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# Availability of Substituent Entropy Constants $\sigma_{s^\circ}$ and Descriptor $\mu^2/\alpha$ as Predictors of Relative Retention Values on Gas-Liquid Chromatography of Substituted Propane and Butane Derivatives

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Under apolar conditions, the logarithm of the relative retention values $\log \gamma$ of substituted *n*-propane and *n*-butane derivatives can be expressed by a linear combination of the substituent entropy constant $\sigma_{s^\circ}$ and descriptor $\mu^2/\alpha$. There seems to be a clear physical basis for this result in terms of the enthalpy of dissolution, $\Delta H_s^\circ$.

**Keywords**——gas-liquid chromatography; relative retention value; three-body problem; substituent entropy constant $\sigma_{s^\circ}$; descriptor $\mu^2/\alpha$; regression analysis

## Introduction

In the previous study[1] on quantitative structure–activity relationships (QSAR), two kinds of novel descriptors—substituent entropy constant $\sigma_{s^\circ}$ and descriptor $\mu^2/\alpha$—were derived from a consideration of the modified Lennard–Jones 12, 6 potential. The former represents both dispersion and repulsion force, and the latter represents both induction and orientation force.

These two descriptors are useful for weak interactions, exemplified by biological responses. They may also be applicable to gas-liquid chromatography (GLC), where a weak interaction occurs between the solute and the stationary liquid. Thus, we examined the applicability of the descriptors to the relative retention values ($\log \gamma$) of substituted *n*-propane and *n*-butane series on GLC under apolar conditions.

## Experimental

**Relative Retention Value log $\gamma$ and Experimental Conditions**——The index $\log \gamma$ is defined by Eq. 1;

$$\log \gamma = \log[t_{R(R)}/t_{R(H)}] \quad (1)$$

where $t_{R(R)}$ and $t_{R(H)}$ are the adjusted retention time (s) of substrate and reference, respectively.

The relative retention values were all measured on a Yanagimoto TCD G1880 gas chromatograph under the following conditions: mobile phase = He; stationary phase = 20% squalane + Chromosorb W; column = glass column treated with $Me_2SiCl_2$, followed by anhydrous methanol; column temperature = 80 °C; reference = *n*-butane.

**Substituent Entropy Constant $\sigma_{s^\circ}$ of *n*-Propane and *n*-Butane Derivatives**——The substituent entropy constant $\sigma_{s^\circ}$ given by Eq. 2 was determined from the absolute entropy $S^\circ_{298}$ (g) compiled in the references[2];

$$\sigma_{s^\circ} = \log[S^\circ_{298}(g)(R)/S^\circ_{298}(g)(H)] \quad (2)$$

where (R) and (H) mean the substrate and reference, respectively.

**Descriptor $\mu^2/\alpha$ of Substituted *n*-Propane and *n*-Butane Derivatives**——The values of dipole moment are all cited from a data book,[3] and polarizability $\alpha$ was calculated by means of Clausius–Mossotti's equation, using the refractive index observed with the $Na_D$ line at 20°C.

**Regression Analysis**——Regression analyses were carried out using the program MVA,[4] developed in our laboratory.

## Results and Discussion

### GLC as a Three-Body Problem

From the previous study[1] on the two kinds of novel QSAR descriptors $\sigma_{s^\circ}$ and $\mu^2/\alpha$, the free-energy-average polar potential (*cf.* Eq. 3) represents the potential energy of a pair of polar molecules a and b.

$$\phi^{\text{av.}} = 4\varepsilon^\circ[(\sigma^\circ/r)^{12} - (\sigma^\circ/r)^6] - 1/r^6(\mu_a^2\mu_b^2/3kT + \alpha_a\mu_b^2 + \alpha_b\mu_a^2) \tag{3}$$

Equation 3 should be valid for QSAR analyses, when a biological response produced by a substrate–receptor interaction occurs in a hydrophobic field. However, GLC requires substrate and mobile and stationary phases, namely, this situation should be treated as a "three-body problem." For example, when we specify a substrate and mobile and stationary phases by the numbers 1, 2, and 3, the total potential energy $U_{123}$ of a system composed of the three factors could be given by Eq. 4;

$$U_{123} = \phi_{12} + \phi_{23} + \phi_{31} + \Delta\phi_{123} \tag{4}$$

where $\phi_{12}$, $\phi_{23}$ and $\phi_{31}$ mean the potential energies of the 12, 23 and 31 pairs, $\Delta\phi_{123}$ means an additional minor increment of the whole system, and $\phi_{23}$ becomes constant when 2 and 3 are specified. It follows that we can regard $E_{\text{dis.}}$ (total), $E_{\text{ind.}}$ (total) $E_{\text{ori.}}$ (total) as the sum of $\phi_{12}$ and $\phi_{31}$.

