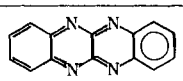
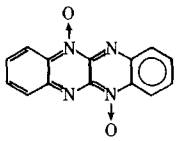
Table II—Quinoxalino[2,3-*b*]quinoxalines

Compound	Structure	Synthetic Method	Melting Point	Anthelmintic Activity[a], mg/kg
XLII		C[b]	>350°, >350° (1)	NA
XLIII[c]		F[d]	>350°	100

[a] NA = not active at 400 mg/kg. [b] See Ref. 1. [c] *Anal.*—Calc. for $C_{18}H_{18}N_4O_2$: C, 63.63; H, 3.05; N, 21.20. Found: C, 63.46; H, 3.00; N, 21.09. [d] See Ref. 4. The melting point was not given.

Method B: 5,12-Diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (IX)—A suspension of 1.0 g (0.004 mole) of I in 50 ml of acetic anhydride was refluxed for 20 hr until a clear solution was obtained. Excess acetic anhydride was evaporated, and the residue was crystallized from ethyl acetate, 0.95 g (70%), mp 203–204°.

5,12 - Diformyl -5,12- dihydroquinoxalino[2,3 - *b*]quinoxaline (VIII)—A mixture of 2.3 g (0.01 mole) of I, 0.94 g (0.02 mole) of 98–100% formic acid, and 4.12 g (0.020 mole) of *N,N'*-dicyclohexylcarbodiimide in 100 ml of dry dioxane was heated at 100° for 22 hr and then cooled. The dicyclohexylurea was filtered off, and the filtrate was evaporated. The residue was dissolved in benzene and filtered, and petroleum ether was added to the filtrate to crystallize the product, 1.1 g (37.9%), mp 225°.

5,12 - Dibenzoyl -5,12- dihydroquinoxalino[2,3 - *b*]quinoxaline (XIII)—A mixture of 1.0 g (0.004 mole) of I and 2 ml of benzoyl chloride in 10 ml of pyridine was allowed to stand at room temperature for 3 days. Addition of petroleum ether precipitated the product, which was crystallized from ethyl acetate, 0.23 g (12%), mp 219–220°.

8-Amino-5,12-diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (XXIX)—A suspension of 1.09 g (0.0030 mole) of 5,12-diacetyl-8-nitro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (XXVIII) and 0.11 g of palladium-on-carbon in 50 ml of dimethoxyethane was reduced with hydrogen at 25 psi. After filtration and evaporation of the solvent, the residue was crystallized from a mixture of ethyl acetate and ether, 300 mg (33%), mp 192–196°.

Methyl *N*-(5,12-Diacetyl-5,12-dihydroquinoxalino[2,3-*b*]-quinoxalin-8-yl)carbamate (XXX)—A solution of 0.74 g (0.0022 mole) of XXIX in 12.5 ml of pyridine was acylated by treatment with 2 g of methyl chloroformate at room temperature for 90 hr. The product was precipitated by addition of water and crystallized from methylene chloride, 0.125 g (14%), mp 229–231°.

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Molecular Connectivity and Steric Parameters

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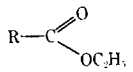
Abstract □ The possible relationship between molecular connectivity indexes, $^m\chi$, and E_s, a thermodynamically derived parameter used to estimate steric effects in organic reactions and sometimes used in biological structure–activity relationships, was investigated. The extended χ terms, $^2\chi$, $^3\chi$, and $^4\chi$, were correlated significantly to E_s (r = 0.961). Aralkyl esters deviated from the correlations, possibly due to intramolecular interactions.

Keyphrases □ Molecular connectivity indexes—relationship to E_s parameter used to estimate steric effects in organic reactions □ Steric parameters—E_s used to estimate steric effects in organic reactions correlated to molecular connectivity indexes □ Topological indexes—molecular connectivity indexes, relationship to E_s parameter used to estimate steric effects in organic reactions

The way atoms are connected to one another in a compound must ultimately influence the compound's physical and chemical properties. Changes in chemical structure most often lead to changes in biological activity. In correlating chemical structure and biological activity, statistical regression analyses, in which various physicochemical properties are used as surrogates for chemical structure, are used. These analyses have been called quantitative structure–activity relationships. The use of this term is unfortunate, since the properties of a molecule are not a description of the structure but rather are consequences of the structure. One is not relating structure to property but property to property. Norrington *et al.* (1) suggested the use of the term property–activity relationships to differentiate these methods from structure-based ones such as methods employing quantum mechanical calculations or the Free and Wilson approach (2).

