(3) L. Kanal, *IEEE Trans. Inform. Theory*, **IT-20**, 697 (1974).
(4) Y. C. Martin, "Quantitative Drug Design-A Critical Introduction," Dekker, New York, N.Y., 1977.
(5) A. J. Stuper and P. C. Jurs, *J. Pharm. Sci.*, **67**, 745 (1978).
(6) A. Cammarata and G. K. Menon, *J. Med. Chem.*, **19**, 739 (1976).
(7) G. K. Menon and A. Cammarata, *J. Pharm. Sci.*, **66**, 304 (1977).
(8) W. J. Dunn, III, and S. Wold, *J. Med. Chem.*, **21**, 1001 (1978).
(9) W. J. Dunn, III, and Y. C. Martin, *ibid.*, **21**, 922 (1978).
(10) D. F. Andrews, in "Discriminant Analysis and Applications," T. Cacoullos, Ed., Academic, New York, N.Y., 1973, pp. 37–47.
(11) E. Fix and J. L. Hodges, U. S. School of Aviation Medicine, Project 21-49-004, Report 4, Randolph Field, Tex., 1951; reprinted in "Machine Recognition of Patterns," A. K. Agrawala, Ed., IEEE Press, New York, N.Y., 1977, pp. 261–279.
(12) T. M. Cover and P. E. Hart, *IEEE Trans. Inform. Theory*, **IT-13**, 21 (1967).
(13) N. J. Nilsson, "Learning Machines," McGraw-Hill, New York, N.Y., 1965.
(14) S. Wold, *Pattern Recognition*, **8**, 127 (1976).
(15) S. Wold and M. Sjöstrom, in "Chemometrics–Theory and Practice," B. R. Kowalski, Ed., ACS Symposium Series No. 52, American Chemical Society, Washington, D.C., 1977, pp. 243–282.
(16) R. Gnanadesikan, "Methods for Statistical Analysis of Multivariate Observations," Wiley, New York, N.Y., 1977, pp. 203–225.
(17) D. L. Duewer, J. R. Koskinen, and B. R. Kowalski, "ARTHUR," available from Alice M. Harper, Department of Chemistry, University of Georgia, Athens, GA 30602.
(18) A. M. Harper, D. L. Duewer, B. R. Kowalski, and J. L. Fasching, in "Chemometrics–Theory and Practice," B. R. Kowalski, Ed., ACS Symposium Series No. 52, American Chemical Society, Washington, D.C., 1977, pp. 14–52.
(19) M. J. Green and B. N. Lutsky, in "Annual Reports in Medicinal Chemistry," vol. 11, F. H. Clarke, Ed., Academic, New York, N.Y., 1976, chap. 16, pp. 149–157.
(20) L. B. Kier and L. H. Hall, *Eur. J. Med. Chem.*, **12**, 307 (1977).
(21) D. F. Andrews, *Biometrics*, **28**, 125 (1972).
(22) P. E. Hart, *IEEE Trans. Inform. Theory*, **IT-14**, 515 (1968).
(23) J. H. Friedman, F. Baskett, and L. J. Shustek, *IEEE Trans. Comput.*, **C-24**, 1000 (1975).
(24) J. T. Tou and P. Gonzales, "Pattern Recognition Principles," Addison-Wesley, Reading, Mass., 1974, pp. 181–186.
(25) D. S. Fullerton, in "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 7th ed., C. O. Wilson, O. Gisvold, and R. F. Doerge, Eds., Lippincott, Philadelphia, Pa., 1977, chap. 20, pp. 731–823.
(26) W. C. Cutting, "Cutting's Handbook of Pharmacology," 5th ed., Appleton-Century Crofts, New York, N.Y., 1972.
(27) "BMDP-Biomedical Computer Programs-1977," W. J. Dixon, Ed., University of California Press, Berkeley, Calif., 1977, pp. 711–733.
(28) R. A. Eisenbeis and R. B. Avery, "Discriminant Analysis and Classification Procedures—Theory and Applications," Heath, New York, N.Y., 1972.

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Structural Information from Molecular Connectivity $^4\chi_{PC}$ Index

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Abstract □ The molecular connectivity $^4\chi_{PC}$ index was examined for its ability to describe uniquely molecules containing substituted benzene rings. The subgraphs comprising this index were shown to encode information about the number, placement, and type of ring substituents. Several examples illustrate the ability of the index to describe structure-influencing properties.

