was contaminated with the meso cis isomer or that partial loss of optical configuration is involved in the (*R*)-(+)-pulegone → (*R*)-(+)-**5** transformation, perhaps in the dehydration of 1,3-dimethylcyclohexanol to dimethylcyclohexene.

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Significance of "Volume" and "Bulk" Parameters in Quantitative Structure–Activity Relationships

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Much use has been made in recent years of parameters for QSAR[1] which are usually considered as measures of volume or bulk. The significance of these parameters is not yet known. Many authors have suggested that they measure steric effects. Others have questioned this. It is of considerable interest to understand the significance of correlations with these parameters. They are as follows: van der Waals volume,[2] V_W; molar refractivity,[3] *MR*; molar volume (Exner[4]), V_M; Traube's rule volume,[5] V_T; parachor;[6] and molecular weight, W_M.

All of these parameters have been used to obtain QSAR. The first question we must consider is whether these parameters are interrelated or not. Values of *MR*, V_M, V_T, parachor, and W_M (sets 1–5, respectively) have therefore been correlated with the corresponding V_W values, which were generally taken from or calculated according to the method of Bondi.[2] The values of V_W for H were obtained by averaging the quantities $V_{W,MH_n} - V_{W,MH_{n-1}}$, where M and n are the following: C, 4; N, 3; O, 2; S, 2; and P, 3. The correlation equation is

$$Q = mV_W + c \qquad (1)$$

The values of the parameters used in the correlations are given in Table I. Results of the best correlations are given in Table II. Results of other correlations are given in Table VI of the supplementary material (see paragraph at end of paper). The results show clearly that *MR*, V_M, V_T, and parachor are significantly correlated with V_W and are therefore interrelated to each other. The Traube volume (set 3) and parachor (set 4) are very closely related to V_W, the correlation equations accounted for >98.5% of the variance of the data. If the *MR* values for alkyl groups (set 1B) and for groups with lone pairs (set 1A) are correlated separately with V_W, the results are very much improved.

We have also separately correlated *MR* values for π-bonded substituents in which the π orbitals include all of the atoms present except hydrogen (set 1C) and partially π-bonded substituents in which one or more of the atoms other than hydrogen are not π bonded (set 1D). Included in set 1D are the CO_2H and $CONH_2$ groups as they seem to fit best in this set. The results are of great interest, although excellent correlations accounting for ≧97.8% of the variance of the data were obtained for all sets, as the m and c values were significantly different for 1A and 1B. Sets 1C and 1D have essentially the same slope but different intercepts (the difference in the intercepts is probably significant). These results further decrease the likelihood that *MR* is measuring steric effects since if that were the case, we would expect an excellent correlation with V_W. Such a correlation would be independent of group type. Figures 1–3 show plots of sets 1A–1D, 3 and 4, and 6.

Table I. Values of "Volume" and "Bulk" Parameters Used in Correlations

1A. *MR* Values[a]

F^b, 0.92; Cl^b, 6.03; Br^b, 8.88; I^b, 13.94; Me, 5.65; H, 1.03; $NH_2{}^b$, 5.42; OH^b, 2.85; $PH_2{}^b$, 12.19; SH^b, 9.22; NO_2, 7.36; CN, 6.33; C_2H_5, 9.55

1B. *MR* Values for Alkyl Groups[a]

Me, 5.65; Et, 10.30; Pr, 14.96; *i*-Pr, 14.98; Bu, 19.59; *t*-Bu, 19.62; c-C_4H_7, 17.88; c-C_5H_9, 22.02; Am, 24.25; c-C_6H_{11}, 26.29; c-C_3H_5, 17.53

1C. *MR* Values for π-Bonded Substituents[a]

CN, 6.33; CHO, 6.88; C≡CH, 9.55; CH=CH_2, 10.99; CH=CHCHO, 16.88; Ph, 25.36; Bz, 30.33; C≡CPh, 61.94; CH=CHPh, 34.17; CH=CHBz, 40.25; NO_2, 7.36; CH=$CHNO_2$, 33.74; CH=CHCN, 16.23

1D. *MR* Values for Partially π-Bonded Substituents[a]