From the definition of the Lennard–Jones 12, 6 potential, and the mixture rule of the force constant $\varepsilon/k$, Eq. 5 is obtained as follows:

$$E_{\text{dis.}}(\text{total}) = (\varepsilon_{11}\varepsilon_{22})^{1/2} + (\varepsilon_{11}\varepsilon_{33})^{1/2}$$
$$= \varepsilon_{11}{}^{1/2}(\varepsilon_{22}{}^{1/2} + \varepsilon_{33}{}^{1/2}) \tag{5}$$

When both mobile and stationary phases are specified, $\varepsilon_{22}{}^{1/2} + \varepsilon_{33}{}^{1/2}$ becomes constant, and we obtain Eq. 6:

$$E_{\text{dis.}}(\text{total}) \propto \varepsilon_{11}{}^{1/2} \tag{6}$$

As shown in the previous report,[1] according to the linear relation between $\varepsilon_{11}$ and absolute entropy $S^\circ_{298}$ (g), $E_{\text{dis.}}$(total) becomes linear with respect to $S^\circ_{298}$ (g)$^{1/2}$, *i.e.* substituent entropy constant $\sigma_{s^\circ}$, and an analogous argument holds for the repulsion interaction.

Furthermore, the total $E_{\text{ind.}}$(total) and orientation $E_{\text{ori.}}$(total) are expressed as below;

$$E_{\text{ind.}}(\text{total}) = E_{\text{ind.}}(12) + E_{\text{ind.}}(31)$$
$$\simeq \mu_1^2/\alpha_1 + \mu_2^2/\alpha_2 + \mu_1^2/\alpha_1 + \mu_3^2/\alpha_3$$

When 2 and 3 are specified, Eq. 7 is obtained:

$$E_{\text{ind.}}\ (\text{total}) = 2\,\mu_1^2/\alpha_1 + \text{constant} \tag{7}$$

An analogous treatment can be applied to $E_{\text{ori.}}$ (total),

$$E_{\text{ori.}}(\text{total}) = E_{\text{ori.}}\,(12) + E_{\text{ori.}}(31)$$
$$\simeq \mu_1^2/\alpha_1(\mu_2^2/\alpha_2 + \mu_3^2/\alpha_3)/3\boldsymbol{k}T$$

When both 2 and 3 are specified, Eq. 8 is obtained;

$$E_{\text{ori.}}(\text{total}) = \mu_1^2/\alpha_1 \times \text{constant} \qquad (8)$$

Thus, we are able to utilize the descriptors $\sigma_{s^\circ}$ and $\mu^2/\alpha$ for the evaluation of relative retention values. Furthermore, the participation of $E_{\text{ori.}}$ need not be considered under apolar conditions, where the term $\mu^2/\alpha$ could be ascribed to the contribution of $E_{\text{ind.}}$

**Estimation of Unknown $\boldsymbol{\sigma_{s^\circ}}$**

For the estimation of the descriptor $\sigma_{s^\circ}$, the corresponding value of $S^\circ_{298}$ (g) is essential, but this is not always available. For instance, in the *n*-BuR series, we lack $S^\circ_{298}$ (g) values for R = I, OMe, COMe. In this work, from the linear relation (*cf.* Eq. 9) between 13 congeners of *n*-PrR and *n*-BuR (*cf.* Tables I and II), the unknown values of the latter series could be estimated as given in parentheses in Table II.

$$\sigma_{s^\circ}(n\text{-BuR}) = 0.927\ (\pm 0.027)\sigma_{s^\circ}(n\text{-PrR}) + 0.066\ (\pm 0.007) \qquad (9)$$

$$n = 13 \quad r = 0.999 \quad s = 2.05 \times 10^{-3} \quad F = 5.86 \times 10^3$$

R = H, Me, Et, *n*-Pr, *n*-Bu, Cl, Br, OH, $NH_2$, CHO, $NO_2$, SH, SMe

**Relative Retention Value of *n*-Propane and *n*-Butane Derivatives**

In this work, as the retention index, the logarithm of the relative retention value is used. The thermodynamics of log $\gamma$ is known to described by Eq. 10;

$$\log\gamma = -[H^\circ_s(\text{R}) - H^\circ_s(\text{H})]/2.303\,\boldsymbol{R}T + \text{constant} \qquad (10)$$

where $\Delta H^\circ_s$ means the enthalpy of dissolution. Consequently, the analysis of log $\gamma$ by means of the novel descriptors $\sigma_s$ and $\mu^2/\alpha$ has a clear molecular basis.