Keyphrases □ Molecular connectivity—description of molecules containing substituted benzene rings by $^4\chi_{PC}$ index □ Structure–activity relationships—molecules containing substituted benzene rings, interpretation of structure–activity relationship from molecular connectivity $^4\chi_{PC}$ index

Since the development of a new method of molecular structure quantitation called molecular connectivity, it has been utilized in numerous structure–activity relationship studies (1–7). The numerical indexes computed for each molecule are rich in information content; hence, constellations of indexes are of considerable value in describing structural features contributing to the numerical value of a physical property or biological activity. This study explored the information content of one important index, $^4\chi_{PC}$, and revealed how it plays a prominent role in several structure–activity relationship analyses.

THEORY

The molecular connectivity description of molecular structure gives rise to several numerical indexes of the general form $^m\chi_t$, where m is the order of the molecular fragment and t is the type. Indexes may be of the simple connectivity (unweighted adjacency) or valence level. The indexes are weighted counts of fragments within a molecule, conveying information about topological features such as molecular size, branching, cyclization, unsaturation, and heteroatom location and type.

One distinct advantage of a molecular connectivity analysis of structure in a structure–activity relationship study is that the indexes correlating with activity in a regression analysis can be interpreted directly in terms of structural fragments meaningful to the medicinal chemist (8–10). Depending on the study, various indexes will emerge from searches with one or more variables, each conveying various amounts of structural information.

It has become apparent in the studies conducted in these laboratories that certain patterns of index appearance are found in analyses of molecular structure using molecular connectivity. One noteworthy appearance is the $^4\chi_{PC}$ (or the $^4\chi^v_{PC}$) index in studies on the structures of molecules containing substituted benzene rings. This index frequently is important as a second or third variable in regression analyses on molecules in which the benzene rings possess different numbers, positions, and types of substituents.

This recurrence led to the belief that the $^4\chi_{PC}$ index carries a high degree of information content in these structural classes that is common to many drug molecules. The purpose of this report is to analyze and

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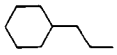
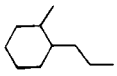
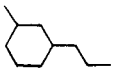
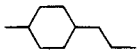
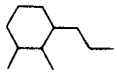
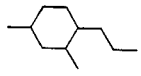
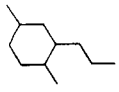
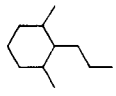
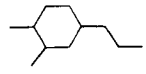
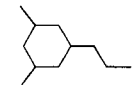
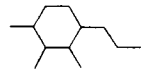
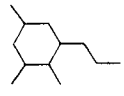
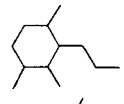
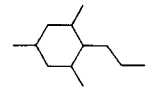
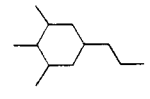
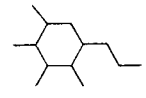
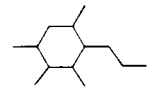
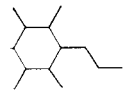
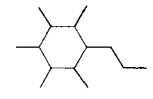
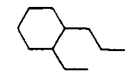
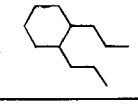
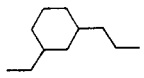
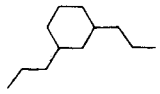
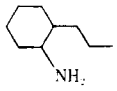
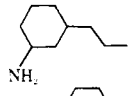
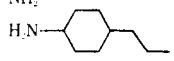
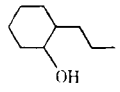
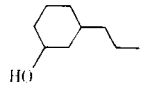
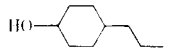
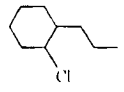
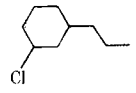
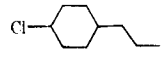
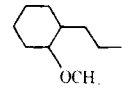
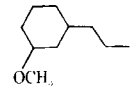
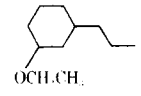
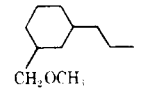
Table I—Molecular Connectivity Indexes for Several Substituted Benzenes

