Rational Estimation of the QSAR (Quantitative Structure–Activity Relationships) Descriptors σ_{S°, and Their Applications for Medicinals Now Available

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Rational estimation of the descriptor σ_{S°, representing the dispersion and repulsion energies in the van der Waals interaction for both aliphatic and aromatic moieties, enabled us to present the descriptors of several important medicinals now available. In this work, the fundamental rule for the estimation of the descriptor for a substrate having a variety of binding modes and the correction value ΔS° necessary for aliphatic heterocycle formation are confirmed, and the descriptors for several important moieties are established according to the concept of quantitative structure–activity relationship analogy. Furthermore, several kinds of herbicides, antiinflammatory agents, hypocholesterolemics, analgesics, sympathetic stimulants, and antipsychotics are concerned in this work.

Keywords entropy constant; absolute entropy; regression analysis; quantitative structure–activity relationship

Introduction

In our previous reports[1a–c] on the estimation of the descriptors σ_{S° for several kinds of substituted methanes, as well as benzenes, the basic treatments were revealed to potentially allow us to estimate an unknown descriptor, per our proposal. In this work, from the demand of quantitative structure–activity relationship (QSAR), we have modified and improved our empirical equations for substituted methanes having $\Sigma\sigma_{S^\circ}(\text{mono}) \geqq 0.4$. Furthermore, the estimation of the correction values, ΔS° value, in the formation of aliphatic heterocycles from a linear molecule, and the precise estimation of unknown important moieties among analogs have been established. Using the prerequisite stated above, we are able to estimate the descriptor σ_{S° for several important varieties of medicinals now available.

TABLE Ia. Analogs and Their Descriptors σ_{S°. Aromatic Amines and Hydrocarbons

	S°_{298} (g)	Arom. σ_{S°	$n \times R\ln 2 / n$	$n \times R\ln 3 / n$
Ph–NH_2	76.28	0.074	1	0
	74.10	0.061	0	1
Ph–NHMe	81.6	0.103	0	1
Ph–NHEt	91.11[a)]	0.151	0	1
Ph–NMe_2	87.5	0.134	1	2
	91.06	0.151	0	1
Ph–NEt_2	105.57[a)]	0.215	1	2
	109.13	0.229	0	1
Ph–NMeEt	96.33	0.175	0	2
	98.51	0.185	0	1
Ph–NH–*n*-Pr	100.80	0.195	0	1
Ph–NH–*n*-Bu	110.53	0.235	0	1
Ph–NH–iso-Pr	98.22	0.184	0	2
	100.40	0.193	0	1
Ph–Me	76.64	0.076	3	1
	79.39	0.091	1	1
Ph–Et	86.15	0.127	1	1
Ph–*n*-Pr	95.76	0.173	1	1
Ph–iso-Pr	92.87	0.159	1	2
	93.05	0.169	1	1
Ph–$CHEt_2$	110.59	0.235	1	2
	112.77	0.244	1	1
Ph–*sec*-Bu	102.33	0.202	0	2
	103.13	0.205	1	1
Ph–*n*-Bu	105.04	0.213	1	1
Ph–*n*-C_5H_{11}	114.47	0.250	1	1
Ph–iso-Bu	102.33	0.202	1	2
	104.51	0.211	1	1

a) Corrected values. Estimations are carried out using linear relation, $\sigma_{S^\circ}(\text{Ph–N=}) = 1.077\,\sigma_{S^\circ}(\text{Ph–C=}) - 0.034$. $R\ln 2$ = entropy of mixing of two optical isomers or that of the presence of plane of symmetry. $R\ln 3$ = entropy of internal symmetry of CH_3. Including $R\ln 2$ of racemate.

TABLE Ib. Analogs and Their Descriptors σ_{S°. Aliphatic Primary-Amines and Hydrocarbons

	S°_{298} (g)	Ali. σ_{S°	$n \times R\ln 3 / n$	$n \times R\ln 2 / n$
$MeNH_2$	57.98	0.115	1	1
$EtNH_2$	68.08	0.184	1	1
n-$PrNH_2$	77.48	0.241	1	1
iso-$PrNH_2$	76.68	0.236	2	1
	78.86	0.248	1	1
n-Bu–NH_2	86.76	0.290	1	1
sec-Bu–NH_2	83.90	0.275	2	1
	86.08	0.286	1	1
tert-Bu–NH_2	80.76	0.259	3	1
	85.12	0.281	1	1
$PhCH_2$–NH_2	89.50	0.303	0	1
	87.32	0.293	1	1
n-$C_5H_{11}NH_2$	96.26	0.335	1	1
Me–Me	54.85	0.091	2	3
Me–Et	64.51	0.161	2	3
Me–*n*-Pr	74.12	0.221	2	3
Me–iso-Pr	70.42	0.199	3	3
	75.36	0.229	2	3
Me–*n*-Bu	83.40	0.273	2	3
Me–*sec*-Bu	82.12	0.266	3	3
	84.30	0.277	2	3
Me–*tert*-Bu	73.23	0.216	4	6
	81.73	0.264	2	3
Me–CH_2Ph	86.15	0.287	1	3
	83.97	0.275	2	3
n-C_6H_{14}	92.83	0.319	2	3

—=estimated values. Estimations are carried out using linear relation, $\sigma_{S^\circ}(\text{R–NH}_2) = 0.956\,\sigma_{S^\circ}(\text{R–Me}) + 0.030$. $R\ln 3$ = entropy of internal symmetry of CH_3. $R\ln 2$ = entropy of the presence of plane of symmetry. Including $R\ln 2$ of racemate.

TABLE Ic. Analogs and Their Descriptors σ_{S°. Aliphatic Secondary-Amines and Hydrocarbons

	S°_{298} (g)	Ali. σ_{S°	$n \times R\ln 3 / n$	$n \times R\ln 2 / n$
Me–NH–Me	65.24	0.166	2	1
	66.62	0.175	2	0
Et–NH–Et	84.18	0.277	2	1
	85.56	0.284	2	0
n-Bu–NH–iso-Bu	120.0	0.431	3	0
	122.18	0.438	2	0
Et–NH–Me	74.91	0.226	2	0
n-Pr–NH–Me	84.44	0.278	2	0
n-Pr–NH–Et	93.88	0.324	2	0
n-Pr–NH–*n*-Pr	103.41	0.366	2	0
	102.03	0.360	2	1
Me–CH_2–Me	64.51	0.161	2	2
	65.89	0.170	2	1
Et–CH_2–Et	83.40	0.273	2	2
	84.78	0.280	2	1
2-Me-*n*-C_8H_{17}	118.52	0.425	3	1
	120.70	0.433	2	1
Et–CH_2–Me	74.12	0.221	2	1
n-Pr–CH_2–Me	83.40	0.273	2	1
n-Pr–CH_2–Et	92.83	0.319	2	1
n-Pr–CH_2–*n*-Pr	102.27	0.361	2	1

—=estimated values. Estimations are carried out using linear relation, σ_{S°(–NH–) = 1.000 σ_{S°(–CH_2–) + 0.005. $R\ln 3$ = entropy of internal symmetry of CH_3. $R\ln 2$ = entropy of the presence of plane of symmetry.

TABLE Id. Analogs and Their Descriptors σ_{S°. Aliphatic Tertiary-Amines and Hydrocarbons

	S°_{298} (g)	Ali. σ_{S°	$n \times R\ln 3 / n$	$n \times R\ln 2 / n$
Me_3N	69.02	0.190	3	3
	71.78	0.207	3	1
Et_3N	96.90	0.338	3	3
	99.66	0.350	3	1
Et–NMe_2	80.46	0.258	3	1
Me–NEt_2	89.03	0.301	3	1
sec-Bu–NMe_2	97.37	0.340	4	1
	99.55	0.349	3	1
n-Pr–NMeEt	99.76	0.350	3	0
	98.38	0.344	3	1
n-Pr–NMe_2	89.34	0.303	3	1
n-Pr–NEt_2	108.09	0.385	3	1
Me_3CH	70.42	0.199	3	3
	73.18	0.216	3	1
Et_3CH	98.35	0.344	3	3
	101.11	0.356	3	1
Et–$CHMe_2$	82.12	0.266	3	1
Me–$CHEt_2$	90.77	0.309	3	1
sec-Bu–$CHMe_2$	98.96	0.347	4	1
	101.14	0.356	3	1
n-Pr–CHMeEt	101.37	0.357	3	0
	99.99	0.351	3	1
n-Pr–$CHMe_2$	90.95	0.310	3	1
n-Pr–$CHEt_2$	109.51	0.391	3	1

—=estimated values. Estimations are carried out using linear relation, σ_{S°(–N=) = 1.021 σ_{S°(–CH=) – 0.014. $R\ln 3$ = entropy of internal symmetry of CH_3. $R\ln 2$ = entropy of the presence of plane of symmetry. Including $R\ln 2$ of racemate.