Table I—Ester Hydrolysis Data [a] *versus* Molecular Connectivity Index



R	$^1\chi$	log k/k_0 (obs)	log k/k_0 (calc)
H	0.000	1.24	0.58
CH_3	0.707	0.00	0.38
C_2H_5	1.207	−0.07	−0.04
C_3H_7	1.707	−0.36	−0.58
n-C_4H_9	2.207	−0.39	−0.66
n-C_5H_{11}	2.707	−0.40	−0.71
$(CH_3)_2CHCH_2CH_2$	2.563	−0.35	−0.84
$C_6H_5CH_2$	2.264	−0.38	−0.93
$C_6H_5CH_2CH_2$	2.764	−0.43	−0.53
$C_6H_5CH_2CH_2CH_2$	3.264	−0.45	−1.22
$(CH_3)_2CH$	1.563	−0.47	−0.43
cyclo-C_6H_{11}	3.225	−0.79	−0.30
$(CH_3)_2CHCH_2$	2.063	−0.93	−1.23
cyclo-$C_6H_{11}CH_2$	3.725	−0.98	−1.27
$CH_3CH(CH_2CH_3)_2$	2.100	−1.13	−1.28
$C_6H_5CHCH_3$	3.185	−1.19	−1.58
$C_6H_5CHC_2H_5$	3.315	−1.50	−1.71
$(CH_3)_3C$	1.854	−1.54	−0.99
$(C_6H_5)_2CH$	4.808	−1.76	−1.73
$(CH_3CH_2)_2CH$	2.639	−1.98	−1.32
$C_6H_5CH{=}CH$	2.941	−1.99	−1.17
C_6H_5	2.265	−2.55	−0.93

[a] Data from Ref. 15.

BACKGROUND

Attempts have been made to develop a numerical description of a molecule derived not from experimental measurements of a property but from knowledge of the molecular structure itself (3–5). The molecular topological approach transcribes molecular structure into a topological graph from which is derived a number, the topological index. Attempts are then made to correlate these indexes to physicochemical properties. One such correlation, suggested by Randić (6) to describe the effects of branching, subsequently was developed into the molecular connectivity index, χ (7).

Molecular connectivity is a term used to describe molecular structure in terms of the attachments of constituent atoms in a molecule. Knowing the manner in which the atoms are attached permits calculation of χ, which seemingly encodes within it the additive and constitutive natures of a molecule. In a series of studies (7–10), χ was correlated significantly to several physicochemical properties.

One physicochemical property that correlated in a highly significant manner with χ ($r > 0.9990$) is molar refraction (5, 7). This property, often used in property–activity relationships (11), reflects the bulk or steric nature of a group (11, 12). Since χ shows such significant correlation to one steric parameter useful in property–activity relationships, its correlation with another parameter used to estimate steric effects, the E_s value of Taft (13), was investigated and is the subject of this report.

The parameter E_s has been particularly useful in reactions where the substituent is near the reaction center. It also was employed in property–activity relationship studies (14), but its usefulness is limited by the lack of experimental data. By showing a correlation between χ or extended terms of χ, it might be feasible to use these terms as estimators of steric hindrance terms in structure–activity relationships.

It seemed plausible that use of extended terms in χ ($^m\chi$) might be especially likely to yield good correlations, since these terms allow the inclusion of cluster subgraphs (5). Clusters of substituents around a reaction center would seem logically important in determining E_s values.

EXPERIMENTAL

Chi (χ) terms are computed from a hydrogen-suppressed formula or graph of the molecule. The simplest term, designated $^1\chi$ and called a connectivity χ, is computed by:

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

where the sum is over all connections or edges in the hydrogen-suppressed graph, and δ_i and δ_j are numbers assigned to each atom reflecting the number of atoms adjacent or connected to atoms i and j, which are formally bonded. The nature of the atom is not considered in the calculation.

