4.83; N, 5.16; S, 11.82. Found: C, 66.10; H, 5.23; N, 5.20; S, 11.93.

***endo*-7-Thiabicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Acid Anhydride (3).** 2*H*-Thiopyran[4] (0.50 g, 5.1 mmol), maleic anhydride (0.50 g, 5.1 mmol) and xylene (about 1 mL) were sealed in a glass tube under vacuum. The sample was heated at 150 °C for 2 h and cooled to give a black tarry mixture. Isolation and purification by chromatography on silica gel using benzene gave 3 (0.19 g, 0.97 mmol, 19%). An analytical sample was prepared by repeated recrystallization from methylcyclohexane: mp 148–148.5 °C; NMR ($CDCl_3$) δ 2.62 (d of d, 1 H, J = 10, 3 Hz, H-8′), 3.10 (d of d, 1 H, J = 10, 3 Hz, H-8), 3.22 (d of d, 1 H, J = 9, 3 Hz, H-3), 3.65 (m, 1 H, H-4), 3.70 (d of d, 1 H, J = 9, 3 Hz, H-2), 4.02 (d of d of d, 1 H, J = 7, 4, 2 Hz, H-1), δ 6.28 (d of d of d, 1 H, J = 8, 7, 2 Hz, H-5), 6.58 (d of d of d, 1 H, J = 8, 7, 2 Hz, H-6); IR (KBr) 1770 cm^{-1} (very strong), 1850, 1220, 1070 cm^{-1} (all strong); mass spectrum *m/e* 196 (parent). Anal. Calcd for $C_9H_8O_3S$ (196.22): C, 55.09; H, 4.11; S, 16.34. Found: C, 55.04; H, 4.17; S, 16.58.

Methyl *endo*-7-Thiabicyclo[2.2.2]oct-5-ene-2-carboxylate (4). 2*H*-Thiopyran[4] (1.69 g, 17.2 mmol) and methyl acrylate (1.55 g, 18.0 mmol) were sealed in a glass tube under vacuum and heated at 150 °C for 36 h. Distillation (bp 100–170 °C (1 torr)) gave 4 (1.28 g, about 80% pure by NMR, 32%) which was further purified by preparative gas chromatography at 180 °C: NMR ($CDCl_3$) δ 1.75–1.97 (m, 2 H, H-3, 3′), 2.27–2.68 (m, 1 H, H-8′), 2.85–3.35 (m, 3 H, H-2, -4, -8), 3.64 (s, 3 H, -OCH_3), 3.78 (d of d of d, 1 H, J = 8, 5, 2 Hz, H-1), 6.06–6.60 (m, 2 H, H-5, -6); IR (neat) 1735, 1210, 1180 cm^{-1} (all strong); mass spectrum *m/e* 184 (parent). Anal. Calcd for $C_9H_{12}O_2S$ (184.26): C, 58.67; H, 6.56; S, 17.40. Found: C, 58.43; H, 6.79; S, 17.64.

***cis,trans*-3-Methyl-*N*-phenylcyclohexane-1,2-dicarboximide (5).** Adduct **2** (0.25 g, 0.92 mmol), Raney nickel[5] (about 2 mL), and ethanol (15 mL) were heated at reflux for 10 min and filtered through Celite. The Celite was washed with hot ethanol and the ethanol portions were concentrated at reduced pressure. The product was recrystallized (methylcyclohexane, charcoal) to give 0.12 g (0.49 mmol, 54%) of product: mp 108.5–110 °C; NMR ($CDCl_3$) δ 1.24 (d, 3 H, J = 6 Hz), 1.0–2.0 (broad signal, 6 H), 2.25 (broad signal, 1 H), 2.57 (m, 1 H), 3.1 (broad signal, 1 H), 7.36 (m, 5 H); mass spectrum *m/e* 243 (parent).

***cis,cis*-3-Methyl-*N*-phenylcyclohex-4-ene-1,2-dicarboximide (6).** *N*-Phenylmaleimide (1.00 g, 5.8 mmol) and *trans*-piperylene (0.59 g, 8.7 mmol) were sealed in a tube under vacuum and heated for 1 h at 150 °C. The resulting solid was recrystallized (methylcyclohexane, charcoal) to give 0.96 g (4.0 mmol, 69%) of product, mp 116.5–117 °C (lit.[6] mp 116–117 °C).