Molecule	Number of $^3\chi_C$ Terms	$^3\chi_C$	$^3\chi_C^v$	Number of $^4\chi_{PC}$ Terms	$^4\chi_{PC}$	$^4\chi_{PC}^v$
I 	1	0.204	0.118	3	0.433	0.219
II 	2	0.402	0.102	7	1.020	0.561
III 	2	0.493	0.285	5	0.777	0.390
IV 	2	0.493	0.285	5	0.841	0.412
V 	3	0.595	0.371	11	1.638	0.942
VI 	3	0.691	0.413	9	1.360	0.729
VII 	3	0.691	0.413	9	1.369	0.732
VIII 	3	0.607	0.377	11	1.500	0.856
IX 	3	0.676	0.407	9	1.514	0.821
X 	3	0.781	0.451	7	1.047	0.535
XI 	4	0.787	0.496	15	2.245	1.317
XII 	4	0.883	0.538	13	1.919	1.089
XIII 	4	0.800	0.502	15	2.127	1.240
XIV 	4	0.896	0.544	13	1.772	1.001
XV 	4	0.868	0.531	13	2.053	1.173
XVI 	5	0.980	—	19	2.800	1.673
XVII 	5	0.992	—	19	2.673	1.593
XVIII 	5	0.992	—	19	2.693	1.601
XIX 	6	1.098	0.713	25	3.448	2.192
XX 	2	0.333	0.204	8	0.992	0.554
XXI 	2	0.333	0.204	8	0.943	0.524

(*continued*)

Table I—*Continued*

Molecule	Number of $^3\chi_C$ Terms	$^3\chi_C$	$^3\chi_C^v$	Number of $^4\chi_{PC}$ Terms	$^4\chi_{PC}$	$^4\chi_{PC}^v$
XXII 	2	0.408	0.236	6	0.873	0.455
XXIII 	2	0.408	0.236	6	0.813	0.421
XXIV 	—	—	—	7	1.020	0.404
XXV 	—	—	—	5	0.777	0.314
XXVI 	—	—	—	5	0.841	0.331
XXVII 	—	—	—	7	1.020	0.356
XXVIII 	—	—	—	5	0.777	0.291
XXIX 	—	—	—	5	0.841	0.305
XXX 	—	—	—	7	1.020	0.633
XXXI 	—	—	—	5	0.777	0.425
XXXII 	—	—	—	5	0.841	0.449
XXXIII 	—	—	—	8	0.992	0.400
XXXIV 	—	—	—	6	0.873	0.352
XXXV 	—	—	—	6	0.813	0.332
XXXVI 	—	—	—	6	0.813	0.385

reveal the information about benzene ring substitution encoded in the $^4\chi_{PC}$ index.

The $^4\chi_{PC}$ index describes the molecular fragment represented as Fragment A.

Fragment A

The index is calculated using the standard algorithm described previously (1, 7, 8). Each atom in the fragment is assigned a δ value based on the number of atoms bonded to it (adjacency) in the original molecule. A valence delta (δ^v) is assigned on the basis of adjacency or, in the case of heteroatoms or unsaturated carbons, use of the prescription $\delta^v = Z^v - h$, where Z^v is the number of valence electrons and h is the number of attached hydrogen atoms. The $^4\chi_{PC}$ (or $^4\chi_{PC}^v$) index then is computed as the sum of the reciprocal square roots of the products of delta values: $^4\chi_{PC} = \Sigma(\delta_i\delta_j\delta_k\delta_l)^{-1/2}$. The $^4\chi_{PC}^v$ index likewise is computed using δ^v values.

The index carries information about the number of benzene ring substituents, the substitution pattern, the length of the substituents up to three bond lengths, and the heteroatom type of substituent. Each category of information will be described, followed by examples of structure–activity relationship studies in which the $^4\chi_{PC}$ index is prominent.

RESULTS AND DISCUSSION

Number of Ring Substituents—The $^4\chi_{PC}$ index appears whenever a branch point in a chain or a ring substituent occurs in a molecular structure. Each ring substituent contributes at least two terms to this index. With substituents longer than one bond length, neglecting hydrogens, the number of terms per substituent is at least three.