An extended term of χ of the order $^2\chi$ is computed from:

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

where i, j, and k are atoms bonded in sequence or in a path, and the sum is over all distinct sets of two-edge paths. In general, extended terms of χ, $^m\chi_p$, are computed for linear paths, p, of m bonds by:

$$^m\chi_p = \sum_{s=1}^{n_m} \prod_{i}^{m+1} (\delta_i)_s^{-1/2} \qquad \text{(Eq. 3)}$$

where n_m is the number of paths with m edges, and s identifies a particular subgraph.

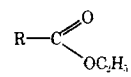
Terms describing nonlinear arrangements of bonds such as clusters of three bonds, $^3\chi_C$, and circuits (or chains) of six atoms, $^6\chi_{CH}$, are computed in the same way. Examples of these extended term calculations are shown in Ref. 10.

Briefly, the nature of χ may be summarized by stating that it is a nonempirical, simply computed number (or numbers) that is a weighted count of bonds and connected sets of bonds. The weighting is based on the connectivity of each atom in a bond formula or graph of the molecule. The expectation is that χ or terms of χ encode within them structural information that is adequate to relate to numerous geometrical, physical, and even biological properties.

RESULTS AND DISCUSSION

To quantitate the steric effect of substituents on reactions rates, Taft (15) studied the esterification and hydrolysis rates of a series of aliphatic

Table II—Aliphatic E_s Values *versus* Molecular Connectivity Indexes [a]



R	E_s(obs[b])	E_s(calc)	$^1\chi$	$^2\chi$	$^3\chi$	$^4\chi$
CH_3	0.00	0.27	0.707	0.000	0.000	0.000
CH_3CH_2	−0.07	0.04	1.207	0.500	0.000	0.000
$(CH_3)_2CH$	−0.47	−0.37	1.563	1.394	0.000	0.000
$(CH_3)_3C$	−1.54	−0.92	1.854	2.561	0.000	0.000
$CH_3(CH_2)_2$	−0.36	−0.60	1.707	0.854	0.354	0.000
$CH_3(CH_2)_3$	−0.39	−0.87	2.207	1.207	0.604	0.250
$(CH_3CH_2)_2CH$	−1.98	−1.81	2.639	1.683	0.866	0.289
$CH_3(CH_2)_4$	−0.40	−0.73	2.707	1.561	0.854	0.427
$(CH_3)_2CHCH_2CH_2$	−0.38	−1.36	2.563	2.036	0.781	0.408
$(CH_3)_3CCH_2$	−1.74	−2.06	2.354	2.811	0.750	0.000
$(CH_3CH_2CH_2)_2CH$	−2.11	−1.87	3.639	2.443	1.394	0.961
$(CH_3)_2CHCH_2CH(CH_3)$	−1.85	−1.88	3.247	3.462	0.961	1.045
$(CH_3)_2CHCH_2CHCH_2(CH_3)_2$	−2.47	−2.51	4.625	4.072	1.971	1.633
$(CH_3)_3CCH_2C(CH_3)_2$	−2.57	−1.78	3.561	5.109	1.362	1.436
$[(CH_3)_3CH_2]_2CH$	−3.18	−3.50	4.932	6.030	1.802	1.804
$(CH_3)_3CC(CH_3)_2$	−3.90	−3.28	3.104	4.134	2.030	0.000
$(CH_3CH_2)_3C$	−3.80	−4.22	3.536	2.561	2.250	0.750
$(CH_3)_3CH_2C(CH_3)C(CH_3)_3$	−4.00	−3.72	4.811	6.548	2.731	1.436

[a] Since the functional group $COOC_2H_5$ remains constant, a connection value, $\delta = 2$, was arbitrarily assigned to this group to facilitate calculations. [b] Data from Ref. 11.

and aryl esters. These studies led to the linear free energy-derived parameters, E_s, which are measures of the influence of steric factors associated with substituents in reaction rates.

Logically, groups clustering around a reaction center, *e.g.*, the C(=O)O$^-$ group of esters, will have the greatest influence on reaction rates dependent on steric effects. Extended χ terms, *e.g.*, $^2\chi$ and $^3\chi$, should reflect this clustering; therefore, a good correlation of E_s with these parameters should be expected.