CO_2H, 6.93; $CONH_2$, 9.81; CONHMe, 14.57; Ac, 11.18; CH=CHAc, 21.10; CO_2Me, 12.87; CH=$CHCO_2H$, 17.91; C≡CMe, 14.14; CH=$CHCO_2Et$, 27.21; CO_2Et, 17.47

2. V_M Values[c]

F, 15.11; Cl, 22.96; Br, 26.19; I, 32.93; Me, 31.48; H, 14.90; NH_2, 17.67; OH, 10.25; SH, 25.81; NO_2, 24.51; CN, 22.67; C_2H_5, 33.22

3. V_T Values[d]

c-C_5H_9, 77.4; *t*-Bu, 67.5; OH, 5.4; NH_2, 17.2; H, 3.1; *i*-Pr, 51.4; Me, 19.2; F, 7.4; Br, 17.7; CH_2OH, 21.5; SMe, 34.7; Et, 35.3; CF_3, 32.1; Cl, 13.2; OMe, 24.7; CN, 13.2; Ac, 34.6

4. Parachor Values[e]

NH_2, 45.5; NHEt, 128.5; OH, 29.8; OEt, 115.3; Me, 55.33; H, 15.5; F, 26.1; Cl, 55.2; Br, 68.0; NO_2, 75.7

5, 6. W_M Values[a]

H, 1.0; F, 19.0; Cl, 35.4; Br, 79.9; I, 126.9; Me, 15.0; NH_2, 16.0; OH, 17.0; PH_2, 33.0; SH, 33.1; NO_2, 46.0; CN, 26.0; C_2H_5, 25.0

[a] All *MR* and W_M values are from C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973). [b] Members of set 1A. [c] O. Exner, *Collect. Czech. Chem. Commun.*, **32**, 1 (1967). [d] J. P. Tollenaere, H. Moereels, and M. Protiva, *Eur. J. Med. Chem.-Chim. Ther.*, **11**, 293 (1976). [e] P. Ahmad, C. A. Fyle, and A. Mellors, *Biochem. Pharmacol.*, **24**, 1103 (1975).

The correlation of W_M with V_W is *not* significant. Obviously, W_M is not measuring volume. Since the mass of a substituent is of chemical significance only when the rate constant for substituent–skeletal group bond breaking is involved, and this is not a likely process in the biological data of interest, the W_M must be related to some other factor of importance. Such a factor may be the polarizability of the group. *MR* is known to be a measure of polarizability. It is significantly, although poorly, correlated (set 7, Table VI, supplementary material) with the total number of electrons in the substituent, n_e, by the equation

$$Q = mn_e + c \qquad (2)$$

A correlation of W_M with eq 2 is indeed successful (set 6, Table II). The regression equation accounts for >99% of the data. A relationship between molar refractivity and number of electrons has long been known. The equation represents the type of relationship

$$MR = {}^4\!/_3(N_0\alpha_0)\,\frac{s\nu_e{}^2}{\nu_V{}^2 - \nu_i{}^2} \qquad (3)$$

in which ν_e, ν_V, and ν_i are the frequencies of vibration of the electron, the electrical oscillator, and the light, respectively,

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Table II. Correlations with Equations 1 and 2

set	m	c	r^a	F^b	s_{est}^c	s_m^c	s_c^c	n^d	$100R^{2e}$
1A	0.968	−4.94	0.989	269.7^f	0.712	0.0589^f	0.794^f	8	97.82
1B	0.442	−0.197	0.9994	7178^f	0.230	0.00522^f	0.217^j	11	99.87
1C	0.564	−1.58	0.999	4130^f	0.634	0.00878	0.373^i	13	99.73
1D	0.546	−2.85	0.992	522.1^f	0.767	0.0239	0.831^i	10	98.49
3	1.60	−4.14	0.993	1064^f	2.56	0.0490^f	1.16^i	17	98.61
4	4.05	2.83	0.996	896.5^f	3.69	0.135^f	2.28^j	10	99.12
6	2.45	−5.95	0.997	1958^f	2.59	0.0553^f	1.20^f	13	99.44

[a] Correlation coefficient. [b] F test. The superscript indicates the footnote for the confidence level (CL). [c] Standard errors of the estimate, m, and c. Superscripts indicate the footnote for the CL of Student's t test. [d] Number of points in the set. [e] Percent of the data accounted for by the regression equation. [f] 99.9% CL. [g] 80% CL. [h] 90.0% CL. [i] 99.0% CL. [j] 50% CL. [k] 95.0% CL. [l] 99.5% CL.

