\,^1\chi^v - 0.789\ (\pm 0.329) \qquad \text{(Eq. 2)}$$

$$r = 0.914 \quad s = 0.291 \quad n = 14$$

The calculated and observed values are listed in Table II.

The inclusion of the Hammett sigma value for each substituent in a multiple regression with $^1\chi^v$ does not improve the relationship. The re-

Table II—Cytochrome P-450 Conversions by Substituted Phenols

Phenol Substituent	$^1\chi^v$	Obs. pC^a	Calc. pC
H	2.134	1.07	0.95
3-Hydroxy	2.268	0.81	1.06
3-Amino	2.333	0.46	1.11
4-Methyl	2.545	1.48	1.29
4-Carboxy	2.722	1.15	1.43
3-Methyl	2.545	1.50	1.29
2-Chloro	2.653	1.60	1.38
3-Ethyl	3.105	1.82	1.74
4-Bromo	3.037	2.04	1.69
2-Iodo	3.766	2.09	2.28
2,4-Dichloro	3.165	2.11	1.79
2,4,6-Trichloro	3.604	2.21	2.15
2,3,4,6-Tetrachloro	4.208	2.65	2.64
Pentachloro	4.734	2.90	3.07

[a] Reference 3.

sults are interesting in that a single term, $^1\chi^v$, is capable of producing a fairly good correlation with biological potency. This is accomplished in a group of molecules containing oxygen, nitrogen, chlorine, bromine, and iodine in three different ring positions and singly as well as multiply substituted. The $^1\chi^v$ term thus encodes within it sufficient structural information to describe the salient features influencing biological activity.

From a mechanistic point of view, it might be concluded that the electronic influence of the substituent on the ring or on the phenolic hydroxyl group is not the critical process. The substituent itself must be participating in a characteristic way in some critical event leading to the activity.

Sweet-Tasting Nitroanilines—A series of substituted nitroanilines was reported to possess sweet taste potency of up to 4000 times the level of sucrose (4). Kier studied these and other sweet-tasting molecules and predicted that the substituent is a third member of the pharmacophore that may participate in a dispersion interaction (5).

The connectivity indexes $^1\chi$ and $^1\chi^v$ were calculated for these molecules and compared with the log of the relative (molar) sweetness to sucrose (Table III). The relationship is:

$$\log RS = 0.350\ (\pm 0.160)^1\chi + 0.694\ (\pm 0.153)^1\chi^v - 3.856\ (\pm 0.689) \quad \text{(Eq. 3)}$$

$$r = 0.953 \quad s = 0.222 \quad n = 9$$

In this case, the structural characteristics influencing the receptor role of the substituent are best quantified by the combination of the simple connectivity, $^1\chi$, and the valence connectivity, $^1\chi^v$, terms. The correlation is quite good and is of potential value in drug design.

Inhibition of *Aspergillus niger*—A group of substituted benzyl alcohols exhibited an inhibitory influence on the mold *A. niger* (6). The potency of these molecules is expressed as log $1/c$ for the minimum inhibitory concentration (Table IV).

Calculation of the $^1\chi^v$ values for each molecule reveals a fair correlation with log $1/c$ (0.890). The electronic influence of the substituents on the ring might be an additional structural factor influencing the activity. Accordingly, the use of the Hammett sigma term is suggested as a second term in a multiple regression analysis. The correlation improves in this case:

$$\log 1/c = 0.990\ (\pm 0.106)^1\chi^v + 0.656\ (\pm 0.197)\sigma - 1.268\ (\pm 0.361) \quad \text{(Eq. 4)}$$

$$r = 0.937 \quad s = 0.286 \quad n = 19$$

An inspection of other chi terms reveals that the fourth-order term, $^4\chi_P{}^v$, described previously (7), gives a significantly improved correlation along with σ:

$$\log 1/c = 1.987^4\chi_P{}^v + 0.507\sigma + 0.365 \quad \text{(Eq. 5)}$$

$$r = 0.962 \quad s = 0.217 \quad n = 19$$

These results indicate that both a connectivity structural characteristic and an electronic influence contribute to the activity within the series. Furthermore, the superiority of the $^4\chi_P{}^v$ term over the first-order term, $^1\chi^v$, is of interest. The $^4\chi_P{}^v$ term describes the important connectivity feature in a superior manner, resulting in a fine correlation.