Table I presents a number of substituted phenethylamines that were chosen to illustrate the information content of the $^4\chi_{PC}$ index. In the first 19 entries, the number of $^4\chi_{PC}$ terms and the $^4\chi_{PC}$ and $^4\chi_{PC}^v$ values for all possible methyl derivatives are reported. By plotting the number of

Table II—Solubility of Alkyl Benzenes

Molecule	Observed ln S^a	Calculated ln S
Benzene	1.64	1.66
Toluene	2.25	2.24
Ethylbenzene	2.84	2.76
o-Xylene	2.78	2.71
m-Xylene	2.76	2.84
p-Xylene	2.73	2.82
Propylbenzene	3.34	3.34
Isopropylbenzene	3.38	3.26
1,2,4-Trimethylbenzene	3.32	3.31
Butylbenzene	3.94	3.89
sec-Butylbenzene	3.67	3.79
tert-Butylbenzene	3.60	3.69
tert-Amylbenzene	4.15	4.08

[a] Molal solubility in water.

methyl substituents *versus* the $^4\chi_{PC}$ value in Fig. 1, it is obvious that the $^4\chi_{PC}$ values correlate closely with the number of methyl substituents. In other words, the $^4\chi_{PC}$ index carries significant information about the number of single-atom ring substituents (exclusive of hydrogen).

This information content is not unique to the $^4\chi_{PC}$ index. It also is encoded in the $^0\chi$, $^1\chi$, and $^3\chi_C$ indexes. However, the information about the number of substituents encoded in $^4\chi_{PC}$ establishes a base from which the greater utility of this index can be established in molecules containing benzene rings. The $^0\chi$, $^1\chi$, and $^3\chi_C$ indexes fail to perform as well as the $^4\chi_{PC}$ index in encoding additional structural information among substituted benzenes.

Orientation of Ring Substituents—The $^4\chi_{PC}$ index encodes information about the orientation of ring substituents. In general, the greater the adjacency or crowding of single-vertex substituents, the larger is the numerical value of the $^4\chi_{PC}$ index. This effect is illustrated in Fig. 2. In considering the six trisubstituted rings (V–X) in Table I, a plot of the number of adjacent pairs *versus* the $^4\chi_{PC}$ values shows an increase in value with an increased pairing of the substituents. The same effect is illustrated in Fig. 2 with the five tetrasubstituted rings (XI–XV) in Table I. Since there is no quantitative way of describing crowding, it is difficult to illustrate this effect in quantitative terms. In fact, the use of $^4\chi_{PC}$ may be a more meaningful way of quantifying crowding or adjacency of ring substituents.

Other indexes fail to discriminate among substitution isomers in every case. Molecule pairs III, IV; VI, VII; and XVII, XVIII have identical $^3\chi_C$ index values.

An examination of the $^4\chi_{PC}$ terms in these cases makes it apparent why it encodes this information. In Fig. 3, the skeletons of III and IV are shown. The $^3\chi_C$ fragments for each skeleton are identical with respect to the atomic δ values. As a result, the $^3\chi_C$ indexes for III and IV are equivalent.

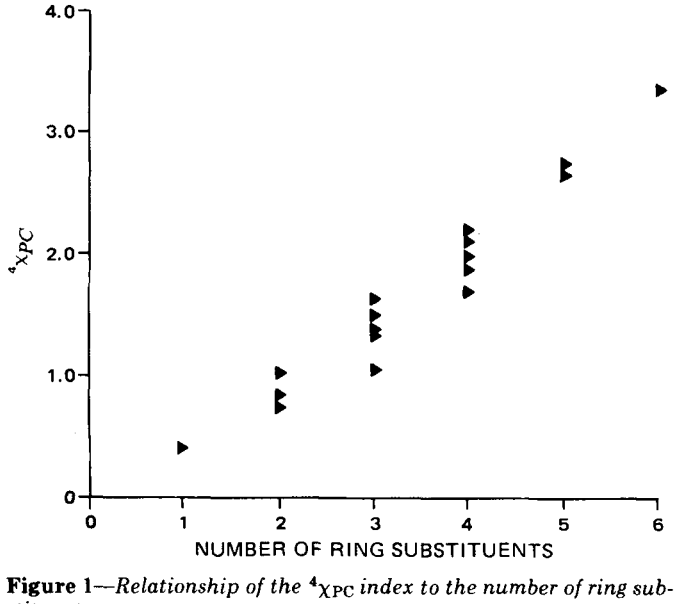


Figure 1—*Relationship of the $^4\chi_{PC}$ index to the number of ring substituents.*

Table III—Cytochrome P-450 Conversion by Substituted Phenols

Substituent	Observed pC^a	Calculated pC
None	1.07	1.02
3-Hydroxy	0.81	1.09
4-Methyl	1.48	1.40
4-Carboxy	1.15	1.30
3-Methyl	1.50	1.44
2-Chloro	1.60	1.36
3-Ethyl	1.82	1.83
4-Bromo	2.04	2.03
2-Iodo	2.09	2.23
2,4-Dichloro	2.11	1.89
2,4,6-Trichloro	2.21	2.33
2,3,4,6-Tetrachloro	2.65	2.59
Pentachloro	2.90	2.92

[a] From Ref. 12.

