CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 36, No. 10 October 1988

Regular Articles

[Chem. Pharm. Bull. 36(10)3743—3752(1988)]

On the Novel Quantitative Structure–Activity Relationships (QSAR) Descriptors σ_{s° and μ^2/α Deduced from the Modified Lennard–Jones 12, 6 Potentials

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(Received January 22, 1988)

From the evaluation of the force constant derived from the modified Lennard–Jones 12,6 potential, the substituent entropy constant σ_{s° has been deduced and revealed to be an effective descriptor representing both attractive (in other words, dispersion) and repulsive forces. Furthermore, for polar molecules, an additional descriptor μ^2/α was proved to be a reasonable one representing both induction and orientation forces. These two kinds of quantitative structure–activity relationships (QSAR) descriptors are applied to many substituted methane and benzene derivatives and shown to be useful.

Keywords——quantitative structure–activity relationship; van der Waals force; Lennard–Jones 12,6 potential; intermolecular force; substituent entropy constant σ_{s°, QSAR descriptor μ^2/α; standard entropy $S^\circ_{298}(g)$

Studies on intermolecular forces by means of the modified Lennard–Jones 12,6 potential have long been accepted as a promising approach to the evaluation of the interaction between pairs of apolar or polar molecules, and numerous force constants determined from this approach have been compiled by Hirschfelder *et al.*[1)]

These force constants, namely, effective diameter and potential minimum ε/k, are given for associated molecules in the gas phase originally, and are determined from the 2nd virial coefficient, gas viscosity, or their combination. This background shows that these force constants reflect the weak molecular interactions. In recent years, chemical reactions *in vitro*, involving large enthalpy changes, have been evaluated in terms of thermodynamics and quantum chemistry, but, on the other hand, drug-receptor interaction or biological responces can be classified in the category of weak molecular interactions. This situation has prompted us to extend these force constants determined by the modified Lennard–Jones 12,6 potential equation for the evaluation of the relative contributions of their components, and, furthermore, to examine the chemical significance of two novel quantitative structure–activity relationships (QSAR) descriptors, substituent entropy constant σ_{s° and descriptor μ^2/α.

TABLE I. Relative Weights of $E_{\text{dis.}}$, $E_{\text{ind.}}$ and $E_{\text{ori.}}$ (erg cm^6) × 10^{-60}, Based on CH_4, MeCl and $Me_2C=O$ as References

	CH_4		MeCl			$Me_2C=O$		
	$E_{\text{dis.}}$	$E_{\text{ind.}}$	$E_{\text{dis.}}$	$E_{\text{ind.}}$	$E_{\text{ori.}}$	$E_{\text{dis.}}$	$E_{\text{ind.}}$	$E_{\text{ori.}}$
MeF	162.0	8.5	254.8	28.4	92.9	325.4	52.6	220.3
MeCl	178.2	9.1	282.3	31.9	99.1	362.4	60.0	235.1
Me_2O	219.2	4.4	349.5	28.7	47.9	450.7	60.5	113.6
$MeCO_2Me$	247.1	5.9	393.2	36.6	83.9	506.3	73.5	198.9
$MeCO_2Et$	351.8	8.2	559.9	47.5	89.8	721.1	98.4	213.0
$Me_2C=O$	226.9	21.6	362.4	60.0	253.1	468.0	105.0	557.6
$MeNO_2$	193.2	31.1	306.1	71.9	339.3	393.0	116.8	804.9
MeCN	182.3	41.0	287.8	87.5	446.7	368.4	136.9	1059.6

General Consideration

Attractive parts of weak intermolecular interactions, in a broad sense, can be classified into three kinds of groups, namely, dispersion, induction, and orientation interactions, and, of the three, the dispersion term is defined as van der Waals force.[2)]

The three kinds of energies are given by Eqs. 1—3;

$$E_{\text{dis.}} = -3/2\alpha_A\alpha_B/r^6_{AB} \cdot I_A I_B/(I_A+I_B) \tag{1}$$

$$E_{\text{ind.}} = -(\alpha_A\mu^2_B+\alpha_B\mu^2_A)/r^6_{AB} \tag{2}$$

$$E_{\text{ori.}} = -\mu^2_A\mu^2_B/r^6_{AB} \cdot 1/3kT \tag{3}$$

where

α = polarizability × 10^{-24} (cm^3)
I = ionization potential (eV)
μ = dipole moment × 10^{-18} (erg$^{1/2}$ cm$^{3/2}$)
k = Boltzmann constant 1.380 × 10^{-16} (erg/K)
r = intermolecular separation × 10^{-8} (cm)

Practically, r_{AB} could not be readily estimated, whereas the relative weights of these three kinds of energies could be easily obtained, even if the common denominator r_{AB} is unknown. The results are summarized in Table I.

