QUANTITATIVE DRUG DESIGN STUDIES. II.¹⁾ DEVELOPMENT AND APPLICATION OF NEW ELECTRONIC SUBSTITUENT PARAMETERS

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New electronic substituent parameters for quantitative drug design were developed from the standpoint of the frontier orbital theory using the extended Hückel method. Each substituent was characterized by three constants (E , Re , I), which were derived from the SOMO (solely occupied molecular orbital) energy and the coefficient of the SOMO hybrid orbital responsible for bonding to the parent moiety. These correspond to the SOMO-SOMO energy difference (E), the resistivity of the path (Re), and the flow intensity (I) respectively, when the frontier electron flow occurs between the standard parent and the substituent. They can be regarded as major factors governing the electronic inductive-field effect of the substituent. As the result of analyses of various kinds of biological data, they were found to be excellent and widely applicable parameters to the structure-activity problems.

In this paper, the new frontier substituent constant values for 150 kinds of substituents and 58 kinds of equations to which the new constants were successfully applied are presented.

Keywords — drug design; Hansch analysis; substituent; electronic parameter; frontier orbital; extended Hückel method; SOMO; molecular connectivity

In the extrathermodynamic approach such as Hansch analysis, the electronic property of substituents is generally regarded as one of the main factors governing the strength of biological activity of derivatives.²⁾ Traditionally, Hammett's σ constants³⁾ and Swain-Lupton's F , R constants^{4,5)} have been used as excellent ones to express this property, but all these constants are experimentally determined ones which were originally developed in the field of physical organic chemistry to explain equilibrium or reaction rates of organic compounds. Up to the present, several parameters have been devised for the properties other than the electronic one in the area of quantitative structure-activity relationships, that is, π ⁶⁾ and f ⁷⁾ constants as hydrophobic parameters, and Verloop-Hoogenstraaten multidimensional steric constants⁸⁾ and van der Waals volume constants as steric ones.⁹⁾ But, for the electronic property, such widely applicable constants have not been devised yet.

The purpose of the present investigation is to try to develop theoretically new electronic substituent constants which nicely work in the quantitative drug design studies¹⁰⁾ from the standpoint of the frontier orbital method.^{11,12)}

CALCULATIONS

Calculations were performed using Facom 230-75 and M-200 computers of the Nagoya University Computation Center. Atomic coordinates of substituents were calculated for assumptive molecular models made up by standard bond lengths and angles¹³⁾ or X-ray analysis data.¹⁴⁾ Electronic states of substituents were estimated using the extended Hückel method,¹⁵⁾ including d -orbitals for the third-row atoms in the periodic table. Table I shows valence-state ionization potential values used in the calculations.

Since d -orbital values of silicon and chlorine were not available in literatures, they assumed 0 eV. The following concept on the substituent

moiety was introduced. As shown in eq. (1), a molecule (R-X) is cut off at the bond between R and X into two new moieties, and termed a parent (R·) and a substituent (·X) respectively.

Two electrons belonging to the R-X bond distribute themselves between the parent and the substituent one by one. Thus, both the parent and the substituent may possess odd electrons. The extended Hückel calculations were carried out to such substituent moieties. Since spin states are not taken into consideration in the extended Hückel method, the highest occupied molecular orbital (HOMO) of the substituent moiety becomes the solely occupied molecular orbital (SOMO). The substituent SOMO energy is given the symbol E_{SOMO} or $E_{\text{SOMO}}^{\text{S}}$, and the SOMO coefficient of the hybrid orbital which participates in bonding to the parent moiety, ϕ_{SOMO} or $\phi_{\text{SOMO}}^{\text{S}}$, hereinafter.

Since coefficients of valence orbitals such as s , p_x , p_y , p_z , etc. are only obtained for each consti-

tuent atom by the extended Hückel calculations, it is necessary to express hybrid orbital states by linear combinations of these valence orbitals. They can be obtained from the following equations,¹⁶⁾ using SOMO valence orbitals of the atom directly connected with a parent, if the bond axis between parent and substituent moieties agrees with X-axis and the bonding direction of the substituent is faced toward $-X$ direction.

$$\Phi_{sp^3} = \frac{1}{2} \chi(s) - \frac{\sqrt{3}}{2} \chi(p_x) \quad (2)$$

$$\Phi_{sp^2} = \frac{1}{\sqrt{3}} \chi(s) - \sqrt{\frac{2}{3}} \chi(p_x) \quad (3)$$

$$\Phi_{sp} = \frac{1}{\sqrt{2}} \chi(s) - \frac{1}{\sqrt{2}} \chi(p_x) \quad (4)$$

$$\begin{aligned} \Phi_{sp^3 d^2} = & \frac{1}{\sqrt{6}} \chi(s) - \frac{1}{\sqrt{12}} \chi(d_{z^2}) \\ & + \frac{1}{2} \chi(d_{x^2-y^2}) - \frac{1}{\sqrt{2}} \chi(p_x) \end{aligned} \quad (5)$$

That is, ϕ_{SOMO} of CH_3 may be calculated from eq. (2), C_6H_5 from eq. (3), $\text{C}\equiv\text{CH}$ from eq. (4), SF_5 from eq. (5), and so on. The n -fold degenerated SOMO hybrid orbital coefficients of substituents were estimated from eq. (2) to (5) after average valence orbital coefficient values were assumed using the expression of $[\sum \chi(i)^2/n]^{1/2}$. In Table II, E_{SOMO} and ϕ_{SOMO} values of 150 kinds of substituents are listed.

According to Table II, it can be seen that substituents in which oxygen or nitrogen atoms participate in bonding to a parent have generally lower E_{SOMO} values, and those in which the oxygen atom is attached to a parent have smaller ϕ_{SOMO} values than in the other cases. It may be considered that E_{SOMO} of substituents is the concept corresponding to the electronegativity in the case of atom species.

RESULTS AND DISCUSSION

New Electronic Substituent Constants

From the standpoint of the frontier orbital theory in which the frontier orbitals are regarded to be most responsible for the chemical properties of the molecule such as reactivity, etc., it may be

TABLE I. Valence-State Ionization Potentials used in Extended Hückel Calculations^{a)}

Atom	s	p	d (eV)
H	13.595		
B	15.15	8.53	
C	21.43	11.42	
N	27.50	14.49	
O	35.30	17.76	
F	37.24 ^{b)}	20.98	
Si	17.93	8.99	0.00 ^{c)}
S ^{d)}	20.77	11.98	2.00
Cl	25.00 ^{b)}	15.09	0.00 ^{c)}

a) H.O.Pritchard and H.A. Skinner, *Chem. Rev.*, **55**, 745 (1955).

b) A.G.Turner, "Methods in Molecular Orbital Theory," Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1974, p.133.

c) The values are not available in the literatures, so assume 0 eV.

d) D.T.Clark, *Tetrahedron*, **24**, 2663 (1968).