TABLE Ie. Analogs and Their Descriptors σ_{S°. for Secondary-Alkylbenzene Derivatives

	Arom. σ_{S°	$n \times R\ln 3 / n$	$n \times R\ln 2 / n$	σ_{S° (MeR)
Ph–$CHMe_2$	0.159	2	1	
	0.166	2	0	
Ph–CH(Me)Et	0.202	2	0	
Ph–CH(Me)–*n*-Pr	0.242	2	0	
Ph–CH(OH)Me	0.179	1	0	
	0.169	2	0	
Ph–$CH(Me)CO_2Et$	0.281	2	0	
Ph–CH(Me)Et	0.202	2	0	0.091
Ph–$CHEt_2$	0.237	2	1	0.161
	0.243	2	0	
Ph–CH(Et)–*n*-Pr	0.283	2	0	0.221
Ph–CH(OH)Et	0.219	1	0	0.110
	0.210	2	0	
Ph–$CH(Et)CO_2Et$	0.322	2	0	0.289

Including $R\ln 2$ for racemate. —=observed values. Estimations are carried out using linear relation, σ_{S°(PhCHMeR) = 0.587 σ_{S°(MeR) + 0.111 and σ_{S°(PhCHEtR) = 0.606 σ_{S°(MeR) + 0.147. $R\ln 3$ = entropy of internal symmetry of CH_3. $R\ln 2$ = entropy of the presence of plane of symmetry.

TABLE If. Analogs and Their Descriptors σ_{S°. Secondary-Alcohols and Hydrocarbons

	Ali. σ_{S°	$n \times R\ln 3 / n$	$n \times R\ln 2 / n$
Me_2CHOH	0.221	2	1
	0.229	2	0
EtMeCHOH	0.285	2	0
n-PrMeCHOH	0.330	2	0
Et_2CHOH	0.323	2	1
	0.329	2	0
Ph–CH(OH)Me	0.338	1	0
Ph–CH(OH)Et	0.379	1	0
Ph–CH(OH)–*n*-Pr	0.413	1	0
p-Cl–PhCH(OH)Me	0.358	1	0
p-Cl–PhCH(OH)Et	0.401	1	0
p-Cl–PhCH(OH)–*n*-Pr	0.432	1	0
Me_2CHMe	0.199	3	3
	0.224	3	0
EtMeCHMe	0.266	3	1
	0.273	3	0
n-PrMeCHMe	0.310	3	1
	0.317	3	0
Et_2CHMe	0.309	3	1
	0.316	3	0
Ph–$CHMe_2$	0.319	2	1
	0.326	2	0
Ph–CHMeEt	0.361	2	0
Ph–CHMe–*n*-Pr	0.402	2	0
p-Cl–Ph–$CHMe_2$	0.340	2	0
	0.334	2	1
p-Cl–Ph–CHMeEt	0.386	2	0
p-Cl–Ph–CHMe–*n*-Pr	0.422	2	0

Including $R\ln 2$ for racemate. —=observed values. Estimations are carried out using linear relation, $\sigma_{S^\circ}(R_1R_2CHOH) = 1.086\,\sigma_{S^\circ}(R_1R_2CHMe) - 0.014$ and σ_{S°(–PhCHOHR) = 0.931 σ_{S°(–PhCHMeR) + 0.039. $R\ln 3$ = entropy of internal symmetry of CH_3. $R\ln 2$ = entropy of the presence of plane of symmetry.

Experimental

Absolute Entropy S°_{298}(g)/e.u. Observed absolute entropies cited in this work are all taken from the data sources.[2a,b]

Substituent Entropy Constant σ_{S°[1a] Descriptor is defined as $\sigma_{S^\circ} = \log\{S^\circ_{298}(g)_A / S^\circ_{298}(g)_B\}$, where the subscript A denotes substituted benzene or methane, and B represents unsubstituted ones, respectively.

Descriptor σ_{S° for $C_6H_{6-n}R_n$ (n=2, 3, 4): Estimations are carried out according to the following equations, Eqs. 1—9[1b]

$$\sigma_{S^\circ}(12) = 0.859\Sigma\sigma_{S^\circ}(\text{mono}) - 0.011 \quad (1)$$

$$\sigma_{S^\circ}(13) = 0.894\Sigma\sigma_{S^\circ}(\text{mono}) - 0.013 \quad (2)$$

$$\sigma_{S^\circ}(14) = 0.905\Sigma\sigma_{S^\circ}(\text{mono}) - 0.022 \quad (3)$$

$$\sigma_{S^\circ}(123) = 0.779\Sigma\sigma_{S^\circ}(\text{mono}) - 0.021 \quad (4)$$

TABLE Ig. Analogs and Their Descriptors σ_{S°. Aliphatic Primary- and Secondary-Amides *vs.* Their Amines

	S°_{298} (g)	Ali. σ_{S°	$n\times R\ln 3/n$	$n\times R\ln 2/n$
$HCONH_2$	59.38	0.125	0	1
	57.2	0.109	1	1
$MeCONH_2$	69.10	0.191	1	1
$EtCONH_2$		0.242	1	1
n-$PrCONH_2$		0.294	1	1
MeCONHMe		0.227	2	0
MeCONH–*n*-Bu	105.2	0.373	2	0
MeCONHEt		0.290	2	0
MeCONH–*n*-Pr		0.335	2	0
HCH_2NH_2	57.98	0.115	1	1
$MeCH_2NH_2$	68.08	0.184	1	1
n-$PrNH_2$	77.48	0.241	1	1
n-$BuNH_2$	86.76	0.290	1	1
EtNHMe		0.226	2	0
Et–NH–*n*-Bu		0.366	2	0
Et–NH–Et	84.18	0.277	2	1
	85.56	0.284	2	0
Et–NH–*n*-Pr		0.324	2	0

Estimations are carried out using linear relation, $\sigma_{S^\circ}(RCONH_2)=0.972\,\sigma_{S^\circ}(RCH_2NH_2)+0.012$ and $\sigma_{S^\circ}(MeCONHR)=1.012\,\sigma_{S^\circ}(MeCH_2NHR)+0.003$. ___=estimated values. $R\ln 3$=entropy of internal symmetry of CH_3. $R\ln 2$= entropy of the presence of plane of symmetry.

