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Solute-Stationary Phase Interaction in Gas-Liquid Chromatography. Evaluation of the Relative Retention Value for Substituted Halogenobenzene Derivatives

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Separation coefficients log γ for substituted halogenobenzene derivatives given by gas-liquid chromatography have been evaluated by regression analysis, using three kinds of descriptors, namely, σ_{s°, μ^2/α and $\Sigma\sigma_\pi^\pm$. For the *ortho*-disubstituted series, the descriptor $\Sigma\sigma_\pi^\pm$, correcting the *ortho* effect due to the vicinal substituent group, is required. This correction can be achieved by evaluating the intensity drop of the p(^{1}La) band of ultraviolet absorption spectra. The $\Sigma\sigma_\pi^\pm$ of the regression equation indicates the contribution of the charge-transfer interaction between the substrate and stationary liquid.

Keywords quantitative structure–activity relationship; gas-liquid chromatography; relative retention value; halogenobenzene derivative; regression analysis; substituent entropy constant σ_{s°; descriptor μ^2/α; substituent constant $\sigma_\pi^\pm$

Our novel quantitative structure–activity relationship (QSAR) descriptors[1,2] σ_{s°—substituent entropy constant—and μ^2/α for aromatic, as well as aliphatic compounds, have been revealed to be effective in the evaluation of weak intermolecular interaction represented by QSAR, gas-liquid chromatography (GLC),[3] solubility in liquid, physical absorption, *etc.*

In this work, as an example of the solute-stationary liquid interaction, the authors examined the relative retention value log γ for substituted halogenobenzene derivatives, and found that an additional descriptor $\sum\sigma_\pi^\pm$, signifying the contribution of the charge-transfer interaction, is necessary for *meta*- and *para*-disubstituted series; their corrections for the *ortho*-disubstituted series from the evaluation of the intensity drop of p(^{1}La) band of ultraviolet absorption spectra are also shown to be successful.

Experimental

Measurement of Relative Retention Value log γ and GLC Experimental Condition The data summarized in Tables I and II were all measured under the same condition described in our previous report,[3] except that the 10% Apiezon L was used as a stationary liquid at 180 °C.

Substituent Entropy Constant σ_{s° of Substituted Halogenobenzene Derivatives The values were determined from the absolute entropy S°_{298} (g)[4] in the usual way, but some of them were also estimated statistically by Kawaki *et al.*[2]

Descriptor μ^2/α for Halogenobenzene Derivatives All of the dipole moments μ/debye were cited from reference.[5] Polarizability $\alpha/10^{24}\,\text{cm}^3$ was determined in the usual way, or estimated statistically as in our previous report.[6]

Substituent Constant $\sigma_\pi^\pm$ Data cited were from reference.[7]

Regression Analysis Regression 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 1.21) developed by Takagi *et al.*[8a] The abbreviation *AIC*[8b] in the regression equation denotes Akaike's information criterion; values in brackets are standard regression coefficients. Bootstrap calculation was carried out on a HITAC M680H plus S820/80 system at the Institute for Molecular Science, in Okazaki.

Results and Discussion

Relative Retention Value log γ for Monohalogeno-, *meta*-, and *para*-Substituted Halogenobenzene Derivatives The regression analyses for 17 congeners in Table I, as well as those of 25 congeners in Table II, excluding the *ortho*-series, afforded the following results given by Eqs. 1 and 2:

$$\begin{aligned}
&\log\gamma = 17.93\sigma_{s^\circ} + 4.635\sum\sigma_\pi^+ - 0.918\mu^2/\alpha - 0.180 \qquad (1)\\
&\qquad (\pm 1.58)\ (\pm 0.738)\quad (\pm 0.458)\quad (\pm 0.233)\\
&\qquad [0.807]\quad [0.420]\quad [-0.145]\\
&n=17,\quad r=0.994,\quad s=0.068,\quad AIC=-37.628
\end{aligned}$$

$$\begin{aligned}
&\log\gamma = 17.01\sigma_{s^\circ} + 4.601\sum\sigma_\pi^+ - 1.374\sum\sigma_\pi^- - 0.895\mu^2/\alpha - 0.117 \qquad (2)\\
&\qquad (\pm 1.94)\ (\pm 1.225)\quad (\pm 1.084)\quad (\pm 0.410)\quad (\pm 0.285)\\
&\qquad [0.949]\quad [0.570]\quad [-0.274]\quad [-0.364]\\
&n=25,\quad r=0.983,\quad s=0.111,\quad AIC=-32.536
\end{aligned}$$

The results allow these conclusions: (1) The major contribution comes from the dispersion and repulsion forces. (2) The term expressed by $\sum\sigma_\pi^\pm$ accounts for the secondary weight of the energy composition. As shown in our previous report,[9] the values of log γ for halogenobenzenes are expressed by the sum of the linear combination of σ_{s° and the resonance effect parameter, $\sum R$.[10] This is consistent

