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Substituent Entropy Constant σ_s and Descriptor μ^2/α of *sym*-Disubstituted Benzene Derivatives. Estimation and Validity of Novel Quantitative Structure–Activity Relationships Descriptors

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The values of substituent entropy constant σ_s of *sym*-disubstituted benzene derivatives have been determined by inter- or extrapolation of the linear relation between five observed values and those of monosubstituted benzene derivatives.

Analysis of the quantitative structure–activity relationships (QSAR) by means of σ_s thus estimated, together with the additional descriptor μ^2/α , is shown to be more effective than approaches hitherto used for the evaluation of actinidin-catalyzed hydrolysis of substituted phenyl hippurates, and the reaction between thiamine and substituted aniline derivatives with thiaminase.

Keywords—QSAR; substituent entropy constant σ_s ; descriptor μ^2/α ; *sym*-disubstituted benzene; actinidin-catalyzed hydrolysis; substituted phenyl hippurate; thiaminase; thiamine; substituted aniline

In the previous report,¹⁾ the authors have discussed the origin of the two kinds of novel quantitative structure–activity relationships (QSAR) descriptors σ_s and μ^2/α . The former is an effective descriptor representing the energies of both dispersion E_{dis} and repulsion E_{rep} forces from the evaluation of the force constants ϵ/k and σ determined empirically by applying the Lennard–Jones 12, 6 potential. The latter covers both induction E_{ind} and orientation E_{ori} forces.

These two kinds of novel descriptors proved to be effective for QSAR analyses of biological responses, including the inhibition of enzyme activity, *etc.* For practical purposes, the descriptor σ_s , called the substituent entropy constant,²⁾ is determined from the absolute entropy $S_{298}^\circ(\text{g})$ of the pure material by the use of Eq. 1;

$$\sigma_s = \log[S_{298}^\circ(\text{g})(\text{B})/S_{298}^\circ(\text{g})(\text{A})] \quad (1)$$

where (A) and (B) denote the reference benzene and substituted benzenes, respectively. The data on $S_{298}^\circ(\text{g})$ compiled in the literature³⁾ generally do not extend to polysubstituted benzene derivatives. Thus we tried to estimate the unknown σ_s values of *sym*-disubstituted benzene derivatives, and in addition, the descriptor μ^2/α was also estimated empirically. In this work, the validities of these descriptors have been examined in the QSAR analyses of actinidin-catalyzed hydrolysis of substituted phenyl hippurates and of the reaction of thiamine and substituted aniline derivatives with thiaminase.

Experimental

Numerical Treatment—QSAR analyses were carried out by using an NEC PC-9801 type personal computer utilizing the multiregression analysis program MR compiled in the multivariate analysis program package MVA.⁴⁾

The standard deviation (S.D.) is given by $S.D. = [S_{se}/(n-k-1)]^{1/2}$, where n and k denote the number of observations and variables, and S_{se} denotes the sum of squares of the residuals. The values into parentheses in the regression equations denote the 95% confidence levels.

Results and Discussion

Substituent Entropy Constant σ_S of Monosubstituted Benzene and Methane Derivatives

In this work, the values of σ_S determined by Eq. 1 are compared using two kinds of linear relations between monosubstituted methanes and benzenes as shown in Fig. 1; the results are summarized in Table I.

Alkanes and alkylbenzene derivatives afforded a linear relation and the values of σ_S are $R \ln N$ (e.u.) higher than those of halide, cyanide, *etc.* with lower symmetry number. These results also support the view that σ_S estimated for monosubstituted benzene derivatives reliably represent both dispersion and repulsive interaction energies.