TABLE II. E_{SOMO} , ϕ_{SOMO} and Frontier Electronic Substituent Constant Values of 150 Kinds of Substituents

No.	Substituent	E^a_{SOMO}	ϕ_{SOMO}	E	Re	I
1	Br	-0.504	0.500	0.05	1.97	-2.11
2	Cl	-0.555	0.500	0.55	1.97	-1.46
3	F	-0.771	0.500	2.71	1.97	1.32
4	SF ₅	-0.385	0.933	-1.15	-1.63	0.61
5	I	-0.463	0.500	-0.36	1.97	-2.63
6	NO	-0.477	0.473	-0.23	2.18	-2.62
7	NO ₂	-0.518	0.811	0.18	-0.64	1.40
8	N ₃	-0.527	0.569	0.27	1.41	-1.30
9	SO ₃ ⁻	-0.431	0.933	-0.68	-1.63	1.71
10	H	-0.500	1.000	0.	0.	0.
11	OH	-0.653	0.577	1.53	1.35	0.52
12	SH	-0.440	0.577	-0.59	1.35	-2.44
13	B(OH) ₂	-0.383	0.703	-1.16	0.28	-2.30
14	NH ₂	-0.533	0.707	0.33	0.25	0.19
15	NHOH	-0.504	0.629	0.05	0.91	-1.09
16	SO ₂ NH ₂	-0.394	0.909	-1.06	-1.44	0.42
17	NH ₃ ⁺	-0.540	0.912	0.40	-1.47	3.81
18	NHNH ₂	-0.478	0.666	-0.21	0.60	-1.13
19	NHSO ₂ NH ₂	-0.527	0.668	0.27	0.58	-0.36
20	CCl ₃	-0.388	0.909	-1.12	-1.44	0.28
21	CF ₃	-0.440	0.982	-0.60	-2.01	2.94
22	OCF ₃	-0.652	0.571	1.52	1.39	0.45
23	SO ₂ CF ₃	-0.408	0.896	-0.91	-1.34	0.52
24	SCF ₃	-0.439	0.572	-0.61	1.39	-2.49
25	CN	-0.474	0.738	-0.26	-0.02	-0.41
26	NCO	-0.554	0.436	0.55	2.45	-1.88
27	NCS	-0.461	0.223	-0.39	3.70	-3.74
28	SCN	-0.452	0.517	-0.48	1.83	-2.68
29	CO ₂ ⁻	-0.449	0.923	-0.50	-1.55	1.94
30	CHCl ₂	-0.392	0.890	-1.08	-1.29	0.07
31	CHF ₂	-0.411	0.915	-0.89	-1.49	0.91
32	CHO	-0.405	0.884	-0.95	-1.24	0.26
33	CO ₂ H	-0.444	0.935	-0.55	-1.65	2.07
34	CH ₂ Cl	-0.407	0.900	-0.92	-1.38	0.58
35	CH ₂ F	-0.417	0.924	-0.82	-1.56	1.22
36	CH=NOH	-0.437	0.864	-0.63	-1.08	0.64
37	CONH ₂	-0.410	0.910	-0.90	-1.45	0.80
38	NHCHO	-0.529	0.792	0.29	-0.48	1.31
39	CH ₂ NO ₂	-0.482	0.581	-0.18	1.32	-1.84
40	CONHOH	-0.424	0.913	-0.76	-1.48	1.16
41	OCONH ₂	-0.535	0.108	0.35	4.07	-3.18
42	CH ₃	-0.430	0.931	-0.70	-1.62	1.64
43	NHCONH ₂	-0.525	0.743	0.26	-0.06	0.54
44	NHCSNH ₂	-0.425	0.095	-0.74	4.09	-4.29
45	CH ₂ OH	-0.415	0.927	-0.85	-1.59	1.21
46	OCH ₃	-0.531	0.226	0.31	3.68	-3.00

No.	Substituent	$E^{a)}_{\text{SOMO}}$	ϕ_{SOMO}	E	Re	I
47	SOCH ₃	-0.393	0.695	-1.06	0.35	-2.21
48	SO ₂ CH ₃	-0.399	0.734	-1.01	0.01	-1.74
49	OSO ₂ CH ₃	-0.527	0.140	0.28	3.99	-3.21
50	SCH ₃	-0.419	0.799	-0.80	-0.54	-0.65
51	CH ₂ NH ₂	-0.396	0.885	-1.04	-1.25	0.08
52	NHCH ₃	-0.488	0.582	-0.11	1.31	-1.73
53	NHSO ₂ CH ₃	-0.508	0.538	0.08	1.66	-1.80
54	CH ₂ NH ₃ ⁺	-0.407	0.926	-0.93	-1.58	1.00
55	NH ₂ CH ₃ ⁺	-0.491	0.716	-0.08	0.17	-0.38
56	C ₂ F ₅	-0.414	0.905	-0.85	-1.41	0.82
57	C≡CH	-0.468	0.799	-0.31	-0.54	0.28
58	CH=CCl ₂	-0.425	0.885	-0.75	-1.25	0.72
59	OCF ₂ CHF ₂	-0.514	0.209	0.14	3.75	-3.22
60	CH=CHCl	-0.423	0.891	-0.77	-1.30	0.76
61	CH ₂ CCl ₃	-0.417	0.916	-0.83	-1.50	1.06
62	CH ₂ CF ₃	-0.429	0.918	-0.71	-1.52	1.38
63	CH ₂ CN	-0.447	0.809	-0.53	-0.62	0.00
64	CH=CHNO ₂	-0.425	0.000	-0.75	4.18	-4.34
65	CH ₂ SCN	-0.413	0.876	-0.87	-1.18	0.31
66	OCH ₂ CO ₂ ⁻	-0.525	0.279	0.26	3.43	-2.91
67	CH=CH ₂	-0.409	0.875	-0.90	-1.17	0.21
68	COCH ₃	-0.403	0.868	-0.97	-1.11	-0.04
69	SCOCH ₃	-0.431	0.828	-0.69	-0.78	-0.02
70	CH ₂ CO ₂ H	-0.428	0.924	-0.72	-1.56	1.46
71	CO ₂ CH ₃	-0.443	0.931	-0.57	-1.62	1.95
72	OCOCH ₃	-0.534	0.203	0.34	3.78	-3.02
73	OCH ₂ CO ₂ H	-0.522	0.270	0.23	3.48	-2.97
74	CH ₂ CH ₂ Cl	-0.415	0.920	-0.84	-1.53	1.10
75	CHClCH ₃	-0.392	0.900	-1.08	-1.37	0.22
76	CH ₂ CONH ₂	-0.443	0.818	-0.57	-0.70	0.06
77	CONHCH ₃	-0.411	0.900	-0.89	-1.37	0.64
78	NHCOCH ₃	-0.497	0.548	-0.03	1.58	-1.88
79	CSNHCH ₃	-0.366	0.691	-1.34	0.39	-2.69
80	NHCSCH ₃	-0.419	-0.023	-0.80	4.18	-4.39
81	C ₂ H ₅	-0.407	0.910	-0.93	-1.45	0.72
82	CH ₂ CH ₂ OH	-0.425	0.924	-0.75	-1.56	1.40
83	CH ₂ OCH ₃	-0.413	0.925	-0.87	-1.57	1.12
84	CH(OH)CH ₃	-0.398	0.912	-1.02	-1.47	0.56
85	OC ₂ H ₅	-0.497	0.000	-0.03	4.18	-3.62
86	CH(OH)CH ₂ OH	-0.412	0.917	-0.88	-1.50	0.95
87	CH ₂ SO ₂ CH ₃	-0.424	0.884	-0.75	-1.24	0.69
88	SC ₂ H ₅	-0.419	0.000	-0.81	4.18	-4.39
89	NHC ₂ H ₅	-0.478	0.437	-0.22	2.45	-2.80
90	N(CH ₃) ₂	-0.475	0.610	-0.25	1.07	-1.69
91	SO ₂ N(CH ₃) ₂	-0.411	0.906	-0.89	-1.42	0.75
92	NH(CH ₃) ₂ ⁺	-0.480	0.758	-0.19	-0.19	-0.05
93	CH ₂ C≡CH	-0.420	0.771	-0.80	-0.30	-0.97
94	CH=CHCHO	-0.407	0.854	-0.93	-1.00	-0.14

