Examination of the Interrelationship Between Aliphatic Group Dipole Moment and Polar Substituent Constants

WEN-YEN LI, ')NG-RU GUO, and ERIC J. LIEN ×

Received February 1 33, from the *Section of Biomedicinal Chemistry, School of Pharmacy, University of Southern California, Los Angeles, CA 90033.* Acceptec ›ublication March 29, 1983.

Abstract □ The relationships between 210 aliphatic group dipole moments (μ) and Taft polar constants (σ^*) are explored, and they are shown to be correlated by a general equation: $\mu = -a \cdot \sigma^* - b \cdot n' - c$, where a, b, and c are constants. The value n' is a parameter reflecting the attenuating factor due to the number and electronic nature of the interval atoms between the most electronegative atom and the first atom connected to the acetate in the measurement of σ^*. The μ and σ^* values of over 214 aliphatic substituents are compiled for future correlation studies. Comparative examples using σ^* and μ in quantitative structure-activity relationships are presented.

Keyphrases □ Dipole moment—aliphatic group, correlation with Taft polar substituent constants, quantitative structure-activity relationships □ Taft polar substituent constants—correlation with aliphatic group dipole moment, quantitative structure-activity relationships □ Quantitative structure-activity relationships—interrelationships between aliphatic group dipole moment and Taft polar substituent constants, applications

In addition to the electronic parameters like the Hammett σ constant and Taft polar constant (σ^*), the group dipole moment, a free energy-related parameter, has been used to study drug-receptor interactions and quantitative structure-activity relationships, especially if σ or other electronic parameters fail to give meaningful correlations (1). It has been reported (1) that the correlation between the aromatic group dipole moment (μ) and σ_m or σ_p varies drastically, or fails completely, if noncongeneric groups are pooled together.

The Taft polar constant (σ^*), which describes mainly the magnitude of inductive electron-withdrawing power of the substituent in the aliphatic system X—CH_2COOR on the reactive center, is defined by (1):

$$\sigma^* = (1/2.48)[\log (K_X/K_0)_B - \log (K_X/K_0)_A] \quad \text{(Eq. 1)}$$

in which B and A designate base- and acid-catalyzed hydrolyses of the ester with the substituent α to the carbonyl group. Although there are problems associated with the definition of σ^*, it is a reasonably accurate measure of the inductive effect, *i.e.*, the inductive electron-withdrawing power of an atom or group of atoms in a molecule. One may expect a better correlation between the aliphatic dipole moment μ, a measure of the charge separation in the group, and σ^* than that of μ and σ_m or σ_p. There have been some reports about the correlation of σ^* values with dipole moments (2), but they mainly involve some limited congeneric series of substituents. The present report attempts to make a wider exploration of the problem and to compile a table of aliphatic group dipole moments and σ^* for future use in correlation studies.

EXPERIMENTAL

A total of 214 substituent groups (for which both μ and σ^* were available) were analyzed to examine the relationship between μ and σ^*. Taft polar constants (σ^*) were taken from Hansch and Leo (3) and Perrin (4). The aliphatic group dipole moments (μ) were taken from the corresponding aliphatic molecular dipole moments (5), where the group is attached to an alkyl group, $CH_3(CH_2)_n$ — X (n = 0–6), assuming the dipole moment value of the alkyl group to be zero. The sign is assigned by comparison of the electronegativities between the substituent and the alkyl group to which the substituent group is connected. A negative sign indicates an electron-withdrawing group. All the regression lines were derived by a computer[1] *via* the method of nonweighted least-squares fit.

RESULTS AND DISCUSSION

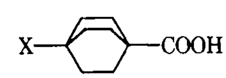
Equation 2 shows the overall correlation between σ^* and μ of 214 substituent groups:

$$\mu = -0.676\sigma^* - 1.055$$

$$n = 214 \quad r = 0.583 \quad s = 1.031 \quad \text{(Eq. 2)}$$

It is obvious that the correlation is not good, and only 34% ($r^2 = 0.34$) of the variance in the data can be explained by this equation. Since the exact number of n in $CH_3(CH_2)_nR$ will not affect the dipole moment, but will affect the σ^* value of such an $R(CH_2)_n$ group attached to an acetate used in the acid- and base-catalyzed hydrolyses, the attenuated polar effect due to different n values needs to be corrected.

According to an alternative approach to the definition of localized effect, a new parameter σ' was proposed by Roberts and Moreland (6) using the pK_a of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids:



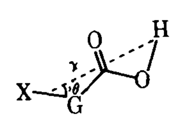
where

$$\sigma'X = \frac{-pK_X + pK_H}{\rho'} \quad \text{(Eq. 3)}$$

Kirkwood and Westheimer used Eq. 4 to describe the effect of the substituent on the acid strength of a series of XG—COOH (7):

$$\log K_X/K_H = \frac{c\mu_x \cdot \cos\theta}{2.303 \cdot RTD \cdot r^2} \quad \text{(Eq. 4)}$$

where c is the electric charge on the proton, μ_x is the moment of the X—G bond, r is the distance between the proton and the center of the dipole, θ is the angle made by the distance r and the X—G bond, and D is the dielectric constant.



Combining Eq. 4 with the Hammett equation, one obtains (7):

$$\rho' \cdot \sigma_x = \frac{c\mu_x \cdot \cos\theta}{2.303 \cdot RTD \cdot r^2} \quad \text{(Eq. 5)}$$

Equation 5 indicates that the localized effect of the constituent group is not only dependent on its dipole moment, but also inversely proportional to the square of the distance from the center of the dipole to the reaction site. Accurately determining the distance and the electrical effect of G between X and the reaction site is not easy. The polar effect of the substituent group is some combination of the inductive (through a bond) and field (through space) effects; therefore, the interval atom number between the most electronegative atom (where the negative inductive effect predominates) and the first atom of the group connecting the reaction site in the measurement of σ^*, as well as their electronic character, need to be considerd to fully reflect the effect of G on the magnitude of σ^*. This requires the addition of an attenuating parameter in correlating μ with σ^*.

Each interval atom exerts a shielding effect to transmit the inductive electron-withdrawing power as measured by σ^*. The higher the interval atom number (n), the greater will be the total shielding effect. When going over three —CH_2— the inductive effect of the group becomes insignificant.

[1] Model 370/185; IBM.