The original hydrolysis data of a mixture of esters were examined first (Table I) (15). These data did not give a good correlation with any χ term. The best correlation was given when extended χ terms were utilized:

$$E_s = -0.566(\pm0.235)^2\chi - 1.22(\pm0.548)^3\chi + 2.14(\pm0.880)^4\chi + 0.387(\pm0.304) \quad \text{(Eq. 4)}$$
$$r = 0.738 \quad s = 0.610 \quad n = 22.0$$

This quality of correlation was not as high as expected and did not match previous correlations with other physicochemical properties (7–10). The problem is complex because combined with the purely topological aspect is a variable influence due to interactions across space. Since it was suspected that the aryl esters were leading to anomalous results, the aryl esters were deleted and the E_s values for 18 aliphatic esters were examined (13). Table II lists the data of E_s, their extended χ terms, and calculated E_s values using the equation giving the best fit.

The resulting correlation equations, correlation coefficients, and standard errors are:

$$E_s = -0.976(\pm0.135)^1\chi + 0.991(\pm0.397) \quad \text{(Eq. 5)}$$
$$r = 0.868 \quad s = 0.768 \quad n = 19$$

$$E_s = -1.161(\pm0.185)^3\chi - 0.056(\pm0.231) \quad \text{(Eq. 6)}$$
$$r = 0.904 \quad s = 0.662 \quad n = 19$$

$$E_s = -0.218(\pm0.018)^2\chi - 1.24(\pm0.261)^3\chi + 0.138(\pm0.241) \quad \text{(Eq. 7)}$$
$$r = 0.922 \quad s = 0.620 \quad n = 19$$

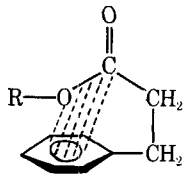
$$E_s = -0.544(\pm0.133)^2\chi - 1.40(\pm0.199)^3\chi + 1.09(\pm0.328)^4\chi + 0.403(\pm0.208) \quad \text{(Eq. 8)}$$
$$r = 0.961 \quad s = 0.460 \quad n = 19$$

The index $^1\chi$ does not give a good correlation with E_s ($r = 0.868$) and reflects primarily path length and, in general, steric bulk characteristics. It does not represent adequately steric influence around a reactive site. In terms of single χ parameters, $^3\chi$ gave the best correlation ($r = 0.904$, $s = 0.662$). A dual-parameter fit with $^2\chi$ and $^3\chi$ improved the correlation ($r = 0.922$, $s = 0.620$), and the three-parameter equation with $^2\chi$, $^3\chi$, and $^4\chi$ gave the best correlation ($r = 0.961$, $s = 0.460$).

These data suggest that extended χ terms are a good measure of intramolecular steric effects, especially when substituents are surrounding the reaction center and especially for aliphatic substituents. Previous high correlations with molar refraction (5, 7) indicate that $^1\chi$ terms give adequate representation of general bulk or steric bulk characteristics.

The poor correlation of χ terms with the aryl esters might be explained as follows. The aryl esters were of the form $C_6H_5(CH_2)_nCOOR$, where n varied from 1 to 3. With sufficient flexibility, there is a possibility for the ester group to fold over the aromatic ring, enabling the π-electrons of the phenyl ring to interact with the ester functional group (Structure I). This intramolecular interaction might be sufficient to affect hydrolysis of the ester moiety.

Several studies (16, 17) reported a similar problem when investigating the effects of the side chains of phenylpropyl derivatives on partition coefficients. The interaction of the side-chain substituent with the π-electrons of the phenyl ring was suggested to result in a folding together of these two portions of the molecule, leading to a more compact structure and a greater than expected water solubility (16).



I

The use of extended χ terms as a measure of the effect of clustering about a reaction center or potential pharmacophoric group is a potentially powerful structure–activity relationship tool in drug analysis. For example, if a drug molecule possesses a site particularly susceptible to metabolic attack, *e.g.*, an ester group, calculation of χ cluster terms about that group should reflect the relative effect of steric hindrance of immediate neighbors on metabolic attack. Another possible application could be the determination of the effect of steric hindrance about a pharmacophoric group affecting the approach of drug to receptor features.

Structure–activity relationships in which $^1\chi$ terms are significantly correlated to biological activity might be viewed as reflecting a generalized dependence of activity on bulk, since $^1\chi$ was correlated significantly to molar refraction (7). It could also reflect a dependence on solubility or partitioning ability since $^1\chi$ also showed a significant correlation with these properties (8, 9). If, however, biological activity correlated significantly with extended χ terms, *e.g.*, $^3\chi$, then one should suspect the influence of steric hindrance effects about some pharmacophoric group.

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