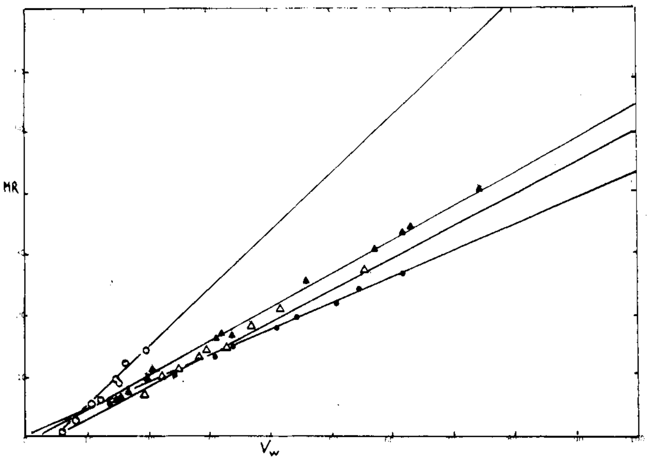

Figure 1. Group molar refractivities vs. van der Waals volumes: ● set 1A; ○ set 1B; ▲ set 1C; △ set 1D.

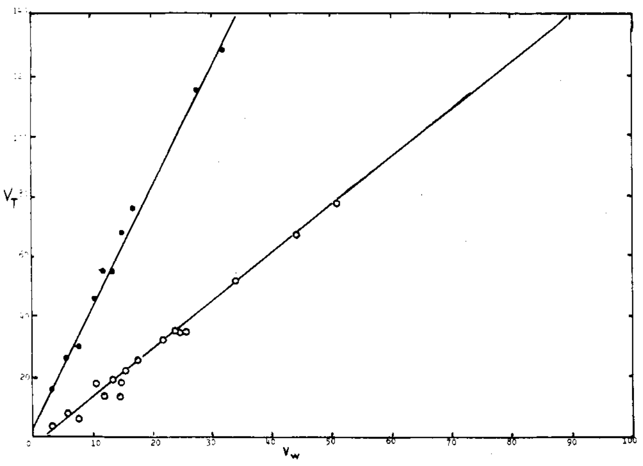

Figure 2. V_T vs. V_W; parachlor vs. V_W: ○ set 3; ● set 4.

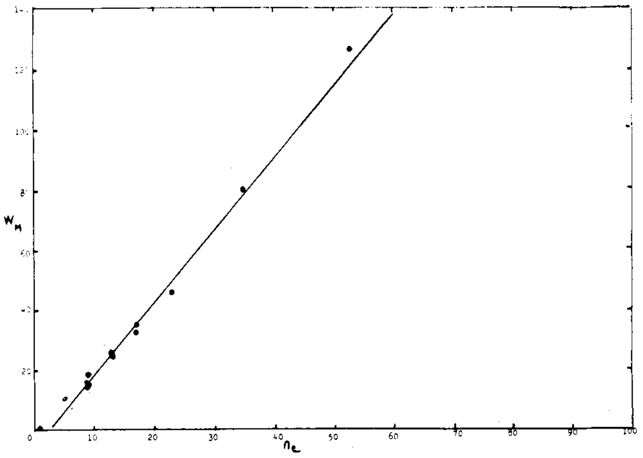

Figure 3. Set 6. W_M vs. n_e.

α_0 is the polarizability in the absence of an externally applied field, N_0 is Avogadro's number, and s is the number of dispersion electrons per molecule.