Furthermore, a weak association is inevitably accompanied with a repulsive force operating between the molecules in question. In this work, the authors tried to utilize the modified Lennard–Jones 12,6 potential[3)] to examine this problem.

Apolar Like and Unlike Pairs

The Lennard–Jones 12,6 potential between an apolar like pair AA is given by Eq. 4 as below;

$$\phi_{AA} = 4\varepsilon^\circ_{AA}[(\sigma^\circ_{AA}/r)^{12} - (\sigma^\circ_{AA}/r)^6] \tag{4}$$

where

$\sigma^\circ_{AA} = r^\circ_{AA}(1/2)^{1/6}$
r°_{AA} = separation at potential minimum × 10^{-8} (cm)
σ°_{AA} = effective diameter × 10^{-8} (cm)
ε°_{AA} = potential minimum expressed as ε°/k (K)

The first term of the right-hand side of Eq. 4 is a repulsive term and the second is an attractive term, due to the contribution from the dispersion force in the apolar pair AA. In the case of an apolar unlike pair AB, the two kinds of force constants could be obtained by an empirical mixture rule,[4] as given by Eq. 5;

$$r^{\circ}_{AB}=(r^{\circ}_{AA}+r^{\circ}_{BB})/2 \qquad \varepsilon^{\circ}_{AB}=(\varepsilon^{\circ}_{AA}\varepsilon^{\circ}_{BB})^{1/2} \tag{5}$$

Polar Unlike and Like Pair by Free-Energy-Average Potential[3]

For a polar unlike pair AB, the angle-averaged potential can be given by the free-energy-average polar potential according to Eq. 6;

$$\phi^{\text{av.}}_{AB}=4\varepsilon^{\circ}_{AB}[(\sigma^{\circ}_{AB}/r)^{12}-(\sigma^{\circ}_{AB}/r)^{6}]-1/r^{6}[(\alpha_{A}\mu^{2}_{B}+\alpha_{B}\mu^{2}_{A})+\mu^{2}_{A}\mu^{2}_{B}/3\boldsymbol{k}T] \tag{6}$$

Furthermore, for a polar like pair AA, Eq. 6 can be transformed to Eq. 7;

$$\phi^{\text{av.}}_{AA}=4\varepsilon^{\circ}_{AA}[(\sigma^{\circ}_{AA}/r)^{12}-(\sigma^{\circ}_{AA}/r)^{6}]-1/r^{6}(2\alpha_{A}\mu^{2}_{A}+\mu^{4}_{A}/3\boldsymbol{k}T) \tag{7}$$

In Eqs. 6 and 7, σ° and ε° denote apolar fractions of the force constants in the polar pairs, and can be obtained according to Eqs. 8 and 9;
For the AB pair

$$\begin{gathered}\phi^{\text{av.}}_{AB}=4\varepsilon_{AB}[(\sigma_{AB}/r)^{12}-(\sigma_{AB}/r)^{6}]\\ \sigma^{6}_{AB}=(\sigma^{\circ}_{AB})^{6}/F \qquad \varepsilon_{AB}=\varepsilon^{\circ}_{AB}F^{2}\\ F=1+\mu^{2}_{A}\mu^{2}_{B}/[12\boldsymbol{k}T\varepsilon^{\circ}_{AB}(\sigma^{\circ}_{AB})^{6}]+(\alpha_{A}\mu^{2}_{B}+\alpha_{B}\mu^{2}_{A})/4\varepsilon^{\circ}_{AB}(\sigma^{\circ}_{AB})^{6}\end{gathered} \tag{8}$$

For the AA pair

$$\begin{gathered}\phi^{\text{av.}}_{AA}=4\varepsilon_{AA}[(\sigma_{AA}/r)^{12}-(\sigma_{AA}/r)^{6}]\\ \sigma^{6}_{AA}=(\sigma^{\circ}_{AA})^{6}/F \qquad \varepsilon_{AA}=\varepsilon^{\circ}_{AA}F^{2}\\ F=1+\mu^{4}_{A}/[12\boldsymbol{k}T\varepsilon^{\circ}_{AA}(\sigma^{\circ}_{AA})^{6}]+\alpha_{A}\mu^{2}_{A}/2\varepsilon^{\circ}_{AA}(\sigma^{\circ}_{AA})^{6}\end{gathered} \tag{9}$$

Experimental

Absolute Entropy S°_{298}(g) (e.u.) and Substituent Entropy Constant $\sigma_{s^{\circ}}$——All the values of absolute entropy S°_{298}(g) are cited from the literature,[5,6] and the substituent entropy constant $\sigma_{s^{\circ}}$[7] is defined by Eq. 15.