In contrast, III and IV give rise to differing sets of $^4\chi_{PC}$ fragments because $^4\chi_{PC}$ fragments *b* and *c* of III contain ring atoms that are positions of substitution. Compound IV does not have such fragments. Since a $^4\chi_{PC}$ fragment has a path-three feature, it is able to distinguish *ortho*-, *meta*-, and *para*-substitution patterns. Thus, in Fig. 3, the $^4\chi_{PC}$ index differentiates between the structures, thereby conveying information in numerical form.

Length of Ring Substituents—The effect on the numerical value of $^4\chi_{PC}$ is illustrated by two series of compounds, II, XX, and XXI and III, XXII, and XXIII. With the *ortho*-substitution series (II, XX, and XXI), lengthening the chain by one atom results in a consistent decrease in the $^4\chi_{PC}$ value. With the *meta*-substitution series (III, XXII, and XXIII), there is a decline in the $^4\chi_{PC}$ value beyond one bond length. Substituents with bond lengths of four or more are not distinguishable from those of three-bond length. On the other hand, a branched substituent such as an isopropyl group gives rise to additional $^4\chi_{PC}$ fragments and, hence, an increased numerical value of this index.

An interesting observation can be made about the $^4\chi_{PC}$ indexes and structures discussed in these two series. A ranking of these six compounds based on the extent of interaction between substituent groups is speculated as II, XX, XXI, XXIII, XXII, and III. This ranking closely parallels the decline in the value of their respective $^4\chi_{PC}$ indexes.

Heteroatom-Type Substituent—From Table I, it can be seen for XXIV–XXXVI that the $^4\chi_{PC}$ index is equivalent for all similarly substituted derivatives with the same number of bonds. Thus, XXIV, XXVII, and XXX have identical $^4\chi_{PC}$ indexes. The valence level index $^4\chi^v_{PC}$ must be employed to differentiate between substituents containing atoms of differing δ^v values; XXIV, XXVII, and XXX have different $^4\chi^v_{PC}$ indexes. The larger the δ^v for the heteroatom vertex in these molecules, the smaller is the numerical value of the $^4\chi^v_{PC}$ index.

The $^4\chi^v_{PC}$ index thus can add to the information encoded in the $^4\chi_{PC}$ index the presence of heteroatoms of various kinds in the substituent groups. In addition, the $^4\chi^v_{PC}$ index can distinguish between substituents

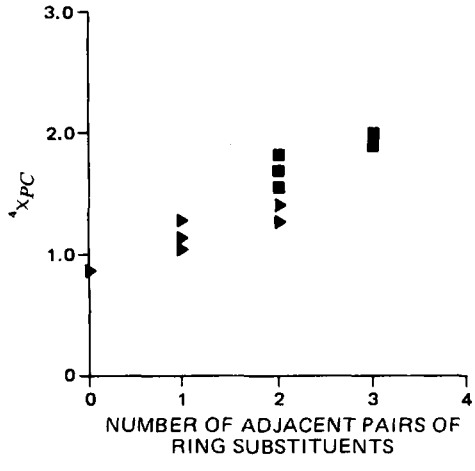


Figure 2—*Relationship of the $^4\chi_{PC}$ index to the number of adjacent pairs of ring substituents, showing the disubstituted (▲) and trisubstituted (●) phenalkylamines in Table I.*