0022-3549/84/0400-0553$01.00/0

Table I—Correlation Equations for Anticonvulsant Activity of Substituted Benzyl *N,N*-Dimethyl Carbamates

a	b	c	Constant	n	r	s	$F_{1,x}$[a]	Eq. No.
$-\log ED_{50} = -a(\log p)^2 + b(\log p) + c\cdot\sigma +$ constant								
0.191	0.795		2.541	20	0.702	0.212		12
0.200	0.836	−0.150	2.252	20	0.720	0.213	$F_{1,16} < 0$	13
0.217	0.905		2.481	18	0.814	0.175		14
0.245	1.040	−0.324	2.392	18	0.876	0.150	$F_{1,14} = 6.3$	15
$-\log ED_{50} = -a(\log p)^2 + b(\log p) + c\cdot\mu_{ph} +$ constant								
0.219	0.898	0.077	2.565	20	0.801	0.183	$F_{1,16} = 6.4$	16
0.213	0.882		2.499	18	0.800	0.182		17
0.262	1.077	0.102	2.486	18	0.940	0.106	$F_{1,14} = 29.4$	18
$-\log ED_{50} = -a(\log p)^2 + b(\log p) + c\cdot\sigma^* +$ constant								
0.212	0.895	−0.208	2.575	20	0.740	0.206	$F_{1,16} = 2.08$	19
0.217	0.905		2.481	18	0.814	0.175		20
0.250	1.058	−0.253	2.501	18	0.860	0.158	$F_{1,14} = 4.42$	21
$-\log ED_{50} = -a(\log p)^2 + b(\log p) + c\cdot\mu +$ constant								
0.205	0.758	0.129	2.965	20	0.891	0.139	$F_{1,16} = 22.4$	22
0.217	0.905		2.481	18	0.814	0.175		23
0.226	0.861	0.118	2.863	18	0.946	0.102	$F_{1,14} = 30.8$	24

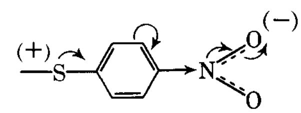
[a] $F_{1,16;0.95} = 4.49$; $F_{1,14;0.95} = 4.60$; $F_{1,16;0.99} = 8.53$; $F_{1,14;0.99} = 8.86$.

However, different types or locations of the interval atom will have different electronic environments which may produce different shielding effects. Thus, n' as an attenuating parameter reflecting the environmental factor of G should not only be the atom number, but be determined on the basis of its contribution to the electron-withdrawing power. Among the environmental factors contributing appreciably to the electron-withdrawing power, the intrinsic electronegativity of the atoms is the most important. If the interval atoms are such that their electronegativity is higher than an sp^3-hybrid carbon atom ($—CH_2—$) such as O, N, S, sp^2-, sp-hybrid carbon atom, or the sp^3-carbon atom attached by two electronegative atoms ($—CCl_2—$, $—CBr_2—$) or groups like NO_2, $—C_6H_5$, their shielding effect is smaller than that of $—CH_2—$. This is not only due to electron delocalization of p or d orbitals formed for transmission of inductive action, but also the additive inductive effect on their neighboring atom. Generally, this effect can be shown by causing a downfield shift in NMR spectrum of the proton attached to these atoms. Daily and Shoolery (8) have proposed a scale of electronegativity of substituent groups obtained from shifts in the NMR spectra of ethyl and methyl derivatives; it was strikingly demonstrated that the electronegativities obtained in this manner are essentially equal to the electronegativities of the Pauling scale of the first atom in the group.

For the reasons mentioned above, the following rough rules are suggested as an initial premise to determine the n' values introduced into the regression analysis as a parameter:

1. For each $—CH_2—$ and other atom that has less electronegativity than a carbon atom, $n' = 1$.
2. For N, S, —CH=CH—, —C≡C—, =C=O, and carbon atoms to which two halogen atoms or electronegative groups are attached simultaneously, n' = 0.5 each. For the conjugated system $—C_6H_4—$, —CH=CH—CH=CH—, and —CH=CH—, $n' = 1$.
3. Carbon or other atoms to which three or more oxygen or halogen atoms are attached are assigned $n' = 0$, for example, $—CCl_3$, $—SO_3R$.

The above method is employed to determine the n' values of each group. For example, with a *p*-nitrophenyl sulfide group, the $—NO_2$ withdraws electrons from all atoms, the negative pole of this group is toward oxygen atoms, the interval atoms include one sulfur atom ($n' = 0.5$), one benzine ring ($n' = 1$), and a nitrogen atom ($n' = 0.5$); therefore, the total $n' = 0.5 + 1 + 0.5 = 2.0$.



By introducing the n' into the regression analysis together with σ^* values, Eq. 6 was obtained:

$$\mu = -0.853\sigma^* - 1.045n' - 0.160$$
$$n = 214 \quad \gamma = 0.801 \quad s = 0.762 \qquad \text{(Eq. 6)}$$

Comparison with Eq. 2 shows that the correlation coefficient is markedly improved. An *F*-test indicates that the interval atom factor n' is statistically highly significant ($F_{1,211} = 171$) for studying the relationship between σ^* and μ.

By deleting those groups which deviate greater than 2 *SD* from this regression and by dividing the 210 substituents into two subgroups, the following equations were obtained. For subgroup I:

$$\mu = -0.687\sigma^* - 0.760$$
$$n = 177 \quad r = 0.686 \quad s = 0.755 \qquad \text{(Eq. 7)}$$
$$\mu = -0.853\sigma^* - 0.942n' - 0.028$$
$$n = 177 \quad r = 0.921 \quad s = 0.406 \qquad \text{(Eq. 8)}$$

Table II—Anticonvulsant Activity and Physicochemical Parameters of Substituted Benzyl *N,N*-Dimethyl Carbamates