No.	Substituent	E^a SOMO	ϕ SOMO	E	Re	I
95	CH=CHCO ₂ H	-0.411	0.877	-0.89	-1.19	0.28
96	CH ₂ COCO ₂ H	-0.419	0.910	-0.81	-1.45	1.01
97	cyclopropyl	-0.406	0.899	-0.94	-1.36	0.52
98	CH ₂ CH=CH ₂	-0.410	0.912	-0.89	-1.47	0.85
99	C(CH ₃)=CH ₂	-0.406	0.876	-0.94	-1.18	0.16
100	CH=CH(CH ₃)	-0.410	0.857	-0.89	-1.02	-0.04
101	COC ₂ H ₅	-0.400	0.848	-1.00	-0.95	-0.39
102	CH ₂ CH ₂ CO ₂ H	-0.410	0.913	-0.90	-1.47	0.83
103	CH ₂ CO ₂ CH ₃	-0.428	0.924	-0.72	-1.56	1.45
104	CH ₂ OCOCH ₃	-0.412	0.927	-0.88	-1.59	1.14
105	CO ₂ C ₂ H ₅	-0.442	0.928	-0.57	-1.59	1.88
106	C ₂ H ₄ CONH ₂	-0.407	0.902	-0.92	-1.38	0.60
107	NHCOC ₂ H ₅	-0.483	0.439	-0.17	2.43	-2.73
108	NHCO ₂ C ₂ H ₅	-0.497	0.040	-0.03	4.16	-3.61
109	CH ₂ CH(CO ₂ ⁻)NH ₃ ⁺	-0.409	0.900	-0.90	-1.37	0.62
110	C ₃ H ₇	-0.408	0.899	-0.92	-1.36	0.57
111	CH(CH ₃) ₂	-0.393	0.910	-1.06	-1.45	0.42
112	CH ₂ OC ₂ H ₅	-0.413	0.923	-0.87	-1.56	1.09
113	OC ₃ H ₇	-0.489	0.000	-0.10	4.18	-3.69
114	OCH(CH ₃) ₂	-0.487	0.000	-0.12	4.18	-3.71
115	NH ₂ C ₃ H ₇ ⁺	-0.474	0.533	-0.26	1.71	-2.29
116	N(CH ₃) ₃ ⁺	-0.477	0.792	-0.23	-0.48	0.35
117	Si(CH ₃) ₃	-0.315	0.955	-1.85	-1.80	-0.75
118	CH=C(CH ₃) ₂	-0.412	0.852	-0.88	-0.98	-0.08
119	COC ₃ H ₇	-0.398	0.838	-1.02	-0.86	-0.55
120	C ₂ H ₄ NHCOCH ₃	-0.418	0.917	-0.81	-1.50	1.10
121	C ₄ H ₉	-0.407	0.887	-0.93	-1.27	0.36
122	iso-C ₄ H ₉	-0.407	0.893	-0.93	-1.31	0.43
123	sec-C ₄ H ₉	-0.393	0.892	-1.07	-1.31	0.12
124	C(CH ₃) ₃	-0.386	0.916	-1.14	-1.50	0.35
125	OC ₄ H ₉	-0.485	0.180	-0.15	3.86	-3.58
126	N(C ₂ H ₅) ₂	-0.462	0.582	-0.37	1.31	-2.10
127	C ₅ H ₁₁	-0.406	0.882	-0.93	-1.23	0.26
128	iso-C ₅ H ₁₁	-0.404	0.879	-0.95	-1.20	0.17
129	tert-C ₅ H ₁₁	-0.409	0.893	-0.91	-1.32	0.50
130	C ₆ H ₅	-0.396	0.836	-1.03	-0.85	-0.62
131	N=NC ₆ H ₅	-0.441	0.440	-0.59	2.42	-3.23
132	OC ₆ H ₅	-0.461	0.180	-0.38	3.86	-3.82
133	SOC ₆ H ₅	-0.402	0.611	-0.98	1.06	-2.74
134	SO ₂ C ₆ H ₅	-0.402	0.809	-0.98	-0.62	-0.85
135	SC ₆ H ₅	-0.423	0.475	-0.76	2.16	-3.28
136	NHSO ₂ C ₆ H ₅	-0.465	0.198	-0.34	3.79	-3.74
137	C ₆ H ₁₃	-0.406	0.879	-0.93	-1.21	0.22
138	COC ₆ H ₅	-0.401	0.770	-0.99	-0.29	-1.33
139	C ₆ H ₄ CO ₂ H- <i>o</i>	-0.397	0.834	-1.02	-0.84	-0.62
140	C ₆ H ₄ CO ₂ H- <i>m</i>	-0.398	0.828	-1.01	-0.78	-0.68
141	C ₆ H ₄ CO ₂ H- <i>p</i>	-0.396	0.835	-1.04	-0.84	-0.63
142	CONHC ₆ H ₅	-0.411	0.898	-0.89	-1.35	0.61

No.	Substituent	E^a_{SOMO}	ϕ_{SOMO}	E	Re	I
143	NHCOC ₆ H ₅	-0.460	0.326	-0.40	3.17	-3.47
144	CH ₂ C ₆ H ₅	-0.415	0.759	-0.85	-0.20	-1.21
145	OCH ₂ C ₆ H ₅	-0.466	0.101	-0.34	4.08	-3.88
146	OTs	-0.460	0.013	-0.40	4.18	-3.99
147	N(C ₆ H ₅)COCH ₃	-0.452	0.346	-0.48	3.05	-3.49
148	O(CH ₂) ₃ C ₆ H ₅	-0.458	0.067	-0.42	4.14	-3.99
149	O(CH ₂) ₃ OC ₆ H ₅	-0.460	0.016	-0.39	4.18	-3.98
150	1-adamantyl	-0.377	0.846	-1.23	-0.93	-0.87

a) Unit: a.u.

thought that SOMO reflects electronic properties of the substituent most excellently. Thus, if we assume that the inductive effect of the substituent occurs mainly by the electron flow through the bond between the parent and the substituent, it may be likely that the inductive field effect concerning the frontier electron is centered at E_{SOMO} and ϕ_{SOMO} .

Let us consider SOMO's of both the parent and the substituent as illustrated in Fig. 1.