TABLE Ih. Analogs and Their Descriptors σ_{S°. Aliphatic Secondary-Ketones, Tertiary-Amides and Tertiary-Amines

	Ali. σ_{S°	$n\times R\ln 3/n$	$n\times R\ln 2/n$
MeCO–iso-Pr	0.298	3	1
MeCO–*sec*-Bu	0.341	3	1
	0.347	3	0
MeCO–$CHEt_2$	0.376	3	1
	0.382	3	0
MeCOCH(Me)–*n*-Pr	0.376	3	1
	0.382	3	1
MeCOCH(Et)–*n*-Pr	0.417	3	1
	0.422	3	0
$MeCONMe_2$	0.290	3	1
MeCON(Me)–Et	0.334	3	1
$MeCONEt_2$	0.370	3	1
MeCON(Me)–*n*-Pr	0.370	3	1
MeCON(Et)–*n*-Pr	0.412	3	1
$MeCH_2NMe_2$	0.258	3	1
$MeCH_2N$(Me)–Et	0.301	3	1
$MeCH_2NEt_2$	0.338	3	3
	0.350	3	1
$MeCH_2N$(Me)–*n*-Pr	0.344	3	1
	0.350	3	0
$MeCH_2N$(Et)–*n*-Pr	0.385	3	1

___=observed values. Estimations are carried out using linear relation, $\sigma_{S^\circ}(MeCONR_1R_2)=0.961\,\sigma_{S^\circ}(MeCH_2NR_1R_2)+0.042$ and $\sigma_{S^\circ}(MeCONR_1R_2)=1.026\,\sigma_{S^\circ}(MeCOCHR_1R_2)-0.016$. $R\ln 3$=entropy of internal symmetry of CH_3. $R\ln 2$=entropy of the presence of plane of symmetry. Including $R\ln 2$ for racemate.

$$\sigma_{S^\circ}(124)=0.765\Sigma\sigma_{S^\circ}(\text{mono})-0.007 \quad (5)$$

$$\sigma_{S^\circ}(135)=0.817\Sigma\sigma_{S^\circ}(\text{mono})-0.033 \quad (6)$$

$$\sigma_{S^\circ}(1234)=0.704\Sigma\sigma_{S^\circ}(\text{mono})-0.024 \quad (7)$$

TABLE Ii. Analogs and Their Estimated Descriptors σ_{S°. Secondary-Alkylbenzenes, Phenylcarbinyl Ketones and Aromatic Tertiary-Amides

	Arom. σ_{S°	Ali. σ_{S°		Arom. σ_{S°	Ali. σ_{S°
PhCH(Me)Et	0.202	0.362	PhCH(*n*-Pr)COMe	0.305	0.465
PhCH(Me)–*n*-Pr	0.242	0.402	PhCH(iso-Pr)COEt	0.326	0.486
$PhCH(Et)_2$	0.237	0.397	PhCH(*sec*-Bu)COEt	0.365	0.525
PhCH(Et)–*n*-Pr	0.283	0.443	$PhCH(CHEt_2)COEt$	0.390	0.550
$PhCH(n\text{-}Pr)_2$	0.308	0.468	PhN(Me)COMe	0.224	0.384
PhCH(Et)–*n*-Pr	0.283	0.443	PhN(Me)COEt	0.259	0.419
PhCH(*n*-Pr)–iso-Pr	0.304	0.464	PhN(Et)COMe	0.265	0.425
PhCH(*n*-Pr)–*sec*-Bu	0.343	0.503	PhN(Et)COEt	0.300	0.460
$PhCh(n\text{-}Pr)CHEt_2$	0.368	0.528	PhN(*n*-Pr)COEt	0.335	0.495
PhCH(Me)COMe	0.230	0.390	PhN(*n*-Pr)COMe	0.301	0.461
PhCH(Me)COEt	0.264	0.412	PhN(iso-Pr)COEt	0.322	0.482
PhCH(Et)COMe	0.271	0.430	PhN(*sec*-Bu)COEt	0.362	0.522
PhCH(Et)COEt	0.304	0.464	$PhN(CHEt_2)COEt$	0.388	0.548
PhCH(*n*-Pr)COEt	0.339	0.499			

Including $R\ln 2$ for racemate. ___=observed values.

TABLE Ij. Descriptors σ_{S° for Ph–NHR, Ph–CH_2R, Ph–COR and Me–R Series

R	Ph–NHR	Ph–CH_2R	Ph–COR	Me–R
Me	0.103	0.127	0.141	0.091
Et	0.151	0.173	0.180	0.161
n-Pr	0.195	0.213	0.215	0.221
n-Bu	0.235	0.250	0.243	0.273
CO_2H	0.166	0.185		0.181
CO_2Me	0.222	0.238		0.254
CO_2Et	0.248	0.262		0.289
CONHMe	0.202	0.219		0.227
COMe	0.182	0.200		0.200
COEt	0.226	0.241		0.259
CO–*n*-Pr	0.260	0.273		0.305
$CONH_2$	0.175	0.194		0.191
CONHEt	0.249	0.263		0.290
CONH–*n*-Pr	0.282	0.294		0.335
CONH–*n*-Bu	0.311	0.321		0.373
$CONMe_2$	0.246	0.260		0.286
CON(Me)Et	0.281	0.293		0.334
$CONEt_2$	0.309	0.319		0.370
NH_2		0.141	0.135	0.115
NHMe		0.177	0.183	0.166
NHEt		0.218	0.217	0.226
NH–iso-Pr		0.250	0.243	0.271
NH–*n*-Pr		0.254	0.247	0.278
NH–*n*-Bu		0.287	0.274	0.324
NH–*sec*-Bu		0.280	0.268	0.314
$NH–CHEt_2$		0.304	0.288	0.349
NMe_2		0.193	0.196	0.190
N(Me)Et		0.241	0.235	0.258
NEt_2		0.270	0.260	0.302
N(Me)–iso-Pr		0.259	0.251	0.285
N(Et)–*n*-Pr		0.305	0.289	0.351
N(Et)–iso-Pr		0.298	0.283	0.340

Estimations are carried out using linear relations, $\sigma_{S^\circ}(PhCH_2R)=0.696\,\sigma_{S^\circ}(MeR)+0.061$, $\sigma_{S^\circ}(PhNHR)=1.073\,\sigma_{S^\circ}(PhCH_2R)-0.033$, and $\sigma_{S^\circ}(PhCOR)=0.829\,\sigma_{S^\circ}(PhCH_2R)+0.036$.

$$\sigma_{S^\circ}(1235)=0.702\Sigma\sigma_{S^\circ}(\text{mono})-0.018 \quad (8)$$

$$\sigma_{S^\circ}(1245)=0.706\Sigma\sigma_{S^\circ}(\text{mono})-0.023 \quad (9)$$

Descriptor σ_{S° for $CH_{4-n}R_n$ (n=2, 3, 4)[1c]: For a substrate having $\Sigma\sigma_{S^\circ}(\text{mono})\geqq 0.4$, the estimations are carried out according to Eqs. 10—12, revised from our previous study.

$$\sigma_{S^\circ}(AB)=0.681\,\Sigma\,\sigma_{S^\circ}(\text{mono})+0.068 \quad (10)$$

$$\sigma_{S^\circ}(ABC)=0.582\Sigma\sigma_{S^\circ}(\text{mono})+0.078 \quad (11)$$

$$\sigma_{S^\circ}(ABCD)=0.521\Sigma\sigma_{S^\circ}(\text{mono})+0.088 \quad (12)$$

TABLE Ik. Analogs and Their Descriptors σ_{S°. Aliphatic Esters and Ketones

R_A–CO–O–R_B	S°	σ_{S°	$R\ln 2$	$R\ln 3$
MeCO–O–COMe	93.20	0.321	×1	×2
	94.58	0.327	×0	×2
HCOMe	72.0	0.209	×0	×1
		0.195	×0	×2
MeCO–OMe	79.90	0.245	×0	×2
MeCO–OEt	86.7	0.289	×0	×2
EtCO–OMe		0.289	×0	×2
sec-Bu–CO–O–*sec*-Bu		0.473	×2	×4
		0.496	×0	×2
sec-Bu–CO–O–CH(Me)–*n*-Pr		0.504	×2	×4
		0.525	×0	×2
sec-Bu–CO–O–CH(Me)–$(CH_2)_2OH$		0.516	×2	×3
		0.530	×0	×2
tert-Pent–CO–O–CH(Me)–*n*-Pr		0.517	×1	×5
		0.540	×0	×2
MeCO–CH_2–COMe	94.73	0.328	×2	×2
	97.49	0.340	×0	×2
HCO–Et	72.83	0.214	×0	×1
		0.201	×0	×2
MeCO–Et	80.81	0.259	×0	×2
MeCO–*n*-Pr	89.91	0.305	×0	×2
EtCO–Et	88.44	0.298	×1	×2
	89.82	0.305	×0	×2
sec-Bu–CO–CH_2–*sec*-Bu		0.485	×2	×4
		0.507	×0	×2
sec-Bu–CO–CH_2–$CH(CH_3)$–*n*-Pr		0.515	×2	×4
		0.536	×0	×2
sec-Bu–CO–CH_2–$CH(CH_3)(CH_2)_2OH$		0.527	×2	×3
		0.541	×0	×2
tert-Pent–CO–CH_2–$CH(CH_3)$–*n*-Pr		0.528	×1	×5
		0.550	×0	×2

—=estimated values. Estimations are carried out according to a linear relation, $\sigma_{S^\circ}(R_ACOOR_B)=1.014\,\sigma_{S^\circ}(R_ACOCH_2R_B)-0.018$, where the following descriptors are used: $\sigma_{S^\circ}[CH_3–CO–CH(CH_3)–CH_2–CH_3/\text{racemic}]=0.347$ and $\sigma_{S^\circ}[CH_3–CO–C(CH_3)_2–CH_2–CH_3]=0.365$. $R\ln 2$=entropy of mixing of two optical isomers or that of the presence of the plane of symmetry. $R\ln 3$=entropy of internal symmetry of CH_3.