X	$\log 1/ED_{50}$[a] Obs.	$\log 1/ED_{50}$[a] Calc.	log p[a]	σ[a]	μ_{ph}[b]	σ^*[c]	μ[c]
H	3.71	3.67	2.16	0.00	0.03	0.75	−0.38
p-CH_3	3.58	3.55	2.63	−0.15	0.36	0.59	−0.10
p-F	3.50	3.44	2.30	0.17	−1.43	0.81	−1.78
m-OCH_3	3.49	3.53	2.09	0.13	−0.65	0.62	−1.25
p-OCH_3	3.46	3.52	2.20	−0.12	−1.30	0.42	−1.23
m-NH_2	3.45	3.35	1.06	−0.14	0.80	0.16	−1.44
m-Cl	3.41	3.28	2.82	0.37	−0.80	0.85	−1.82
p-Cl	3.35	3.22	2.93	0.27	−1.59	0.92	−1.90
m-$N(CH_3)_2$	3.29[d]	3.46	2.28	−0.15	0.80	0.16	−1.60
m-O-*i*-Pr	3.21	3.35	2.80	0.04	−0.65	0.62	−1.25
p-OCH_2Ph	3.19[d,e]	3.09	3.27	−0.42	−1.35	0.42	−1.23
p-NO_2	3.19	3.16	1.95	0.82	−4.13	1.14	−4.43
p-CN	3.16	3.15	1.67	0.69	−4.08	1.05	−4.41
p-Br	3.15	3.18	3.01	0.26	−1.57	0.90	−1.91
p-I	3.14	3.02	3.32	0.27	−1.36	0.87	−1.76
p-CF_3	3.10	3.14	3.08	0.53	−2.61	0.96	−1.94
m-OPh	2.92	2.91	3.55	0.25	−0.58	0.35	−1.38
p-*tert*-Bu	2.47	2.55	4.14	−0.17	0.52	0.43	0.00
p-$OCON(CH_3)_2$	3.09	3.21	1.59	0.22	−3.70	1.40[f]	−3.90
p-SCH_3	2.88[e]	3.19	2.12	0.08	−1.34	0.66	−4.08

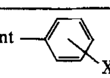
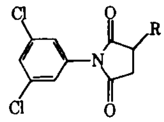
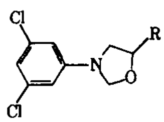
[a] Taken from Ref. 11; $\log 1/ED_{50}$ calculated using Eq. 24. [b] Value along the *para*-direction. [c] The value of substituent  [d] Outliers in Eq. 16. [e] Outliers in Eqs. 13, 19, and 22. [f] Calculated from Eq. 10.

Table III—Antifungal Activity and Physicochemical Parameters

R	pI_{50} Obs.[a]	pI_{50} Calc.[b]	Log MW	Log p[a]	μ



R	Obs.	Calc.	Log MW	Log p	μ
H	5.58	5.63	2.39	1.90	−0.02
Me	5.62	5.69	2.41	2.22	0.00
Et	5.73	5.77	2.44	2.76	0.00
n-Pr	5.83	5.85	2.46	3.30	0.08
Isopr	5.89	5.83	2.46	3.17	0.08
n-Bu	5.99	5.94	2.49	3.84	0.08
Ph	6.00	5.89	2.51	3.36	−0.38
S—Me	5.49	5.52	2.46	1.28	−1.45
S—Et	5.68	5.58	2.48	1.82	−1.47
S—*n*-Pr	5.70	5.64	2.50	2.36	−1.47
S—*n*-Bu	5.79	5.69	2.52	2.90	−1.47
S—*n*-Pent	5.65	5.75	2.54	3.44	−1.47
CH_2—S—Et	5.48	4.64	2.50	2.36	−1.47
CH_2—S—*n*-Pr	5.62	5.69	2.52	2.90	−1.47
CH_2—S—Isopr	5.68	5.69	2.52	2.77	−1.47
SOMe	5.06	5.10	2.49	−0.94	−3.88
SO—*n*-Pr	5.25	5.21	2.53	0.14	−3.88
SO_2Me	5.11	5.07	2.51	−1.37	−4.26
SO_2Et	5.27	5.13	2.53	−0.83	−4.26
SO_2—*n*-Pr	4.92	5.19	2.55	−0.29	−4.26
SO_2—*n*-Bu	5.15	5.22	2.56	0.25	−4.26
CH_2-SO_2-Et	5.38	5.19	2.55	−0.29	−4.26



R	Obs.	Calc.	Log MW	Log p	μ
H	5.47	5.63	2.39	2.77	−0.02
Me	5.80	5.69	2.41	3.09	0.00
Et	5.95	5.77	2.44	3.63	0.00
Isopr	5.83	5.83	2.46	4.04	0.08
tert-Bu	5.90	5.92	2.49	4.45	0.08
Ph	5.79	5.89	2.51	4.23	−0.38

[a] Taken from Ref. 12. [b] Calculated from Eq. 31.

For subgroup II:

$$\mu = -0.635\sigma^* - 2.666$$

$$n = 33 \quad r = 0.787 \quad s = 0.648 \qquad \text{(Eq. 9)}$$

$$\mu = -0.763\sigma^* - 0.853n' - 1.820$$

$$n = 33 \quad r = 0.940 \quad s = 0.366 \qquad \text{(Eq. 10)}$$

The first subgroup includes 180 substituent groups of no distinct structural relationship, but the second subgroup includes 33 substituent groups characterized structurally as amido, sulfonyl, sulfone, nitrophenyl, and amino groups.

All the equations have very similar slopes, and n' shows similar contribution to the overall correlation. Thus, the relationship between the dipole moment and polar substituent constant σ^* may be presented by the following:

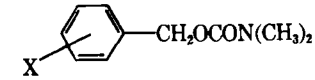
$$\mu = -a \cdot \sigma^* - b \cdot n' - c \qquad \text{(Eq. 11)}$$

n' is a complex factor including the number and electronic nature of the interval atoms. Whether n' can be expressed more accurately by the chemical shift values of these atoms in ^1H- or ^{13}C-NMR remains to be studied. Careful examination of the data shows that for practical application of the equation, the range of the value of n' is limited to 0–2.5, and the total value of n' generally should not be greater than the value of σ^* or μ to obtain a reasonable result (*Appendix*).

In Eq. 11, c is a constant representing the types of substituent groups. Substituents in the second subgroup, like amido, sulfonyl, sulfone, amino, and nitrophenyl groups, have considerably larger μ values with relatively small σ^* values. For amines and amides this may be due to the lone pair electron on the nitrogen atom decreasing the inductive electron-withdrawing power of C=O and SO_2—, while at the same time increasing the dipole moment through its resonance effect. For sulfonyl and sulfone groups, the relatively large dipole moment values may be due to presence of much larger mesomeric moments (9, 10).