Toxicity of Diethyl Phenyl Phosphates—A series of ring-substituted diethyl phenyl phosphates was toxic to the housefly (8) (Table V). An analysis using molecular connectivity and the Hammett sigma term reveals a very good correlation with the toxic concentration, pC, according to:

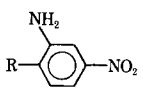
$$pC = 2.512\ (\pm 0.184)\sigma + 0.382\ (\pm 0.154)^1\chi^v - 1.350\ (\pm 0.420) \quad \text{(Eq. 6)}$$

$$r = 0.975 \quad s = 0.295 \quad n = 13$$

The predicted results are shown in Table V.

Equation 6 reveals that both a connectivity feature and an electronic influence play important roles in the activity of these molecules. The wide

Table III—Relative Sweet Taste of Nitroanilines



R	$^1\chi$	$^1\chi^v$	Obs. Log RS^a	Calc. Log RS
Propoxy	6.647	4.264	1.406	1.426
Iodo	5.109	4.279	0.675	0.899
Ethoxy	6.147	3.764	0.885	0.904
Bromo	5.109	3.556	0.566	0.398
Chloro	5.109	3.166	0.365	0.127
Methoxy	5.647	3.176	0.293	0.321
Methyl	5.109	3.064	0.337	0.561
Fluoro	5.109	2.452	−0.591	−0.368
Hydrogen	4.716	2.653	−0.538	−0.366

[a] Reference 4. Data converted to molar basis.

Table IV—Inhibition of *Aspergillus niger* by Substituted Benzyl Alcohols *versus* Chi and Hammett Sigma Terms

R	σ	$^4\chi_P{}^v$	Obs. Log $1/C^a$	Calc. Log $1/C$
Hydrogen	0	0.574	1.51	1.51
4-Chloro	0.23	0.718	2.07	1.91
2,4-Dichloro	0.45	1.153	3.07	2.88
3,4-Dichloro	0.60	0.980	3.07	2.61
2,4,5-Trichloro	0.82	1.365	3.32	3.49
3,4,5-Trichloro	0.97	1.400	3.63	3.64
2-Bromo	0.20	1.024	2.15	2.50
4-Bromo	0.23	0.851	2.27	2.17
4-Iodo	0.28	1.107	2.75	2.70
4-Methyl	−0.17	0.684	1.79	1.64
2,4-Dimethyl	−0.31	1.008	2.14	2.21
3,5-Dimethyl, 4-chloro	0.09	1.238	3.05	2.87
3,5-Dimethyl, 4-iodo	0.14	1.575	3.42	3.56
2-Nitro	0.76	0.786	2.49	2.31
4-Nitro	0.78	0.697	2.00	2.14
4-Cyano	0.63	0.676	1.67	2.03
2-Hydroxy	0.17	0.623	1.39	1.42
3-Hydroxy	0.17	0.635	1.39	1.63
4-Hydroxy	0.17	0.586	1.39	1.35

[a] Reference 6.

Table V—Toxicity of Substituted Diethyl Phenyl Phosphates *versus* Sigma and Chi Terms

Phenyl Substituent	σ	$^1\chi^v$	Obs. pC^a	Calc. pC
4-Nitro	1.24	2.358	2.40	2.66
4-Sulfoxymethyl	0.92	3.059	2.10	2.12
4-Cyano	0.88	2.295	1.85	1.74
3-Nitro	0.71	2.358	1.48	1.33
3-Sulfopentafluoro	0.68	1.530	1.38	0.94
4-Chloro	0.23	2.423	0.04	0.15
3-*tert*-Butyl	−0.10	3.571	−0.24	−0.24
Hydrogen	0	1.911	−0.82	−0.62
4-Carboxy	0.35	2.499	0.25	0.48
4-*tert*-Butyl	−0.20	3.571	−0.24	−0.49
3-Methoxy	0.12	2.433	−0.25	−0.12
4-Methoxy	−0.11	2.433	−0.25	−0.69
4-Methyl	−0.17	2.321	−1.32	−0.89

[a] Reference 8.

diversity of groups is a severe challenge for the connectivity concept, and the good correlation is testimony to the ability of the method to describe structural characteristics important in this case.