Ionization Potential——Data are cited from reference 8.

Dipole Moment——Data are cited from reference 9.

Polarizability——The values of polarizability are cited from reference 10, and some of them are calculated from the Lorentz–Lorenz equation $n^{2}-1/n^{2}+2\cdot M/d=4/3\pi N\alpha$, using the refractive index n^{20}_{D}.[11]

Regression Analyses——Regression analyses were carried out on an NEC PC-9801 personal computer using the program MVA[12] developed in our laboratory.

Results and Discussion

Linear Relations between Apolar Potential Minima $\varepsilon^{\circ}_{AA}/k$ (K) and S°_{298}(g)

Apolar potential minima $\varepsilon^{\circ}_{AA}/k$ (K) determined from the Lennard–Jones 12,6 potential among apolar like pairs have been estimated on the bases of 2nd virial coefficient, gas viscosity, or their combinations. Tee *et al.*[13] applied the last method, together with the Kihara rigid-spherical-core model,[14] and obtained force constants of aliphatic apolar hydrocarbon pairs (see Table II).

Some additional data on apolar $\varepsilon^{\circ}_{AA}/k$ (K)[3] estimated from Eq. 9 are also presented in Table II. They were derived from the gas viscosity data of aliphatic polar like pairs.

Table II. Empirical Force Constants of Apolar and Polar Like Pairs, Cube Root of Polarizability and $S^\circ_{298}(g)$

	Apolar				Polar			
	σ°_{AA} (Å)		ε°_{AA}/k (K)		σ_{AA} (Å)	ε_{AA}/k (K)	$\alpha^{1/3}$ (Å)	$S^\circ_{298}(g)$ (e.u.)
	a)	b)	a)	b)				
CH_4	3.678	3.505	166.78	232.20			1.379	44.52
C_2H_4	4.200	3.912	219.01	328.21				52.45
C_2H_6	4.221	3.977	274.48	425.32			1.649	54.85
C_3H_8		4.519		493.71			1.855	64.51
CMe_4	5.638	5.395	357.13	625.88			2.169	73.23
n-C_4H_{10}	5.003	4.830	398.92	672.33			2.016	74.12
n-C_5H_{12}	5.282	5.396	474.15	777.37			2.156	83.40
n-C_7H_{16}	5.715	5.996	621.23	1023.30			2.393	102.27
	c)		c)		c)	c)		
$CHCl_3$	5.355		344.3		5.350	348.2	2.043	70.66
CH_2Cl_2	4.921		362.3		4.910	382.1	1.896	64.59
MeCl	4.449		228.2		4.357	293.5	1.657	56.04
Et_2O	5.660		320.42		5.655	449.0	2.074	81.90
EtOH	4.575		327.8		4.531	367.6	1.722	67.54
$MeCO_2Me$	5.026		422.1		5.002	446.9	1.909	79.8
$MeCO_2Et$	5.314		463.7		5.293	486.7	2.066	86.70
$Me_2C=O$	5.085		310.4		4.917	464.8	1.856	70.49

a) Reference 13. b) Reference 14. c) Reference 3.

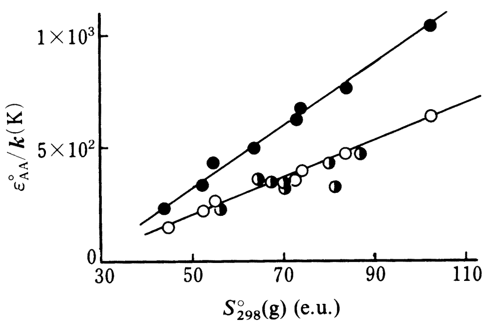

Fig. 1. Correlations between ε°_{AA}/k(K) and $S^\circ_{298}(g)$ (e.u.)

●, ref. 6; ○, ref. 5; ◑, ref. 3.