It may be supposed that the electron transfer and the bond formation take place between them by the SOMO-SOMO energy difference as the driving force. The frontier electron may flow from the moiety with higher SOMO energy to that with lower SOMO energy. Therefore, a substituent whose SOMO energy is higher than a parent possesses the electron-donating property, and the electron-acceptable property in the opposite case. Since ϕ_{SOMO} forms the passage of the frontier electron flow, it may be associated with the resistance against the flow. But, it is impossible to determine $E^{\text{P}}_{\text{SOMO}}$ and $\phi^{\text{P}}_{\text{SOMO}}$ of the parent in Fig. 1 definitely, because various kinds of the lead structures are available in the lead optimization problems. Thus, the assumptive parent whose $E^{\text{P}}_{\text{SOMO}}$ is zero was adopted as a standard to obtain substituent constants. This seems reasonable since the chemical modifications are usually carried out on the same lead structure in the extrathermodynamic approach such as Hansch analysis. The next problem was to establish the concrete functional formula of the resis-

FIG. 1. SOMO-SOMO Interaction between Parent and Substituent Moieties

In this case, the frontier electron flows from the substituent to the parent through the lobes of $\phi^{\text{S}}_{\text{SOMO}}$ and $\phi^{\text{P}}_{\text{SOMO}}$ hybrid orbitals by the energy difference of $(E^{\text{S}}_{\text{SOMO}} - E^{\text{P}}_{\text{SOMO}})$.

TABLE III. Cross Correlation Matrix for Electronic Substituent Constants

	E	Re	I
E	1.000		
Re	0.526	1.000	
I	-0.190	-0.912	1.000
F	0.258	0.166	-0.046
R	-0.420	-0.419	0.284
σ_m	0.123	0.029	0.037
σ_p	-0.147	-0.182	0.150

tance. Although ϕ_{SOMO} 's are zero, for example in $\text{CH}=\text{CHNO}_2$ (No. 64) and OC_2H_5 (No. 85) of Table II, the frontier electron may flow even in such cases by using occupied or unoccupied orbitals near SOMO. Therefore, the SOMO resistance of the substituent (Re_{SOMO}) was defined in the following formula.

$$Re_{\text{SOMO}}(\text{X}) = \exp[-\phi_{\text{SOMO}}^2(\text{X})] \quad (\text{X} \neq \text{H}) \quad (6)$$

Eq. (6) is one of the simplest expressions that satisfies both requirements that the resistance should decrease monotonously, and that the frontier electron may flow even if ϕ_{SOMO} equals zero. However Re_{SOMO} of the hydrogen (H) should be estimated using eq. (7), because there exist no occupied or unoccupied orbitals except SOMO in this moiety.

$$Re_{\text{SOMO}}(\text{H}) = 1/[\exp\{\phi_{\text{SOMO}}^2(\text{H})\} - 1] \quad (7)$$

The frontier electron current intensity (I_{SOMO}) may also be defined as follows from the analogy to Ohm's law in the field of electrical engineering.

$$I_{\text{SOMO}}(\text{X}) = E_{\text{SOMO}}(\text{X})/Re_{\text{SOMO}}(\text{X}) \quad (8)$$

Thus, we have obtained the new electronic substituent parameters (E_{SOMO} , Re_{SOMO} , I_{SOMO}), which uniquely define the electronic state of each substituent.

Frontier substituent constant values of 150 kinds of substituents are shown in Table II. They are adjusted values, which are expressed in values relative to the hydrogen values as the standards using the following equations so that they may be easily handled.

$$E(\text{X}) = -10 \cdot [E_{\text{SOMO}}(\text{X}) - E_{\text{SOMO}}(\text{H})] \quad (9)$$

$$Re(\text{X}) = 10 \cdot [Re_{\text{SOMO}}(\text{X}) - Re_{\text{SOMO}}(\text{H})] \quad (10)$$

$$I(\text{X}) = -10 \cdot [I_{\text{SOMO}}(\text{X}) - I_{\text{SOMO}}(\text{H})] \quad (11)$$

Since zero was employed as $E_{\text{SOMO}}^{\text{P}}$ for convenience and the substituents possess the negative $E_{\text{SOMO}}^{\text{S}}$ values as shown in Table II, these constants may be regarded as measures concerned

with the electron attractive properties of the substituent. Thus, the large E value means that the frontier electron flows by the strong propelling power, and the low Re value expresses the small resistance of the passage. Similarly, the substituent with the large I value can accept a large quantity of frontier electron from the standard parent.

If the parent is known, it is also possible to take into account $E_{\text{SOMO}}^{\text{P}}$ and $\phi_{\text{SOMO}}^{\text{P}}$ in defining the substituent constants. In such a case, a functional formula of the resistivity may contain both $\phi_{\text{SOMO}}^{\text{P}}$ and $\phi_{\text{SOMO}}^{\text{S}}$.

Relationships among Electronic Substituent Constants

Table III shows the cross correlation matrix of electronic substituent constants including conventional ones.

The BMDP8D program,¹⁷⁾ which can handle the data containing missing values, was used for the calculation of the matrix in Table III. The extremely high coefficient ($r = -0.912$) is found between Re and I , and the somewhat high coefficient ($r = 0.526$) between E and Re with respect to the frontier substituent constants. Judging from the results, it is advisable at least not to use both Re and I simultaneously in the same equation to avoid collinearity problems.

According to Table III, there exist no apparent correlations between the frontier constants and the conventional ones (F , R , σ_m , σ_p). But the frontier constants are expected to be one of the important factors influencing the inductive-field effect of the substituent, since they are associated with the frontier electron transfer through the bond between the parent and the substituent. The following equation was obtained as the result of investigating the relationships between the frontier constants and the Swain-Lupton's F constant using 97 kinds of substituents in Table II for which the F constant values are available.

$$F = -1.21 E_{\text{SOMO}} (1 + 0.39 DO + 0.54 DB + 1.13 CH) + 0.16 I_{\text{SOMO}} - 0.28 \quad (12)$$

$n = 97, r = 0.794, s = 0.137$

TABLE IV. Results of Stepwise Multiple Regression Analyses applied to Various Kinds of Biological Data Using Frontier Substituent Constants as Electronic Parameters