SUMMARY

These studies reveal the contribution that molecular connectivity may make in structure–activity studies. Recent advances made in this method, namely the treatment of heteroatoms (1) and the development of extended connectivity terms (7), make possible the consideration of a wide variety of molecules typically found in drug studies. Most importantly, molecular connectivity, as developed to this point, is capable of revealing good relationships with biological activities (9–13). It is expected that this method of structural analysis will find wide application in structure–activity studies.

Furthermore, the method of molecular connectivity relates molecular structure directly to biological activity. No intermediate physical properties are required for satisfactory correlation. The medicinal chemist's intuition concerning structure and activity can be applied directly and quantitatively to drug studies. The demonstrated ability to handle a variety of heteroatoms greatly strengthens the method of molecular connectivity.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 10, 1976, from **Eastern Nazarene College, Quincy, MA 02170,* and the *‡Massachusetts College of Pharmacy, Boston, MA 02115.*

Accepted for publication June 23, 1976.

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Bioavailability of Digoxin–Hydroquinone Complex: A New Oral Digoxin Formulation

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Abstract □ A new oral digoxin formulation, a digoxin–hydroquinone complex (99% dissolution at 5 min), was evaluated in 12 healthy human volunteers with reference to bioavailability and extent and time of peak serum digoxin levels. This preparation was compared with a commercial digoxin tablet (26% dissolution at 5 min), digoxin elixir, and a parenteral digoxin solution. Bioavailability was assessed by the 24-hr area under the serum digoxin–time curve and 48-hr digoxin excretion in urine. The bioavailability of the complex was similar to that of the elixir but not statistically different from that of the tablet. The tablet was less bioavailable than the elixir. There was less interindividual variation in bioavailability with the complex than with the elixir. Peak serum digoxin levels were higher with the complex than the tablet and were achieved more quickly.

Keyphrases □ Digoxin—bioavailability of complex with hydroquinone compared to other digoxin dosage forms, humans □ Bioavailability—digoxin–hydroquinone complex compared to other digoxin dosage forms, humans □ Complexes—digoxin–hydroquinone, bioavailability compared to other digoxin dosage forms, humans □ Dosage forms, various—digoxin and digoxin–hydroquinone complex, bioavailability compared, humans □ Cardiotonic agents—digoxin–hydroquinone complex, bioavailability compared to other digoxin dosage forms, humans

The bioavailability of oral digoxin preparations has been studied recently (1–11), and several studies (4–10) showed that the bioavailability of solid digoxin dosage forms correlated with the dissolution rate but not the disintegration rate (11). This finding led to the assertion that existing *in vitro* dissolution tests are adequate for predicting commercial digoxin tablet bioavailability. Other investigations (12–16), however, demonstrated that the *in vitro* dissolution rate of commercial digoxin tablets need not correlate with bioavailability, since tablets that did not meet USP XVIII dissolution specifications showed *in vivo* bioavailability characteristics comparable to tablets that did. Thus, the relationship between bioavailability and dissolution rate appears to be unresolved.

The main cause of the unsatisfactory dissolution of digoxin tablets is related primarily to digoxin's low water solubility. Although improved formulation technology has resulted in significant improvement, an intrinsically more soluble form of digoxin should enhance dissolution. Higuchi and Ikeda (17) recently developed such a form by complexing digoxin and hydroquinone. This approach utilizes the concept of free energy of dissolution of molecular complexes (18). The digoxin–hydroquinone[1] complex is more readily soluble than digoxin itself, and total dissolution of digoxin occurs within 5 min (17).

This paper reports a comparison of the bioavailability in humans of the complex with that of a digoxin tablet[2] of

[1] Lot 828-264, supplied by Pennwalt Corp., Pharmaceutical Division, Rochester, N.Y.

[2] Lanoxin, lot 022-1, supplied by the Food and Drug Administration.