## REFERENCES

(1) R. Baugh, R. T. Calvert, and J. T. Fell, *J. Pharm. Sci.*, **66**, 733 (1977).

(2) L. Lachman, C. J. Swartz, and J. Cooper, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 213 (1960).

(3) C. J. Swartz, T. Urbanyi, and J. Cooper, *ibid.*, **49**, 165 (1960).

(4) L. Lachman, S. Weinstein, C. Swartz, T. Urbanyi, and J. Cooper, *J. Pharm. Sci.*, **50**, 141 (1961).

(5) J. T. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N.Y., 1972, p. 347.

(6) R. A. Umberger, *Anal. Chem.*, **27**, 768 (1955).

(7) A. J. Khoury and L. J. Cali, *J. Pharm. Sci.*, **56**, 1485 (1967).

(8) J. M. Talmage, M. H. Penner, and M. Geller, *ibid.*, **54**, 1194 (1965).

(9) J. A. Waters, Y. Kondo, and B. Witkop, *ibid.*, **61**, 321 (1972).



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# Quantitative Structure–Activity Relationships and Carminative Activity II: Steric Considerations


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**Abstract** □ The unexplained variation in the relationships between carminative activities and octanol–water distribution coefficients of various classes of compounds was explained. The steric substituent constant ($E_s$) value, van der Waals volume, and molecular connectivity were introduced into a previously derived correlation. Each parameter brought about an improvement, and molecular connectivity was the most successful. Correlations containing molecular connectivity terms explained the excess variation. The results were in agreement with a mechanism in which carminative activity depended on the availability of the oxygen atom in the functional group of the molecule and was reduced when the substituent attached to the oxygen hindered the interaction between the oxygen atom and the receptor.



**Keyphrases** □ Carminative activities—various oxygen-containing compounds, related to solubility, steric considerations □ Solubility—various oxygen-containing compounds, related to carminative activities, steric considerations □ Structure–activity relationships—carminative activities of various oxygen-containing compounds related to solubility, steric considerations


Recently, the carminative activities of 34 alcohols, esters, ethers, phenols, and carbonyl compounds were described (1). Carminative activity was expressed as the ability to produce a 50% inhibition ($ID_{50}$) of a standard response to carbachol in the guinea pig isolated ileum preparation. Regression analysis revealed a significant rectilinear relationship between log $1/ID_{50}$ and the logarithms of the octanol–water distribution coefficients (log $P$), but the correlation equation explained only 50% of the variation.

However, each chemical class of compounds, in isolation, produced more precise correlations, indicating the influence of factors other than solubility on carminative activity. Electronic distributions were unimportant, and it was suggested that the variation was due to the oxygen atom being shielded by the group attached to it. Consequently, the bulkier the group, the lower would be the carminative activity. Therefore, the hypothesis was tested by introducing steric parameters into the correlation equation between log $P$ and log $1/ID_{50}$.

## EXPERIMENTAL

The $ID_{50}$ results and octanol–water distribution coefficients were reported previously (1). The compounds examined and other data are listed in Table I. All compounds consist of an oxygen joined to two chemical groups, one of which may be hydrogen. In choosing the groups to which to assign steric parameters, the decision was unambiguous with four of the five ethers since they each had two identical groups linked to oxygen. The vinyl group was chosen for the fifth compound, ethyl vinyl ether, since it was the smaller group. Similarly, values for hydrogen were given to all of the alcohols and phenols. The smaller groups were chosen because it was considered that interaction between oxygen and the receptor site would take place along the path of least resistance.

In each compound, the groups are located on opposite sides of the oxygen atom so that it is unlikely that both groups would interfere at once. Therefore, the probability of interaction through the bulkier group would be low. No logical way of allocating steric parameters to the carbonyl compounds, in accord with these assignments, was possible, so this class of compounds was omitted from the correlations. It was suggested previously (1) that the carbonyl oxygen of the esters, and not the ether oxygen, was responsible for carminative activity. Parameters for $CH_3C=$ were assigned, therefore, to the esters (since they are all acetates).

## RESULTS AND DISCUSSION

Taft (2) assigned substituent constants ($E_s$), which are a measure of steric effects on reaction rates, to a range of substituent groups. The best correlation of log $1/ID_{50}$ against log $P$, reported previously (1), and the $E_s$ value is:

$$\log 1/ID_{50} = 0.128 + \underset{8.8}{0.521(0.059)} \log P + \underset{4.7}{0.360(0.077)} E_s \quad \text{(Eq. 1)}$$

$$n = 22 \quad r = 0.915 \quad s = 0.220 \quad F_{2,19} = 49\alpha(0.001) = 10.2$$

where $n$ represents the number of results considered (reduced from 26 to 22 because an $E_s$ value for $CH_3C=$ was not available), $r$ is the correlation coefficient, and $s$ is the standard deviation. The figures in parenthesis following the coefficient in log $P$ and $E_s$ represent their standard errors ($p = 0.05$), and the figures below the coefficients are the ratios of the coefficients to their standard errors. Comparison of these values with $t$ values obtained from statistical tables indicated that both physical parameters are related to log $1/ID_{50}$ ($p < 0.001$).