TABLE I. Typical Substituent Entropy Constants σ_S

R	MeR	PhR	R	MeR	PhR
H	0.000	0.000	C ₆ H ₅	0.236	0.164
Me	0.091	0.076	NMe ₂	0.190	0.134
Et	0.161	0.127	NHMe	0.166	0.103
<i>n</i> -Pr	0.221	0.173	NH ₂	0.115	0.074
iso-Pr	0.199	0.159	NHPh	0.263	0.181
<i>n</i> -Bu	0.273	0.213	OH	0.110	0.069
iso-Bu	0.266	0.200	OMe	0.156	0.127
<i>sec</i> -Bu	0.266	0.202	SH	0.136	0.097
<i>tert</i> -Bu	0.210	0.173	F	0.078	0.051
<i>n</i> -C ₅ H ₁₁	0.319	0.250	Cl	0.099	0.067
<i>n</i> -C ₆ H ₁₃	0.361	0.284	Br	0.122	0.083
<i>n</i> -C ₇ H ₁₅	0.399	0.316	I	0.135	0.094
<i>n</i> -C ₈ H ₁₇	0.434	0.345	CF ₃	0.188	0.142
<i>n</i> -C ₉ H ₁₉	0.466	0.373	CHO	0.152	0.127
<i>n</i> -C ₁₀ H ₂₁	0.496	0.398	COMe	0.200	0.142
<i>n</i> -C ₁₁ H ₂₃	0.524	0.423	CO ₂ H	0.181	0.137
<i>n</i> -C ₁₂ H ₂₅	0.551	0.446	CO ₂ Me	0.254	0.200
<i>n</i> -C ₁₃ H ₂₇	0.575	0.468	CN	0.120	0.077
<i>n</i> -C ₁₄ H ₂₉	0.600	0.489	C \equiv CH	0.125	0.077
<i>n</i> -C ₁₆ H ₃₃	0.642	0.528	CH=CH ₂	0.156	0.108
CH ₂ Br	0.188	0.150			

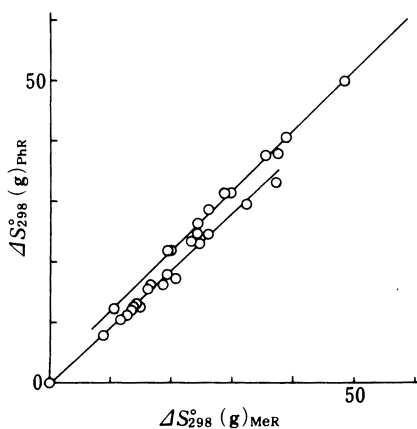


Fig. 1. Correlation between the Increment of Absolute Entropy $\Delta S_{298}^{\circ}(\text{g})$ of Benzene (PhR) and Methane (MeR) Derivatives

Estimation of σ_s of *sym*-Disubstituted Benzene Derivatives

For *sym*-disubstituted benzene derivatives, the observed five absolute entropies $S_{298}^\circ(\text{g})$ afforded linear relations with those of monosubstituted benzenes as given by Eqs. 2, 3, and 4; $n = 5$ ($R = \text{F, Cl, Br, Me, Et}$).^{3c)}

$$S_{298}^\circ(\text{g}), (1, 2) = 1.96(0.15)S_{298}^\circ(\text{g})_{\text{mono}} - 65.39(0.18) \quad (2)$$

$$r = 0.999, \quad F = 1767, \quad \text{S.D.} = 0.49$$

$$S_{298}^\circ(\text{g}), (1, 3) = 2.05(0.10)S_{298}^\circ(\text{g})_{\text{mono}} - 71.84(0.11) \quad (3)$$

$$r = 1.000, \quad F = 3976, \quad \text{S.D.} = 0.34$$

$$S_{298}^\circ(\text{g}), (1, 4) = 2.05(0.06)S_{298}^\circ(\text{g})_{\text{mono}} - 73.20(0.07) \quad (4)$$

$$r = 1.000, \quad F = 10724, \quad \text{S.D.} = 0.21$$

The unknown values of $S_{298}^\circ(\text{g})$ of *sym*-disubstituted benzene derivatives could be estimated from Eqs. 2, 3 and 4 by inter- or extrapolations, and transformed to σ_s by Eq. 1. The values of σ_s thus obtained are summarized in Table II and their validity was also confirmed by the gas liquid chromatographic (GLC) method.⁴⁾

Estimation of Descriptor μ^2/α of *sym*-Disubstituted Benzene Derivatives

For the estimation of the novel QSAR descriptor μ^2/α , the values of dipole moment μ (debye) and polarizability α ($\times 10^{-24} \text{ cm}^3$) are necessary. The former are usually available in the literature⁵⁾ or could be determined as the vector sum of those of monosubstituted benzene derivatives. In addition, the polarizability could also be estimated as the simple sum $\Sigma \Delta\alpha_{\text{mono}}$ of the excess polarizability $\Delta\alpha_{\text{mono}}$ of monosubstituted benzene derivatives, where $\Delta\alpha = \alpha_{\text{PhR}} - \alpha_{\text{PhH}}$ (cf. Table IIIa). The $\Delta\alpha$ of disubstituted benzene derivatives are given by Eqs. 5, 6 and 7 (cf. Table IIIb);

