1554 Chem. Pharm. Bull. 37(6) 1554—1555 (1989) Vol. 37, No. 6

# Feasibility of Estimating the Novel Quantitative Structure–Activity Relationship (QSAR) Descriptor $\sigma_{s^\circ}$ by Means of Gas-Liquid Chromatography. I. Halogenobenzene Derivatives

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**The separation coefficients (log $\gamma$) of halogenobenzene derivatives obtained by means of gas-liquid chromatography have been subjected to the regression analysis, using the novel quantitative structure–activity relationship (QSAR) descriptor $\sigma_{s^\circ}$, together with the sum of Swain–Lupton's resonance parameter $\Sigma R$. The result indicates that the former is the major determinant, whereas the latter is minor. From the above result, the successful estimation of unknown values of $\sigma_{s^\circ}$ has been achieved for polyhalogenobenzene derivatives. Furthermore, the values of $S^\circ_{298}$(g) agree well with observed values determined by statistical thermodynamics.**

**Keywords** gas-liquid chromatography; halogenobenzene derivative; separation coefficient; regression analysis; substituent entropy constant $\sigma_{s^\circ}$; Swain–Lupton's resonance parameter $R$; absolute entropy

## Introduction

In our previous work[1)] on the development of the two kinds of novel quantitative structure–activity relationship (QSAR) descriptors $\sigma_s$ and $\mu^2/\alpha$, the absolute entropy $S^\circ_{298}$(g) was a requisite for the estimation of the former. However, the descriptors were originally determined from the temperature dependency of the specific heat of the pure material or from the statistical thermodynamic treatment of vibrational spectroscopy data. Although data thus determined are compiled in the literature,[2)] there are deficiencies in the field of aromatic compounds, especially polysubstituted derivatives. Hence, we have applied parametric and statistical procedures to disubstituted benzene derivatives, with like or unlike substituent groups, and obtained useful results.[3)]

In this work, in contrast to the above procedures, we employed gas-liquid chromatography (GLC), because the separation coefficient (log $\gamma$) observed in GLC could be determined by the weak molecular interactions among the three components, *i.e.*, substrate, mobile phase and stationary phase. In the preceding report,[4)] the relative separation coefficients of aliphatic polar compounds have been successfully evaluated by the linear combination of the novel QSAR descriptors $\sigma_{s^\circ}$ and $\mu^2/\alpha$.

We have now examined log $\gamma$ values of polysubstituted halogenobenzene derivatives, and concluded that the GLC method is reasonable for the estimation of the descriptor $\sigma_{s^\circ}$ (in other words, the absolute entropy).

## Experimental

**Experimental Conditions of GLC** Preparation of Stationary Phase: Chromosorb W coated with 10% Apiezon L or 20% squalane was used as the stationary phase. The stationary liquids were dissolved in appropriate amounts of cyclohexane or toluene and added to the carrier, then the solvent was removed *in vacuo*.

Dimethyldichlorosilane (DMCS) Treatment of Glass-Column Wall: A glass column filled with a 5% toluene solution of DMCS was left for 5—6 h at 55—60 °C on a water bath. The solution was decanted off, and the column was filled with anhydrous $CH_3OH$ for 1 h. The column was further washed with anhydrous $CH_3OH$ and dried in a desiccator after the removal of the solvent by decantation.

Measurement Conditions: Separation coefficients were all measured under the following conditions. Apparatus, Yanagimoto TCD G1880 gas chromatograph; column, DMCS treated 2.0 m glass column, 3.4 mm i.d. mobile phase, He with 1.5 kg/cm² gauge pressure; temperature, 180 °C (column) and 230 °C (column gate) for Apiezone L and 160 °C (column) and 200 °C (column gate) for squalane.

Sample: All materials were of JIS grade. For liquid material, 1 $\mu$l was used. For solid materials, a saturated solution in benzene was prepared and 1 $\mu$l was injected. All measurements were carried out in a steady state.