(1) Hypnotic activity of barbiturates against rats ^{a)}	
$-\log\text{MED}$	$= - 0.296f^2 + 2.127f - 0.853Re + 0.044MR - 3.991$
	(0.167) (1.315) (0.584) (0.029) (2.957)
$n=15, r=0.885, s=0.119, F_{4,10}=9.06, F_{1,10}(Re)=10.044(1\%)$	
(2) Toxicity of barbiturates against rats ^{a)}	
$-\log\text{MLD}$	$= - 0.030f^2 - 1.510E - 0.496Re + 0.038MR - 1.880$
	(0.022) (0.983) (0.573) (0.027) (3.046)
$n=15, r=0.821, s=0.114, F_{4,10}=5.18, F_{1,10}(Re)=3.66(10\%), F_{1,10}(E)=11.57(1\%)$	
(3) Toxicity of benzoic acids against mosquito larvae ^{b)}	
$\log(1/C)$	$= 0.503\pi + 0.033Re + 1.588$
	(0.085) (0.045) (0.091)
$n=13, r=0.988, s=0.102, F_{2,10}=206.75, F_{1,10}(Re)=2.68(25\%)$	
(4) Toxicity of diethyl phenylphosphates against houseflies ^{b)}	
$\log(1/C)$	$= - 2.499\pi - 3.157E_m + 2.600E_p + 0.920$
	(1.129) (1.836) (1.635) (0.427)
$n=9, r=0.945, s=0.392, F_{3,5}=13.83, F_{1,5}(E_m)=19.58(1\%), F_{1,5}(E_p)=16.71(1\%)$	
(5) Carcinogenic activity of dimethylaminoazobenzenes ^{b)}	
$\log A$	$= - 0.084MR_o - 0.860\pi_p + 0.082MR_p + 0.311I_p + 0.860$
	(0.033) (0.637) (0.074) (0.140) (0.163)
$n=15, r=0.922, s=0.143, F_{4,10}=14.14, F_{1,10}(I_p)=24.18(0.5\%)$	
(6) Relative localization rates of benzeneboronic acids in brain tissue ^{c)}	
$\log C_b$	$= 0.266\pi_{o,p} + 0.163E_{o,p} - 0.051MR_m - 0.699H-D + 1.661$
	(0.186) (0.131) (0.035) (0.307) (0.194)
$n=25, r=0.913, s=0.268, F_{4,20}=25.07, F_{1,20}(E_{o,p})=6.79(2.5\%)$	
(7) Localization ratio of tumor to brain tissues ^{c)}	
$\log(C_t/C_b)$	$= - 0.100E_{o,p} + 0.046MR_m + 0.886H-D - 0.440$
	(0.152) (0.042) (0.281) (0.214)
$n=25, r=0.844, s=0.317, F_{3,21}=17.39, F_{1,21}(E_{o,p})=1.89(25\%)$	
(8) Hypnotic activity of barbiturates against rabbits ^{c)}	
$\log(1/C)$	$= - 0.472f^2 + 0.325MR + 5.611Re + 16.462$
	(0.275) (0.190) (5.980) (17.832)
$n=9, r=0.896, s=0.173, F_{3,5}=6.81, F_{1,5}(Re)=5.82(10\%)$	
(9) Narcotic activity of <i>p</i> -aminobenzoates against goldfishes ^{d)}	
$\log(1/C)$	$= - 0.241f^2 + 1.461f + 0.767E + 3.686$
	(0.149) (0.630) (0.748) (0.432)
$n=9, r=0.989, s=0.061, F_{3,5}=77.54, F_{1,5}(E)=6.96(5\%)$	
(10) Bacteriostatic activity of sulfanililides against <i>Escherichia coli</i> ^{e)}	
(i) <i>m, p</i> -forms	
$\log(1/C)$	$= 1.445\pi^2 - 1.311\pi + 0.459E_p - 0.115Re_p + 5.018$
	(0.547) (0.453) (0.412) (0.087) (0.172)
$n=17, r=0.909, s=0.219, F_{4,12}=14.32, F_{1,12}(E_p)=5.93(5\%), F_{1,12}(Re_p)=8.46(2.5\%)$	
(ii) all	
$\log(1/C)$	$= 1.346\pi^2 - 1.151\pi + 0.444E_p - 0.127Re_p + 0.987E_o$
	(0.637) (0.505) (0.479) (0.098) (0.701)
	$+ 0.181I_o + 5.018$
	(0.130) (0.177)

$$n=22, r=0.897, s=0.266, F_{6,15}=10.35, F_{1,15}(E_p)=3.90(10\%), F_{1,15}(Re_p)=7.55(2.5\%), F_{1,15}(E_o)=8.99(1\%), F_{1,15}(I_o)=8.74(1\%)$$

- (11) Human liver mitochondria MAO inhibition of N-phenoxyethyl cyclopropylamines^{f)}

$$\log(1/C) = - \underset{(0.169)}{0.235 I_m} + \underset{(0.034)}{0.097 MR_p} + \underset{(0.396)}{5.989}$$

$$n=9, r=0.955, s=0.399, F_{2,6}=30.88, F_{1,6}(I_m)=11.53(2.5\%)$$

- (12) Rat liver MAO inhibition of N-phenoxyethyl cyclopropylamines^{f)}

$$\log(1/C) = \underset{(0.294)}{0.755 E_m} + \underset{(0.375)}{0.743 \pi_p} - \underset{(0.148)}{0.231 I_p} + \underset{(0.238)}{5.315}$$

$$n=18, r=0.917, s=0.404, F_{3,14}=24.57, F_{1,14}(I_p)=11.46(0.5\%), F_{1,14}(E_m)=30.63(0.5\%)$$

- (13) Inhibitory potency of chloramphenicols against *Escherichia coli*^{g)}

$$\log A = - \underset{(0.249)}{0.505 \pi^2} + \underset{(0.136)}{0.093 I} + \underset{(0.064)}{0.092 MR} + \underset{(0.581)}{0.960}$$

$$n=9, r=0.923, s=0.222, F_{3,5}=9.59, F_{1,5}(I)=3.03(25\%)$$

- (14) Diuretic activity of sulfonamides against rats^{h)}

$$\log(1/C) = - \underset{(0.253)}{0.808 H-D} + \underset{(0.172)}{0.261 H-A} + \underset{(0.059)}{0.060 I_p} + \underset{(0.121)}{0.254}$$

$$n=15, r=0.918, s=0.140, F_{3,11}=19.70, F_{1,11}(I_p)=4.70(10\%)$$

- (15) Natriuretic activity of sulfonamides against rats^{h)}

$$\log(1/C) = - \underset{(0.249)}{0.750 H-D} + \underset{(0.169)}{0.279 H-A} + \underset{(0.059)}{0.058 I_p} + \underset{(0.117)}{0.266}$$

$$n=15, r=0.913, s=0.137, F_{3,11}=18.29, F_{1,11}(I_p)=4.73(10\%)$$

- (16) Carbonic anhydrase inhibitory activity of sulfonamidesⁱ⁾

(i) 0.2°C

$$\log(1/K_I) = \underset{(0.419)}{0.531 \pi_{o,p}} + \underset{(0.080)}{0.141 MR} - \underset{(0.618)}{0.604 D} + \underset{(0.173)}{0.147 I_{o,p}} - \underset{(0.732)}{0.479}$$

$$n=18, r=0.816, s=0.414, F_{4,13}=6.47, F_{1,13}(I_{o,p})=3.41(10\%)$$

(ii) 15 °C

$$\log(1/K_I) = \underset{(0.419)}{0.573 \pi_{o,p}} + \underset{(0.080)}{0.130 MR} - \underset{(0.618)}{0.554 D} + \underset{(0.173)}{0.148 I_{o,p}} - \underset{(0.732)}{0.338}$$

$$n=18, r=0.804, s=0.414, F_{4,13}=5.96, F_{1,13}(I_{o,p})=3.46(10\%)$$

- (17) Rabbit liver cytochrome P-450 conversion to P-420 by anilines^{j)}

$$\log(1/C) = \underset{(0.172)}{0.806 \pi} + \underset{(0.053)}{0.046 Re} + \underset{(0.100)}{0.917}$$

$$n=7, r=0.988, s=0.076, F_{2,4}=84.23, F_{1,4}(Re)=5.80(10\%)$$

- (18) Anesthetic activity of aliphatic ethers against mice^{k)}

$$-\log ED_{50} = - \underset{(0.054)}{0.158 f^2} + \underset{(0.364)}{1.068 f} + \underset{(0.031)}{0.038 MR} + \underset{(0.337)}{0.492 Re} + \underset{(1.175)}{1.732}$$