Equation 1 explains 84% of the variation and is a significant improvement on the corresponding equation containing log $P$ alone. The relationship is confirmed by the figures shown below the equation, which are the results of analysis of variance of the observed results about the regression, followed by an $F$ test.

Kier and coworkers (3, 4) developed a range of parameters, collectively termed molecular connectivity ($\chi$), related to the topological structure of organic groups. The simplest term, the zero-order connectivity, is designated ${}^0\chi^v$ and is calculated from:

$${}^0\chi^v = \sum (\delta_i)^{-1/2} \quad \text{(Eq. 2)}$$

where $\delta_i$ is a number assigned to each nonhydrogen atom and reflects the




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**Table I—Steric Parameters**

| Compound | Hindering Group | $E_s$ | $V_w$, nm$^3$ × $10^{-1}$ | Molecular Connectivity $^0\chi^v$ | Molecular Connectivity $^1\chi^v$ |
|---|---|---|---|---|---|
| Isobutyl alcohol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| *n*-Butyl acetate | $CH_3C=$ | — | 0.364 | 1.500 | 0.704 |
| 1,2-Dihydroxybenzene | H | 1.24 | 0.022 | 0.000 | 0.000 |
| 1,3-Dihydroxybenzene | H | 1.24 | 0.022 | 0.000 | 0.000 |
| 1,4-Dihydroxybenzene | H | 1.24 | 0.022 | 0.000 | 0.000 |
| *o*-Cresol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| *m*-Cresol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| *p*-Cresol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| Dibutyl ether | $CH_3(CH_2)_3$ | −0.39 | 0.651 | 3.121 | 1.996 |
| Diethyl ether | $CH_3CH_2$ | −0.07 | 0.343 | 1.707 | 0.996 |
| 3,4-Dimethylphenol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| Diisopropyl ether | $(CH_3)_2CH$ | −0.47 | 0.497 | 2.577 | 1.390 |
| Dipropyl ether | $CH_3(CH_2)_2$ | −0.36 | 0.497 | 2.414 | 1.495 |
| Ethyl acetate | $CH_3C=$ | — | 0.364 | 1.500 | 0.704 |
| Ethyl vinyl ether | $CH_3C=$ | — | 0.301 | 1.284 | 0.644 |
| Eugenol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| Hexanol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| Menthol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| 2-Methoxyphenol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| 4-Methoxyphenol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| 1-Pentanol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| 2-Phenoxyethanol | H | 1.24 | 0.022 | 0.000 | 0.000 |
| Isopropyl acetate | $CH_3C=$ | — | 0.364 | 1.500 | 0.704 |
| *n*-Propyl acetate | $CH_3C=$ | — | 0.364 | 1.500 | 0.704 |
| Salicylaldehyde | H | 1.24 | 0.022 | 0.000 | 0.000 |
| Thymol | H | 1.24 | 0.022 | 0.000 | 0.000 |

number of atoms bonded to it. A similar term is derived for each bond by calculating the product of the numbers associated with the two atoms of the bond. These values are summed to give the first-order connectivity, $^1\chi^v$. In general, extended terms of $\chi$ ($^m\chi_p^v$) are computed for linear paths, $p$, of $m$ bonds by:

$$^m\chi_p^v = \sum_{j=1}^{N_s} \left[ \prod_{i=1}^{m+1} (\delta_i)_j \right]^{-1/2} \quad \text{(Eq. 3)}$$

where $N_s$ is the number of distinct paths with $m$ edges. Detailed information on the significance and calculation of connectivities was reported previously (4, 5). Murray (6) demonstrated relationships between $E_s$ values and connectivity. Therefore, correlations similar to Eq. 1 were attempted with connectivity terms in place of $E_s$. This substitution provided the advantage that a steric parameter could be allocated to the esters. Connectivities are given in Table I. The best correlations obtained are represented by Eqs. 4–6:

$$\log 1/ID_{50} = 0.563 + 0.537(0.048) \log P - 0.242(0.039)\,{}^0\chi^v \quad \text{(Eq. 4)}$$
$$\qquad\qquad 11.3 \qquad\qquad 6.2$$
$$r = 0.937 \quad n = 26 \quad s = 0.186 \quad F_{2,23} = 83.0\alpha(0.001) = 9.47$$
$$t(\phi = 24; p = 0.001) = 3.75$$

$$\log 1/ID_{50} = 0.531 + 0.553(0.045) \log P - 0.433(0.064)\,{}^1\chi^v \quad \text{(Eq. 5)}$$
$$\qquad\qquad 12.3 \qquad\qquad 6.8$$
$$r = 0.944 \quad n = 26 \quad s = 0.056 \quad F_{2,23} = 9.46\alpha(0.001) = 9.47$$

$$\log 1/ID_{50} = 0.478 + 0.577(0.048) \log P + 0.351(0.284)\,{}^0\chi^v$$
$$\qquad\qquad 12.0 \qquad\qquad 1.2$$
$$-1.036(0.493)\,{}^1\chi^v \quad \text{(Eq. 6)}$$
$$\qquad 2.1$$
$$r = 0.948 \quad n = 26 \quad s = 0.054 \quad F_{3,22} = 65.0\alpha(0.001) = 7.80$$
$$t(\phi = 23; p = 0.03) = 1.06$$