1, 2-series;

$$\Delta\alpha(1, 2) = 0.989(0.008)\Sigma\Delta\alpha - 0.013(4.466) \quad (5)$$

$$n = 43, \quad r = 1.000, \quad F = 57371, \quad \text{S.D.} = 0.071$$

TABLE II. Observed and Estimated Values of σ_s on the *sym*-Disubstituted Benzene Derivatives

	Mono	1, 2	1, 3	1, 4
NO ₂	0.115	0.187	0.192	0.187
CN	0.076	0.121	0.124	0.118
CF ₃	0.141	0.230	0.237	0.232
COMe	0.141	0.230	0.237	0.232
CO ₂ Me	0.200	0.321	0.327	0.326
F	0.051	0.078	0.076	0.069
Cl	0.066	0.103	0.106	0.097
Br	0.081	0.128	0.134	0.128
I	0.094	0.151	0.155	0.150
Me	0.076	0.117	0.123	0.117
Et	0.127	0.208	0.213	0.207
OMe	0.127	0.207	0.213	0.208
OH	0.069	0.108	0.110	0.104
NH ₂	0.074	0.117	0.119	0.113
NMe ₂	0.134	0.218	0.223	0.219

—, observed values.

TABLE IIIa. Polarizability α [10^{-24} cm³] of Monosubstituted Benzene Derivatives

	$\alpha^a)$	$\Delta\alpha_{\text{mono}}^b)$		$\alpha^a)$	$\Delta\alpha_{\text{mono}}^b)$
H	10.380	0	Et	14.179	3.800
NO ₂	12.978	2.599	<i>n</i> -Pr	16.035	5.655
CN	12.478	2.098	iso-Pr	16.024	5.645
COMe	14.557	4.178	<i>n</i> -Bu	17.876	7.497
COEt	16.181	5.802	iso-Bu	17.917	7.537
CHO	12.659	2.279	<i>sec</i> -Bu	17.848	7.469
CF ₃	12.199	1.819	<i>tert</i> -Bu	17.833	7.453
CO ₂ Me	15.198	4.819	<i>n</i> -Pent	19.714	9.334
CO ₂ Et	16.886	6.506	CH=CH ₂	14.436	4.056
F	10.336	-0.044	OMe	13.155	2.775
Cl	12.352	1.973	OEt	14.919	4.539
Br	13.471	3.092	OH	11.147	0.767
I	15.515	5.136	NH ₂	12.127	1.747
Me	12.309	1.929	NMe ₂	16.209	5.830

a) Obtained from n_D^{20} and D_4^{20} by applying the following equation; $\alpha = [(n^2 - 1)/(n^2 + 2)](M/D)(3/4\pi N)$ where M and N mean molar weight and Avogadro's number, respectively. b) $\alpha_R - \alpha_H$.

1,3-series;

$$\Delta\alpha(1,3) = 1.003(0.0008)\Sigma\Delta\alpha - 0.023(2.518) \quad (6)$$

$$n = 31, \quad r = 1.000, \quad F = 62276, \quad \text{S.D.} = 0.065$$

1,4-series;

$$\Delta\alpha(1,4) = 1.011(0.009)\Sigma\Delta\alpha - 0.055(1.271) \quad (7)$$

$$n = 35, \quad r = 1.000, \quad F = 56311, \quad \text{S.D.} = 0.068$$

The values of descriptor μ^2/α are summarized in Table IV.