**Method of Data Analysis** Data analyses were carried out on NEC PC-9801/M/VX and EPSON PC-286V personal computers using a program package for multivariate analyses, MVA (version 1.2),[5)] developed in our laboratory.

## Results and Discussion

**Selection of Stationary Liquid** Selection of the stationary liquid in an important factor in the determination of the relative magnitude of the log $\gamma$ value. In the previous work,[4)] in order to minimize the contributions from orientation, induction, and hydrogen bonding interactions, squalane (McReynolds' number = 0[6)]) was used. However, for halogenobenzene derivatives, the retention time becomes longer as the vapor pressure of the substrate becomes higher. In this work, therefore, Apiezone L, which is slightly more polar than squalane, was used as the stationary liquid. The two kinds of log $\gamma$ showed a good correspondence to each other as indicated by Eq. 1:

$$\log\gamma(\text{Ap.}) = 0.861(\pm 0.006)\log\gamma(\text{Sq.}) - 0.038(\pm 0.065) \tag{1}$$

$$n=16 \quad r=0.993 \quad s=0.038 \quad F=928.2$$

where (Ap.) and (Sq.) mean Apiezon L and squalane used as stationary liquids, respectively. Substrates are PhR (R = H, Et, *n*-Bu, 1,2,3,4-$Me_4$, 1,2,3,5-$Me_4$, $CO_2Me$, $CO_2Et$, $NO_2$, $NMe_2$, NHEt, $NEt_2$, SMe, O-*n*-Bu, *m*-di-$OEt_2$, I, 1,2,4-$Cl_3$). Judging from the result of Eq. 1, it is permissible to replace squalane with Apiezon L in the evaluation of log $\gamma$.

**Evaluation of log $\gamma$ of Halogenobenzene Derivatives** First, we carried out regression analyses using the data listed in Table I, obtaining the following regression equations:

$$\log\gamma = 25.291(\pm 12.950)\sigma_{s^\circ} - 1.246(\pm 0.968) \tag{2}$$

$$n=4 \quad r=0.986 \quad s=0.097 \quad F=70.61$$

PhX (X = F, Cl, Br, I)

$$\log\gamma = 11.079(\pm 10.191)\sigma_{s^\circ} - 0.491(\pm 1.100) \tag{3}$$

$$n=12 \quad r=0.608 \quad s=0.679 \quad F=5.87$$

PhX (X = F, Cl, Br, I, *o*-$F_2$, *m*-$F_2$, *p*-$F_2$, *o*-$Cl_2$, *m*-$Cl_2$, *p*-$Cl_2$, $F_6$, $Cl_6$)

TABLE I. $\log\gamma$, $\sigma_{S^\circ}$ and $\sum R$ of Halogenobenzene Derivatives

| | X | $\log\gamma$ | $\sigma_{S^\circ}$ [8] | $\sum R$ [7] |
|---|---|---|---|---|
| 1 | F | −0.025 | 0.051 | −0.60 |
| 2 | Cl | 0.537 | 0.066 | −0.24 |
| 3 | Br | 0.782 | 0.081 | −0.18 |
| 4 | I | 1.105 | 0.094 | −0.12 |
| 5 | *o*-$F_2$ | 0.000 | 0.078 | −1.20 |
| 6 | *m*-$F_2$ | −0.051 | 0.076 | −1.20 |
| 7 | *p*-$F_2$ | −0.109 | 0.069 | −1.20 |
| 8 | *o*-$Cl_2$ | 1.026 | 0.103 | −0.48 |
| 9 | *m*-$Cl_2$ | 0.980 | 0.106 | −0.48 |
| 10 | *p*-$Cl_2$ | 0.980 | 0.097 | −0.48 |
| 11 | $F_6$ | −0.477 | 0.153 | −3.60 |
| 12 | $Cl_6$ | 2.529 | 0.215 | −1.44 |