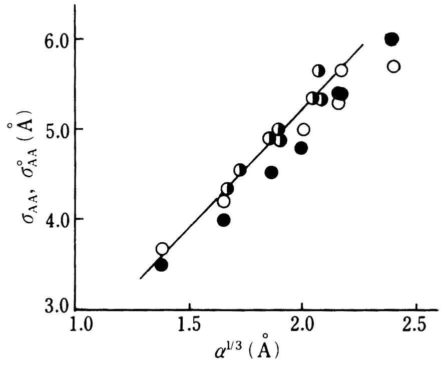

Fig. 2. Correlations between Effective Diameter σ°_{AA}, σ_{AA} (Å) and Cube Root of Polarizability (Å)

●, ref. 6; ○, ref. 5; ◑, ref. 3.

In this work, for the first time, the authors have found that the values of ε°_{AA}/k (K) are linearly related to the absolute entropy $S^\circ_{298}(g)$ of the substrates as shown in Fig. 1.

In any event, the three different approaches confirm that ε°_{AA}/k (K) increases proportionally to $S^\circ_{298}(g)$, and the result of regression analysis of the combined data[3,13] can be expressed by Eq. 10.

$$\varepsilon^\circ_{AA}/k = 7.570(\pm 1.048)S^\circ_{298}(g) - 175.227(\pm 0.428) \qquad (10)$$

$$n = 14 \qquad r = 0.997 \qquad F = 247.60 \qquad \text{S.D.} = 20.09$$

Table III. Estimation of Unknown Force Constants $\varepsilon^{\circ}_{AA}/k$ (K) and σ°_{AA} (Å), σ_{AA} (Å)

	$\varepsilon^{\circ}_{AA}/k$ (K)	σ°_{AA} (Å), σ_{AA} (Å)
C_3H_8	313.11	4.827
iso-C_4H_{10}	357.85	5.307
n-C_6H_{14}	527.50	5.962
n-C_8H_{18}	669.21	6.524
n-C_9H_{20}	739.68	6.773
MeOH	258.46	3.878
$MeNO_2$	322.35	4.459
MeCN	265.27	4.273
MeBr	269.51	4.691
MeI	284.35	5.146
PhF	372.31	5.698
PhMe	404.94	6.038
PhCl	391.92	6.043
$PhNO_2$	481.09	6.143
Ph-1,3,5-Me_3	521.89	6.594

Consequently, by use of Eq. 10, unknown values of $\varepsilon^{\circ}_{AA}/k$ (K) could be estimated (Table III).

Estimation of Intermolecular Separation at Potential Minimum

As stated in the previous section, the conversion of σ to σ°, as well as ε to ε° can be achieved by determining the factor F in Eqs. 8 and 9, and the transformed values of ε° and σ° become essential in Eqs. 6 and 7 for the determination of the $E_{\mathrm{dis.}}$ and $E_{\mathrm{rep.}}$ terms. The original σ_{AA} should be determined empirically. The three kinds of data[3,13,14] are linearly related to the cube root of the polarizability $\alpha^{1/3} \times 10^{-8}$ (cm) as shown in Fig. 2, because the polarizability represents the actual volume of the substrate molecule.

Regression analyses of the data in columns (a) and (c) of Table II afforded Eqs. 11 and 12 for the apolar and polar groups, respectively.

$$\sigma^{\circ}_{AA}=2.134(\pm 0.512)\alpha^{1/3}+0.739(\pm 1.380) \tag{11}$$

$$n=6 \qquad r=0.985 \qquad F=133.69 \qquad \mathrm{S.D.}=0.155$$

$$\sigma_{AA}=2.615(\pm 0.532)\alpha^{1/3}+0.019(\pm 53.746) \tag{12}$$

$$n=8 \qquad r=0.980 \qquad F=144.80 \qquad \mathrm{S.D.}=0.090$$

Of the above two equations, Eq. 12 is better than Eq. 11, because the former passes through the origin, and when the unknown σ_{AA} of polar pair is estimated by Eq. 12, the corresponding σ°_{AA} could be obtained from Eq. 9.

