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Studies on Quantitative Structure-Activity Relationships. IV.[1] Usefulness of the Novel Substituent Entropy Constant σ_{s° and the Sign of the Enthalpy Parameter

Yoshio Sasaki,*,[a] Tatsuya Takagi,[a] Akihiro Iwata,[a] and Hideko Kawaki[b]

Faculty of Pharmaceutical Sciences, Osaka University,[a] Yamadaoka 1-6, Suita 565, Japan and Faculty of Pharmacy, Kinki University,[b] Kowakae 3-4-1, Higashi-Osaka 577, Japan

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Biological response (BR) can be expressed by the equation $BR=a(\sigma_{s^\circ})^2+b\sigma_{s^\circ}+c\sigma_i+d\sigma_\pi+e$ for quantitative structure-activity relationships (QSAR) analyses.

The values of σ_i and σ_π originally take + or − sign depending on the electronic character of the substituent group and can be used to describe strong drug-site interactions.

On the contrary, original chemical significance is lost in $|\sigma_i|$ and $|\sigma_\pi|$, which can be applied to weak drug-site interaction, where dipole-dipole or dispersion interaction could be predominant.

The coefficient c of the BR equation becomes the same in *meta*- and *para*-substituted benzene series. When σ_π is real, $\sigma_\pi/_m+\sigma_\pi/_p$ gives a better result than $\sigma_\pi/_{m,p}$, while on the other hand, when σ_π is absolute, $|\sigma_\pi|/_{m,p}$ gives a good result.

As regards the entropy term $a(\sigma_{s^\circ})^2+b\sigma_{s^\circ}$, the *ortho*-substituted benzene series requires the + sign for a and the − for b, whereas for *meta*- and *para*-substituted series, this is reversed. When the relative weight of the entropy term decreases and the contribution of the enthalpy term becomes predominant, the quantum chemical index could often be used as an effective scale for BR.

Keywords——quantitative structure-activity relationships; substituent constant; substituent entropy constant σ_{s°; regression analysis; 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(R-substituted phenyl)-*s*-triazines; 9-(R′-substituted anilino)acridines; dihydrofolate reductase inhibition; poly [*d*(A−T)] binding; *E. coli*; *A. niger*

Introduction

In the previous report[2] of a quantitative structure–activity relationships (QSAR) study on biological response (BR) to drugs, the contribution of the entropy term was given by a quadratic equation of the substituent entropy constant σ_{s°, together with a linear combination of the substituent constants σ_i and σ_π in the equation $BR=a(\sigma_{s^\circ})^2+b\sigma_{s^\circ}+c|\sigma_i|+d|\sigma_\pi|+e$. Here, σ_i and σ_π are written as absolute values.

As the sign of the σ_{s° is always +, in this work, in order to define the explicit chemical significance, we attempted to determine the signs of the two parameters in two kinds of combinations, namely, (σ_i, σ_π) and $(|\sigma_i|, |\sigma_\pi|)$.

Detailed discussions are presented for four kinds of QSAR examples.

Experimental

Substituent Entropy Constants σ_{s°——The values are all cited from the previous report.[2)]
Substituent Constants σ_i and σ_π——The values are all cited from references.[3)]
Regression Analyses——The regression analyses were carried out on a personal computer (NEC PC8001) using the program NEC TSS LIBRARY TSS/LIB-6 and our own programs coded in basic. The standard deviation SD was calculated by means of the equation, $SD=[S_{se}/(n-k-1)]^{1/2}$, where n and k are the number of observations and that of variables, respectively. S_{se} denotes the sum of the squares of residuals. ** in the F test denotes 99% statistical confidence.

Results and Discussion

It is well known that the substituent entropy constant σ_{s° always takes the + sign, but σ_i and σ_π may take + or − sign, namely, σ_i is − for all alkyl substituent groups and + for others, but σ_π is + for electron-attracting substituent groups and − for electron-donating ones.

In addition, from the statistical view point, the weight of an alkyl group in σ_i must be minor, but the relative weight of electron-donating and -attracting groups is counter balanced in σ_π.

Consequently, the following tentative conclusions were reached.

1) As regards the sign of σ_i, the choice of a real or absolute value does not produce a statistically significant difference in the regression equation.

2) The choice of σ_π or $|\sigma_\pi|$ has a serious effect on a regression equation, and the original chemical significance of σ_π is lost.

In view of the above discussion, we propose a tentative rationalization for the choice of real or absolute enthalpy parameters. When the substituent constants σ_i and σ_π lose their signs, they also lose both orientation of the electronic effect and the original chemical significance. This may be related to dipole-dipole or dispersion type interaction between the site and drug.

Recently, in order to confirm the physicochemical meaning of current QSAR parameters, cluster analysis was carried out by Takagi, *et al.*,[1)] who showed that σ_i and $|\sigma_i|$ belong to the same cluster, whereas σ_π and $|\sigma_\pi|$ belong to different ones.

QSAR analyses (Examples 1—4) were examined in this work, on the basis of the above discussion.

Example 1. Poly [*d*(A—T)] Binding of 9-(R′-Substituted anilino)-acridines[4)]

The final results of the regression equations are as follows.