TABLE Il. Amino Acids R–$CH(NH_2)$COOH and Their Descriptors σ_{S°

	R	σ_{S° (cal)	π	I
Gly	H	0.270	0.00	0
Ala	Me	0.303	0.31	0
Val	iso-Pr	0.366	1.22	0
Leu	iso-Bu	0.405	1.70	0
Ile	*sec*-Bu	0.405	1.80	0
Ser	$HOCH_2$	0.356	−0.04	1
Thr	MeCH(OH)	0.372	0.26	1
Asp	HOOC–CH_2–	0.392	−0.77	2
Asn	H_2NOC–CH_2–	0.400	−0.60	2
Glu	HOOC–$(CH_2)_2$–	0.430	−0.64	2
Gln	H_2NOC–$(CH_2)_2$–	0.434	−0.22	2
Cys	$HSCH_2$–	0.367	1.54	1
Met	MeS–$(CH_2)_2$–	0.443	1.23	1
Lys	H_2N–$(CH_2)_4$–	0.467	−0.99	3
Hyl	H_2N–$CH_2CH(OH)$–$(CH_2)_2$–	0.504		
Phe	Ph–CH_2–	0.430	0.79	1
Tyr	*p*-HO–Ph–CH_2–	0.454	0.96	1
tert-Leu	*tert*-Bu	0.383		
γ-Me–Leu	Neopentyl	0.416		
Norvaline	*n*-Pr	0.379		
Norleucine	*n*-Bu	0.420		
Homoalanine	Et	0.344		
Pro	–$(CH_2)_3$–	0.329		
Hyp	–CH_2–$CH(OH)$–CH_2–	0.375		

TABLE IIa. Carbocycles and Their ΔS°/e.u. for Cyclization from Linear Molecules

	Cyclic					Linear		
	S°	$R\ln 2$	Cor. S°	Cor. σ_{S°		S°	Cor. S°	ΔS°
C3	56.75	×3	60.89	0.136	C2–C	64.51	65.89	5.00
C4	63.45	×4	68.95	0.190	C3–C	74.12	75.50	6.55
C5	70.00	×5	76.90	0.237	C4–C	83.40	84.78	7.88
C6	71.28	×3	75.42	0.229	C5–C	92.83	94.21	18.79

TABLE IIb. N-, S-, and O-Heterocycles and Their ΔS° for Cyclization from Linear Molecules

Cyclic						
	S°	Cor. S°	Cor. σ_{S°		S°	ΔS°
C2=N	59.90	61.28	0.139	C2–N	68.08	6.86
C3=N	67.07	68.45	0.187	C3–N	77.48	9.03
C4=N	73.97	75.35	0.229	C4–N	86.76	11.41
C5=N	72.85	74.23	0.222	C5–N	96.26	22.03
C2=S	61.07	62.39	0.147	C2–S	70.77	8.38
C3=S	68.17	69.55	0.194	C3–S	80.40	10.85
C4=S	73.94	75.32	0.228	C4–S	89.68	14.36
C5=S	77.26	78.64	0.247	C5–S	99.28	20.64
C2=O	57.94	59.32	0.125	C2–O	67.54	8.22
C3=O	65.46	66.84	0.176	C3–O	77.63	10.79
C4=O	72.68	74.06	0.221	C4–O	86.80	12.74
C5=O	71.31	72.70	0.213	C5–O	96.21	23.51

Linear					
	S°	ΔS°		S°	ΔS°
C–N–C	65.24	5.34			
C–N–C2	74.91	6.46			
C2–N–C2	85.56	10.21	C–N–C3	84.44	9.09
C2–N–C3	93.88	19.65	C–N–C4	93.88	19.65
C–S–C	69.70	7.31			
C–S–C2	79.62	10.07			
C2–S–C2	89.34	14.02	C–S–C3	88.84	13.52
C2–S–C3	98.97	20.33	C–S–C4	98.43	19.79
C–O–C	65.21	5.89			
C–O–C2	74.24	7.40			
C2–O–C2	83.28	9.22	C–O–C3	83.52	9.46
C2–O–C3	89.97	17.27	C–O–C4	98.43	25.73

—=estimated values. $R\ln 2$=entropy of the presence of plane of symmetry.

where A, B, C, and D denote substitutent groups.

Estimation of Descriptors σ_{S° among Analogs: Details of the estimation of the descriptor for several kinds of important moieties are summarized in Tables Ia—k, where calculations are carried out according to the concept of QSAR analogy referencing the parent compounds, *etc.* When the descriptor of the parent is known, the proportional relation affords that of the analog, where additional correction should be required for the element of symmetry, and the results summarized in Tables Ia—k could be expressed by the empirical equations written in the margin.

Amino Acids and Their Descriptors σ_{S°: Descriptors σ_{S° obtained in our previous study[1c] are revised, using Eqs. 10—12, and the results are summarized in Table Il.

Correction Values ΔS° for Aliphatic Heterocycle Formation from a Linear Molecule Correction value ΔS° by the ring formation could be regarded as the difference of S° between linear and cyclic compounds, as arranged in Table IIa, b, where lack of data for secondary-amines are supplied from Table Ic, and those of the cyclic series are estimated from empirical relations as follows:

$$\sigma_{S^\circ}(–NH–)=0.891\,\sigma_{S^\circ}(–CH_2–)+0.018 \quad (13)$$

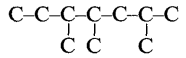
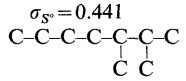
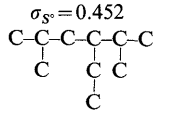
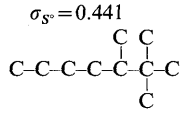
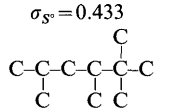
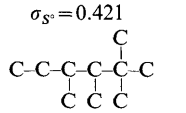
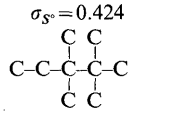
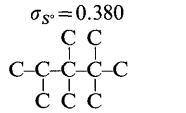
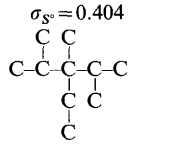
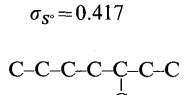
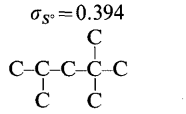
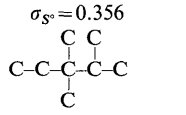
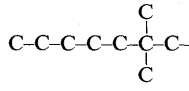
	ref.	$\Sigma\sigma_{S^\circ}$ (mono)	σ_{S° (cal)	S° (cal)	$n \times R \ln 2$	cor. S° (cal)	cor. σ_{S° (cal)
	C-3	0.546	0.440	122.57	1	121.19	0.435
	C-4	0.623	0.441	122.78	1[a]	124.16	0.445
$S^\circ = 122.90$ e.u.	C-5	0.580	0.416	115.95	1[a]	117.32	0.421
$\sigma_{S^\circ} = 0.441$							
	C-3	0.609	0.432	120.50	1[a]	121.88	0.437
	C-4	0.566	0.453	126.47	1	125.10	0.449
$S^\circ = 126.01$ e.u.	C-5	0.568	0.455	126.87	1	125.49	0.450
$\sigma_{S^\circ} = 0.452$							
	C-3	0.626	0.442	123.28	1[a]	124.66	0.447
	C-4	0.546	0.440	122.57	1	121.19	0.435
$S^\circ = 122.90$ e.u.							
$\sigma_{S^\circ} = 0.441$							
	C-2	0.626	0.414	115.53	3	111.40	0.398
	C-3	0.580	0.416	115.91	1[a]	117.29	0.421
$S^\circ = 120.56$ e.u.	C-4	0.534	0.432	120.28	1	118.91	0.427
$\sigma_{S^\circ} = 0.433$							
	C-3	0.573	0.411	114.83	1[a]	116.20	0.417
	C-4	0.512	0.417	116.21	1	114.83	0.411
$S^\circ = 117.45$ e.u.	C-5	0.540	0.393	109.92	1	108.54	0.387
$\sigma_{S^\circ} = 0.421$							
	C-2	0.620	0.411	114.70	3	110.57	0.395
	C-3	0.573	0.411	114.83	1[a]	116.20	0.417
$S^\circ = 118.14$ e.u.	C-4	0.565	0.407	113.60	1[a]	114.98	0.412
$\sigma_{S^\circ} = 0.424$							
	C-2	0.557	0.378	106.35	3	102.22	0.361
	C-3	0.559	0.379	106.61	1	105.23	0.374
$S^\circ = 106.69$ e.u.							
$\sigma_{S^\circ} = 0.380$							
	C-2	0.586	0.393	110.12	3	105.99	0.377
	C-3	0.597	0.399	111.57	1	110.19	0.394
$S^\circ = 112.80$ e.u.							
$\sigma_{S^\circ} = 0.404$							
	C-3	0.650	0.427	118.91	1	117.53	0.422
$S^\circ = 116.23$ e.u.							
$\sigma_{S^\circ} = 0.417$							
	C-3	0.525	0.383	107.62	1[a]	109.00	0.389
	C-4	0.487	0.400	111.74	1	110.36	0.394
	C-5	0.470	0.388	108.80	1	107.42	0.383
$S^\circ = 110.32$ e.u.							
$\sigma_{S^\circ} = 0.394$							
	C-2	0.539	0.369	104.08	3	99.94	0.351
	C-3	0.415	0.351	99.81	1	98.43	0.345
$S^\circ = 101.15$ e.u.							
$\sigma_{S^\circ} = 0.356$							
	C-2	0.466	0.349	99.49	1	98.11	0.343
	C-3	0.542	0.370	104.46	1	103.08	0.365
$S^\circ = 103.14$ e.u.							
$\sigma_{S^\circ} = 0.365$							
	C-3	0.662	0.433	120.63	1	119.25	0.428
	C-4	0.557	0.447	124.70	1	123.32	0.442
	C-5	0.553	0.445	123.92	1	122.54	0.440
$S^\circ = 124.47$ e.u.							
$\sigma_{S^\circ} = 0.447$							

Chart 1. Fragmentation Mode, σ_{S° (cal) and S°_{298} (g) (cal)

ref. = reference position. *a*) Racemate. $R \ln 2$ = entropy of mixing of two optical isomers or that of the presence of plane of symmetry.

7 6 5 4 3 2 1
Me–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–OH

n-octanol: S°_{298} (g) = 124.12 e.u.: ali. σ_{S° = 0.445

ref.		$\Sigma\sigma_{S^\circ}$ (mono)	σ_{S° (AB)	$(S^\circ - R\ln 2)$/e.u.	ali. σ_{S° (cal)
2-C	*n*-C6 + C1 − OH	= 0.361 + 0.182 = 0.543	0.438	120.62	0.433
3-C	*n*-C5 + C2 − OH	= 0.319 + 0.241 = 0.560	0.449	123.91	0.446
4-C	*n*-C4 + C3 − OH	= 0.273 + 0.289 = 0.562	0.451	124.31	0.446
5-C	*n*-C3 + C4 − OH	= 0.221 + 0.334 = 0.555	0.446	122.93	0.441
6-C	*n*-C2 + C5 − OH	= 0.161 + 0.375 = 0.536	0.433	119.29	0.428

C_6H_5–CH_2–CH_2–CH_2–CH_2–CH_2–CH_3

n-hexylbenzene: S°_{298} (g) = 123.78 e.u.: arom. σ_{S° = 0.284

ref.		$\Sigma\sigma_{S^\circ}$ (mono)	σ_{S° (AB)	$(S^\circ - R\ln 2)$/e.u.	arom. σ_{S° (cal)
1-C	*n*-C5 + Ph	= 0.319 + 0.236 = 0.555	0.446	122.93	0.281
2-C	*n*-C4 + C − Ph	= 0.273 + 0.284 = 0.557	0.447	123.32	0.283
3-C	*n*-C3 + C − C − Ph	= 0.221 + 0.333 = 0.554	0.445	122.74	0.281
4-C	C2 + C − C − C − Ph	= 0.161 + 0.373 = 0.534	0.431	118.91	0.267

Chart 2. Fragmentation Mode and σ_{S° (cal)

TABLE IIIa. Calculated Descriptors σ_{S° for Substituted Penoxyacetic Acids, Diphenyl Ethers and Hydroquinone Diphenyl Ethers

Ph–O–CH_2COOH		Ph–O–Ph		PhO–Ph–OPh	
Substituent	σ_{S°	Substituent	σ_{S°	Substituent	σ_{S°
H	0.223		0.224		
2-Cl	0.243		0.243		
4-Cl	0.245		0.240		
2,4-Cl_2	0.265		0.265		
2-Me-4-Cl	0.272		0.273		
2,4,6-Cl_3	0.282		0.278		
4-Cl-α-Me	0.273	4-Cl-2′-Me	0.269		
4-Cl-α-Me_2	0.287	4-Cl-2′,6′-Me_2	0.284		
		4-OCH_2COOH	0.386	4-PhO	0.383
		4-OCHMeCOOH	0.415	4-PhO-2′-Me	0.404
		4-$OCMe_2$COOH	0.429	4-PhO-2′,6′-Me_2	0.427

TABLE IIIb. Thyroxine Analogs and Their Descriptors σ_{S°

	σ_{S°
4-(4′-Cl-PhO–)-Ph–O–CHMeCOOH	0.429
4-(4′-Cl-PhO–)-Ph–O–Ph-2′-Me	0.417
Thyronine	0.438
4-(4′-Cl-PhO–)-Ph–O–Ph = 2′-NH_2	0.428
Thyroxine	0.531
1-(3′,5′-I_2-4′-HO-C_6H_2–)-2,6-I_2-4-(2″-H_2N-C_6H_4–)hydroquinone	0.517

$$\sigma_{S^\circ}(\text{–O–}) = 0.944\,\sigma_{S^\circ}(\text{–}CH_2\text{–}) - 0.00 \quad (14)$$

ΔS° = 18.79 e.u. obtained at cyclohexane formation is reasonable, because the observed and calculated S°_{298}(g) of *n*-butyl-cyclohexane and *cis*- and *trans*-decalin mutually agree, as shown below:

	obsd. S°_{298}(g)/e.u.	$R\ln 2$	calcd. S°_{298}(g)/e.u.
n-decane	130.7	0	
n-butyl-cyclohexane	109.58	1	130.17 − 18.79 − 1.38 = 110.0
trans-decalin	109.58	1	109.58 − 18.79 − 1.38 = 89.41
cis-decalin	90.28	0	109.58 − 18.79 = 90.791

Regression Analyses Computation was carried out on NEC PC9801/M/VX and Epson PC-286V personal computers using a program package for multi-variate analyses (MVA) developed by Takagi, *et al.*[3]

Results and Discussion

Selection of Optimal Descriptor σ_{S° When an actual substrate is submitted for the estimation of the descriptor σ_{S°, several estimation routes are inherently concerned. Eventually, in order to get an optimal value, we must select a best fit, especially when the substrate has a concurrent variety of substitution modes. This situation is important for molecules having aliphatic residues.