In a weak interaction such as a bioreaction, the biological response, BR , could be given by Eq. 8;

$$BR = E_{\text{rep}} + E_{\text{dis}} + E_{\text{CT}} + E_{\text{ES}} + E_{\text{PL}}$$

$$BR = a\sigma_S + b\sigma_\pi + c(\mu^2/\alpha) + d \quad (8)$$

where E_{CT} , E_{ES} and E_{PL} are the energies of charge transfer, electrostatic and polarization interactions, respectively. The descriptors σ_S , σ_π and μ^2/α correspond to $E_{\text{rep}} + E_{\text{rep}}$, E_{CT} and $E_{\text{ES}} + E_{\text{PL}}$, respectively; the quantum chemical approach given by Aida and Nagata,⁷⁾ as well as the statistical thermodynamical treatment given by Sasaki *et al.*²⁾ support these correspondences.

Examples of QSAR Analyses

Actinidin-Catalyzed Hydrolysis of Substituted Phenyl Hippurates at 25°C and pH 6.0⁸⁾ (cf. Table V).

3-substituted series;

$$\log(1/K_m) = 4.274\sigma_S + 5.124\sigma_{S^*(x)} + 2.870 \quad (9)$$

$$(1.308) \quad (1.520) \quad (0.062)$$

$$n = 16, \quad r = 0.936, \quad F = 45.75, \quad \text{S.D.} = 0.132$$

where the subscript x means halogen and the relation of σ_S and $\sigma_{S^*(x)}$ is $r = -0.124$.
3- and 4-substituted series;

TABLE IIb. Polarizability α [10^{-24} cm³] of Disubstituted Benzenes

	α_{obs}	α_{calcd}		α_{obs}	α_{calcd}		α_{obs}	α_{calcd}
1,2-R ₁ R ₂								
Me ₂	14.191	14.184	F, Me	12.140	12.232	NH ₂ , Et	15.796	15.855
Et ₂	17.886	17.886	Cl, Me	14.189	14.227	NH ₂ , CH=CH ₂	16.199	16.109
Et, Me	16.034	16.035	Cl, Et	16.078	16.078	NH ₂ , Cl	14.065	14.047
<i>n</i> -Pr, Me	17.889	17.860	Cl, iso-Pr	17.927	17.904	NO ₂ , Me	14.842	14.847
iso-Pr, Me	17.868	17.871	Cl, CH=CH ₂	16.336	16.332	NO ₂ , Et	16.714	16.698
<i>n</i> -Bu, Me	19.677	19.693	Br, Et	17.212	17.185	NO ₂ , OMe	15.698	15.684
iso-Bu, Me	19.762	19.733	Br, iso-Pr	19.042	19.011	NO ₂ , OEt	17.533	17.430
<i>sec</i> -Bu, Me	19.697	19.665	Br, CH=CH ₂	17.359	17.439	CN, Me	14.345	14.351
<i>tert</i> -Bu, Me	19.675	19.650	(OMe) ₂	15.632	15.856	COMe, OMe	17.137	17.246
<i>n</i> -Pr, Et	19.739	19.722	OMe, Cl	15.022	15.065	CHO, Me	14.566	14.531
iso-Pr, Me	19.734	19.708	OEt, Me	16.802	16.767	CO ₂ Me, OMe	17.695	17.665
(iso-Pr) ₂	21.422	21.537	OH, Me	13.101	13.034	(CO ₂ Me) ₂	19.498	19.471
F ₂	10.472	10.370	OH, Cl	13.029	13.077	CO ₂ Et, OMe	19.597	19.551
Cl ₂	14.269	14.270	NH ₂ , Me	13.838	14.004	(CO ₂ Et) ₂	23.261	23.242
Br ₂	16.555	16.485						
1,3-R ₁ R ₂								
Me ₂	14.255	14.227	<i>tert</i> -Bu, iso-Pr	23.456	23.497	OH, Me	13.006	13.062
Et ₂	17.974	17.980	F ₂	10.397	10.269	OH, Cl	13.167	13.106
Et, Me	16.115	16.104	Cl ₂	14.327	14.315	NH ₂ , Me	14.048	14.045
iso-Pr, Me	17.957	17.955	Br ₂	16.522	16.560	NH ₂ , Cl	14.019	14.089
<i>n</i> -Pr, Me	17.976	17.966	F, Me	12.197	12.248	NH ₂ , Br	15.289	15.211
<i>n</i> -Bu, Me	19.812	19.813	Cl, Me	14.253	14.271	NMe ₂ , Me	18.122	18.141
iso-Bu, Me	19.862	19.854	Cl, Et	16.089	16.148	NO ₂ , Me	14.898	14.899
<i>sec</i> -Bu, Me	19.801	19.785	Br, Me	15.343	15.394	COMe, Me	16.330	16.483
<i>n</i> -Pent, Me	21.684	21.656	OMe, Me	14.974	15.077	COMe, OMe	17.466	17.332
<i>n</i> -Pr, Et	19.842	19.842	OEt, Me	16.901	16.846	CO ₂ Et, OMe	19.630	19.669
iso-Pr, Et	19.966	19.831						
1,4-R ₁ R ₂								
Me ₂	14.272	14.226	(<i>n</i> -Pr) ₂	21.768	21.762	Br, CH=CH ₂	17.630	17.553
Et ₂	17.994	18.009	<i>n</i> -Pr, iso-Pr	21.859	21.751	OMe, Me	14.980	15.082
Et, Me	16.134	16.117	(iso-Pr) ₂	21.700	21.740	OEt, Me	16.873	16.865
<i>n</i> -Pr, Me	17.978	17.994	(<i>sec</i> -Bu) ₂	25.357	25.430	OEt, Cl	16.878	16.909
iso-Pr, Me	18.045	17.983	F, Me	12.204	12.231	OH, Me	12.995	13.051
<i>n</i> -Bu, Me	19.824	19.856	Cl, Me	14.266	14.270	OH, iso-Bu	18.832	18.722
iso-Bu, Me	19.857	19.897	Cl, Et	16.150	16.161	NH ₂ , Et	15.911	15.933
<i>sec</i> -Bu, Me	19.750	19.828	Cl, iso-Pr	18.009	18.027	NMe ₂ , Me	17.988	18.170
<i>tert</i> -Bu, Me	19.789	19.828	Cl, CH=CH ₂	16.561	16.421	NO ₂ , Et	16.875	16.795
<i>n</i> -Pr, Et	19.841	19.885	Br, Me	15.450	15.402	COMe, Cl	16.500	16.544
iso-Pr, Et	19.868	19.874	Br, Et	17.278	17.293	CO ₂ Et, OMe	19.845	19.710
<i>tert</i> -Bu, Et	21.724	21.703	Br, iso-Pr	19.148	19.159			