$$n=28, r=0.966, s=0.103, F_{4,23}=79.43, F_{1,23}(Re)=9.04(1\%)$$

- (19) Excretion response of benzoic acids against rabbits^{l)}

$$RBR = \underset{(0.128)}{0.391 \pi} - \underset{(0.022)}{0.059 MR} - \underset{(0.069)}{0.044 I} + \underset{(0.158)}{1.990}$$

$$n=8, r=0.988, s=0.082, F_{3,4}=52.51, F_{1,4}(I)=3.10(25\%)$$

- (20) Hypnotic activity of barbiturates against rats^{l)}

$$-\log MHD = - \underset{(0.179)}{0.278 f^2} + \underset{(1.604)}{1.582 f} - \underset{(0.740)}{0.412 I} + \underset{(0.036)}{0.058 MR} + \underset{(3.560)}{0.206}$$

$$n=14, r=0.898, s=0.119, F_{4,9}=9.33, F_{1,9}(I)=1.61(25\%)$$

- (21) Toxicity of barbiturates against rabbits^{l)}

$$-\log\text{MLD} = - \frac{0.046f^2}{(0.031)} + \frac{0.069MR}{(0.038)} - \frac{0.966Re}{(0.435)} - \frac{0.982}{(1.906)}$$
 $n=11, r=0.904, s=0.077, F_{3,7}=10.39, F_{1,7}(Re)=27.43(0.5\%)$
- (22) Toxicity of aliphatic ethers against mice^{l)}

$$-\log\text{LD}_{50} = - \frac{0.238f^2}{(0.117)} + \frac{1.105f}{(0.668)} + \frac{0.114MR}{(0.042)} + \frac{0.511E}{(0.557)} - \frac{0.329}{(1.053)}$$
 $n=25, r=0.937, s=0.151, F_{4,20}=36.20, F_{1,20}(E)=3.68(10\%)$
- (23) Bacteriostatic activity of phenylmethacrylates against *Streptococcus faecalis*^{l)}

$$-\log\text{MIC} = - \frac{0.031\pi^2}{(0.010)} + \frac{0.177Re}{(0.033)} + \frac{2.862}{(0.129)}$$
 $n=8, r=0.988, s=0.069, F_{2,5}=106.35, F_{1,5}(Re)=178.92(0.5\%)$
- (24) Growth inhibitory activity of aliphatic alcohols against mouse fibroblast L-cells^{m)}

$$-\log\text{ID}_{50} = - \frac{0.857f_2}{(0.389)} + \frac{0.194MR_2}{(0.052)} - \frac{1.200Re_2}{(1.020)} - \frac{1.351}{(1.785)}$$
 $n=13, r=0.952, s=0.223, F_{3,9}=28.99, F_{1,9}(Re_2)=7.09(5\%)$
- (25) Toxicity of aliphatic alcohols against mice^{m)}

$$-\log\text{LD}_{50} = - \frac{1.129f_2}{(0.382)} - \frac{4.862E_2}{(1.970)} - \frac{1.299Re_2}{(1.387)} - \frac{2.587}{(3.407)}$$
 $n=13, r=0.917, s=0.221, F_{3,9}=15.89, F_{1,9}(E_2)=31.13(0.5\%), F_{1,9}(Re_2)=4.49(10\%)$
- (26) Antielectroshock activity of 5- α -thienylhydantoinsⁿ⁾
 (i) mice

$$\log(1/C) = - \frac{0.245f^2}{(0.188)} + \frac{0.611f}{(0.509)} - \frac{0.123I}{(0.207)} + \frac{2.629}{(0.274)}$$
 $n=7, r=0.928, s=0.067, F_{3,3}=6.16, F_{1,3}(I)=3.62(25\%)$
 (ii) rats

$$\log(1/C) = - \frac{0.660f^2}{(0.185)} + \frac{2.306f}{(0.684)} + \frac{1.415E}{(0.503)} + \frac{2.486}{(0.165)}$$
 $n=7, r=0.990, s=0.029, F_{3,3}=47.79, F_{1,3}(E)=78.30(0.5\%)$
- (27) Anticonvulsant activity of 4-benzoylpyridines against mice^{o)}

$$\log(1/C) = - \frac{0.121\pi^2}{(0.067)} + \frac{0.173\pi}{(0.101)} - \frac{0.227E_o}{(0.184)} - \frac{0.079I_o}{(0.083)} + \frac{3.273}{(0.104)}$$
 $n=13, r=0.928, s=0.129, F_{4,8}=12.46, F_{1,8}(E_o)=8.07(2.5\%), F_{1,8}(I_o)=4.77(10\%)$
- (28) Inhibitory activity of O-phenyl-DL-homoserines against rat liver ATP: L-methionine S-adenosyltransferase^{p)}

$$\text{pl}_{50} = \frac{2.279\pi^2}{(0.764)} - \frac{0.953\pi}{(0.508)} + \frac{0.061I_p}{(0.064)} + \frac{1.684}{(0.125)}$$
 $n=11, r=0.956, s=0.121, F_{3,7}=25.06, F_{1,7}(I_p)=5.27(10\%)$
- (29) Inhibitory activity of 9-phenylguanines against rabbit liver guanine deaminase^{q)}

$$\log(1/C) = - \frac{0.501Re_o}{(0.319)} + \frac{0.068MR_m}{(0.027)} - \frac{0.129Re_m}{(0.153)} + \frac{0.388\pi_p}{(0.203)} + \frac{1.058D}{(0.505)} + \frac{5.115}{(0.281)}$$
 $n=29, r=0.877, s=0.475, F_{5,23}=15.30, F_{1,23}(Re_o)=10.58(0.5\%), F_{1,23}(Re_m)=3.03(10\%)$
- (30) Inhibitory activity of phenyl methylcarbamates against bovine erythrocyte acetylcholinesterase^{r)}
 (i) *p*-form

$$\log(1/K_d) = \frac{0.065MR}{(0.026)} + \frac{0.048I}{(0.090)} + \frac{1.989}{(0.248)}$$
 $n=10, r=0.921, s=0.180, F_{2,7}=19.58, F_{1,7}(I)=1.60(25\%)$
 (ii) *m*-form