On the basis of the correlations obtained, σ^* expresses the total electronic effect of the substituent, including the X and G in the group. Thus if interaction between drug and receptor is controlled by the total electronic nature (X + G) of the substituent through transmission toward the reactive site, σ^* constants may be a suitable descriptor of electronic effects for QSAR. If, on the other hand, the interaction is intermolecular in nature and is controlled directly by the electronic nature of the X portion of the substituent, then dipole moment μ as a measure of the charge separation in the group may give a more meaningful correlation.

For instance, Eqs. 12–24 (Table I) show the QSAR between the anticonvulsant activity and physicochemical parameters (Table II) of substituted benzyl *N*,*N*-dimethyl carbamates reported by Yamauea *et al.* (11):



Equations 13 and 15 were obtained by using simultaneously Hammett σ constant and Hansch's π, but in Eqs. 16 and 18, the aromatic group dipole moment μ_{ph} was used as an electronic parameter instead of σ. When the substituted benzene is regarded as an aliphatic substituent group of CH_3—$OCON(CH_3)_2$, Eqs. 19 and 21, and 22 and 24 are obtained by using *the Taft polar constant σ^* and aliphatic group dipole moment μ as the electronic parameters*, respectively.

According to the correlation coefficient and *F*-test, the dipole moment (whether aromatic group moment μ_{ph} or aliphatic group moment μ) gives a statistically more significant correlation than the Hammett σ or Taft σ^*. Among these electronic parameters used, the aliphatic group dipole moment seems to be the best, giving the highest degree of correlation in the case examined (Eq. 24).

Takayama *et al.* (12) reported the QSAR of antifungal 1-(3,5-dichlorophenyl)-2,5-pyrrolidinediones and 3-(3,5-dichlorophenyl)-2,4-oxazolidinediones and showed that the activity becomes greater with the increasing hydrophobicity of the substituents on the imido ring, independent of the electronic (σ^*) and steric effects (E_s) (Table III). Reexamination with aliphatic group dipole moment μ as an electronic parameter and log MW as a measure of bulk is shown by Eqs. 25–31 (Table IV). The correlation with μ or log p alone is statistically significant, although the improvement in regression with log p by introducing μ or log MW is generally not very significant ($F_{1,25}$ = 2.58 or 0.25, respectively) because of considerable covariance between log p and μ or μ and log MW. Among the two parameter equations, the combination of log MW and μ gives the highest correlation (Eq. 31), and the combination of log p and μ gives a slightly lower correlation (Eq. 30). The addition of log MW is statistically significant at the 99.9% level, as indicated by an *F*-test ($F_{1,25}$ = 21.80). This suggests that both the size of the molecule (13) and the dipole moment of the substituent group are important in determining the antifungal activity of the compounds examined.

The existence of the covariance among log p, log MW, and μ is shown in the following squared correlation matrix:

	log MW	log p	μ
log MW	1	0.13	0.50
log p		1	0.81
μ			1

Use of these three parameters simultaneously or the addition of (log p)^2 does not result in a further improvement in correlation.

Table IV—Equations Correlating Antifungal Activity with Physicochemical Constants

Equation	*n*	*r*	*s*	$F_{1,25}$	Eq. No.
$pI_{50} = -2.352(\log MW) + 11.442$	28	0.378	0.281		25
$pI_{50} = 0.153\mu + 2.582$	28	0.871	0.145		26
$pI_{50} = 0.158(\log p) + 5.258$	28	0.907	0.128		27
$pI_{50} = (\log p)^2 + 0.159(\log p) + 5.258$	28	0.907	0.130		28
$pI_{50} = -0.350(\log MW) + 0.155(\log p) + 6.133$	28	0.908	0.130	0.25	29
$pI_{50} = 0.113(\log p) + 0.050\mu + 5.428$	28	0.915	0.125	2.58	30
$pI_{50} = 2.879(\log MW) + 0.212\mu - 1.252$	28	0.934	0.111	21.80	31

Appendix Aliphatic Dipole Moments and Taft Polar Constants (σ*)
$CH_3(CH_2)_nR$, where *n* = 0–6