$$\log(1/K_m) = 4.473\sigma_{S(3)} + 5.221\sigma_{S(x),(3)} + 0.768\mu^2/\alpha_{(4)} + 2.839 \quad (10)$$

(0.997) (1.468) (0.207) (0.042)

$$n=23, \quad r=0.945, \quad F=52.63, \quad \text{S.D.}=0.137$$

where the subscripts (3) and (4) denote *meta* and *para* substituted positions, and the correlation of σ_S and μ^2/α is $r = -0.227$.

Equation 10 suggests that σ_S is effective separately for halogen and nonhalogen series in all *meta* congeners, whereas the μ^2/α term operates for the *para* series only.

The result of Carroti *et al.*⁽⁸⁾ is given by Eq. 13;

TABLE IV. The Values of Polarizability α [10^{-24} cm³] and the Descriptor μ^2/α [10^{-12} erg]

	α			μ^2/α		
	1, 2	1, 3	1, 4	1, 2	1, 3	1, 4
NO ₂	15.510	15.571	15.581	2.399	0.947	0.007
CN	14.519	14.693	14.568	3.092	1.019	0
COMe	18.634	18.739	18.773	1.342	0.446	0.400
CF ₃	13.967	14.007	14.004	1.198	0.315	0.029
CO ₂ Me	19.498	20.025	20.070	0.402	0.180	0.241
F	10.472	10.397	10.236	0.550	0.194	0
Cl	14.269	14.327	14.314	0.361	0.155	0
Br	16.555	16.522	16.577	0.277	0.147	0
I	20.290	20.667	20.711	0.144	0.079	0.002
Me	14.191	14.255	14.272	0.019	0.010	0
Et	17.886	17.974	17.994	0.020	0.007	0.003
OMe	15.632	15.926	15.937	0.111	0.159	0.210
OH	11.885	11.896	11.876	0.569	0.367	0.165
NH ₂	13.824	13.862	13.858	0.154	0.234	0.162
NMe ₂	21.903	22.054	22.114	0.358	0.115	0.070

—, observed values.