We have extended this work by examining the correlation of MR with the equation

$$MR = a_c n_c + a_\sigma n_\sigma + a_\pi n_\pi + a_n n_n + a_0 \qquad (4)$$

where n_c is the total number of core electrons, n_σ is the total number of σ-bonding electrons, n_π is the total number of π-bonding electrons, and n_n is the total number of nonbonding electrons. The results obtained for correlations with eq 4 are as follows: $r = 0.983$; $F = 321.6$ (99.9% confidence level); $s_{est} = 1.78$; $s_c = 0.0248$ (99.9% confidence level); $s_\pi = 0.145$ (99.9% confidence level); $s_\sigma = 0.0243$ (99.9% confidence level); $s_n = 0.0431$ (90.0% confidence level); $s_0 = 0.539$ (90.0% confidence level); $r_{c\pi} = 0.064$; $r_{c\sigma} = 0.218$; $r_{cn} = 0.312$ (95.0% confidence limit); $r_{\pi\sigma} = 0.096$; $r_{\pi n} = 0.064$; $r_{\sigma n} = 0.086$; $n = 50$; $100R^2 = 96.62$; $a_c = 0.320$; $a_\pi = 0.680$; $a_\sigma = 0.684$; $a_n = -0.0825$; $a_0 = 0.991$. There is no significant difference between a_σ and a_π. Thus, correlation with an equation such as 4a would be entirely satisfactory.

$$MR = a_c n_c + a_b n_b + a_n n_n + a_0 \qquad (4a)$$

In this equation, n_b is the number of bonding electrons in the group. It is interesting to note that the nonbonding electrons make the smallest contribution to MR and that a_n is barely significant. The results are excellent; eq 4 accounts for >96% of the variance of the data.

Having established interrelationships among the "volume" or "bulk" parameters, we may now consider what it is that they do measure. Consider the υ steric parameters and V_W values of the C_nH_{2n+1} alkyl groups. We will consider the alkyl groups as an example because a considerable body of evidence has been accumulated which suggests that the electrical effects of alkyl substituents, in solution at least, are constant.[7] Values of υ and V_W for C_4, C_5, and C_6, isomeric alkyl groups are collected in Table III. For the C_4, C_5, and C_6 groups, respectively, the ratio of υ_L/υ_S, where υ_L is the υ value of the largest isomer and υ_S is that of the smallest isomer, is 1.8, 2.4, and 3.1, respectively. Rate constants for a wide range of organic reactions are known to be dependent on υ, including acid- or base-catalyzed ester,[8-11] amide,[12,13] and thioester hydrolyses,[14] elimination reactions,[15] acetal and ketal formation and hydrolysis,[16] esterification of carboxylic acids,[5] carbonyl addition reactions of aldehydes and ketones,[17] and addition reactions of acetylenes.[18] The van der Waals volume is the same for all of a set of C_nH_{2n+1} isomeric groups, whereas the υ values can show considerable variation. The steric effects of alkyl groups on rate or equilibrium constants seem to invariably depend on υ rather than on V_W; that is, groups with the same volume

Table III. Comparison of ν With V_W for Isomeric C_4, C_5, and C_6 Alkyl Groups[a]

C_4	V_W	ν	C_4	V_W	ν
Bu	44.36	0.68	*sec*-Bu	44.35	1.02
i-Bu	44.35	0.98	*t*-Bu	44.34	1.24

$\nu_L/\nu_S = 1.82$

C_5	V_W	ν	C_5	V_W	ν
Am	54.59	0.68	*i*-Am	54.58	0.68
i-PrCHMe	54.57	1.29	PrCHMe	54.58	1.05
Et_2CH	54.58	1.51	*t*-$BuCH_2$	54.57	1.34
$EtMe_2C$	54.57	1.63	*sec*-$BuCH_2$	54.58	1.00

$\nu_L/\nu_S = 2.50$

C_6	V_W	ν	C_6	V_W	ν
$AmCH_2$	64.82	0.73	*i*-$Pr(CH_2)_3$	64.81	0.68
t-$Bu(CH_2)_2$	64.80	0.70	*sec*-$Bu(CH_2)_2$	64.81	(0.72)
$PrCHMeCH_2$	64.81	(1.07)	Et_2CHCH_2	64.81	(1.13)
$EtMe_2CCH_2$	64.80	(1.48)	BuCHMe	64.81	1.07
PrCHEt	64.81	(1.56)	*i*-PrCHEt	64.80	2.11
i-BuCHMe	64.80	1.09	*sec*-BuCHMe	64.80	(1.56)
i-BuCHMe	64.79	2.11	$PrMe_2C$	64.80	(1.65)
i-$PrMe_2C$	64.79	(2.00)	Et_2MeC	64.80	(2.00)

$\nu_L/\nu_S = 3.10$

[a] Values in parentheses are estimated as described in ref 10.