TABLE II. Observed and Calculated Values of $\sigma_{S^\circ}$

| | X | $\sigma_{S^\circ\text{obs.}}$ [8] | $\sigma_{S^\circ\text{calcd.}}$ | $\Delta\sigma_{S^\circ}$ |
|---|---|---|---|---|
| 1 | F | 0.051 | 0.053 | 0.002 |
| 2 | Cl | 0.066 | 0.068 | 0.002 |
| 3 | Br | 0.081 | 0.078 | −0.003 |
| 4 | I | 0.094 | 0.092 | −0.002 |
| 5 | *o*-$F_2$ | 0.078 | 0.079 | 0.001 |
| 6 | *m*-$F_2$ | 0.076 | 0.076 | 0.000 |
| 7 | *p*-$F_2$ | 0.069 | 0.073 | 0.004 |
| 8 | *o*-$Cl_2$ | 0.103 | 0.102 | −0.001 |
| 9 | *m*-$Cl_2$ | 0.106 | 0.100 | −0.006 |
| 10 | *p*-$Cl_2$ | 0.097 | 0.100 | 0.003 |
| 11 | $F_6$ | 0.153 | 0.151 | −0.002 |
| 12 | $Cl_6$ | 0.215 | 0.218 | 0.003 |

$$\log\gamma = 13.078(\pm 2.005)\sigma_{s^\circ} - 0.289(\pm 0.236) \qquad (4)$$

$n=7 \quad r=0.991 \quad s=0.093 \quad F=281.1$

PhX (X = Cl, Br, I, *o*-$Cl_2$, *m*-$Cl_2$, *p*-$Cl_2$, $Cl_6$)

Equations 2, 3 and 4 prompted us to introduce a new descriptor $\sum R$ (sum of the Swain–Lupton's mesomeric parameter, $R$[7]) mainly for fluorine compounds, to take account of the charge transfer interaction.

The introduction of $\sum R$ afforded a successful regression equation as follows:

$$\log\gamma = 19.416(\pm 1.140)\sigma_{s^\circ} + 0.781(\pm 0.053)\,\mathrm{M}\,R - 0.587(\pm 0.107) \qquad (5)$$

$n=12 \quad r=0.997 \quad s=0.065 \quad F=868.6$

PhX (X = F, Cl, Br, I, *o*-$F_2$, *m*-$F_2$, *p*-$F_2$, *o*-$Cl_2$, *m*-$Cl_2$, *p*-$Cl_2$, $F_6$, $Cl_6$)

When the descriptor $\sigma_{s^\circ}$ is taken as a subordinate variable, Eq. 5 can be converted to Eq. 6:

$$\sigma_{s^\circ} = 0.051(\pm 0.003)\log\gamma - 0.040(\pm 0.003)\sum R + 0.031(\pm 0.004) \qquad (6)$$

$n=12 \quad r=0.998 \quad s=0.003 \quad F=993.1$

The calculated $\sigma_{s^\circ}$ values obtained from Eq. 6 are listed in Table II.

From Eq. 6, we are able to estimate the values of $\sigma_{s^\circ}$ from the observed log $\gamma$ and descriptor $\sum R$, and they can be converted to $S^\circ_{298}$(g) (Table III), giving agreement within $< \pm 3$ e.u. with the observed values obtained by statistical thermodynamic analysis by Aleman and Lielmesz.[8]