- $$\log(1/K_d) = \begin{matrix} 0.204MR & 0.192I & 1.790 \\ (0.069) & (0.196) & (0.605) \end{matrix}$$
- $n=10, r=0.939, s=0.409, F_{2,7}=26.13, F_{1,7}(I)=5.39(10\%)$
- (iii) all
- $$\log(1/K_d) = \begin{matrix} 0.198MR_m & 0.069MR_p & 0.187I_m & 1.857 \\ (0.038) & (0.030) & (0.132) & (0.307) \end{matrix}$$
- $n=19, r=0.949, s=0.310, F_{3,15}=44.91, F_{1,15}(I_m)=9.10(1\%)$
- (31) Inhibition of rat liver microsomal epoxidation of aldrin by 5-phenoxyethylimidazoles^{s)}
- $$pI_{50} = - \begin{matrix} 0.435D & 0.182E & 6.133 \\ (0.144) & (0.069) & (0.093) \end{matrix}$$
- $n=8, r=0.970, s=0.072, F_{2,5}=40.14, F_{1,5}(E)=45.01(0.5\%)$
- (32) Herbicidal activity of ethyl N-chloroacetyl-N-phenylglycinates^{t)}
- (i) the rice plant
- $$pI_{50} = \begin{matrix} 0.579\pi_o & 0.221I_o & -0.073MR_m & 4.602 \\ (0.281) & (0.091) & (0.041) & (0.361) \end{matrix}$$
- $n=28, r=0.896, s=0.410, F_{3,24}=32.44, F_{1,24}(I_o)=24.94(0.5\%)$
- (ii) barnyard-grass
- $$pI_{50} = \begin{matrix} 0.562\pi_o & 0.203I_o & 4.417 \\ (0.208) & (0.082) & (0.200) \end{matrix}$$
- $n=28, r=0.843, s=0.374, F_{2,25}=30.59, F_{1,25}(I_o)=26.47(0.5\%)$
- (33) Sweet taste potency of *m*-nitroanilines^{u)}
- $$\log RS = \begin{matrix} 0.717^1\chi & -0.299E & -3.423 \\ (0.460) & (0.289) & (2.518) \end{matrix}$$
- $n=9, r=0.896, s=0.325, F_{2,6}=12.22, F_{1,6}(E)=6.36(5\%)$
- (34) Rabbit liver cytochrome P-450 conversion to P-420 by phenols^{u)}
- $$\log(1/C) = \begin{matrix} 0.736^1\chi^v & -0.231E_m & 0.113Re_p & -0.568 \\ (0.263) & (0.258) & (0.158) & (0.773) \end{matrix}$$
- $n=14, r=0.946, s=0.254, F_{3,10}=28.67, F_{1,10}(E_m)=3.94(10\%), F_{1,10}(Re_p)=2.55(25\%)$
- (35) Inhibitory activity of benzyl alcohols against *Aspergillus niger*^{u)}
- $$\log(1/C) = \begin{matrix} 2.050^4\chi_p^v & -0.080I_{3,5} & 0.102Re_4 & 0.362 \\ (0.501) & (0.094) & (0.117) & (0.439) \end{matrix}$$
- $n=19, r=0.950, s=0.254, F_{3,15}=46.50, F_{1,15}(I_{3,5})=3.38(10\%), F_{1,15}(Re_4)=3.37(10\%)$
- (36) Tumor-inhibitory activity of cycloheximide cinnamates against mice^{v)}
- $$TW = \begin{matrix} 0.162MR_o & 1.483E_o & -1.168\pi_p & -1.784E_p & -0.368I_p & 2.713 \\ (0.090) & (1.124) & (0.728) & (1.371) & (0.414) & (0.439) \end{matrix}$$
- $n=15, r=0.862, s=0.537, F_{5,9}=5.22, F_{1,9}(E_o)=8.90(2.5\%), F_{1,9}(E_p)=8.67(2.5\%), F_{1,9}(I_p)=4.06(10\%)$
- (37) Immunosuppressive activity of cycloheximide cinnamates against mice^{v)}
- $$HT = - \begin{matrix} 0.517MR_m & 1.343I_m & -0.666\pi_{o,p} & 0.190MR_{o,p} & 4.815 \\ (0.390) & (1.072) & (1.127) & (0.196) & (1.785) \end{matrix}$$
- $n=15, r=0.861, s=1.161, F_{4,10}=7.15, F_{1,10}(I_m)=7.80(2.5\%)$
- (38) Viral neuraminidase inhibition of 1-phenoxyethyl-3,4-dihydroisoquinolines^{w)}
- $$\log(1/C) = \begin{matrix} 0.096\pi^2 & -0.023Re_p & 2.726 \\ (0.046) & (0.024) & (0.068) \end{matrix}$$
- $n=15, r=0.823, s=0.087, F_{2,12}=12.59, F_{1,12}(Re_p)=4.03(10\%)$
- (39) Inhibitory activity of phenyl N-methylcarbamates against bovine erythrocyte acetylcholinesterase^{x)}
- (i) *o*-form

$$\Delta \log(1/K_d) = -1.646\pi + 0.339E + 0.283MR - 1.309H-A - 0.139$$

(1.800) (0.310) (0.205) (1.776) (0.532)

$n=15, r=0.872, s=0.346, F_{4,10}=7.93, F_{1,10}(E)=6.02(5\%)$

(ii) *m*-form

$$\Delta \log(1/K_d) = 0.521\pi - 0.156Re + 0.084MR - 0.046$$

(0.304) (0.089) (0.040) (0.403)

$n=21, r=0.911, s=0.401, F_{3,17}=27.65, F_{1,17}(Re)=13.57(0.5\%)$

(iii) *p*-form

$$\Delta \log(1/K_d) = 0.122I + 0.027MR + 0.663H-A + 0.116$$

(0.072) (0.021) (0.222) (0.275)

$n=19, r=0.873, s=0.216, F_{3,15}=16.07, F_{1,15}(I)=12.59(0.5\%)$

(iv) all

$$\Delta \log(1/K_d) = 0.531\pi_m - 0.156Re_m + 0.078MR_m - 0.350\pi_o + 0.244E_o$$

(1.071) (0.073) (0.028) (0.381) (0.232)

$$+ 0.135MR_o + 0.125I_p + 0.033MR_p + 0.689H-A_p + 0.024$$

(0.040) (0.107) (0.024) (0.317) (0.246)

$n=53, r=0.892, s=0.341, F_{9,43}=18.67, F_{1,43}(Re_m)=18.60(0.5\%), F_{1,43}(E_o)=4.51(5\%), F_{1,43}(I_p)=5.22(5\%)$

(40) Toxicity of 1-phenyl-3,3-dimethyltriazenes against rats^{v)}

$$-\log LD_{50} = -0.713\pi^2 + 0.822\pi + 0.066Re + 2.462$$

(0.508) (0.464) (0.053) (0.122)

$n=8, r=0.956, s=0.087, F_{3,4}=14.32, F_{1,4}(Re)=11.53(5\%)$

(41) Analgesic activity of 1-methyl-4-piperidinol benzoates against mice^{z1)}

$$-\log ED_{50} = -0.435\pi_m - 0.076I_m - 0.185\pi_p + 1.434$$

(0.497) (0.066) (0.180) (0.140)

$n=11, r=0.872, s=0.142, F_{3,7}=7.42, F_{1,7}(I_m)=7.69(5\%)$

(42) Inhibitory activity of benzamidines against human serine proteases^{z2)}

(i) C1s

$$\log(1/K_I) = 0.416\pi_m + 0.160Re_m - 3.321E_{o,p} - 1.214I_{o,p} + 3.177$$

(0.313) (0.169) (1.472) (0.696) (0.376)

$n=16, r=0.889, s=0.554, F_{4,11}=10.40, F_{1,11}(Re_m)=4.33(10\%), F_{1,11}(E_{o,p})=24.60(0.5\%), F_{1,11}(I_{o,p})=14.64(0.5\%)$

(ii) plasmin

$$\log(1/K_I) = -0.192I_m + 0.095MR_m - 1.017I_{o,p} - 1.057E_{o,p} + 3.417$$

(0.148) (0.100) (0.649) (1.266) (0.329)