***cis,cis*-3-Methyl-*N*-phenylcyclohexane-1,2-dicarboximide (7).** Adduct **6** (0.25 g), Raney nickel (about 2 mL), and ethanol (15 mL) were heated at reflux for 10 min and filtered through Celite. The Celite was washed with hot ethanol (2 × 15 mL), and the ethanol portions were concentrated at reduced pressure. Two recrystallizations (methylcyclohexane, charcoal) gave white needles: mp 90 °C; NMR ($CDCl_3$) δ 2.22 (d, 3 H, J = 7 Hz), 1.0–2.4 (broad signal, 7 H), 2.98 (m, 2 H), 7.04 (m, 5 H); mass spectrum *m/e* 243 (parent); mmp (with **5**) 85–87 °C.

Reduction of 4. Adduct 4 (0.55 g), Raney nickel (about 6 mL), and ethanol (15 mL) were heated at reflux for 45 min and filtered through Celite. The Celite was washed with hot ethanol, and the combined ethanol fractions were concentrated at reduced pressure. The resulting liquid was purified by preparative gas chromatography (column temperature 150 °C) to give methyl 3-methylcyclohexanecarboxylate.

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Registry No.—1, 289-72-5; **2,** 69927-41-9; **3,** 69979-92-6; **4,** 69927-42-0; **5,** 53288-19-0; **6,** 69979-93-7; **7,** 53288-20-3; *N*-phenylmaleimide, 941-69-5; maleic anhydride, 108-31-6; methyl acrylate, 96-33-3; *trans*-piperylene, 2004-70-8; *trans*-methyl methylcyclohexanecarboxylate, 7605-53-0.

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Absolute Configurations and Rotations of *trans*-3,5-Dimethylcyclohexanone, *trans*-3,5-Dimethylcyclohexene, and *trans*-1,3-Dimethylcyclohexane

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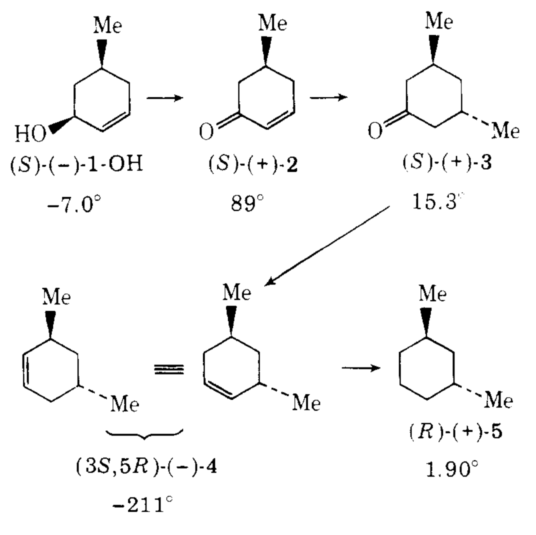
In another study it became important to know the absolute configuration and rotation of *trans*-3,5-dimethylcyclohexene (4). This paper describes the correlations that provide this information. We have also converted active 4 to *trans*-1,3-dimethylcyclohexane (5) to establish the absolute rotation and configuration of the latter.

The optical configuration and rotation of 4 were correlated with 5-methyl-2-cyclohexenone (2) as outlined in Scheme I. Optically active 5-methyl-2-cyclohexenone (2) was prepared from active *cis*-5-methyl-2-cyclohexenol (1-OH)[1] by oxidation with manganese dioxide as reported earlier.[2] It has been shown[2] that this reaction proceeds with complete preservation of optical configuration. The absolute rotation for 1-OH (7.0°)[1,3] was originally determined by complete resolution, and in this work we have confirmed this value by direct determination of enantiomeric compositions of active 1-OH with a chiral NMR shift reagent, tris(heptafluorobutyrylcamphorato)europium, $Eu(hfbc)_3$.[4] For example, a sample of 1-OH, $[\alpha]^{25}{}_{\mathrm{D}}$ −2.32°, was found to be 34 ± 0.5% optically pure and a sample of (−)-1-OAc, found to be 52% optically pure with $Eu(hfbc)_3$, was converted to (+)-2, $[\alpha]^{25}{}_{\mathrm{D}}$ 46°, which corresponds to 52% optical purity.[5] These experiments confirm the original absolute rotation for 2[2,5] as well as for 1-OH.[1] Attempts to determine enantiomeric compositions of active 2 and 3 with chiral NMR shift reagents[4] were unsuccessful. The absolute configuration of 2 was established earlier[2] by corre-