No.	Formula	R	*n*′	μR, Debye	σ*	WLN	Solvent[a]	Temp., °C
1	BH_2O_2	—$B(OH)_2$	0.5	−1.16	0.95	*BQQ	G	115
2	Br	—Br	0.0	−1.97	2.84	*E	CCl_4	25
3	Cl	—Cl	0.0	−1.93	2.68	*G	CCl_4	25
4	ClO_2S[b]	—SO_2Cl	0.0	−2.28	5.00	*SWG	B	25
5	Cl_2PS	—$PSCl_2$	0.0	−3.00	3.70	*PS&GG	B	20
6	ClS	—SCl	0.5	−2.00	2.50	*SG	G	—
7	F	—F	0.0	−1.90	3.21	*F	G	NS
8	FO_2S	—SO_2F	0.0	−3.39	4.70	*SWF	B	25
9	F_4P	—PF_4	0.0	−2.55	2.80	*PFFFF	G	31–70
10	I	—I	0.0	−1.79	2.46	*I	CCl_4	25
11	NHCHO	—NHCHO	1.0	−3.86	1.62	*MVH	B	25
12	NCO	—NCO	1.0	−2.81	2.25	*NCO	B	20
13	H_2NO	—NHOH	0.5	−0.80	0.30	*MQ	B	25
14	NH_2	—NH_2	0.0	−1.35	0.62	*Z	B,CHx	25
15	NO	—NO	0.5	−2.30	2.08	*NO	G	NS
16	NO_2	—NO_2	0.5	−3.59	4.25	*NW	G	20
17	NH_2O_2S	—SO_2NH_2	0.5	−4.60	2.61	*SWZ	D	30
18	NO_3	—ONO_2	0.5	−3.08	3.86	*ONW	G	−78
19	N_2H_3	—$NHNH_2$	0.5	−1.82	0.40	*MZ	G	25
20	N_3	—N=N=N	0.0	−2.17	2.62	*NNN	G	NS
21	OH	—OH	0.0	−1.66	1.55	*Q	B	25
22	SH	—SH	0.0	−1.51	1.68	*SH	B	25
23	SO_2CH_3	—$S(O)OCH_3$	0.5	−2.83	2.84	*SO&O1	B	25
24	SO_3CH_3	—SO_2CH_3	0.0	−4.16	3.62	*OSWI	D	25
25	$SeCH_3$	—$SeCH_3$	1.0	−1.41	0.95	*-Se-1	G	NS
26	CClO	—COCl	0.5	−2.48	1.81	*VG	CCl_4	25
27	CCl_3	—CCl_3	0.0	−1.84	2.65	*XGGG	CHx	25
28	CF_3	—CF_3	0.0	−1.94	2.61	*XFFF	B	25
29	CN	—CN	0.5	−3.63	3.30	*CN	B	30
30	CNS	—SCN	1.0	−3.89	3.43	*SCN	B	25
31	CNSe	—SeCN	1.5	−3.91	3.61	*-Se-CN	B	25
32	$CHBr_2$	—$CHBr_2$	0.5	−1.90	1.90	*YEE	CHx	25
33	$CHCl_2$	—$CHCl_2$	0.5	−1.96	1.94	*YGG	B	25
34	CHO	—CHO	0.5	−2.58	2.15	*VH	B	25
35	CHO_2	—COOH	0.5	−1.65	2.08	*VQ	B	30
36	CH_2Br	—CH_2Br	1.0	−1.97	1.00	*1E	CCl_4	25
37	CH_2Cl	—CH_2Cl	1.0	−1.93	1.05	*1G	CCl_4	25
38	CH_2I	—CH_2I	1.0	−1.79	0.85	*1I	CCl_4	25
39	CH_2NO	—$CONH_2$	0.5	−3.73	1.68	*VZ	B	25
40	CH_2NO_2	—CH_2NO_2	1.5	−3.29	1.73	*1NW	B	25
41	CH_2ClO	—OCH_2Cl	0.0	−1.90	2.56	*01G	B	0
42	CH_2SH	—CH_2SH	1.0	−1.52	0.62	*1SH	G	−50
43	CH_3	—CH_3	0.0	0.0	0.0	*1	G	—
44	CH_3N_2S[b]	—$NHCSNH_2$	0.0	−0.16	1.80	*MYZUS	B	25
45	CH_3O	—OCH_3	0.0	−1.27	1.81	*01	B	25
46	CH_3OS	—$S(O)CH_3$	0.5	−3.88	2.88	*SO&1	B	20
47	CH_3O_2S	—SO_2CH_3	0.5	−4.26	3.68	*SW1	B	25
48	CH_3O_3S	—SO_2OCH_3	0.0	−4.18	3.62	*SW01	D	25
49	CH_3S	—SCH_3	0.0	−1.45	1.56	*S1	B	25
50	CH_4N	—$NHCH_3$	0.0	−1.01	−0.81	*M1	G	NS
51	CH_4N	—CH_2NH_2	1.0	−1.35	0.50	*1Z	B,CHx	25
52	C_2H	—C≡CH	0.0	−0.78	1.30	*1UU1	NS	NS
53	C_2HS	—SCCH	0.0	−1.69	2.00	*S1UU1	G	−53
54	C_2H_2Cl	—CHCHCl	1.0	−1.64	0.87	*1U1G	G	—
55	$C_2H_2NO_2$	—$CHCHNO_2$	1.5	−3.99	1.75	*1U1NW	B	20
56	$C_2H_2Cl_3$	—CH_2CCl_3	1.0	−1.84	0.75	*1XGGG	CHx	25
57	C_2H_2OCl	—$COCH_2Cl$	0.5	−2.27	2.50	*V1G	CCl_4	25
58	C_2H_3	—$CH{=}CH_2$	0.0	−0.40	0.56	*1U1	G	−78
59	$C_2H_3Br_2$	—$CHBrCH_2Br$	1.0	−1.43	1.38	*YE1E	B	25
60	$C_2H_2Cl_3$	—$CHClCHCl_2$	1.0	−2.07	1.08	*YGYGG	—	—
61	$C_2H_3Cl_2$	—CCl_2CH_3	0.5	−2.33	1.53	*XGG1	I	31–55
62	C_2H_3O	—CH_2CHO	1.5	−2.23	0.62	*1VH	B	25
63	C_2H_3O	—$COCH_3$	0.5	−2.77	1.81	*V1	B	30
64	$C_2H_3O_2$	—CH_2COOH	1.5	−1.68	1.08	*1VQ	B	25
65	$C_2H_3O_2$	—$COOCH_3$	0.5	−1.75	2.00	*V01	B	25
66	$C_2H_3O_2$	—$OCOCH_3$	0.0	−1.81	2.56	*OV1	B	25
67	C_2H_3S	—$SCH{=}CH_2$	0.0	−1.38	1.31	*S1U1	B	25
68	C_2H_4Br	—$CHBrCH_3$	1.0	−2.08	1.25	*YE	CCl_4	25
69	C_2H_4Br	—CH_2CH_2Br	2.0	−1.97	0.44	*2E	CCl_4	25
70	C_2H_4Cl	—$CHClCH_3$	1.0	−2.05	1.00	*YG	CCl_4	25
71	C_2H_4Cl	—CH_2CH_2Cl	2.0	−1.93	0.41	*2G	CCl_4	25
72	C_2H_4I	—CH_2CH_2I	2.0	−1.79	0.41	*2I	CCl_4	25
73	C_2H_4NO	—$NHCOCH_3$	1.0	−3.81	1.40	*MV1	B	25
74	C_2H_4NO	—CH_2CONH_2	1.5	−3.75	0.31	*1VZ	B	25
75	$C_2H_4NO_2$	—$CH_2CH_2NO_2$	2.5	−2.69	0.50	*2NW	B	30
76	C_2H_5	—C_2H_5	0.0	0.0	−0.10	*2	G	NS
77	C_2H_5O	—OC_2H_5	0.0	−1.27	1.68	*02	B	25
78	C_2H_5O	—CH_2OCH_3	1.0	−1.32	0.66	*101	CCl_4	25
79	C_2H_5O	—$CH(OH)CH_3$	1.0	−1.69	0.46	*YQ	CHx	25