$n=17, r=0.811, s=0.484, F_{4,12}=5.76, F_{1,12}(I_m)=7.99(2.5\%), F_{1,12}(I_{o,p})=11.64(1\%), F_{1,12}(E_{o,p})=3.32(10\%)$

(43) Antibacterial activity of 3-formylrifamycin SV N-phenylpiperazinoacetylhydrazones^{z3)}(i) *Staphylococcus aureus*

$$\log(1/C) = -0.309\pi^2 + 0.277\pi + 0.054I + 0.058MR + 7.040$$

(0.222) (0.158) (0.050) (0.036) (0.192)

$n=14, r=0.893, s=0.114, F_{4,9}=8.83, F_{1,9}(I)=6.03(5\%)$

(ii) *Bacillus subtilis*

$$\log(1/C) = 0.194\pi + 0.078E + 5.051$$

(0.095) (0.090) (0.090)

$n=14, r=0.805, s=0.128, F_{2,11}=10.14, F_{1,11}(E)=3.61(10\%)$

(iii) *Clostridium perfringens*

$$\log(1/C) = 0.141\pi + 0.095I + 8.284$$

(0.062) (0.031) (0.067)

$$n = 13, r = 0.936, s = 0.091, F_{2,10} = 35.37, F_{1,10}(I) = 48.26(0.5\%)$$

- (44) Mutagenic activity of 1-phenyl-3,3-dialkyltriazenes against *Salmonella typhimurium* strain TA92^{z 4)}

(i) dimethyl form

$$\log(1/C) = \frac{1.386\pi_m}{(0.633)} + \frac{0.906\pi_p}{(0.341)} + \frac{0.750E_p}{(0.753)} + \frac{0.054MR_p}{(0.058)} + \frac{5.484}{(0.590)}$$

$$n = 15, r = 0.936, s = 0.566, F_{4,10} = 17.76, F_{1,10}(E_p) = 4.91(10\%)$$

(ii) all

$$\log(1/C) = \frac{0.947\pi_p}{(0.314)} + \frac{0.825E_p}{(0.699)} + \frac{0.055MR_p}{(0.057)} + \frac{1.380\pi_m}{(0.599)} + \frac{3.700Re_R}{(3.800)} + \frac{11.455}{(6.140)}$$

$$n = 18, r = 0.935, s = 0.549, F_{5,12} = 16.68, F_{1,12}(E_p) = 6.59(2.5\%), F_{1,12}(Re_R) = 4.50(10\%)$$

- (45) Bovine liver dihydrofolate reductase inhibition of 5-benzyl-2,4-diaminopyrimidines^{z5)}

$$pI_{50} = \frac{0.700\pi_m}{(0.165)} + \frac{0.047Re_p}{(0.054)} + \frac{4.958}{(0.108)}$$

$$n = 23, r = 0.894, s = 0.180, F_{2,20} = 39.71, F_{1,20}(Re_p) = 3.31(10\%)$$

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p) P.B. Hulbert, *Mol. Pharmacol.*, **10**, 315 (1974). I_{50} : 50% inhibitory concentration.

q) C. Silipo and C. Hansch, *Mol. Pharmacol.*, **10**, 954 (1974). D : dummy variable. 1 for substitution where oxygen atom is directly attached to para-position.

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In eq. (12), *DO* and *DB* are the dummy variables. The former assigns 1 to the substituent having the third-row atom attached to the parent, and the latter assigns 1 to the substituent with C=O, C=S, N=O, or S=O groups directly linked to the parent, respectively. *CH* is for the charge on the substituent, that is, +1 for the substituent with a positive charge, and -1 for that with a negative charge.

The fact that the *F* constants are well associated with the frontier constants by such a simple relation as eq. (12) supports the above-mentioned expectation. According to eq. (12), E_{SOMO} may also serve as the propelling power for the other electronic transfers such as *d*-orbital and π -electron participating ones.

The correlations between the frontier constants and those relating the properties other than the electronic one (π , *f*, *MR*, H-A, H-D) are also low. They are at most 0.45.

Application to Biological Data

Various kinds of biological data were analyzed to examine the applicability of the frontier substituent constants to the quantitative drug design problems. The data were taken from the literatures in which Hansch-type regression analyses had been already performed. The results are collected in Table IV. In deriving the equation, π or *f* constants were used as hydrophobic variables according to the type of substitution, that is, π constants for the aromatic substitution, and *f* constants for the aliphatic one, respectively. They were taken from the Pomona College Medicinal Chemistry Parameter Files,²⁾ and not experimentally determined values. As a steric variable, the molar refractivity (*MR*) was employed. Besides, dummy variables such as hydrogen-accepting (H-A) and hydrogen-donating (H-D) properties, *etc.* were added if necessary. Each equation was determined using the forward stepwise multiple regression technique. The

values in parentheses under coefficients of each equation give 95% confidence limits for the coefficients. As for the statistics, *n* is the number of compounds analyzed, *r* is the correlation coefficient, *s* is the standard deviation, and $F_{m,n}$ is the *F* values with degrees of freedom, *m* and *n*. In particular, $F_{1,n}(X)$ shows the partial *F* value adding *X* to the equation. For example, $F_{1,10}(Re) = 10.044(1\%)$ in eq. (1) means that the addition of the *Re* term to the equation is significant at 1% level compared to the equation from which the *Re* term is excluded.

Although coefficients of the π^2 term should be negative theoretically, those of eq. (10), (28) and (38) have positive values. Thus, it may be dangerous to use these equations for the prediction of biological potency of the compound whose π value is beyond the range used in formulating equations. Comparisons with usual electronic parameters were not carried out in this study. It seems meaningless to discuss relative merits of the frontier constants against the conventional ones because large errors might be usually accompanied with the biological data in the literatures examined. According to Table IV, the frontier constants are found to be successfully applicable to various types of the biological data.

CONCLUSIONS

There have so far been numerous reports¹⁸⁻²¹⁾ in which the quantum chemical indices of the molecule are employed as the theoretical electronic parameters. But they do not have the wide applicability, because they are not the physicochemical constants inherently assigned to the substituent. The frontier substituent constants are the first electronic substituent constants that were developed theoretically for the quantitative drug design problems.

The author does not insist on the superiority of them over the conventional constants. But they

are easy to handle and are applicable to both aromatic and aliphatic systems as shown in Table IV. In addition, the definitions are simple and clear enough to understand. Thus, they may be employed as alternatives to conventional parameters in Hansch analysis.

Kier²²⁾ proposed the topological method using the molecular connectivity and proved its utility in the biological regression analyses. However, the concept of molecular connectivity is devoid of any electronic factors of the molecule as pointed out by him. The frontier substituent constants may be used as the electronic variables in the molecular connectivity analysis, as successfully shown in eq. (33)–(35) of Table IV. This approach seems interesting because it adopts only theoretical indices as variables.

The new constants would be much improved if the spin state of the substituent was taken into account. This may be accomplished using the computer programs of the molecular orbital methods for the open shell system such as the CNINDO program.²³⁾ Although three kinds of constants (E , Re , I) were derived from E_{SOMO} and ϕ_{SOMO} in this paper, it may be also possible to use E_{SOMO} and ϕ_{SOMO} as they are.

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