TABLE IVa. Calculated Descriptors σ_{S° for Substituted Phenylacetic Acids and Biphenyls

Phenylacetic acids		Biphenyls	
Substituent	σ_{S°	Substituent	σ_{S°
4-iso-Bu	0.326	4-iso-Bu	0.312
3-Cl-4-cyclo-hex.-α-Me	0.360	3-Cl-4-cyclo-hex.-2′-Me	0.339
4-iso-Bu-α-Me	0.361	4-iso-Bu-2′-Me	0.345
3-PhO-α-Me	0.387	3-PhO-2′-Me	0.371
3-PhCO-α-Me	0.371	3-PhCO-2′-Me	0.355
3-Cl-4-CH_2 = $CHCH_2$O	0.340	3-Cl-4-CH_2 = $CHCH_2$O	0.324

TABLE IVb. Mephenamic Acid 2-CO_2H–C_6H_4–X–C_6H_3-2′,3′-Me_2 (X = NH) Analogs and Their Descriptors σ_{S°

X	σ_{S°
–NH–	0.310
–O–	0.344
–CH_2–	0.347
–CO–	0.336
–S–	0.355

In this work, as shown in Charts 1 and 2, in order to settle the basic principle, we have calculated the descriptors for several substrates having a set of substitution modes by means of Eqs. 10—12, and compared the calculated results with those of the observed. And, the result suggests that the largest of the calculated reaches an optimal value. This empirical rule becomes an effective technique for the estimation of the descriptor of complex molecules, and the positive proof along this line could be prepared in the following sequence.

Substituted Phenoxyacetic Acids, Diphenyl Ethers as Herbicide[4a] and Hypocholesterolemics[4b] As summarized in Tables IIIa, b, the descriptor σ_{S° for phenoxyacetic acid agrees with that of diphenyl ether. Accordingly, the derivatives of the two series could also be expected to have an analogous result, even if the Me group on the side chain is removed on the neighboring phenyl ring. The data arranged in Table IIIa support that O–Ph, arom. σ_{S° = 0.224 could be replaced by O–CH_2–COOH, arom. σ_{S° = 0.221. The descriptors of thyroxine analogs are presented in Table IIIb.

TABLE Va. Analgesics and Their Descriptors σ_{S°

		σ_{S°
1.	Ethyl *p*-aminobenzoate	0.245
2.	Ketamine	0.298
3.	1-Benzyl-1,2,3,4-tetrahydroisoquinoline	0.314
4.	1-Benzyl-*N*-Me-1,2,3,4-tetrahydroisoquinoline	0.326
5.	Mepivacaine	0.355
6.	Lidocaine	0.368
7.	*β*-Eucaine	0.373
8.	Petidine	0.370
9.	Procaineamide	0.382
10.	Procaine	0.383
11.	Tyr–Gly–Gly–Phe–Met– and Tyr–Gly–Gly–Phe–Leu–enkephalin's essential parts *p*-HO–Ph–CH_2–CH–NH_2 + HN–CH_2–CO– + Ph–CH_2–CH	0.409
12.	U-50488	0.441
13.	Tetracaine	0.477
14.	Methadone	0.483
15.	Fentanyl	0.501
16.	Oxybuprocaine	0.523
17.	Sufentanyl	0.543
18.	Dibucaine	0.593

TABLE Vb. Sympathetic Stimulants and Their Descriptors σ_{S°

		σ_{S°
1.	Methamphetamine	0.253
2.	Norepinephrine	0.276
3.	Phenylephrine	0.282
4.	Ephedrine	0.287
5.	Epinephrine	0.294
6.	*d*-Methylephedrine	0.295
7.	Etilefrine	0.310
8.	*l*-Isoproterenol	0.339
9.	Terbutaline	0.362
10.	Sulbutamol	0.404
11.	Propranolol	0.414

TABLE Vc. Antipsychotics and Their Descriptors σ_{S°

		σ_{S°
1.	Haloperidol	0.474
2.	Sulpiride	0.489
3.	Nemonapride	0.504

Substituted Phenylacetic Acids and Biphenyls as Anti-flammatory Agents[4c] Analogy between O–Ph and O–CH_2COOH also suggests that of Ph and CH_2COOH, though the magnitude of the former $\sigma_{S^\circ}=0.185$ does not agree well with the $\sigma_{S^\circ}=0.164$ of the latter, but the correspondence of data is generally favorable as summarized in Table IVa. Furthermore, the estimated descriptors of mephenamic acid[4d] analogs are presented as arranged in Table IVb, where a similar level is observed except concerning the diphenylamine type.

Analgesics,[4d,5a,b] **Sympathetic Stimulant**[4d] **and Anti-psychotics**[5c] In this section, we have estimated the descriptors of entitled medicinals now available, and the results are summarized in Tables Va—c.

This data, together with those given in Tables IIIa, b and IVa, b, point to a gradual increase of σ_{S°, irrespective of the presence or absence of the common part of the chemical structure.

And, as the descriptor σ_{S° denotes the contributions from both dispersion E_{dis} and repulsion E_{rep} in a weak molecular interaction, the data cited above represents the enhancement of E_{dis} and E_{rep}. Furthermore, medicinals with a similar level of σ_{S° are observed among functionally different classes. It is evident, then, that the medicinals having E_{dis} and E_{rep} of potentially similar level meet with different receptors.

Example In order to illustrate the procedure for the estimation of σ_{S°, some examples are given as follows:

Example 1A. 1-Benzyl-1,2,3,4-tetrahydro-isoquinoline

Calculations are carried out followed by the routes given below:

(1) the descriptor of 1-benzyl-tetraline could be determined under six conditions as follows,
   1. 1-Me-tetraline + toluene
   2. 1,5-diphenyl-*n*-pentane
   3. *o*-*n*-Pr-diphenylethane
   4. α-benzyl-*o*-diethylbenzene
   5. 1-phenyl-2-*o*-toluyl-*n*-butane
   6. 1,2-diphenyl-*n*-pentane

(2) combination of fragments in 1, and ring closures in 2—6 lead to 1-benzyl-tetraline, and, conversion of $-CH_2-$ to $-NH-$ affords the descriptor of isoquinoline.

1. 1-Me-tetraline + toluene
   Ph–*n*-Bu $S^\circ = 105.04 - \text{tetraline } S^\circ = 89.2 = 15.84$ e.u.
   Ph–*n*-C_5H_{11} $S^\circ = 114.47 - 15.84 = 98.63$ e.u. and ali. $\sigma_{S^\circ}=0.345$
   0.345
   0.236
   Σ 0.581 $\sigma_{S^\circ}(AB)=0.463$ $S^\circ - \boldsymbol{R}\ln 2 = 128.11$ e.u. and ali. $\sigma_{S^\circ}=0.459$ ($-CH_2-$) and 0.464 ($-NH_2-$), arom. $\sigma_{S^\circ}=0.304$

2. 1,5-diphenyl-*n*-pentane
   a. ref. α-C 0.236 Ph
      0.410 C–C–C–C–Ph
      Σ 0.646 $\sigma_{S^\circ}(AB)=0.508$ $S^\circ - \boldsymbol{R}\ln 2 = 142.02$ e.u.
   b. ref. β-C 0.284 C–Ph
      0.373 C–C–C–Ph
      Σ 0.657 $\sigma_{S^\circ}(AB)=0.515$ $S^\circ - \boldsymbol{R}\ln 2 = 144.36$ e.u.
   c. ref. γ-C 0.333 C–C–Ph
      0.333 C–C–Ph
      Σ 0.666 $\sigma_{S^\circ}(AB)=0.525$ $S^\circ - \boldsymbol{R}\ln 2 = 146.57$ e.u.

   after correcting tetraline ring closure $\Delta = 15.84$ e.u., we get $S^\circ = 130.73$ e.u., ali. $\sigma_{S^\circ}=0.468$ ($-CH_2-$) and $=0.473$ ($-NH-$). That is converted to arom. $\sigma_{S^\circ}=0.318$, including $\boldsymbol{R}\ln 2$ as a racemate.