Scheme I



lation with active 3-methylcyclohexanone. The absolute rotations in Scheme I are $[\alpha]^{25}_{\mathrm{D}}$ (neat).[3]

Optically active **2** was converted to 3,5-dimethylcyclohexanone by conjugate addition of lithium dimethylcuprate according to the method reported by House and Fischer.[6] They observed that this reaction is stereoselective and that **2** gives **3** consisting of ~98% trans isomer. Under these conditions (*S*)-**2** gives (+)-**3** which thus has the 3*S*,5*S* configuration. A distinguishing feature of this correlation is that the cis contaminant is meso and thus it and all subsequent compounds derived from it are optically inactive. Thus observed rotations for **3**, **4**, and **5** can be corrected for contamination by inactive cis isomer. In all cases, the amount of cis isomer in the sample can be determined by capillary gas chromatography.

Optically active **3** was converted to active **4** by a method developed by Shapiro[7] which involves reaction of tosylhydrazone derivative of the ketone with methyllithium. In this manner (*S*)-(+)-**3** was converted to (−)-**4** which thus has the 3*S*,5*R* configuration.

Hydrogenation of (3*S*,5*R*)-(−)-**4** gives (+)-*trans*-1,3-dimethylcyclohexane (**5**). This shows that the latter has the *R* configuration. In an earlier study Mousseron and Granger[8] prepared (+)-**5** by hydrogenation of a mixture of (+)-1,3- and (+)-2,4-dimethylcyclohexene obtained by dehydration of active 1,3-dimethylcyclohexanol.[9] The latter was prepared from 3-methylcyclohexanone derived from (+)-pulegone. The latter is now known to have the *R* configuration;[10] thus the correlation of (+)-**5** with (*S*)-(+)-**2** in Scheme I is in agreement with the correlation of (+)-**5** with (*R*)-(+)-pulegone and (and (*R*)-(+)-3-methylcyclohexanone[11]) that by Mousseron and Granger.

Experimental Section

Materials. *cis*-5-Methylcyclohexenol (1-OH) was prepared and resolved as reported previously:[1] ^{13}C NMR ($(CD_3)_2CO$) δ (from Me_4Si) 67.6 (C-1), 127.2 (C-2), 132.7 (C-3), 41.7 (C-4), 28.6 (C-5), 34.2 (C-6), 22.3 (CH_3); ^{1}H NMR (CCl_4) δ 1.0 (d, 3 H), 1.4–2.2 (m, 5 H), 4.1–4.3 (m, 1 H), 4.2 (s, 1 H), 5.6 (s, 2 H). With $Eu(hfbc)_3$[4] $\Delta\Delta\delta = 0.49$ for the α-H with $R/S = 0.6$. A sample of (−)-**1-OH**, $[\alpha]^{25}_{\mathrm{D}}$ −2.32°,[3] was found to be 34 ± 0.5% optically pure with this shift reagent.[12]