Table IV. Values of *a*/*b* for XG[a]

11. G = Me

Ac, 139.9; CN, 150.5; Pr, 118.0; *i*-Pr, 96.9; Me, 86.03; Am, 140.6; H, 52.66; Cl, 115.2; MeO, 111.4; EtO, 122.3; EtS, 147.5[b]; F, 87.97; OAc, 140.1; MeS, 139.7; Et, 102.6; Ph, 164.5; Me_2N[c], 120.1; CH_2CN, 154.5; CH_2Cl, 126.1; C_2H_5, 101.3; $PhCH_2CH_2$, 176.8; $PhCH_2$, 171.6

12. G = Et

$C_2H_3CH_2$, 131.7; Et, 118.0; CH_2CN, 161.2; H, 86.03; OAc, 144.3; Cl, 126.1; EtO, 129.3; SH, 138.8; CO_2Et, 151.0; EtS, 154.4; Am, 152.6; Bu, 140.6; MeO, 122.3; MeS[b], 147.5; Pr, 130.2; *i*-Pr, 127.4; PhO, 179.1; CN, 154.5; $PhCH_2$, 176.8; $ClCH_2$, 139.4; Ph, 171.6; CO_2Me, 146.4; Me, 102.6

13. G = Pr

C_2H_5, 131.7; Me, 118.0; CN, 172.2; Bu, 152.6; Pr, 140.6; CO_2Me, 153.1; Et, 130.2; Am, 157.6; H, 102.6; Ph, 176.8; Cl, 159.1; CO_2Et, 156.7

14. G = *i*-Pr

C_2H_5, 128.7; Me, 112.7; $PhCH_2$, 180.0; *i*-Pr, 138.6; CO_2Et, 144.8; CO_2Me, 149.7; Et, 127.4; Ph, 176.0; CH_2OAc, 155.5

15. G = Ph

H, 156.0; CN, 193.7; Br, 185.6; Cl, 175.0; Ph, 212.9; $PhCH_2$, 170.5; Et, 171.6; F, 155.0; I, 199.8; EtO, 179.1; Pr, 176.8; *i*-Pr, 176.0; Me, 164.5

[a] From "Handbook of Chemistry and Physics", R. C. Weast, Ed., 48th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1967. [b] Excluded from correlation with eq 13. [c] Excluded from correlation with eq 28 and 29. The basis for the exclusion of points from the correlations is their large deviation from the regression line obtained for the remainder of the set. Only one point of eq 22 was excluded from the correlations of set 11 with eq 13, 28, and 29; only one point of eq 23 was excluded from the correlation of set 12 with eq 13. All other correlations were carried out with the entire set indicated.

but different υ values exhibit *different* reactivities. This strongly suggests that the "volume" or "bulk" parameters are not actually measuring volume or bulk; they do *not* represent steric effects. What then do these parameters measure? A number of authors have proposed that the molar refractivity actually represents the London force interaction between the biologically active species and some receptor site. Interestingly, no known instance of a correlation of some simple, well-understood physical or chemical data with a polarizability substituent parameter seems to exist.

It seemed to us that it would be useful to demonstrate the existence of such a correlation, as this would help to support the argument that bulk or volume parameters are in fact measures of polarizability. For this purpose we have chosen to examine the *a* and *b* constants of the van der Waals equation of state. The *a* constant has the dimensions of energy divided by volume, and the *b* constant is proportional to molar volume. If we consider the ratio *a*/*b*, this quantity has the dimensions of energy and represents the energy due to molecular interactions of the charge-transfer, Debye, Keesom, and London types. If we assume that the charge-transfer interactions are negligible, then the energies of interaction are given by the expressions