3. *o*-*n*-Pr-diphenylethane
   a. α-C ref.
      o-Et-C_6H_4-*n*-Pr 0.173 *n*-Pr
      0.127 Et
      Σ 0.300 $\sigma_{S^\circ}(12)=0.247$
      $S^\circ + \boldsymbol{R}\ln 2 = 114.93$ e.u.
      ali. $\sigma_{S^\circ}=$ 0.412
      0.236 –Pr
      Σ 0.648 $\sigma_{S^\circ}(AB)=0.509$
      $S^\circ - \boldsymbol{R}\ln 2 = 142.48$ e.u.
   b. β-C ref.
      o-Me–C_6H_4–*n*-Pr 0.173 *n*-Pr
      0.076 Me
      Σ 0.249 $\sigma_{S^\circ}(12)=0.203$
      $S^\circ + \boldsymbol{R}\ln 2 = 104.03$ e.u.
      ali. $\sigma_{S^\circ}=$ 0.369
      0.287 –C–Ph
      Σ 0.656 $\sigma_{S^\circ}(AB)=0.515$
      $S^\circ - \boldsymbol{R}\ln 2 = 144.27$ e.u.

4. α-benzyl-*o*-diethylbenzene
   benzyl $-CH_2-$ ref.
   o-Et–C_6H_4–iso-Pr 0.159 iso-Pr
   0.127 Et
   Σ 0.286 $\sigma_{S^\circ}(12)=0.235$
   $S^\circ - \boldsymbol{R}\ln 2 = 111.82$ e.u.

ali. σ_{S° = 0.400
0.236 –Ph
Σ 0.636 σ_{S°(AB) = 0.501
$S^\circ - \boldsymbol{R}\ln 2 = 139.73$ e.u.

5. 1-phenyl-2-*o*-toluyl-*n*-butane
benzyl $-CH_2-$ ref.
o-Me–C_6H_4–*sec*-Bu 0.076 Me
0.202 *sec*-Bu
Σ 0.278 $\sigma_{S^\circ}(12) = 0.288$
$S^\circ + \boldsymbol{R}\ln 2 = 110.09$ e.u.
ali. σ_{S° = 0.393
0.236 –Ph
Σ 0.278 σ_{S°(AB) = 0.496
$S^\circ - \boldsymbol{R}\ln 2 = 138.23$ e.u.

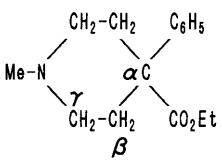
6. 1,2-diphenyl-*n*-pentane
benzyl –CH= ref. 0.236 –Ph
0.284 –C–Ph
0.221 –C–C–C
Σ 0.741 σ_{S°(ABC) = 0.509
$S^\circ = 143.82$ e.u.
among all cases, 2c is the most probable.

Example 1B. 1-Benzyl-1,2,3,4-tetrahydroisoquinoline (**1**) and 1-Benzyl-*N*-Me-1,2,3,4-tetrahydroisoquinoline (**2**)

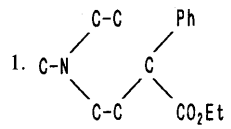
1-benzyl-1,2,3,4-tetrahydroisoquinoline (**1**)
descriptor of **1** could be given from 1-benzyl-naphthalene as below;
1-methyl-naphthalene gives $S^\circ = 90.21$ e.u.
ali. σ_{S° = 0.307
0.236
Σ 0.543 σ_{S°(AB) = 0.438
1-benzyl-naphthalene gives $S^\circ - \boldsymbol{R}\ln 2 = 120.62$ e.u.
and, as ΔS° (tetraline − naphthalene) = 89.2 − 80.22 = 8.93 e.u.,
1-benzyl-tetraline gives $S^\circ = 120.62 + 8.93 = 129.60$ e.u. and ali. σ_{S° = 0.464, and conversion of $-CH_2-$ to –NH– affords ali. $\sigma_{S^\circ} = 0.469$ for 1-benzyl-1,2,3,4-tetrahydroisoquinoline. After including $\boldsymbol{R}\ln 2$ for the presence of racemate, we get arom. $\sigma_{S^\circ} = 0.314$.

1-benzyl-*N*-Me-1,2,3,4-tetrahydroisoquinoline (**2**)
descriptor of **2** could be given from 1-benzyl-2-Me-naphthalene as below;
1,2-Me_2-naphthalene gives $S^\circ = 97.23$ e.u.
ali. σ_{S° = 0.339
0.236
Σ 0.575 σ_{S°(AB) = 0.460
1-benzyl-2-Me-naphthalene gives $S^\circ - \boldsymbol{R}\ln 2 = 126.89$ e.u.
and, as ΔS° (tetraline − naphthalene) = 89.2 − 80.22 = 8.93 e.u.
accordingly, 1-benzyl-2-Me-tetraline gives $S^\circ = 126.89 + 8.93 = 135.87$ e.u. and ali. $\sigma_{S^\circ} = 0.485$.
replacement of =CH–Me to =N–Me affords ali. $\sigma_{S^\circ} = 0.481$ and $S^\circ = 134.76$ e.u. and, after including $\boldsymbol{R}\ln 2$ for racemate, we get arom. $\sigma_{S^\circ} = 0.326$.

Example 2. Petidine

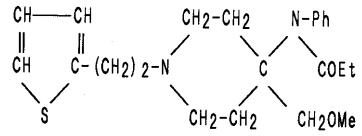


estimations are carried out for three kinds of open chain intermediates as below:

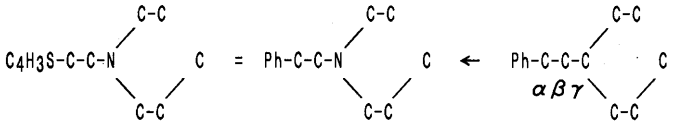


a. ref. α-C ali. σ_{S° 0.236 Ph
0.289 CO_2Et
0.350 MeEtN–*n*-Pr
Σ 0.875 σ_{S°(ABC) = 0.587
after cyclization, $S^\circ - 19.65 = 152.36$ e.u.
b. ref. β-C ali. σ_{S° 0.434 Ph–C–CO_2–Et
0.301 Et_2NMe
Σ 0.735 σ_{S°(AB) = 0.569
c. ref. γ-C ali. σ_{S° 0.478 Ph–C(–CH_2)–CO_2Et
0.258 Me_2N-Et
Σ 0.736 σ_{S°(AB) = 0.569
the result of 1a is the most plausible, and, after subtracting the element of symmetry $\boldsymbol{R}\ln 2 = 1.38$ e.u., we get arom. $\sigma_{S^\circ} = 0.370$.
2. underestimation results when *tert* α-carbon is set up as a reference.

Example 3. Sufentanyl



calculations are carried out under the following conditions:
1. α-Me-thiophene $S^\circ = 76.49$ e.u. could be taken as toluene $S^\circ = 76.64$ e.u.
2. *tert*-N is replaced with –CH=
3. aliphatic σ_{S° for Ph–N–COEt = 0.414; $CH_2OMe = 0.222$
4. in order to avoid underestimation of σ_{S° (cal), the entry of a C1 or C2 unit in $\Sigma\sigma_{S^\circ}$ should be omitted.
5. calculations are carried out for open chain intermediates, and piperidine ring closure is made up at the last step.



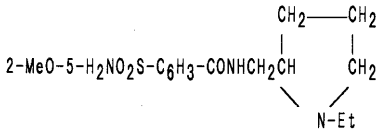
ref.	$\Sigma\sigma_{S^\circ}$	σ_{S° (cal)
α-C	0.627	0.495
β-C	0.641	0.505
γ-C	0.715	0.494

β-C reference is an optimal, and affords $S^\circ - \boldsymbol{R}\ln 2 = 140.88$ e.u. ali. $\sigma_{S^\circ}(-CH_2=) = 0.500$ and $(-N=) = 0.497$
combination of fragments and cyclization
0.497
0.419 Ph–N–COEt
0.222 CH_2OMe
Σ 1.138 gives σ_{S°(ABC) = 0.740 $S^\circ = 244.66 - 19.65 = 225.01$ e.u. and arom. $\sigma_{S^\circ} = 0.541$, after correcting an element of symmetry.