For a polar unlike pair AB, the intermolecular separation r_{AB} could be given by the Eq. 13.

$$\begin{aligned} r^{\circ}_{AA} &= \sigma^{\circ}_{AA}\cdot 2^{1/6} \\ r^{\circ}_{BB} &= \sigma^{\circ}_{BB}\cdot 2^{1/6} \\ r_{AB} \equiv r^{\circ}_{AB} &= (r^{\circ}_{AA}+r^{\circ}_{BB})/2 \end{aligned} \tag{13}$$

Estimations of $E_{\mathrm{dis.}}$, $E_{\mathrm{ind.}}$, and $E_{\mathrm{ori.}}$ between Apolar–Apolar, Apolar–Polar and Polar–Polar Pairs

The energies due to the dispersion, induction and orientation interactions between

TABLE IV. $E_{dis.}$, $E_{ind.}$ and $E_{ori.}$ (cal mol^{-1}) of Apolar–Apolar, Apolar–Polar and Polar–Polar Pairs: Substrate = CH_4, MeC = O and MeCl

	CH_4		$Me_2C=O$			MeCl		
	$E_{dis.}$	$E_{ind.}$	$E_{dis.}$	$E_{ind.}$	$E_{ori.}$	$E_{dis.}$	$E_{ind.}$	$E_{ori.}$
CH_4	662.7		904.1	25.9		775.2	16.5	
C_2H_6	850.2		1159.9	27.5		994.5	18.1	
CMe_4	969.8		1322.3	27.4		1134.4	16.1	
n-C_4H_{10}	1025.0		1398.3	27.7		1198.9	16.5	
n-C_5H_{12}	1117.4		1524.4	22.4		1307.1	16.2	
n-C_7H_{16}	1279.0		1744.9	26.7		1496.1	15.4	
MeCl	775.2	16.5	1057.6	43.3	168.8	906.8	33.5	104.2
CH_2Cl_2	976.8	7.6	1332.5	36.8	81.4	1142.6	25.4	49.2
$CHCl_3$	952.1	2.7	1057.6	43.8	171.0	1113.8	19.5	18.1
Et_2O	1082.3	5.2	1476.5	21.2	29.1	1266.0	17.0	17.1
EtOH	929.1	11.9	1267.5	34.2	123.2	1086.8	28.8	75.5
$MeCO_2Me$	1054.3	8.8	1438.3	36.7	94.3	1233.3	25.8	56.8
$MeCO_2Et$	1105.0	7.7	1507.5	37.7	85.9	1292.6	25.8	51.2
$Me_2C=O$	904.0	25.9	1233.4	53.5	279.4	1057.6	43.3	168.8
CCl_4	1008.1							
$MeNO_2$	921.4	51.9	1257.0	78.9	535.0	1077.8	69.8	328.9
MeCN	835.9	79.5	1140.3	104.3	803.6	977.7	88.7	497.9
Et_3N			1654.2	27.8	11.1	1418.3	16.5	6.4

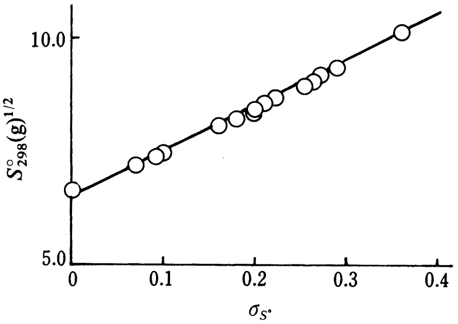

Fig. 3. Correlation between $S^\circ_{298}(g)^{1/2}$ and σ_{S°

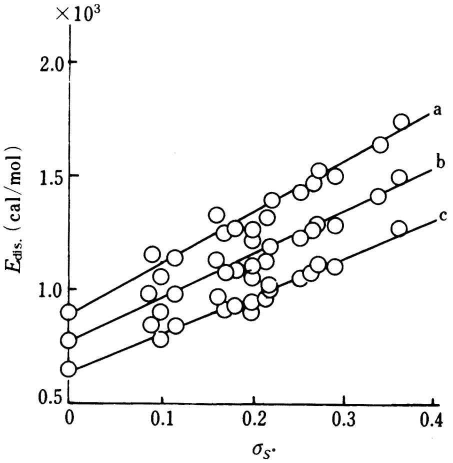

Fig. 4. Correlations between $E_{dis.}$ (cal mol^{-1}) and σ_S

a, $Me_2C=O$; b, MeCl; c, CH_4.

apolar–apolar, apolar–polar, and polar–polar pairs, referring to methane, acetone, and methyl chloride as substrates, have been estimated and the results are shown in Table IV, where the estimations of $E_{dis.}$ were carried out using the mixture rule, *e.g.* $\varepsilon^\circ_{AB}=(\varepsilon^\circ_{AA}\varepsilon^\circ_{BB})^{1/2}$. The values of $E_{ind.}$ and $E_{ori.}$ could not be estimated until the intermolecular separation r°_{AB} (namely, effective apolar diameter σ°_{AA} and σ°_{BB} of the polar like pair) is determined. The data summarized in Table IV suggest that $E_{dis.}$ plays a dominant role among the three kinds of contributions, and $E_{ori.}$ shows a pronounced increase when either partner has a large dipole moment, whereas $E_{ind.}$ always plays a minor role.