TABLE V. $\log(1/K_m)$ Values of Actinidin-Catalyzed Hydrolysis of Substituted Phenyl Hippurates

	$\log(1/K_m)$	$\sigma_{S'(3)}$	$\mu^2/\alpha_{(4)}$	$\sigma_{\pi(4)}^{+a)}$
H	2.77	0	0	0
3-F	3.01	0.051	0	0
3-Cl	3.63	0.066	0	0
3-Br	3.64	0.083	0	0
3-I	3.93	0.095	0	0
3-Me	3.26	0.076	0	0
3- <i>tert</i> -Bu	3.66	0.173	0	0
3-CF ₃	3.47	0.142	0	0
3-CN	3.08	0.077	0	0
3-NO ₂	3.53	0.115	0	0
3,5-Me ₂	3.37	0.123	0	0
3-Me,5-Et	3.52	0.176	0	0
3,5-Cl ₂	3.84	0.106	0	0
3,5-(OMe) ₂	3.60	0.213	0	0
3,5-(NO ₂) ₂	3.90	0.192	0	0
3,4,5-Cl ₃	4.01	0.138	0	-0.070
4-F	2.72	0	0.192	-0.118
4-Cl	3.04	0	0.192	-0.070
4-Me	2.95	0	0.009	-0.078
4-COMe	3.47	0	0.621	0
4-CN	3.62	0	1.134	0
4-NO ₂	3.80	0	1.185	0
4-OMe	2.87	0	0.150	-0.281

a) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Kaishi*, **86**, 873 (1965). M. Sawada, M. Ichihara, Y. Yukawa, T. Nakachi and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, **53**, 2055 (1980).

$$\log(1/K_m) = 0.718\sigma + 0.439\pi'_{(3)} + 3.005 \quad (11)$$

(0.224) (0.174) (0.048)

$$r = 0.862, \quad F = 28.98, \quad \text{S.D.} = 0.206$$

TABLE VI. $\log k$ Values of the Reaction between Thiamine and Substituted Aniline Derivatives with Thiaminase

	$\log k$	σ_s	$\mu^2/\alpha_{(4)}$
4-CN	-3.43	0.077	1.134
4-COMe	-3.34	0.142	0.621
3-NO ₂	-1.86	0.130	0
3-Br	-1.26	0.083	0
4-Br	-1.49	0.083	0.176
3-Cl	-1.15	0.066	0
4-Cl	-1.33	0.066	0.192
H	-0.74	0	0
3-Me	-0.92	0.076	0
4-Me	-1.10	0.076	0.009
4-OMe	-1.36	0.127	0.150

When we compare Eq. 10 with Eq. 11, the chemical meaning of the former is more explicit.

Rate of the Reaction between Thiamine and Substituted Anilines with Thiaminase⁹⁾ (cf. Table VI)

$$\log k = -9.776\sigma_s - 2.004\mu^2/\alpha - 2.475\sigma_{\pi(4)}^+ - 0.506 \quad (12)$$

(3.756) (0.391) (1.700) (0.629)

$$n=11, \quad r=0.986, \quad F=83.6, \quad \text{S.D.}=0.180$$

$$\log k = -7.920\sigma_s - 2.114\mu^2/\alpha_{(4)} - 0.529 \quad (13)$$

(5.294) (0.575) (0.900)

$$n=11, \quad r=0.963, \quad F=50.6, \quad \text{S.D.}=0.276$$

where the relation of σ_s and μ^2/α is $r=0.217$.

Fujita⁹⁾ presented Eq. 14 for the same number of congeners.

$$\log k = 0.685\pi - 1.868\sigma^- + 0.558Es_{(4)} - 1.860 \quad (14)$$

(0.462) (0.565) (0.440) (0.258)

$$n=11, \quad r=0.906, \quad F=18.3, \quad \text{S.D.}=0.433$$

When Eq. 13 is compared with Eq. 14, the former is superior in terms of the number of descriptors, and the correlation coefficient is higher.

In a weak interaction without hydrogen bonding, the two novel descriptors σ_s and μ^2/α are very effective. The energy of hydrogen bonding is much larger than E_{dis} and E_{ori} , and should be treated by using a dummy variable.

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