There is no significant difference between the equations with regard to goodness of fit ($p > 0.05$), but all are better than Eq. 1 ($p < 0.01$). Therefore, $^0\chi^v$ and $^1\chi^v$ are more suitable than $E_s$ for assessing the steric hindrance presented by groups bonded to oxygen in the carminative molecules. There is nothing to choose between the two connectivity terms ($p > 0.05$), and the fit is not improved either by combining them or by incorporating higher order connectivity parameters. No combination of connectivities alone gave a satisfactory correlation with log $1/ID_{50}$. A term involving the distribution coefficient was always essential for a good predictive relationship.

The $E_s$ values are linear functions of van der Waals radii (6–8). Moriguchi *et al.* (9) published a list of van der Waals volumes, $V_w$, for substituent groups and used them as a measure of steric effects on biological activities. Multiple regression analysis of log $P$ and $V_w$ against the carminative activities of the alcohols, esters, ethers, and phenols produced Eq. 7:

$$\log 1/ID_{50} = 0.576 + 0.529(0.057) \log P - 0.893(0.201)V_w \quad \text{(Eq. 7)}$$
$$\qquad\qquad 9.3 \qquad\qquad 4.5$$
$$r = 0.909 \quad n = 26 \quad s = 0.222 \quad F_{2,23} = 55\alpha(0.001) = 9.47$$

It is a significant improvement on the corresponding equation containing log $P$ as the only independent variable, but it is not as good a correlation as Eqs. 4–6.

The $E_s$ values are defined by:

$$E_s = \log \frac{k}{k_0} \quad \text{(Eq. 8)}$$

where $k$ and $k_0$ represent rate constants for the acid hydrolysis of esters ($R_1COOR_2$); $k_0$ is the rate constant when $R_1$ is methyl, and $k$ is the corresponding constant when $R_1$ is the substituent group of interest. The underlying principle of the concept is that acid hydrolysis of esters is not influenced by polar effects and is dependent exclusively on the stereochemistry of the transition state.

In the present work, the groups are attached to oxygen, rather than to carbon, representing a different environment from that used to calculate the parameters. Nevertheless, it can be argued that since the groups are all bonded to the same element, any errors involved in using $E_s$ values would be constant. A more serious objection is that the second group attached to the oxygen varies from compound to compound, although the same criticism can be leveled at Taft's calculations (2) in which a range of alkyl groups ($R_2$) was used. Furthermore, since the second group in each carminative is remote from the first, significant steric interaction on the other side of the oxygen atom would be unlikely. An exception is possible with substituents containing bulky groups alpha to the oxygen; but the only candidate for this situation was 2-methoxyphenol, and its carminative activity is predicted reasonably well by Eq. 1. The principal effect brought about by the second group attached to oxygen would be expected to be polar rather than steric.

The $E_s$ values may give better predictions than van der Waals volumes, which are calculated geometrically, because they are based on chemical considerations. Molecular connectivity was the most successful approach. This method of expressing the stereochemistry of substituent groups is more sophisticated than the van der Waals volume, and the results obtained with carminatives suggest that they are more representative of steric hindrance than either $E_s$ or $V_w$. The failure of the $E_s$ values to match the success achieved with connectivities could be due to inherent errors in their derivation, particularly the assumption that the reaction constants ($\rho_A$ and $\rho_B$) are equal. Taft (2) described $E_s$ values as "nearly quantitative measures of steric factors."

The most important conclusion is that correlations between carminative activity and the distribution coefficient are improved by consideration of a parameter that is a measure of steric factors. All three parameters examined brought about such an improvement. Molecular connectivities were the best parameters and are easily calculated. Previously (1), correlation of the log $1/ID_{50}$ for all compounds against log $P$ gave a relationship that explained only 50% of the variation. But when only one chemical class, hydroxy compounds, was considered, 90% of the variation was accounted for. Inclusion of molecular connectivity terms in the first correlation increased the explained variation from 50 to 88–90%, as shown in Eqs. 4–6. The inference is that steric factors are the sole cause of biological variation resulting from changing the functional groups in the carminatives investigated.

## REFERENCES


(1) B. K. Evans, K. C. James, and D. K. Luscombe, *J. Pharm. Sci.*, **67**, 277 (1978).

(2) R. W. Taft, *J. Am. Chem. Soc.*, **74**, 3120 (1952).

(3) L. H. Hall, L. B. Kier, and W. J. Murray, *J. Pharm. Sci.*, **64**, 1974 (1975).

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

(5) T. D. Paolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, **13**, 31 (1977).

(6) W. J. Murray, *J. Pharm. Sci.*, **66**, 1352 (1977).

(7) M. Charton, *J. Am. Chem. Soc.*, **91**, 615 (1969).

(8) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).

(9) I. Moriguchi, Y. Kanada, and K. Komatsu, *Chem. Pharm. Bull.*, **24**, 1799 (1976).