Table V. $S^\circ_{298}(g)$ (e.u.) and Substituent Entropy Constant σ_{S° of Monosubstituted Methane and Benzene Derivatives

R	MeR		C_6H_5R	
	$S^\circ_{298}(g)$	σ_{S°	$S^\circ_{298}(g)$	σ_{S°
H	44.52	0.000	64.34	0.000
Me	54.85	0.091	76.64	0.076
Et	64.51	0.161	86.15	0.127
n-Pr	74.12	0.221	95.76	0.173
iso-Pr	70.42	0.199	92.87	0.156
n-Bu	83.40	0.273	105.04	0.206
iso-Bu	82.12	0.266	101.97	0.200
sec-Bu	82.12	0.266	102.44	0.202
tert-Bu	73.23	0.210	95.83	0.173
n-C_5H_{11}	92.83	0.319	114.47	0.250
n-C_6H_{13}	102.27	0.361	123.78	0.284
n-C_7H_{15}	111.55	0.399	133.09	0.316
C_6H_5	76.64	0.236	93.85	0.164
NMe_2	69.02	0.190	87.5	0.134
NHMe	65.24	0.166	81.6	0.103
NH_2	57.98	0.115	76.28	0.074
NHC_6H_5	81.6	0.263	97.5	0.181
OH	57.29	0.110	75.43	0.069
OMe	63.83	0.156	86.2	0.127
SH	60.96	0.163	80.51	0.097
F	53.25	0.078	72.33	0.051
Cl	56.04	0.099	74.92	0.067
Br	58.75	0.122	77.53	0.083
I	60.71	0.135	79.84	0.094
CF_3	68.66	0.188	89.05	0.142
CHO	63.15	0.152	86.2	0.127
COMe	70.49	0.200	89.12	0.142
CO_2H	67.52	0.181	88.19	0.137
CO_2Me	79.9	0.245	102.0	0.200
CN	58.19	0.120	76.73	0.077
$C\equiv CH$	59.30	0.125	76.88	0.077
$CH=CH_2$	63.80	0.156	82.48	0.108
CH_2Br	68.71	0.188	90.8	0.150

Definition of Substituent Entropy Constant σ_{s° as an Effective Descriptor Representing Both $E_{\text{dis.}}$ and $E_{\text{rep.}}$

As stated in the foregoing section, the values of ε°/k (K) determined from apolar like pairs and those calculated for polar like pairs are linearly related to $S^\circ_{298}(g)$, so both $E_{\text{dis.}}$ and $E_{\text{rep.}}$ of these two series at potential minima could be related to Eq. 14, using the mixture rule.[4)]

$$\varepsilon^\circ_{AB} = (\varepsilon^\circ_{AA}\varepsilon^\circ_{BB})^{1/2} \propto [S^\circ_{298}(g)_A S^\circ_{298}(g)_B]^{1/2} \qquad (14)$$

When B is specified as a reference and A denotes a partner, Eq. 14 becomes as follows;

$$\varepsilon^\circ_{AB} \propto S^\circ_{298}(g)^{1/2}_A$$

Consequently, when the substituent entropy constant σ_{s° is defined by Eq. 15, this descriptor is linearly related to $S^\circ_{298}(g)^{1/2}_A$ as shown in Fig. 3, and the values of $E_{\text{dis.}}$ (Table IV) are linearly related to σ_{s° of the partners (Fig. 4).