Racemic and optically active **5-methyl-2-cyclohexenone (2)** was prepared from **1-OH** by oxidation with MnO_2.[2] ^{13}C NMR ($CDCl_3$): δ 199.4 (C-1), 129.4 (C-2), 149.7 (C-3), 33.9 (C-4), 30.3 (C-5), 46.2 (C-6), 21.1 (CH_3); ^{1}H NMR agrees with published data.[6] Optically active **2** derived from the above **1-OH**, $[\alpha]^{25}_{\mathrm{D}}$ −2.32,[3] had $[\alpha]^{25}_{\mathrm{D}}$ 43° (*c* 1.6 $CHCl_3$); ORD plain positive.[12,13] A sample of **1-OH**, $[\alpha]^{25}_{\mathrm{D}}$ 1.50° (21% optically pure[2]), gave **2**, $[\alpha]^{25}_{\mathrm{D}}$ −17.4°[3] (20% optically pure[2,5]). An impure sample of (−)-**1-OH**, which gave **1-OAc** shown to be 52% optically pure with $Eu(hfbc)_3$ with $R/S = 0.3$,[4] gave (+)-**2**, $[\alpha]^{25}_{\mathrm{D}}$ 45.9°.[3] This agrees well with the absolute rotation of $[\alpha]^{25}_{\mathrm{D}}$ 89° determined earlier.[5] The optical purity of active **2** could not be determined directly since $Eu(hfbc)_3$ or $Eu(facam)_3$ gave no shift differences for enantiomers.

Correlation of Optically Active 5-Methyl-2-cyclohexenone (2) and *trans*-3,5-Dimethylcyclohexanone (3). Both racemic and optically active **2** were converted to **3** by addition of lithium dimethylcuprate at 0 °C as described previously.[6] The NMR and MS spectra were in agreement with the published data. ^{13}C NMR (C_6D_6): δ 208.6 (C-1), 48.6 (C-2 and −6), 29.6 (C-3 and -5), 39.6 (C-4), 20.9 (CH_3). A sample of (*S*)-(+)-**2**, $[\alpha]^{25}_{\mathrm{D}}$ 43° (*c* 1.6 $CHCl_3$), gave (*S*)-(+)-**3**[12] in 80% yield after purification by preparative GC (5 ft × 1/4 in., 10% FFAP on Chromosorb W) which had $[\alpha]^{25}_{\mathrm{D}}$ 3.92° (*c* 1, $CHCl_3$); negative Cotton effect.[13] Capillary GC (300 ft Ucon Polar) showed that the active sample had 2% of the meso cis isomer.

In another experiment, (*S*)-(+)-**2**, $[\alpha]^{25}_{\mathrm{D}}$ 45.9°[3] (52% optically pure), gave (*S*)-(+)-**3**, bp 63 °C (9.6 mm), $[\alpha]^{25}_{\mathrm{D}}$ 7.9° (corrected for 3% meso isomer shown by capillary GC, 200 ft Ucon LB-2000). This gives a calculated absolute rotation of $[\alpha]^{25}_{\mathrm{D}}$ 15.3°[3] for **3**. The enantiomeric composition could not be determined directly with $Eu(facam)_3$ or $Eu(hfbc)_3$ because of unsuitable shift differences for the enantiomers.

Correlation of Optically Active *trans*-3,5-Dimethylcyclohexanone (3) and *trans*-3,5-Dimethylcyclohexene (4). Racemic **3** was converted to the tosylhydrazone derivative in 85–91% yield by the method reported by Shapiro and Dauben and co-workers.[7b] After purification by recrystallization from ether, the white solid had the following: mp 120–121 °C dec; ^{13}C NMR ($(CD_3)_2CO$) δ 144 (C-1), 39.8 (C-2 and -6), 30 (C-3 and -5), 21.4 (C-4), 21.0 (CH_3); ^{1}H NMR ($CDCl_3$) δ 0.8 (d, 6 H), 1.4 (m, 2 H), 1.75–2.4 (m, 6 H), 2.42 (s, 3 H), 7.3–7.9 (q, 4 H), 8.2 (bs, 1 H).

Anal. Calcd for $C_{15}H_{22}N_2SO_2$: C, 61.19; H, 7.53. Found: C, 60.95; H, 7.52. Mass spectrum: mass (rel intensity) 294 (4.1), 157 (14.3), 140 (14.1), 139 (100), 109 (15.6), 95 (53.4), 91 (36.3), 55 (26.4), and 41 (28.3).