Example 4. *l*-Isoproterenol 3,4-$(HO)_2$–C_6H_3–CH(OH)–CH_2–NH–$CHMe_2$ (α, β, γ)

1. the descriptor belongs to arom. σ_{S° (124) type.
2. phenylcarbinol side chain could be estimated in the following three ways:
a. reference point = α-carbon
ali. σ_{S° 0.236 Ph
0.110 OH
0.315 –C–NH–$CHMe_2$ from C–C–C–$CHMe_2$ $\sigma_{S^\circ} = 0.310$
Σ 0.661 gives σ_{S°(ABC) = 0.463, $S^\circ = 129.20$ e.u. and arom. $\sigma_{S^\circ} = 0.303$
b. reference point = β-carbon
ali. σ_{S° 0.332 PhCH(OH)– optical active
0.271 –NH–$CHMe_2$ from C–C–$CHMe_2$ $\sigma_{S^\circ} = 0.266$
Σ 0.603 gives σ_{S°(AB) = 0.478 $S^\circ - \boldsymbol{R}\ln 2 = 132.65$ e.u. and arom. $\sigma_{S^\circ} = 0.314$
c. reference point = γ-carbon converted from –NH–
ali. σ_{S° 0.373 PhCH(OH)–CH_2– optical active
0.199 Me_2CH–
Σ 0.572 gives σ_{S°(AB) = 0.458, $S^\circ - \boldsymbol{R}\ln 2 = 126.29$ e.u.
and $\sigma_{S^\circ} = 0.453$. And, the conversion of $-CH_2-$ to –NH– gives σ_{S°(–NH–) = 0.458 and $S^\circ = 127.81$ e.u. namely, phenylcarbinyl moiety gives arom. $\sigma_{S^\circ} = 0.298$.
in conclusion, case b is the most reliable, when we sum up the descriptors
0.314
0.138 2 × OH
Σ 0.452 gives $\sigma_{S^\circ}(124) = 0.339$,

Example 5. Sulpiride



estimations are made for five kinds of open chain intermediates given below, and pyrolidine ring closure is done at the last step of estimation.

		ref.	$\Sigma\sigma_{S^\circ}$	σ_{S° (cal)
1.	Ph–CONH–C–C–C–C–C–NH–C–C	α	0.748	0.577
	$\alpha\ \beta\ \gamma$	β	0.743	0.574
		γ	0.731	0.566
2.	Ph–CONH–C–C–N–C–C–C	α	0.728	0.564
	C–C	β	0.727	0.564
3.	Ph–CONH–C–C–N–C–C	α	0.722	0.560
	C C–C	β	0.769	0.526
4.	Ph–CONH–C–C–N–C	α	0.729	0.564
	C–C C–C	β	0.796	0.541
5.	Ph–CONH–C–C–C–C–C	α	0.729	0.564
	N–C–C	β	0.824	0.558

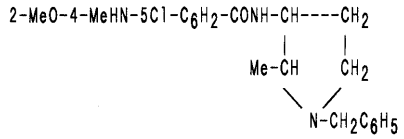
the result suggests that case 1, with α-C reference, is optimal and symmetry correction and pyrolidine ring closure afford $S^\circ = 168.25 - 1.38 - 11.41 = 155.46$ e.u. and arom. $\sigma_{S^\circ} = 0.383$.

then, we sum up the aromatic descriptors:

	0.383	
	0.127	OMe
	0.135	SO_2NH_2
Σ	0.645	gives arom. $\sigma_{S^\circ} = 0.486$

after including $\boldsymbol{R}\ln 2$ as a racemate, we get arom $\sigma_{S^\circ} = 0.489$.

Example 6. Nemonapride



1. the descriptor belongs to a 1,2,4,5-tetrasubstituted benzene derivative, having additional correction of symmetry $2 \times \boldsymbol{R}\ln 2 = 2.76$ e.u.
2. σ_{S° for benzoic amide having *N*-benzyl-pyrrolidine side chain could be estimated from the ring closure of open chain derivatives as below, where additional corrections inherent to symmetry and optical isomers are necessary.

a. Ph–CONH–C–C–C–N–C–Ph (α β γ C–C)
b. Ph–CONH–C–C–N–C–Ph (C C–C)
c. Ph–CONH–C–C–N–C–Ph (C C C)
d. Ph–CONH–C–C–N–C–Ph (C–C C)
e. Ph–CONH–C–C–C–N–C–Ph (C–C)

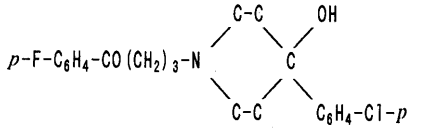
	reference	arom. σ_{S°		reference	arom. σ_{S°
a.	α-C	0.440	d.	α-C	0.429
	β-C	0.439		β-C	
	γ-C	0.442	e.	α-C	0.431
b.	α-C	0.432		β-C	0.429
	β-C			γ-C	0.432
c.	α-C				
	β-C				

(underestimations occur at blanks)

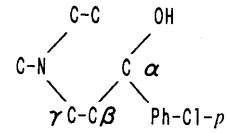
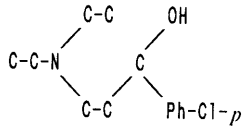
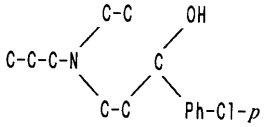
the results suggest that arom. $\sigma_{S^\circ} = 0.440$ obtained for a under α-C reference is the most plausible, and the descriptor of "nemonapride" could be determined as follows:

	0.442	
	0.066	Cl
	0.127	MeO
	0.103	NHMe
Σ	0.738	$\sigma_{S^\circ}(1245) = 0.498$, $S^\circ + 2 \times \boldsymbol{R}\ln 2 = 205.29$ e.u. and, we get arom $\sigma_{S^\circ} = 0.504$.

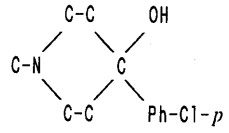
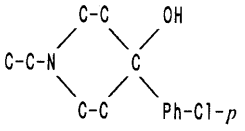
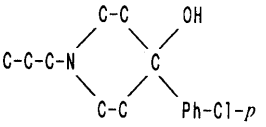
Example 7. Haloperidol



1. descriptors σ_{S° for fragment as aliphatics are as follows: *p*-F–Ph–COMe = 0.317, *p*-F–Ph–COEt = 0.353, *p*-F–Ph–CO–*n*-Pr = 0.384, *p*-Cl–Ph–Me = 0.266, *p*-Cl–Ph–CH(OH)–Me = 0.358, *p*-Cl–Ph–CH(OH)–Et = 0.401
2. descriptors σ_{S° for aliphatic amines, and the corrections ΔS° for piperidine ring closure are cited from Tables Id and II.
3. fragments having *tert* α-C are rejected in advance.

	ref.	$\Sigma\sigma_{S^\circ}$ (mono)	σ_{S° (cal)	S° (cal) e.u.
	β	0.659	0.513	114.95
	γ	0.659		
	β	0.696		
	γ	0.702	0.542	155.16
	β	0.743		
	γ	0.751	0.576	167.66

correction of piperidine ring closure and symmetry.

	S° e.u.	ali. σ_{S°
	144.95 − 19.65 − 1.38 = 123.92	0.445
	155.16	134.13	0.479
	167.66	146.63	0.518

combination to *p*-F–Ph–CO– groups;

0.445	0.479	0.518
0.384	0.353	0.317
Σ 0.829	Σ 0.832	Σ 0.835

from $\Sigma\sigma_{S^\circ} = 0.835$, we get

$\sigma_{S^\circ}(\mathrm{AB}) = 0.637$, $S^\circ - \boldsymbol{R}\ln 2 = 191.62$ e.u., and arom. $\sigma_{S^\circ} = 0.474$.

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