TABLE VI. Products of Polarizability $\alpha_A\alpha_B$ ($\times 10^{-48}$ cm^6) and 6th Power of Intermolecular Separation r^6_{AB} ($\times 10^{-48}$ cm^6) of Apolar and Polar Pairs: Substrate B = CH_4

	α_A	$\alpha_A\alpha_B$	r^6_{AB}
CH_4	2.62	6.86	4397
C_2H_6	4.48	11.74	7703
C_3H_8	6.38	16.72	11242
n-C_4H_{10}	8.19	21.46	15305
iso-C_4H_{10}	8.36	21.90	15671
CMe_4	10.20	26.25	19933
n-C_5H_{12}	10.02	26.25	19503
n-C_6H_{14}	11.80	30.92	23981
n-C_7H_{16}	13.70	35.89	28791
n-C_8H_{18}	15.54	40.71	33776
$CHCl_3$	8.53	22.35	15918
CH_2Cl_2	6.82	17.87	11831
MeCl	4.55	11.92	7849
Et_2O	8.92	23.37	19725
EtOH	5.11	13.39	9260
$Me_2C=O$	6.39	16.74	11996
$MeCO_2Me$	6.96	18.24	12720
$MeCO_2Et$	8.82	23.11	15522

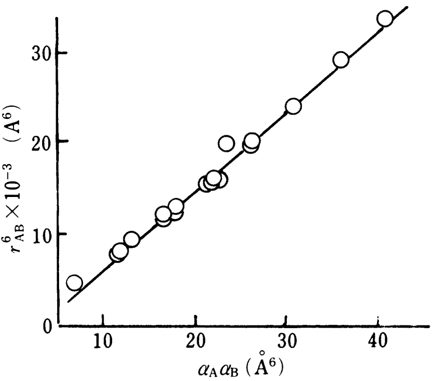

Fig. 5. Correlation between $r^6_{AB} \times 10^{-3}$ (Å^6) and $\alpha_A\alpha_B$ (Å^6)

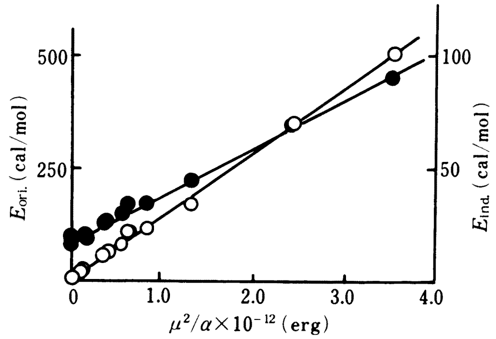

Fig. 6. Correlations of $E_{ind.}$ and $E_{ori.}$ against $\mu^2/\alpha \times 10^{-12}$ (erg)

Substrate = MeCl. ○, $E_{ori.}$; ●, $E_{ind.}$.

$$\sigma_{s^\circ} = \log S^\circ_{298}(g)_A/S^\circ_{298}(g)_B \tag{15}$$

Furthermore, as Eq. 4 suggests an empirical relation between the hard sphere diameter σ° and the separation at potential minimum r°_0, the relative ratio of the two exponential terms (namely, attractive *vs.* repulsive) becomes constant. Thus, the descriptor σ_{s° seems reasonable, embracing both attractive (*i.e.*, dispersion) and repulsive terms.

Substituent Entropy Constants σ_{s° of Typical Monosubstituted Methane and Benzene Derivatives

As shown in the previous section, the substituent entropy constant σ_{s° can be obtained from the absolute entropy $S^\circ_{298}(g)$ determined by measurement of the temperature dependency of the specific heat of the pure material or by statistical mechanical analysis of vibrational spectra; the data are compiled mainly in references 5 and 6. The values of $S^\circ_{298}(g)$

Table VIIa. Values of μ^2/α ($\times 10^{-12}$ erg) of Monosubstituted Benzenes and Methanes

Substituent R	C_6H_5R	MeR
NMe_2	0.15	0.05
NH_2	0.19	
OMe	0.15	0.32
OH	0.19	0.86
iso-Pr	0.01	0.00
tert-Bu	0.00	0.00
Et	0.01	0.00
Me	0.01	0.00
H	0.00	0.00
F	0.19	1.26
Cl	0.19	0.83
Br	0.18	0.58
I	0.11	0.29
CHO	0.61	1.37
COMe	0.62	1.30
CO_2Me	0.23	0.41
CO_2Et	0.23	0.36
CN	1.13	3.52
NO_2	1.19	2.42
CF_3	0.53	
SH	0.10	
SMe	0.12	0.28

Table VIIb. Values of μ^2/α ($\times 10^{-12}$ erg) of Typical Aliphatic Compounds

Compound	μ^2/α	Compound	μ^2/α
Dioxane	0.02	$CHBr_3$	0.08
EtOH	0.57	CH_2I_2	0.09
n-PrOH	0.41	CHI_3	0.06
n-$C_6H_{11}OH$	0.10	$HCONH_2$	3.37
H_2O	2.27	$MeCONH_2$	2.68
CHF_3	0.93	$HCONMe_2$	1.91
CF_4	0.00	MeCONHMe	1.57
CH_2Cl_2	0.35	EtCN	2.64
$CHCl_3$	0.13	$EtNO_2$	1.93
CCl_4	0.00	Et_2O	0.15
CH_2Br_2	0.23	Et_3N	0.03

and $\sigma_{s^{\circ}}$ of typical monosubstituted methane and benzene derivatives are summarized in Table V.