TABLE I. log $\gamma$, $\sigma_{s^\circ}$ and $\mu^2/\alpha$ [erg × $10^{-12}$] of *n*-Propane Derivatives

| Substituent | log $\gamma$ | $\sigma_{s^\circ}$ | $\mu^2/\alpha$ |
|---|---|---|---|
| Me | 0.000 | 0.221 | 0.000 |
| Et | 0.445 | 0.275 | 0.000 |
| *n*-Pr | 0.808 | 0.319 | 0.000 |
| *n*-Bu | 1.158 | 0.361 | 0.000 |
| *n*-Pent | 1.490 | 0.399 | 0.000 |
| Cl | | 0.234 | |
| Br | 0.869 | 0.260 | 0.405 |
| I | 1.158 | 0.256 | 0.312 |
| OMe | 0.395 | 0.273 | 0.175 |
| OH | 0.339 | 0.241 | 0.425 |
| $NH_2$ | 0.374 | 0.241 | 0.238 |
| CHO | 0.553 | 0.268 | 0.814 |
| COMe | 0.888 | 0.305 | 0.737 |
| CN | 0.734 | 0.242 | 1.621 |
| $NO_2$ | 0.964 | 0.281 | 1.498 |
| SH | | 0.257 | |
| SMe | | 0.300 | |

Correlation coefficient $r = -0.318$ between $\sigma_s$ and $\mu^2/\alpha$. $n = 12$ (Me, Et, *n*-Pr, *n*-Bu, *n*-Pent, OMe, OH, $NH_2$, CHO, COMe, CN, $NO_2$).

TABLE II. $\log\gamma$, $\sigma_s$ and $\mu^2/\alpha$ [erg × $10^{-12}$] of *n*-Butane Derivatives

| Substituent | $\log\gamma$ | $\sigma_s$ | $\mu^2/\alpha$ |
|---|---|---|---|
| H | 0.000 | 0.221 | 0.000 |
| Me | 0.445 | 0.275 | 0.000 |
| Et | 0.808 | 0.319 | 0.000 |
| *n*-Pr | 1.158 | 0.361 | 0.000 |
| *n*-Bu | 1.490 | 0.399 | 0.000 |
| Cl | 0.864 | 0.284 | 0.373 |
| Br | 1.180 | 0.298 | 0.338 |
| I | 1.557 | (0.303) | 0.272 |
| OMe | 0.795 | (0.318) | 0.141 |
| OH | 0.767 | 0.290 | 0.293 |
| $NH_2$ | 0.797 | 0.290 | 0.206 |
| CHO | 0.961 | 0.313 | 0.664 |
| COMe | 1.245 | (0.348) | 0.605 |
| SH | 1.165 | 0.304 | 0.156 |
| SMe | | 0.345 | |
| $NO_2$ | | 0.326 | |

Correlation coefficient between $\sigma_s$ and $\mu^2/\alpha$ $r=0.085$. $n=10$ (H, Me, Et, *n*-Pr, *n*-Bu, OMe, OH, $NH_2$, CHO, COMe).

The observed values of $\log\gamma$ for substituted *n*-propane and *n*-butane series are summarized in Tables I and II, together with the descriptors $\sigma_s$ and $\mu^2/\alpha$, and the results of the regression analyses are gived below:

1. *n*-Propane series except halogens

$$\log\gamma = 8.055(\pm 0.898)\sigma_s + 0.308(\pm 0.081)\mu^2/\alpha - 1.762(\pm 0.274)$$

$$n=12 \quad r=0.989 \quad s=0.066 \quad F=208.6^{**}$$

2. *n*-Butane series except halogens and SH

$$\log\gamma = 8.046(\pm 1.112)\sigma_s + 0.336(\pm 0.241)\mu^2/\alpha - 1.739(\pm 0.351)$$

$$n=10 \quad r=0.999 \quad s=0.069 \quad F=159.7^{**}$$

## References

1) Y. Sasaki, T. Takagi, and H. Kawaki, *Chem. Pharm. Bull.*, **36**, 3743 (1988).

2) *a*) D. R. Stull, E. F. Westrum Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," John Wiley and Sons, Inc., New York, 1969; *b*) S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

3) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman & Co., San Francisco, 1963.

4) T. Takagi, K. Tange, N. Iwata, Y. Shindo, A. Iwata, T. Katayama, H. Izaki, S. Fujii, and Y. Sasaki, Proceedings of the 4th Software Conference, Osaka, March 1988, p. 285.