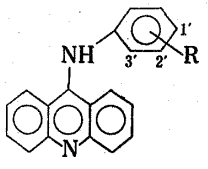
$R_{3'}$(*ortho*)=NO_2, CO_2Me, $CONH_2$, I, Br, Cl, F, *tert*-Bu, iso-Pr, Et, Me, H, OMe, OEt, OH, NH_2
$pI_{50}=+30.78(\pm22.81)(\sigma_{s^\circ})^2-8.52(\pm4.80)\sigma_{s^\circ}+1.51(\pm0.69)|\sigma_\pi|+4.69$
$n=16$, $r=0.851$, $F=10.5$,** $SD=0.16$

$R_{2'}$(*meta*)=NO_2, H, Cl, Me, OH, OMe, NH_2
$pI_{50}=-45.32(\pm60.54)(\sigma_{s^\circ})^2+5.67(\pm8.47)\sigma_{s^\circ}-0.52(\pm0.50)\sigma_\pi+4.82$
$n=7$, $r=0.962$, $F=12.4$,** $SD=0.08$

$R_{1'}$(*para*)=NO_2, SO_2Me, CN, COMe, CO_2Me, $CONH_2$, I, Br, Cl, F, H, Me, OMe, OH, NH_2, NMe_2
$pI_{50}=+2.77(\pm1.47)\sigma_{s^\circ}-1.50(\pm0.28)\sigma_\pi+4.80$
$n=16$, $r=0.955$, $F=67.8$,** $SD=0.13$

$R_{1'}$(*para*)+$R_{2'}$(*meta*)
$pI_{50}=+2.42(\pm1.39)\sigma_{s^\circ 1',2'}-1.47(\pm0.27)\sigma_{\pi 1'}-0.77(\pm0.40)\sigma_{\pi 2'}+4.86$
$n=22$, $r=0.946$, $F=51.2$,** $SD=0.13$

The essentials of the above results are: 1) the signs of a and b are + and − for $R_{3'}$ (*ortho*) series, but this is reversed for $R_{2'}$ (*meta*) and $R_{1'}$ (*para*) series; 2) σ_π requires the absolute value for $R_{3'}$ (*ortho*) series, in contrast to the *meta*-, *para*- and *meta*- + *para*- series.



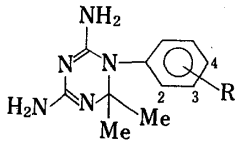
Example 2. Dihydrofolate Reductase Inhibition by 4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(R-substituted phenyl)-*s*-triazines[5]

The derived final regression equations are given below.

R_2(*ortho*)$=CF_3$, I, Cl, F, H, Me, Et, OH, OMe, SMe, NH_2

$$\log 1/C = +116.34(\pm 129.18)(\sigma_{s^\circ})^2 - 36.74(\pm 22.05)\sigma_{s^\circ} + 6.35$$
$n=11$, $r=0.921$, $F=22.2$,** $SD=0.40$

$$\log 1/C = -11.75(\pm 7.41)\sigma_{s^\circ} + 5.79$$
$n=11$, $r=0.875$, $F=29.3$,** $SD=0.47$



R_3(*meta*)$=NO_2$, CN, COMe, CF_3, I, Br, Cl, F, H, *tert*-Bu, Me, OMe, OH

$$\log 1/C = -72.71(\pm 69.27)(\sigma_{s^\circ})^2 + 16.54(\pm 13.44)\sigma_{s^\circ} + 1.17(\pm 1.21)|\sigma_i| - 3.76(\pm 1.36)|\sigma_\pi| + 6.27$$
$n=13$, $r=0.924$, $F=11.7$,** $SD=0.21$

R_4(*para*)$=SO_2Me$, CO_2Me, CO_2Et, CF_3, COMe, I, Br, F, H, Me, *tert*-Bu, OMe, OH, NH_2

$$\log 1/C = -13.00(\pm 50.71)(\sigma_{s^\circ})^2 + 25.66(\pm 12.42)\sigma_{s^\circ} - 3.92(\pm 1.59)|\sigma_\pi| + 6.30$$
$n=14$, $r=0.936$, $F=23.6$,** $SD=0.33$

R_3(*meta*)$+$R(*para*) series

$$\log 1/C = -136.25(\pm 36.63)(\sigma_{s^\circ})^2_{3,4} + 27.66(\pm 8.90)\sigma_{s^\circ 3,4} - 3.82(\pm 0.99)|\sigma_\pi|_{3,4} + 6.19$$
$n=26$, $r=0.926$, $F=43.8$,** $SD=0.28$

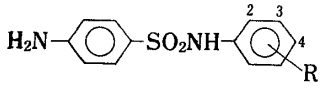
The main features are as follows: 1) for R_2 (*ortho*) series, the signs of a and b are $+$ and $-$, respectively, in contrast to R_3 (*meta*), R_4 (*para*) and R_3 (*meta*) $+R_4$ (*para*) series; 2) for all series σ_π requires the absolute value.

Example 3. Microbiological Activities of Substituted Phenylsulfonamides against *E. coli*[6]

The regression analyses finally gave the following equations.