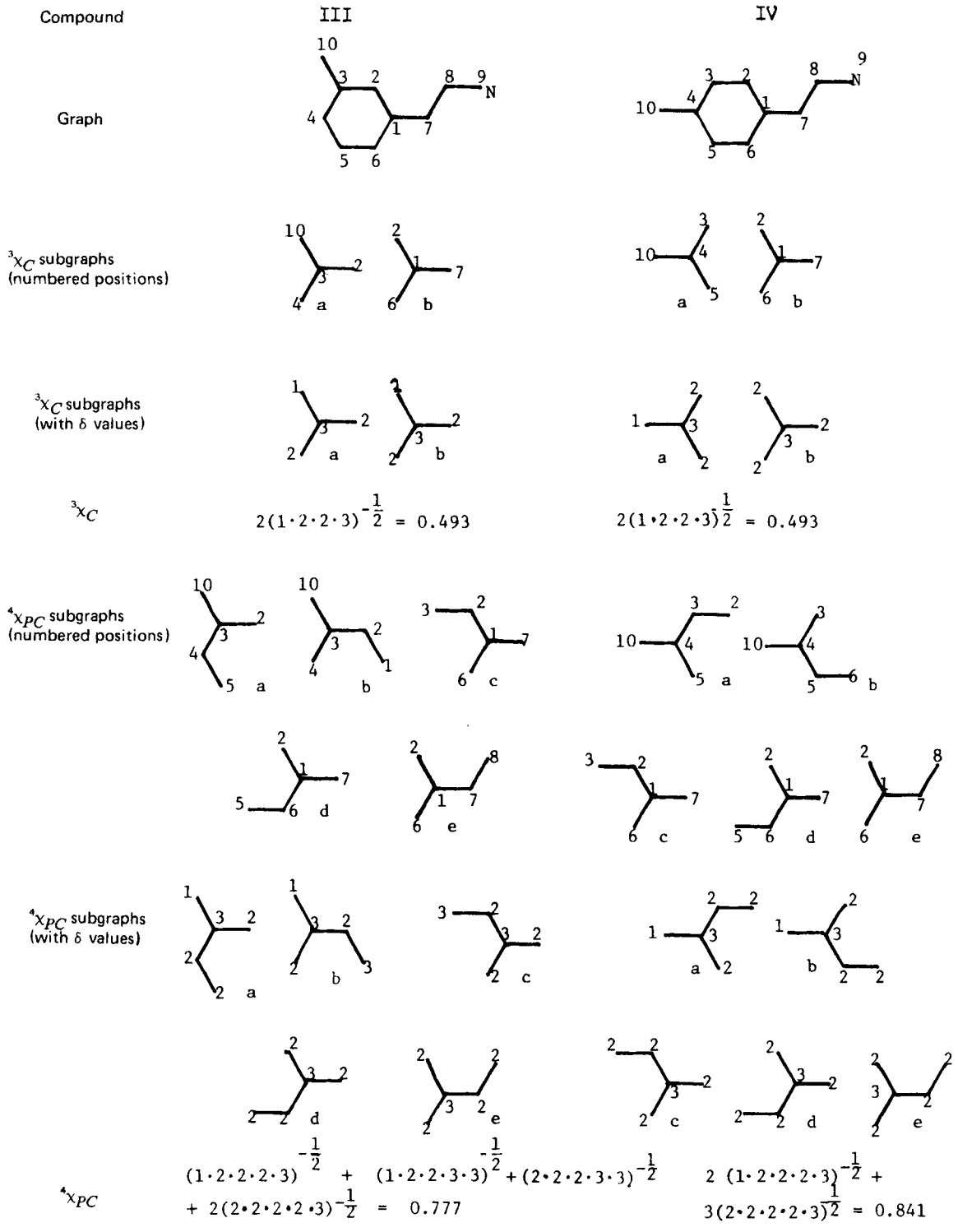


Figure 3—*Comparison of* $^3\chi_C$ *and* $^4\chi_{PC}$ *subgraphs for two molecules.*

containing the same heteroatoms but in different group positions (*e.g.*, XXXV and XXXVI).

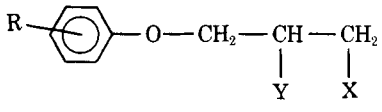
Examples of $^4\chi_{PC}$ Indexes in Structure–Activity Relationship Studies—*Propyl Phenyl Ethers*—The first reported use of $^4\chi_{PC}$ in a structure–activity relationship equation was a study on a series of substituted phenyl propyl ethers active against the fungus *Trichophyton mentagrophytes* (1). The same study later was employed in a detailed subgraph analysis (11).