$$E_{dd} = \frac{-2\mu_1^2\mu_2^2}{3KTr^6} \tag{5}$$

for Keesom,

$$E_{di} = \frac{-\mu_1^2\alpha_2}{r^6} - \frac{\mu_2^2\alpha_1}{r^6} \tag{6}$$

for Debye, and

$$E_{ii} = \frac{-3\alpha_1\alpha_2 h\nu_0}{4r^6} \tag{7}$$

for London forces. In these relationships μ is the molecular dipole moment, α is the molar polarizability, *K* is the Boltzmann constant, *r* is the distance between molecules, *T* is the temperature, ν_0 is the frequency, and *h* is Planck's constant. The subscripts 1 and 2 refer to the interacting molecules. The molar refractivity of a molecule XG is given by the equation

$$MR_{XG} = \frac{n^2 - 1}{n^2 + 2}\frac{W_M}{D} = \tfrac{4}{3}(\pi N_A\alpha) \tag{8}$$

where *D* is the density of the liquid, *n* is the refractive index, and N_A is Avogadro's number. Then,

$$MR_{XG} = c\alpha_{XG} \tag{9}$$

Molar refractivity is additive. Then

$$MR_{XG} = MR_X + MR_G \tag{10}$$

$$= c\alpha_X + c\alpha_G \tag{11}$$

and therefore it is possible, as Hansch and co-workers have done, to obtain MR_X values characteristic of some group, X, and proportional to the polarizability of that group. MR_X can therefore be used as a polarizability parameter. Then for some series of molecules, XG, the total energy of interaction will be given by the relationship

$$E_T = E_{dd} + E_{di} + E_{ii} = m(a/b)_{XG} \tag{12}$$

From eq 5–7, the fact that $MR_X = c\alpha_X$, and the fact that the interaction is between two molecules of the same kind,

$$E_T = a_{dd}\mu_X^4 + a_{di}\mu_X^2 MR_X + a_{ii}MR_X^2 + a_0 \tag{13}$$

where

$$a_{dd} = \frac{-2}{3KTr^6},\ a_{di} = \frac{-2}{r^6},\ a_{ii} = \frac{-3h\nu_0}{4r^6} \tag{14}$$

Data from the literature for the ratio of *a*/*b* for systems of the type XG where G is methyl, ethyl, propyl, isopropyl, and phenyl have been correlated with eq 13. The data used are set forth in Table IV. Values of $100R^2$ are given in Table V. Complete results are given in Table VII (supplementary

Table V. Values of $100R^2$ for Correlations with Equations 13, 28, and 29[a]

set	eq 13	eq 28	eq 29
11	75.31	85.19	83.36
12	85.76	83.72	82.99
13	77.82[b]	95.45	91.97
14	89.78[b]	93.32[d]	92.16
15	51.88[c]	54.17[c]	

[a] Superscripts indicate the footnote for the confidence level (CL) of the F test for the significance of the correlation. In the absence of a superscript, the CL is 99.9%. [b] 99.0% CL. [c] 90.0% CL. [d] 99.5% CL.

material). For the four sets of alkyl derivatives, significant correlations were obtained, accounting for >75% of the variance of the data. The results obtained for the benzene derivatives are poor; the correlation equation accounts for about 50% of the data. This large deviation may well be due to the assumption that charge-transfer interactions are negligible. It should be noted that X groups likely to be involved in hydrogen bonding were not included in the data examined. Deviation from the correlation equations for the alkyl derivatives may be due to the quality of the data. Obviously, in these correlations, MR_X is measuring group polarizability rather than some kind of steric effect. The value of $r\mu^4$ ($\mu^2\alpha$) [r_{12}, Table V] is highly significant in all of the sets studied and probably accounts for the fact that a_{dd} is not significant in any of the sets studied.