The conversion of the tosylhydrazone derivative of **3** to *trans*-3,5-dimethylcyclohexene (**4**) with methyllithium proceeded smoothly using a published procedure.[7b] The product was purified by preparative GC (XF-1150 on 60/80 on Chromosorb W). Capillary GC (275 ft, DC-710) showed the product **4** contained ~1% of the cis isomer. ^{13}C NMR ($CDCl_3$): δ 125.3 (C-1), 132.6 (C-2), 28.6 (C-3), 33.6 (C-4), 24.5 (C-5), 38.1 (C-6), 21.4 (3-Me), 21.6 (5-Me). ^{1}H NMR (CCl_4): δ 1.0 (d, 3 H), 1.05 (d, 3 H), 1.1–1.2 (m, 6 H), 5.6 (s, 2 H).

Anal. Calcd for C_8H_{19}: C, 87.19; H, 12.81. Found: C, 86.8; H, 13.2.

Optically active **3** was converted to **4** in the same manner except that to avoid optical fractionation the tosylhydrazone derivative of **3** was not recrystallized and the product, active **4**, was purified by fractionation with a spinning band column (bp 80 °C). In one experiment (*S*)-(+)-**3**, $[\alpha]^{25}_{\mathrm{D}}$ 7.9° (52% optically pure), gave (3*S*,5*R*)-(−)-**4**, $[\alpha]^{25}_{\mathrm{D}}$ −109°,[3] $[\alpha]^{25}_{\mathrm{D}}$ −115° (*c* 4, $CHCl_3$), both corrected for contamination by 2% inactive cis isomer and 2% toluene. In other experiments, 34% optically pure (+)-**3** gave (−)-**4**, $[\alpha]^{25}_{\mathrm{D}}$ −73.4° (*c* 7.6 $CHCl_3$), and 20% optically pure (−)-**3** gave (+)-**4**, $[\alpha]^{25}_{\mathrm{D}}$ 43.2° (*c*, 8, $CHCl_3$). From these correlations we obtain the following absolute rotations for **4**, $[\alpha]^{25}_{\mathrm{D}}$ 211° (neat) and 215° ($CHCl_3$).[12]

Correlation of Optically Active 5-Methyl-2-cyclohexenone (2) and *trans*-1,3-Dimethylcyclohexane (5). An acetic acid solution of racemic *trans*-3,5-dimethylcyclohexene (**4**)[14] containing 1% cis isomer (100 ft SE-30 capillary column) was hydrogenated in a Parr shaker over platinum oxide at an initial pressure of 40 psi. Hydrogen uptake was rapid. The solution was filtered, diluted with three volumes of water, and extracted with pentane; the dried (Na_2CO_3) pentane extract was concentrated with a fractionation column. Comparison with authentic samples of *cis*- and *trans*-1,3-dimethylcyclohexane (Chem Samples) showed the reduction product to be 99% *trans*- and 1% *cis*-1,3-dimethylcyclohexane. The product had n^{25}_{D} 1.4286 (lit.[8] 1.4265). The ^{13}C and ^{1}H NMR spectra corresponded to published spectra for *trans*-1,3-dimethylcyclohexane (**5**).[15,16]

To establish the absolute rotation and configuration of **5**, (*S*)-(+)-**2**, $[\alpha]^{25}_{\mathrm{D}}$ 32.96°[3] (37% optically pure),[5] was converted to (*R*)-(+)-**5**, $[\alpha]^{25}_{\mathrm{D}}$ 70° (corrected for dilution with 5% meso isomer), without purification of the intermediates, (*S*)-(+)-**3** and (3*S*,5*R*)-(−)-**4**. The (+)-**5** was purified by fractionation, bp 123 °C, and GC with a 100 ft SE-30 capillary column showed the product to contain 4% of the cis isomer. These data show the absolute rotation of **5** to be ~1.9°.[3]

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Registry No.—(+−)-1-OH, 69653-39-0; (S1-(−)-1-OH, 69685-64-9; (+−)-**2**, 54352,35-1; (*S*)-(+)-**2**, 15466,88-3; (+−)-**3**, 54307-72-1; (*S*)-(+)-**3**, 69685-65-0; (+−)-3-tosylhydrazone, 69653-40-3; (+−)-**4**, 69653-41-4; (3*S*,5*R*)-(−)-**4**, 69685-66-1; (+−)-**5**, 69685-67-2; (*R*)-(+)-**5**, 69685-68-3.

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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

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

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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