These 28 molecules are related to log 1/*c* by:

$$\log(1/c) = 2.44\,{}^1\chi - 3.29\,{}^3\chi_P + 2.71\,{}^4\chi^v_{PC} - 1.31 \qquad \text{(Eq. 1)}$$

$$r = 0.957 \quad s = 0.149 \quad n = 28 \quad F = 87.4$$

The compounds in the study included mono-, di-, and tri-ring-substituted derivatives including methyl and chloro groups in varying numbers and ring positions.



X = H, OH Y = H, OH R = Cl, CH_3

The $^4\chi^v_{PC}$ index conveys the type of information described previously. The greater its magnitude, the greater is the calculated log 1/*c* value.

Table IV—Inhibition of *Aspergillus niger* by Substituted Benzyl Alcohols

Substituent	Observed log $1/c$[a]	Calculated log $1/c$
None	1.51	1.29
4-Chloro	2.07	1.93
2,4-Dichloro	3.07	2.61
3,4-Dichloro	3.07	2.66
2,4,5-Trichloro	3.32	3.34
3,4,5-Trichloro	3.63	3.35
2-Bromo	2.15	2.38
4-Bromo	2.27	2.32
4-Iodo	2.75	2.61
4-Methyl	1.79	1.83
2,4-Dimethyl	2.14	2.41
3,5-Dimethyl, 4-chloro	3.05	3.15
3,5-Dimethyl, 4-iodo	3.42	3.83
2-Nitro	2.49	2.13
4-Nitro	2.00	2.13
4-Cyano	1.67	1.83
2-Hydroxy	1.39	1.62
3-Hydroxy	1.39	1.54
4-Hydroxy	1.39	1.56

[a] From Ref. 13.

Thus, the $^4\chi^v_{PC}$ index indicates that multiple substitution of the ring, particularly in the *ortho*-position and in adjacent ring positions, enhances log $1/c$. Furthermore, the $^4\chi^v_{PC}$ index describes the favorable role of chlorine over methyl as the substituent.

Amphetamines—The $^4\chi^v_{PC}$ index emerged as one of three molecular connectivity indexes in a structure–activity relationship study of 23 ring-substituted amphetamines tested as hallucinogenic agents (8). The ring substituents were methoxy and methylenedioxy with a few alkyl groups and a bromo group.

The regression analysis presented the $^4\chi^v_{PC}$ index in reciprocal form:

$$\log MU = \frac{45.16}{^3\chi_P} + 1.29\,{}^6\chi_P - \frac{4.30}{^4\chi^v_{PC}} - 5.59 \qquad \text{(Eq. 2)}$$

$$r = 0.92 \quad s = 0.25 \quad n = 23 \quad F = 35$$

The $^4\chi^v_{PC}$ index describes the favorable role of substituent orientation, substituent length, and heteroatom presence.

Alkyl Benzenes—Molal solubility data are available for 13 alkylbenzenes (Table II). A two-index equation including the $^4\chi_{PC}$ index gives an excellent correlation with ln S:

$$\ln S = 0.782\,{}^0\chi^v - 0.344\,{}^4\chi_{PC} - 1.051 \qquad \text{(Eq. 3)}$$

$$r = 0.994 \quad s = 0.086 \quad n = 13 \quad F = 394$$

The calculated results in Table II reveal the role played by the $^4\chi_{PC}$ index, in concert with the $^0\chi^v$ index, in describing the various types and orientations of substituents on the benzene ring. The $^4\chi_{PC}$ index predicts the favorable influence of substituent branching on solubility. The influence on this physical property is revealed by the quality of the correlation with ln S.

Phenols—A series of heteroatom-substituted phenols are effective in the cytochrome P-450 conversion (12). These derivatives were subjected to molecular connectivity analysis (Table III). The 50% inhibitory concentration, pC, was found to be related to the two indexes by:

$$pC = 0.628\,{}^0\chi^v - 4.99\,{}^4\chi_{PC} - 1.81 \qquad \text{(Eq. 4)}$$

$$r = 0.971 \quad s = 0.161 \quad n = 13 \quad F = 82$$

The $^4\chi_{PC}$ index describes the number, orientation, and complexity of the substituents to the extent that it accounts for 94% of the variation in the data.

