CAN MOLECULAR CONNECTIVITY SERVE AS A STERIC PARAMETER IN QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS?

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Molecular connectivities (χ values) are topological indices devised by Randić (1975), and extensively developed by Kier and Hall (1976). They have been shown to correlate with a number of physicochemical parameters such as partition coefficient (Murray, Hall and Kier, 1975). They are readily calculated from the hydrogen-suppressed molecular graph, from a knowledge of the number of bonds formed by each atom in a molecule, and are able to distinguish between some types of structural isomers. They are used increasingly as structural parameters in quantitative structive-activity relationships. Various orders of the index, depending on how many bonds are considered at a time, may be calculated, and a program is available for calculating up to seventh order χ values.

Since the numerical value of a given order of χ increases with the number of atoms in the molecule, it might be thought that χ values could be utilised as steric parameters, particularly as some of the higher order terms reflect branching in a molecule. Connectivities have, in fact, been so used (Evans, James and Luscombe, 1979).

However, there has been no detailed examination of the utility of χ values as steric parameters. We report here on a correlation of zero- and first-order χ values (including valence-corrected values χ^v) with a number of other parameters widely used as steric terms. The correlation coefficients are shown in Table 1; a total of 35 substituents, of widely varying nature, was used in the analysis.

Table 1. Correlation of molecular connectivities with steric parameters

	E_s	E_s^c	v	MR	L	B_1	B_2	B_3	B_4
$^0\chi$	0.726	0.692	0.734	0.779	0.596	0.464	0.722	0.668	0.569
$^0\chi^v$	0.543	0.475	0.542	0.773	0.765	0.232	0.604	0.544	0.580
$^1\chi$	0.766	0.670	0.773	0.960	0.610	0.581	0.797	0.683	0.710
$^1\chi^v$	0.663	0.525	0.637	0.946	0.701	0.412	0.686	0.593	0.751

E_s = Taft steric constant; E_s^c = Hancock steric constant; v = Charton steric constant; MR = molar refractivity; L, B_1-B_4 = Sterimol parameters (values for these constants taken from Seydel and Schaper (1979)).

It is concluded, from this limited analysis, that first-order χ values model molar volume reasonably well (molar refractivity has units of molar volume, but also contains a polarisability component (Hansch, 1976)), but that χ values do not reflect the same aspects of sterism as do most other steric parameters.

Evans, B.K., James, K.C., Luscombe, D.K. (1979) J. Pharm. Sci. 68: 370-371
Hansch, C. (1976) J. Med. Chem. 19: 1-6
Kier, L.B., Hall, L.H. (1976) Molecular Connectivity in Chemistry and Drug Research, Academic Press, New York
Murray, W.J., Hall, L.H., Kier, L.B. (1975) J. Pharm. Sci. 64: 1978-1981
Randić, M. (1975) J. Am. Chem. Soc. 97: 6609-6615
Seydel, J.K., Schaper, H.-J. (1979) Chemische Struktur und Biologische Aktivität von Wirkstoffen: Methoden de Quantitativen Struktur-Wirkung-Analyse, Verlag Chemie, Weinheim