TABLE III. Calculated and Observed Values of $S^\circ_{298}$(g) of Halogenobenzene Derivatives

| | $\log\gamma$ | $\sum R$ | $\sigma_{S^\circ\text{calcd.}}$ | $S^\circ_{298}$(g) calcd. | $S^\circ_{298}$(g) obsd.[8] | $\Delta S^\circ_{298}$(g) |
|---|---|---|---|---|---|---|
| *o*-$Br_2$ | 1.472 | −0.36 | 0.120 | 84.82 | 86.43 | −1.61 |
| *m*-$Br_2$ | 1.445 | −0.36 | 0.119 | 84.62 | 87.69 | −3.07 |
| *p*-$Br_2$ | 1.438 | −0.36 | 0.119 | 84.62 | 86.33 | −1.71 |
| *o*-$I_2$ | 2.023 | −0.24 | 0.144 | 89.64 | | |
| *p*-$I_2$ | 2.000 | −0.24 | 0.143 | 89.43 | | |
| *o*-Cl,F | 0.523 | −0.84 | 0.091 | 79.34 | 80.74 | −1.40 |
| *m*-Cl,F | 0.469 | −0.84 | 0.088 | 78.79 | 81.02 | −2.23 |
| *p*-Cl,F | 0.469 | −0.84 | 0.088 | 78.79 | 76.90 | 1.89 |
| *o*-Br,F | 0.794 | −0.78 | 0.102 | 81.37 | 83.59 | −2.22 |
| *m*-Br,F | 0.704 | −0.78 | 0.098 | 80.63 | | |
| *p*-Br,F | 0.722 | −0.78 | 0.099 | 80.81 | | |
| *o*-Br,Cl | 1.369 | −0.42 | 0.117 | 84.23 | 86.58 | −2.35 |
| *m*-Br,Cl | 1.213 | −0.42 | 0.109 | 82.70 | | |
| *p*-Br,Cl | 1.203 | −0.42 | 0.109 | 82.70 | | |
| 1,2,3-$Cl_3$ | 1.445 | −0.72 | 0.133 | 87.39 | 88.47 | −1.08 |
| 1,2,4-$Cl_3$ | 1.394 | −0.72 | 0.131 | 86.99 | 89.94 | −2.95 |
| 1,3,5-$Cl_3$ | 1.327 | −0.72 | 0.127 | 86.19 | 86.64 | −0.45 |
| 1,2,4-$Br_3$ | 2.035 | −0.54 | 0.156 | 92.15 | | |
| 1,3,5-$Br_3$ | 1.996 | −0.54 | 0.156 | 91.72 | 95.30 | −3.58 |
| 1-Br-2,3-$Cl_2$ | 1.868 | −0.66 | 0.153 | 91.51 | | |
| 1-Br-3,4-$Cl_2$ | 1.611 | −0.66 | 0.139 | 88.61 | | |
| 1-Br-2,6-$Cl_2$ | 1.654 | −0.66 | 0.142 | 89.22 | | |
| 1,2,3,4-$Cl_4$ | 1.808 | −0.96 | 0.162 | 93.43 | 94.91 | −1.48 |
| 1,2,4,5-$Cl_4$ | 1.741 | −0.96 | 0.158 | 92.57 | 94.03 | −1.46 |
| 1,2,4,5-$Br_4$ | 2.615 | −0.72 | 0.193 | 100.34 | | |
| $F_5$ | −0.410 | −3.00 | 0.130 | 86.79 | 89.63 | −2.84 |

**Acknowledgement** Financial assistance from the Hoan-sha Fund is gratefully acknowledged.

## 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," Wiley, New York, 1969; *b*) S. W. Benson, "Thermochemical Kinetics," Wiley, New York, 1967; *c*) 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) Y. Sasaki, H. Kawaki, F. Masuda and T. Takagi, unpublished.
4) S.-L. Hsiu, H. Kawaki, K. Yokoyama, H. Takai and Y. Sasaki, *Chem. Pharm. Bull.*, **36**, 4474 (1988).
5) 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, 1988, p. 285.
6) W. O. McReynolds, *J. Chromatogr. Sci.*, **8**, 685 (1970).
7) C. G. Swain, S. H. Unger, N. R. Rosenquist and M. S. Swain, *J. Am. Chem. Soc.*, **105**, 492 (1983).
8) H. Aleman and J. Lielmesz, *J. Chem. Eng. Data*, **14**, 335 (1969).