As most QSAR correlations are carried out with some combination of electrical, hydrophobicity, steric, and bulk parameters, we thought it would be interesting to attempt the correlation of some function of a/b with σ and MR rather than with μ and MR. We may rewrite eq 12 in the form

$$E_T = a_{dd}\mu_X^4 + 2a_{dd}^{1/2}a_{ii}^{1/2}\mu_X^2 MR_X + a_{ii}MR_X^2 - a^*\mu_X^2 MR_X \quad (15)$$

where

$$a^* + a_{di} = 2a_{dd}^{1/2}a_{ii}^{1/2} \quad (16)$$

Then

$$E_I = (a_{dd}^{1/2}\mu_X^2 + a_{ii}^{1/2}MR_X)^2 - a^*\mu_X^2 MR_X \quad (17)$$

If

$$a^*\mu_X^2 MR_X \ll (a_{dd}^{1/2}\mu_X^2 + a_{ii}^{1/2}MR_X)^2 \quad (18)$$

then

$$E_T \cong (a_{dd}^{1/2}\mu_X^2 + a_{ii}^{1/2}MR_X)^2 \quad (19)$$

and

$$E_T^{1/2} = a_{dd}^{1/2}\mu_X^2 + a_{ii}^{1/2}MR_X \cong m[(a/b)^{1/2}] \quad (20)$$

The largest value that $a^*\mu_X^2 MR_X$ can have, which occurs when the Debye force is zero is

$$(a^*\mu_X^2 MR_X)_{max} = 2a_{dd}^{1/2}a_{ii}^{1/2}\mu_X^2 MR_X = 2E_{dd}^{1/2}E_{ii}^{1/2} \quad (21)$$

In general

$$E_{ii} \gg E_{dd} \gg E_{di} \quad (22)$$

This is particularly true of the large polar molecules. Then

$$E_{ii} \gg 2E_{dd}^{1/2}E_{ii}^{1/2} \quad (23)$$

and eq 20 should be valid in most cases.

We have shown that for the symmetric X, the dipole moment is given by

$$\mu_{XG} = L\sigma_I + D\sigma_R + h \quad (24)$$

When G is alkyl, the value of P_R, the percent delocalized (resonance) effect, given by[19]

$$P_R = (D \cdot 100)/(L + D) \quad (25)$$

is approximately equal to the P_R value for the σ_m constants. Then

$$\mu_X = \rho|\sigma_{mX}| + h \quad (26)$$

Substituting eq 26 in eq 20, we obtain

$$E_T^{1/2} = a_{dd}^{1/2}(\rho^2\sigma_{mX}^2 + 2\rho_G\sigma_{mX}h_G + h_G^2) + a_{ii}^{1/2}MR_X \quad (27)$$

or

$$(a/b)^{1/2} = a_1\sigma_{mX}^2 + a_2|\sigma_{mX}| + a_3 MR_X + a_0 \quad (28)$$

We have correlated the data for the XG sets in Table IV with eq 28. Values of $100R^2$ are given in Table V. The complete results are given in Table VIII of the supplementary material. Significant correlations were obtained for the alkyl derivatives; in fact, the results are better than those obtained for correlation with eq 13. The correlation equations account for >83% of the variance of the data. In four of the five sets, a_1 values are not significant. This is due to the strong correlation between σ_m^2 and σ_m. The benzene derivatives are again poorly correlated. If we discard the σ^2 term, we obtain eq 29. Values

$$(a/b)^{1/2} = a_2|\sigma_{mX}| + a_3 MR_X + a_0 \quad (29)$$

of $100R^2$ for the correlations of alkyl derivatives with this equation are given in Table V. The complete results are given in Table IX of the supplementary material. The correlations obtained are about as good as those resulting from the use of eq 28; they account for ≧83% of the variance of the data. The results of the correlations with both eq 28 and 29 show that the MR term is dominant, as is seen by comparing the values of F_C which are given by

$$F_C = a_i(w_{max} - w_{min}) \quad (30)$$

where a_i is the regression coefficient of the variable w_i and $w_{i,max}$ and $w_{i,min}$ are the maximum and minimum values, respectively, of w_i. The dominance of the term in MR is in accord with eq 22.