Benzyl Alcohols—A series of benzyl alcohol derivatives modified in the ring are known to inhibit *Aspergillus niger* (13). The molecular connectivity description reveals a correlation with $^1\chi^v$ and $^4\chi_{PC}$ accounting for 88% of the variance in the data:

Table V—Inhibition of *Mycobacterium tuberculosis* by Substituted Phenols

Substituent	Observed pC[a]	Calculated pC
None	0.95	1.02
4-Bromo	1.94	1.92
2-Methyl, 4-bromo	2.35	2.32
2-Ethyl, 4-bromo	2.70	2.70
2-Propyl, 4-bromo	3.18	3.10
2-Butyl, 4-bromo	3.76	3.49
2-Pentyl, 4-bromo	3.99	3.88
2-*sec*-Pentyl, 4-bromo	3.54	3.80
2-Hexyl, 4-bromo	4.26	4.27
2-Cyclohexyl, 4-bromo	3.75	3.88
2-Bromo	1.78	1.83
2-Bromo, 4-*tert*-pentyl	3.39	3.37
2-Bromo, 4-hexyl	4.11	4.20
2-Bromo, 4-propyl, 3,5-dimethyl	3.69	3.61

[a] From Ref. 14.

$$\log 1/c = 0.341\,{}^4\chi_{PC} + 0.979\,{}^1\chi^v - 1.404 \qquad \text{(Eq. 5)}$$

$$r = 0.940 \quad s = 0.268 \quad n = 19 \quad F = 61$$

The results (Table IV) reveal the role of $^4\chi_{PC}$ in describing the number and orientation of ring substituents.

Phenols—A series of alkyl bromophenols was reported as effective in inhibiting *Mycobacterium tuberculosis* (14). A molecular connectivity analysis reveals a high correlation with two variables, including the $^4\chi^v_{PC}$ index:

$$pC = 0.551\,{}^0\chi^v - 0.434\,{}^4\chi^v_{PC} - 1.052 \qquad \text{(Eq. 6)}$$

$$r = 0.992 \quad s = 0.134 \quad n = 14 \quad F = 357$$

The results in Table V show the role of the $^4\chi_{PC}$ index in describing structural information in the relationship.

Conclusion—Because of the structure of the molecular fragment described by $^4\chi_{PC}$, this index is ideally suited to quantifying structural features associated with ring substitution. The fragment may contain up to three consecutive phenyl ring bonds; as a consequence, *ortho-*, *meta-*, and *para*-substitution give rise to different terms, resulting in different $^4\chi_{PC}$ indexes in each case.

The structural information encoded in the $^4\chi_{PC}$ index should make it possible to interpret the structure–activity relationship from molecular connectivity descriptions when this index appears.

REFERENCES

(1) L. B. Kier and L. H. Hall, "Molecular Connectivity in Chemistry and Drug Research," Academic, New York, N.Y., 1976.

(2) L. B. Kier, L. H. Hall, W. J. Murray, and M. Randic, *J. Pharm. Sci.*, **64**, 1971 (1975).

(3) L. B. Kier, W. J. Murray, and L. H. Hall, *J. Med. Chem.*, **18**, 1272 (1975).

(4) T. DiPaolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, **13**, 31 (1977).

(5) L. B. Kier, T. DiPaolo, and L. H. Hall, *J. Theoret. Biol.*, **67**, 585 (1977).

(6) L. H. Hall and L. B. Kier, *Tetrahedron*, **33**, 1953 (1977).

(7) L. B. Kier and L. H. Hall, *Eur. J. Med. Chem.*, **12**, 307 (1977).

(8) L. B. Kier and L. H. Hall, *J. Med. Chem.*, **20**, 1631 (1977).

(9) L. B. Kier, L. H. Hall, and R. J. Simons, *J. Pharm. Sci.*, **67**, 725 (1978).

(10) L. H. Hall and L. B. Kier, *Eur. J. Med. Chem.*, **13**, 89 (1978).

(11) L. H. Hall and L. B. Kier, *J. Pharm. Sci.*, **67**, 1743 (1978).

(12) Y. Ichikawa and T. Yamano, *Biophys. Acta*, **147**, 518 (1967).

(13) D. V. Carter, P. T. Carlton, A. H. Fenton, J. R. Housey, and B. Lessel, *J. Pharm. Pharmacol., Suppl.*, **10**, 149T (1958).

(14) E. Klarmann, V. Shternov, L. Gates, and P. Cox, *J. Am. Chem. Soc.*, **55**, 4657 (1933).