continued

No.	Formula	R	n'	μR, Debye	σ*	WLN	Solvent[a]	Temp., °C
80	C_2H_5O	—CH_2CH_2OH	2.0	−1.66	0.21	*2Q	B	25
81	$C_2H_5O_2S$	—$S(O)OC_2H_5$	0.5	−2.84	2.84	*SO&O2	B	25
82	$C_2H_5O_2S$	—$CH_2SO_2CH_3$	1.5	−4.40	1.32	*1SW1	B	25
83	C_2H_6N	—$N(CH_3)_2$	0.0	−1.26	−0.62	*N1&1	B	25
84	$C_2H_6NO_2S$	—$SO_2N(CH_3)_2$	0.5	−4.71	2.62	*SWN1&1	B	25
85	$C_2H_6NO_2S$	—$NCH_3SO_2CH_3$	1.0	−4.71	2.10	*N1&SW1	B	25
86	C_2H_6OP	—$PO(CH_3)_2$	1.0	−4.20	2.81	*PO&1&1	B	25
87	C_3H_3	—$CCCH_3$	0.0	−0.84	1.20	*1UU2	G	—
88	C_3H_3	—CH_2CCH	1.0	−0.84	0.81	*2UU1	G	35
89	$C_3H_4F_3$	—CH_2CH_2CF	2.0	−1.94	0.32	*2XFFF	—	—
90	C_3H_4N	—CH_2CH_2CN	2.5	−3.51	0.49	*2CN	CCl_4	20
91	C_3H_5	—$C(CH_3)CH_2$	0.0	−0.34	0.48	*YU1	B	25
92	C_3H_5	—CH_2CHCH_2	1.0	−0.35	0.0	*2U1	G	−78
93	C_3H_5	—$CHCHCH_3$	0.0	−0.25	0.36	*1U2	G	NS
94	C_3H_5	—cyclo-C_3H_5	0.0	−0.14	0.15	*AL3TJ	G	—
95	C_3H_5O	—COC_2H_5	0.5	−2.79	1.61	*V2	B	25
96	C_3H_5O	—CH_2CH_2CHO	2.5	−2.23	0.29	*2VH	B	25
97	C_3H_5O	—CH_2COCH_3	1.5	−2.80	0.62	*1V1	B	25
98	$C_3H_5O_2$	—CH_2OCOCH_3	1.0	−1.84	1.06	*1OV1	B	25
99	$C_3H_5O_2$	—$COOC_2H_5$	0.5	−1.81	2.26	*VO2	B	25
100	$C_3H_5O_2$	—CH_2COOCH_3	1.5	−1.84	1.00	*1VO1	B	25
101	C_3H_6NO	—$CON(CH_3)_2$	0.5	−3.81	1.94	*VN1&1	B	25
102	C_3H_6NO	—$NHCOC_2H_5$	1.0	−3.55	1.56	*MV2	G	110
103	C_3H_6NO	—$N(CH_3)COCH_3$	1.0	−3.86	2.25	*N1&V1	B	25
104	C_3H_6NO	—$CH_2CH_2CONH_2$	2.5	−3.78	0.19	*2VZ	B	25
105	C_3H_6NO	—$CH_2NHCOCH_3$	2.0	−3.55	0.43	*1MV1	G	110
106	$C_3H_6NO_2$	—$NHCOOC_2H_5$	1.0	−3.80	1.99	*MVO2	*l*	20
107	$C_3H_6NO_2$	—$OCON(CH_3)_2$	0.0	−3.80	2.87	*OVN1&1	*l*	20
108	C_3H_7	—$CH(CH_3)_2$	0.0	0.08	−0.19	*Y	*l*	—
109	C_3H_7	—C_3H_7	0.0	0.08	−0.12	*3	*l*	—
110	C_3H_7O	—$OCH(CH_3)_2$	0.0	−1.32	1.62	*OY	B	25
111	C_3H_7O	—$CH_2OC_2H_5$	1.0	−1.27	0.58	*1O2	B	25
112	C_3H_7O	—OC_3H_7	0.0	−1.32	1.68	*O3	CCl_4	25
113	C_3H_7O	—$CH_2CH(OH)CH_3$	2.0	−1.77	0.16	*1YQ	D	25
114	C_3H_7O	—$CH_2CH_2OCH_3$	2.0	−1.27	0.24	*2O1	B	25
115	C_3H_7O	—$C(OH)(CH_3)_2$	1.0	−1.72	0.35	*XQ	D	25
116	C_3H_7S	—SC_3H_7	0.0	−1.63	1.38	*S3	B	19
117	C_3H_7S	—$SCH(CH_3)_2$	0.0	−1.61	1.49	*SY	B	20
118	$C_3H_7O_2S$	—$SO_2CH(CH_3)_2$	0.5	−4.50	3.68	*SWY	B	25
119	C_4H_7	—$CHCHC_2H_5$	0.0	−0.34	0.31	*1U3	B	25
120	C_4H_7	—$CHC(CH_3)_2$	0.0	−0.34	0.19	*1UY	B	25
121	C_4H_7	—$CH_2CHCHCH_3$	1.0	−0.34	0.0	*2U2	B	25