We may now draw some conclusions from these results. We have shown that parachor, molar refractivity, molar volume, volume obtained from Traube's rule, and van der Waals volume are all interrelated. The relationship between the molar refractivities of alkyl groups and van der Waals volume is excellent and can be used to estimate MR values of alkyl groups from the corresponding V_W values. Molecular weight is not a function of volume; it is dependent on the total number of electrons in the substituent and therefore is best considered as a crude polarizability parameter. The steric effects observed in simple organic reactions are directionally dependent for nonsymmetric substituents. It is therefore unlikely that "volume" parameters are a measure of steric effects as the term is used in physical organic chemistry. These parameters may represent either the group polarizability, in which case they account for a London interaction between the biologically active molecule(s) and a receptor site, or a hydrophobicity term in which the volume is acting as a crude measure of the surface area. They may therefore be a measure of the number of water molecules surrounding the substituent which are lost when the S-receptor complex is formed. The successful correlation of the a/b ratios with eq 13, 28, and 29 demonstrates clearly that in a simple nonbiological system MR (or any of the other "volume" parameters) can be used as a polarizability parameter since in these data volume is not

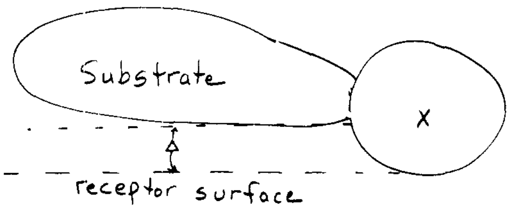

Figure 4. Cross section of the substrate–receptor complex.

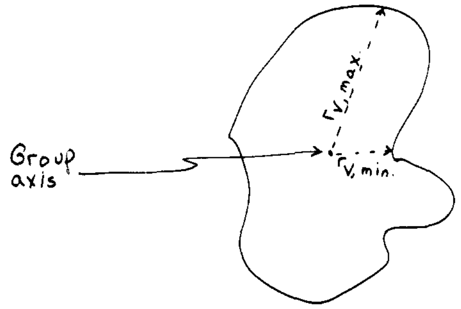

Figure 5. Cross section of the X group perpendicular to the group axis.

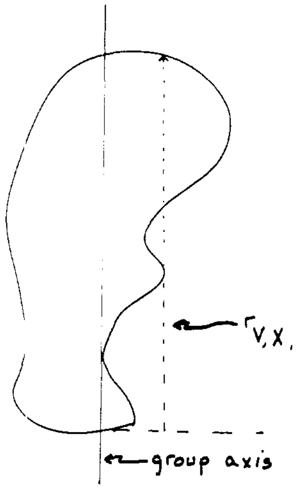

Figure 6. Cross section of the X group including the group axis.

involved and steric effects are not present.

It has been suggested that there may be "steric" effects in biological systems which are entirely different from those encountered in ordinary chemical reactions and that such effects may indeed be volume dependent. We would like to suggest that in biological systems two sources of steric effects are possible: those which are entirely analogous to the steric effects encountered in ordinary chemical reactions, and those which are due to the formation of a complex between the substrate and some receptor site. If the receptor site resembles a planar surface, the steric effect of a group attached to the substrate will depend on how far it extends beyond the rest of the substrate. Its steric effect will therefore be directional, as are the steric effects in ordinary chemical reactions (see Figure 4). If the receptor site is a hole or depression, the steric effect of the attached group X will be dependent on its minimum and maximum perpendicular van der Waals radii and its parallel van der Waals radius (see Figures 5 and 6). Unless the group has considerable symmetry, its appropriate van der Waals radii will not be a simple function of its volume. It follows then that even in a biological system a dependence of steric effects on group volume is not likely.

We suggest that the significance of volume or bulk parameters in QSAR is that they represent some kind of bonding interaction between the biologically active molecule and the receptor site contributing to the formation of a complex and that steric effects (in the sense normally used in physical organic chemistry) are *not* involved.

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Supplementary Material Available: Results of correlations with eq 1 (Table VI), 13 (Table VII), 28 (Table VIII), and 29 (Table IX) (3 pages). Ordering information is given on any current masthead page.

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Cycloadditions with Quadricyclane. Synthesis of Fused-Ring 1,2-Diazetidines

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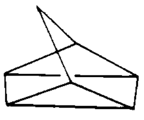
The unique chemical reactivity of molecules containing strained σ bonds has been of considerable experimental and theoretical interest to organic chemists. Most notable of these highly reactive compounds are bicyclo[2.1.0]pentane,[1] bicyclobutanes,[2] and tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane[3] (quadricyclane, Q). The $[2_\pi + 2_\sigma + 2_\sigma]$ cycloadditions of quadricyclane with a variety of dienophiles[3,4] suggest significant interaction



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