R_2(*ortho*)$=$I, Br, Cl, H, Me, OMe, OEt, 2,3-Me_2

$$MIC = +2.21(\pm 1.52)\sigma_i + 2.99(\pm 2.50)\sigma_\pi + 4.86$$
$n=8$, $r=0.905$, $F=11.4$,** $SD=0.27$



R_3(*meta*)$=NO_2$, CF_3, I, Br, Cl, H, Me, OMe, OEt, 3,4-Cl_2, 3,5-Cl_2

$$MIC = +1.47(\pm 0.75)\sigma_i + 4.67$$
$n=11$, $r=0.829$, $F=19.8$,** $SD=0.20$

R_4(*para*)$=NO_2$, SO_2Me, COMe, CN, CF_3, I, Cl, Br, H, Me, OMe, OEt, NMe_2

$$MIC = +1.00(\pm 0.90)\sigma_i + 1.83(\pm 0.56)\sigma_\pi + 4.88$$
$n=13$, $r=0.960$, $F=58.5$,** $SD=0.19$

R_3(*meta*)$+R_4$(*para*)series

$$MIC = +1.14(\pm 0.53)\sigma_{i3,4} + 0.79(\pm 0.67)\sigma_{\pi 3} + 1.77(\pm 0.45)\sigma_{\pi 4} + 4.82$$
$n=23$, $r=0.945$, $F=53.3$,** $SD=0.17$

The regression equations are all expressed as linear combinations of the enthalpy parameters, excluding those of the entropy ones. This is consistent with the results of quantum chemical approaches,[6] because they are originally concerned with the the contribution of the enthalpy term.

Example 4. Antifungal Activities of 5,7-Disubstituted-8-hydroxy-quinolines against *A. niger*[7]

The antifungal activities of 26 derivatives of 5,7-disubstituted-8-hydroxy-quinolines (summarized in Table 1) were determined against various kinds of microbiological systems (*e.g. Aspergillus niger*, *etc.*) by Gershon, *et al.*,[7] but QSAR analyses were unsuccessful. Recently, Lukovits *et al.*[8] successfully applied principal component analysis, but this treatment does not afford an explicit physicochemical meaning to the component factor.

The derived final regression equation is as follows.

$$\log 1/C = +2.96(\pm 2.32)\sum\sigma_{s^\circ 5,7} - 2.99(\pm 1.92)|\sigma_i| - 3.70(\pm 0.75)|\sigma_\pi| + 2.85$$
$n=26$, $r=0.950$, $F=67.6$,** $SD=0.20$

where the values of σ_i and σ_π are all determined by the vector sum. Contrary to our expectation, σ_π requires an absolute value, irrespective of the planar structure of the congener.

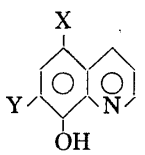


Table I. Structural Details for the 5,7-Disubstituted-8-hydroxyquinolines

No.	5-X	7-Y	No.	5-X	7-Y
1	H	F	14	Br	Cl
2	H	Cl	15	Br	I
3	H	Br	16	Br	NO_2
4	H	I	17	I	F
5	H	NO_2	18	I	Br
6	F	F	19	I	NO_2
7	F	Cl	20	NO_2	F
8	F	Br	21	F	NO_2
9	F	I	22	Cl	NO_2
10	Cl	F	23	Br	NH_2
11	Cl	Br	24	I	NH_2
12	Cl	I	25	NO_2	Cl
13	Br	F	26	NO_2	Br

The regression equations summarized in Examples 1—4 lead to the following conclusions.

1) The coefficient c becomes the same in *meta*- and *para*-substituted series.

2) When σ_π is real, $\sigma_\pi/_m+\sigma_\pi/_p$ gives better results than $\sigma_\pi/_{m,p}$, and, on the other hand, when σ_π is absolute, $|\sigma_\pi|/_{m,p}$ gives a good result.

3) As for the entropy term $a\,(\sigma_s{}^\circ)^2+b\,\sigma_s{}^\circ$, *meta*- and *para*-substituted series take $-$ sign for a and $+$ sign for b, whereas for *ortho*-substituted series this is reversed, namely, the former gives a BR maximum and the latter affords a minimum.

4) The multisubstituted series can be transformed into the monosubstituted series by taking the vector sum for the enthalpy parameter and the simple sum for the entropy parameter.

Additional evidence supporting the above tentative conclusions will be presented in the following report.

Conclusion

The expression of biological response by the equation, $BR=a(\sigma_s{}^\circ)^2+b\,\sigma_s{}^\circ+c\,\sigma_i+d\,\sigma_\pi+e$, is very effective for QASR analysis. As for the entropy term $a\,(\sigma_s{}^\circ)^2+b\,\sigma_s{}^\circ$, $(-a, +b)$ or $(+a, -b)$ correspond to the presence of the BR maximum or minimum, respectively, and e agrees well with that of the reference. For the enthalpy term, the combination of (σ_i, σ_π) is appropriate for strong drug-site interaction, wheras $(|\sigma_i|, |\sigma_\pi|)$ is appropriate for weak drug-site interaction, such as dipole-dipole or dispersion interaction.

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