The majority of available data[5,6)] cover typical aliphatic compounds, but from the practical QSAR view point, $\sigma_{s^{\circ}}$ must apply to various kinds of substitution, especially polysubstituted benzene derivatives. Further work is necessary in this respect.

Descriptor μ^2/α Representing Both $E_{\text{ind.}}$ and $E_{\text{ori.}}$

As given by Eqs. 2 and 3, $E_{\text{ind.}}$ and $E_{\text{ori.}}$ are determined when the dipole moment, polarizability, and intermolecular separation of the two partners are known, but, unfortunately, in the QSAR approach, physicochemical information on the receptor side is usually wanted. Thus, we transformed Eqs. 2 and 3 to Eqs. 16 and 17, respectively.

$$E_{\text{ind.}} = -(\alpha_A\mu_B^2 + \alpha_B\mu_A^2)/r_{AB}^6 \propto (\mu_A^2/\alpha_A + \mu_B^2\alpha_B) \qquad (16)$$

$$E_{\text{ori.}} = -\mu_A^2\mu_B^2/r_{AB}^6 \cdot 1/3kT \propto \mu_A^2/\alpha_A \cdot \mu_B^2/\alpha_B \cdot 1/3kT \qquad (17)$$

These transformations imply a linear relationship of $\alpha_A\alpha_B$ to r_{AB}^6, and this is confirmed to be valid in Fig. 5, based on the data summarized in Table VI.

From this evidence, we conclude that the descriptor μ^2/α effectively represents the contributions of both $E_{\text{ind.}}$ and $E_{\text{ori.}}$. The values of $E_{\text{ind.}}$ and $E_{\text{ori.}}$ (Table IV) are linearly related to μ^2/α as shown in Fig. 6, and values of this descriptor are available for typical aromatics and aliphatics (see Tables, VIIa, b).

Acknowledgement Financial assistance from Hoan-sha is gratefully acknowledged.

References and Notes

1) J. O. Hirschfelder, C. F. Curtiss, and R. B. Bird, "Molecular Theory of Gases and Liquids," Wiley, New York, 1954, and references cited therein.
2) T. M. Reed and K. E. Gubbins, "Applied Statistical Mechanics," McGraw–Hill, London, 1973, and references cited therein.
3) T. M. Reed and K. E. Gubbins, "Applied Statistical Mechanics," McGraw–Hill, 1973, Chapter 5, p. 163.
4) D. W. Calvin and T. M. Reed, III, *J. Chem. Phys.*, **54**, 3733 (1971).
5) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, 1969.
6) *a*) S. W. Benson, "Thermochemical Kinetics," Wiley, New York, 1967; *b*) S. W. Benson, *et al.*, *Chem. Rev.*, **69**, 279 (1969).
7) Y. Sasaki, T. Takagi, Y. Yamasato, A. Iwata, and H. Kawaki, *Chem. Pharm. Bull.*, **29**, 3073 (1981).
8) The Chemical Society of Japan, "Kagaku-Benran II," Chapter 14, 1984.
9) A. L. McClellan, "Tables of Experimental Dipole Moments," Freeman, San Fransisco, 1963.
10) J. Applequist, J. R. Carl, and K.-K. Fung, *J. Am. Chem. Soc.*, **94**, 2952 (1972).
11) Zvi Rappoport, "Handbook of Tables for Organic Compound Identifications," 3rd ed., Chemical Rubber Co., 1967.
12) T. Takagi, K. Tange, N. Iwata, Y. Shindo, A. Iwata, T. Katayama, H. Izaki, S. Fujii, and Y. Sasaki, The 4th Software Conference, Proceedings, Osaka, 1988, p. 285.
13) L. S. Tee, S. Gotoh, and W. E. Stewart, *Ind. Eng. Chem. Fundam.*, **5**, 356 (1966).
14) L. S. Tee, S. Gotoh, and W. E. Stewart, *Ind. Eng. Chem. Fundam.*, **5**, 363 (1966).