122	C_4H_9	—C_4H_9	0.0	0.08	0.25	*4	B	25
123	C_4H_9O	—OC_4H_9	0.0	−1.26	1.68	*O4	B	25
124	$C_4H_{10}N$	—NHC_4H_9	0.0	−1.27	−1.08	*M4	B	20
125	$C_4C_{10}O_3P$	—$OP(OC_2H_5)_2$	0.0	−2.88	3.02	*PO&O2&O2	B	25
126	C_5H_9O	—O-cyclo-C_5H_9	0.0	−1.60	1.62	*OAL5TJ	B	25
127	C_5H_{11}	—C_5H_{11}	0.0	0.10	−0.23	*5	*l*	NS
128	$C_5H_{11}O$	—$O(CH_2)_4CH_3$	0.0	−1.32	1.52	*O5	B	25
129	$C_5H_{11}S$	—$S(CH_2)_4CH_3$	0.0	−1.63	1.35	*S5	D	25
130	$C_5H_{11}O_2$	—$CH(OC_2H_5)_2$	0.5	−1.27	1.14	*YO2&O2	B	25
131	$C_5H_8O_2$	—$CHCHCOOC_2H_5$	1.5	−1.95	1.12	*1U1VO2	B	24
132	$C_6H_2N_3O_6$	—C_6H_2—2,4,6-$(NO_2)_3$	0.0	−1.19	1.62	*R BNW DNW FNW	B	25
133	$C_6H_3Cl_2O$	—OC_6H_3—2,4-Cl_2	0.0	−2.77	3.17	*OR BG DG	B	20
134	C_6H_4Br	—C_6H_4—4-Br	1.0	−1.91	0.86	*R DE	B	25
135	C_6H_4Cl	—C_6H_4—2-Cl	1.0	−1.34	1.05	*R BG	HP	20
136	C_6H_4Cl	—C_6H_4—4-Cl	1.0	−1.90	0.92	*R DG	B	25
137	C_6H_4Cl	—C_6H_4—3-Cl	1.0	−1.82	0.85	*R CG	B	25
138	C_6H_4F	—C_6H_4—3-F	1.0	−1.78	0.82	*R CF	B	25
139	C_6H_4F	—C_6H_4—4-F	1.0	−1.78	0.81	*R DF	B	25
140	C_6H_4I	—C_6H_4—4-I	1.0	−1.76	0.87	*R DI	B	25
141	$C_6H_4NO_2$	—C_6H_4—2-NO_2	1.5	−3.60	1.14	*R BNW	*l*	9–25
142	$C_6H_4NO_2$	—C_6H_4—3-NO_2	1.5	−3.40	1.21	*R CNW	B	25
143	$C_6H_4NO_2$	—C_6H_4—4-NO_2	1.5	−4.43	1.26	*R DNW	B	25
144	C_6H_4BrO	—OC_6H_4—2-Br	0.0	−2.50	2.45	*OR BE	CCl_4	20
145	C_6H_4BrO	—OC_6H_4—3-Br	0.0	−2.05	2.48	*OR CE	B	25
146	C_6H_4BrO	—OC_6H_4—4-Br	0.0	−2.37	2.44	*OR DE	B	25
147	C_6H_4ClO	—OC_6H_4—3-Cl	0.0	−2.06	2.57	*OR CG	B	25
148	C_6H_4ClO	—OC_6H_4—4-Cl	0.0	−2.30	2.62	*OR DG	B	25
149	C_6H_4IO	—OC_6H_4—2-I	0.0	−2.25	2.38	*OR BI	CCl_4	20
150	C_6H_4IO	—OC_6H_4—4-I	0.0	−2.14	2.39	*OR DI	CCl_4	20
151	$C_6H_4NO_3$	—OC_6H_4—2-NO_2	2.0	−4.05	2.78	*OR BNW	B	30, 50
152	$C_6H_4NO_3$	—OC_6H_4—3-NO_2	2.0	−4.00	2.76	*OR CNW	B	20
153	$C_6H_4NO_3$	OC_6H_4—4-NO_2	2.0	−4.00	2.91	*OR DNW	B, D	30, 60
154	C_6H_4BrS	—SC_6H_4—3-Br	0.0	−1.83	1.84	*SR CE	B	30
155	C_6H_4BrS	—SC_6H_4—4-Br	0.0	−1.80	1.83	*SR DE	B	25
156	C_6H_4ClS	—SC_6H_4—3-Cl	0.0	−1.83	2.02	*SR CG	B	30
157	C_6H_4ClS	—SC_6H_4—4-Cl	0.0	−1.81	1.97	*SR DG	B	30
158	C_6H_4FS	—SC_6H_4—4-F	0.0	−1.64	1.77	*SR DF	B	30
159	$C_6H_4NO_2S$	—SC_6H_4—2-NO_2	2.5	−4.93	2.47	*SR BNW	B	NS
160	$C_6H_4NO_2S$	—SC_6H_4—4-NO_2	2.5	−4.43	2.33	*SR DNW	B	25

Continued on next page

Appendix (continued)

No.	Formula	R	n′	μR, Debye	σ*	WLM	Solvent[a]	Temp., °C
161	C_6H_4NOSe	$—SeC_6H_4—4-NO_2$	2.5	−4.38	1.83	*SeR DNW	B	NS
162	$C_6H_4NO_4S$	$—SO_2C_6H_4—4-NO_2$	0.0	−2.80	3.63	*SWR DNW	D	25
163	C_6H_4BrOS	$—S(O)C_6H_4—4-Br$	0.5	−3.26	3.14	*SO&R DE	B	20
164	C_6H_4ClOS	$—S(O)C_6H_4—4-Cl$	0.5	−3.08	3.14	*SO&R DG	B	20
165	C_6H_5	$—C_6H_5$	0.0	−0.38	0.75	*R	CHx	25
166	C_6H_5O	$—OC_6H_5$	0.0	−1.38	2.43	*OR	B	25
167	$C_6H_5O_2$	$—OC_6H_4—2-OH$	0.0	−2.46	2.60	*OR BQ	B	60
168	$C_6H_5O_2S$	$—OSOC_6H_5$	0.0	−3.48	3.25	*OSO&R	B	25
169	$C_6H_5O_2S$	$—SO_2C_6H_5$	0.5	−4.75	3.55	*SWR	B	25
170	$C_6H_5O_3S$	$—OSO_2C_6H_5$	0.0	−4.99	3.62	*OSWR	D	25
171	C_6H_5S	$—SC_6H_5$	0.0	−1.29	1.87	*SR	B	25
172	C_6H_5S	$—C_6H_4—2-SH$	1.0	−1.16	0.72	*R BSH	B	25
173	$C_6H_6NO_2S$	$—NHSO_2C_6H_5$	1.0	−4.62	1.99	*MSWR	B	25–55
174	C_6H_{11}	—cyclohexyl	0.0	0.00	0.18	*AL6TJ	CCl_4	25
175	$C_6H_{11}O$	—O-cyclohexyl	0.0	−1.68	1.81	*O AL6TJ	B	25
176	$C_6H_{13}S$	$—S(CH_3)_5CH_3$	0.0	−1.56	1.33	*S6	B	25
177	C_7H_4NO	$—O—C_6H_4—4-CN$	0.0	−4.39	2.73	*OR DCN	B	20
178	C_7H_4ClO	$—OCO(C_6H_4—4-Cl)$	0.0	−1.94	2.63	*OVR DG	B	25
179	$C_7H_4NO_4$	$—OCO(C_6H_4—4-NO_2)$	0.0	−3.48	2.73	*OVR DNW	B	25
180	C_7H_5O	$—CO(C_6H_5)$	0.5	−2.90	2.26	*VR	B	20
181	C_7H_5O	$—OCOC_6H_5$	0.0	−1.94	2.57	*OVR	B	20
182	C_7H_5O	$—COOC_6H_5$	0.0	−1.69	2.57	*VOR	B	25
183	C_7H_6NO	$—CONHC_6H_5$	1.0	−3.62	1.68	*VNR	B	25
184	C_7H_7	$—CH_2C_6H_5$	1.0	−0.39	0.27	*1R	CHx	25
185	C_7H_7	$—C_6H_5—2-CH_3$	0.0	−0.54	0.62	*R B1	CHx	25
186	C_7H_7	$—C_6H_5—4-CH_3$	0.0	−0.10	0.59	*R D1	*l*	25
187	C_7H_7O	$—CH_2O—C_6H_5$	1.0	−1.38	0.87	*1OR	B	25
188	C_7H_7O	$—OC_6H_4—2-CH_3$	0.0	−1.09	2.29	*OR B1	B	20
189	C_7H_7O	$—OC_6H_4—3-CH_3$	0.0	−1.25	2.33	*OR C1	B	20
190	C_7H_7O	$—OC_6H_4—4-CH_3$	0.0	−1.23	2.30	*OR D1	B	20
191	C_7H_7O	$—C_6H_4—4-OCH_3$	1.0	−1.23	0.42	*R D01	B	20
192	$C_7H_7O_2$	$—OC_6H_4—2-OCH_3$	0.0	−1.26	2.29	*OR B01	B	20
193	$C_7H_7O_2$	$—OC_6H_4—3-OCH_3$	0.0	−1.58	2.42	*OR C01	B	20
194	$C_7H_7O_2$	$—OC_6H_4—4-OCH_3$	0.0	−1.72	2.32	*OR D01	B	20
195	C_7H_7S	$—SCH_2C_6H_5$	0.0	−1.46	1.56	*S1R	D	25
196	C_7H_7S	$—SC_6H_4—3-CH_3$	0.0	−1.38	1.89	*SR C1	B	30
197	C_7H_7S	$—SC_6H_4—4-CH_3$	0.0	−1.49	1.80	*SR D1	B	30
198	C_7H_7OS	$—SC_6H_4—3-OCH_3$	0.0	−1.74	1.89	*SR C01	B	30
199	C_7H_7OS	$—SC_6H_4—4-OCH_3$	0.0	−1.98	1.66	*SR D01	B	30
200	$C_7H_7O_2S$	$—S(O)C_6H_4—4-OCH_3$	0.5	−4.24	3.00	*SO&R D01	B	20
201	$C_7H_7O_2S$	$—SO_2C_6H_4—4-CH_3$	0.5	−5.08	3.32	*SWR D1	D	25
202	$C_7H_7S_2$	$—SC_6H_4—4-SCH_3$	0.0	−1.81	1.69	*SR DS1	B	30
203	C_7H_7Se	$—SeC_6H_4—4-CH_3$	1.0	−1.46	1.23	*-Se⁻ R D1	B	NS
204	$C_7H_{13}O$	$—OCH_2—cyclo-C_6H_{11}$	0.0	−1.41	1.31	*01 A16TJ	B	20
205	C_8H_7	$—CH{=}CHC_6H_5$	0.0	−0.77	0.41	*1U1R	B	25
206	C_8H_9	$—CH(CH_3)C_6H_5$	1.0	−0.40	0.37	*YR	CHx	25
207	$C_8H_7O_2$	$—OC_6H_4—4-COCH_3$	0.0	−3.04	2.91	*OR DV1	B	25
208	C_8H_8NO	$—N(COCH_3)C_6H_5$	1.0	−3.63	1.37	*NR&V1	B	25
209	$C_8H_9O_3S$[b]	$—CH_2OSO_2C_6H_4—4-CH_3$	1.0	−5.30	1.44	*10SWR D1	D	25
210	C_9H_{11}	$—C_6H_4—4-CH(CH_3)_2$	0.0	−0.15	0.56	*R DY	*l*	25
211	$C_{10}H_{13}$	$—C_6H_4—4-C(CH_3)_3$	0.0	0.0	0.52	*R DX	CCl_4	25
212	$C_{12}H_{10}P$	$—P(C_6H_5)_2$	0.5	−1.39	1.06	*PR&R	B	20
213	$C_{12}H_{10}OP$	$—PO(C_6H_5)_2$	1.0	−4.66	1.71	*PO&R&R	B	20
214	$C_{13}H_{11}S_2$	$—CH(SC_6H_5)_2$	0.5	−1.72	1.56	*YSR&SR	B	25

[a] Key: (B) benzene; (D) dioxane; (G) gaseous phase; (CHx) cyclohexane; (HP) heptane; (*l*) liquid; (NS) not stated. [b] Omitted in equations 8 and 10.

REFERENCES

(1) E. J. Lien, Z. R. Guo, R. L. Li, and C. T. Su, *J. Pharm. Sci.*, **71**, 641 (1982).

(2) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N.Y., 1956, p. 614.

(3) C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," Wiley, New York, N.Y., 1979.

(4) D. D. Perrin, in "Physical Chemical Properties of Drugs," S. H. Yalkowsky, A. A. Sinkula, and S. C. Valvani, Eds., Decker, New York, N.Y., 1980, pp. 1–48.

(5) A. L. McClellan, "Tables of Experimental Dipole Moments," Vol. 2, Rahara Enterprises, El Cerrito, Calif., 1974.

(6) J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, **75**, 2167 (1953).

(7) M. Charton, in "Progress in Physical Organic Chemistry," vol. 13, R. W. Taft, Ed., Wiley, New York, N.Y., 1981, p. 122.

(8) B. P. Daily and J. N. Shoolery, *J. Am. Chem. Soc.*, **77**, 3977 (1955).

(9) C. P. Smyth, "Dielectric Behavior and Structure," New York, N.Y., 1955, pp. 254–255.

(10) E. A. Braude and F. C. Machod, "Determination of Organic Structures by Physical Methods," Academic, New York, N.Y., 1955.

(11) C. Yamauea, C. Sonota, T. Tako, M. Tanaka, J. Yamada, C. Horizaka, and T. Fujita, "8th Symposium on Structure–Activity Relationships," Tokyo, 1981, pp. 31–35.

(12) C. Takayama, A. Fujinami, O. Kirino, and Y. Hisada, *Agri. Biol. Chem.* **46**(11), 2755 (1982).

(13) E. J. Lien and P. H. Wang, *J. Pharm Sci.*, **69**. 648 (1980).