TABLE I. Values of log γ and the Descriptors for Halogenobenzene Derivatives

	log γ	σ_{s°	$-\sum\sigma_\pi^\pm$	μ	α	μ^2/α
F	−0.025	0.051	0.118	1.48	10.341	0.212
Cl	0.537	0.066	0.070	1.60	12.352	0.207
Br	0.782	0.081	0.061	1.57	13.471	0.183
I	1.105	0.094	0.068	1.29	15.476	0.108
o-F_2	0.000	0.078	0.236	2.4	10.354	0.556
o-Cl_2	1.026	0.103	0.140	2.3	14.193	0.373
o-Br_2	1.472	0.128	0.085	2.0	16.554	0.242
o-I_2	2.023	0.151	0.059	1.7	20.292	0.142
o-Cl, F	0.523	0.096	0.188	2.37	12.257	0.458
o-Br, F	0.794	0.107	0.179	2.29	13.364	0.392
o-Br, Cl	1.369	0.120	0.131	2.2	15.355	0.315
m-F_2	−0.051	0.076	0.236	1.51	10.208	0.223
m-Cl_2	0.980	0.106	0.140	1.48	14.327	0.153
m-Br_2	1.445	0.134	0.122	1.5	16.522	0.136
m-Cl, F	0.469	0.094	0.188	1.52	12.274	0.188
m-Br, F	0.704	0.106	0.179	1.40	13.405	0.146
m-Br, Cl	1.213	0.120	0.131	1.5	15.456	0.146
p-F_2	−0.109	0.069	0.236	0	10.791	0
p-Cl_2	0.980	0.097	0.140	0	14.474	0
p-Br_2	1.438	0.128	0.122	0	16.577	0
p-I_2	2.000	0.150	0.136	0.19	20.711	0.000
p-Cl, F	0.469	0.084	0.188	0	12.527	0
p-Br, F	0.722	0.097	0.179	0	13.610	0
p-Br, Cl	1.203	0.109	0.131	0	15.557	0

TABLE II. Values of $\log\gamma$ and the Descriptors for Halogenobenzene Derivatives

	$\log\gamma$	σ_{s°	$-\sum\sigma_\pi^\pm$	μ	α	μ^2/α
F	−0.033	0.051	0.118	1.48	10.341	0.212
Cl	0.557	0.066	0.070	1.60	12.352	0.207
Br	0.775	0.081	0.061	1.57	13.476	0.183
I	1.081	0.094	0.068	1.42	15.476	0.108
o-F_2	−0.011	0.078	0.236	2.4	10.354	0.556
o-Cl_2	1.010	0.103	0.140	2.3	14.193	0.373
o-Br_2	1.443	0.128	0.085	2.0	16.554	0.242
o-I_2	2.002	0.151	0.059	1.7	20.292	0.142
o-Cl, Br	1.231	0.120	0.131	2.2	15.355	0.315
o-Cl, I	1.514	0.129	0.114	1.95	17.339	0.219
o-Cl, CH_3	0.802	0.116	0.148	1.40	14.189	0.138
o-Br, CH_3	1.033	0.128	0.139	1.45	15.208	0.138
o-I, CH_3	1.317	0.137	0.140	1.22	17.445	0.085
o-Cl, NO_2	1.327	0.139	−0.069	4.3	14.846	1.245
o-Br, NO_2	1.532	0.153	−0.058	4.2	15.954	1.106
o-I, NO_2	1.803	0.166	−0.071	3.8	17.938	0.805
o-Cl, OCH_3	1.090	0.155	0.351	2.5	15.021	0.416
m-F_2	−0.056	0.076	0.236	1.58	10.208	0.245
m-Cl_2	0.946	0.106	0.140	1.48	14.393	0.152
m-Br_2	1.419	0.134	0.122	1.5	16.563	0.136
m-Cl, Br	1.184	0.119	0.131	1.5	15.436	0.146
m-Cl, I	1.474	0.129	0.138	1.4	17.460	0.112
m-Cl, CH_3	0.799	0.116	0.148	1.78	14.259	0.222
m-Br, CH_3	1.037	0.129	0.139	1.77	15.389	0.204
m-I, CH_3	1.318	0.140	0.148	1.58	17.413	0.143
m-Cl, NO_2	1.358	0.142	−0.262	3.4	14.930	0.774
m-Br, NO_2	1.575	0.159	−0.271	3.44	16.044	0.738
m-I, NO_2	1.859	0.169	−0.264	3.47	18.071	0.666
p-F_2	−0.081	0.069	0.236	0	10.791	0
p-Cl_2	0.967	0.097	0.140	0	14.314	0
p-Br_2	1.415	0.128	0.122	0	16.577	0
p-I_2	1.966	0.150	0.136	0	20.711	0
p-Cl, Br	1.187	0.109	0.131	0	15.557	0
p-Cl, I	1.471	0.120	0.138	0.46	17.497	0.000
p-Cl, CH_3	0.789	0.105	0.148	1.90	14.429	0.250
p-Br, CH_3	1.044	0.119	0.139	1.98	15.512	0.253
p-Cl, NO_2	1.375	0.135	−0.262	2.50	15.059	0.415
p-Br, NO_2	1.592	0.148	−0.271	2.4	16.143	0.357

with the above results. The observed results suggest an effect reflecting the charge delocalization, for which the CH/π type interaction[11] between the polar substance and stationary liquid is a most plausible explanation. Aida and Nagata,[12] in their earlier study on energy composition, ranked the contribution from the charge-transfer interaction second, but the authors conclude that the term $\sum\sigma_\pi^\pm$ can be rationalized as an instance of CH/π interaction, a variation of the hydrogen bonding currently approved by Takagi *et al.*[13] (3) The contribution expressed by the term μ^2/α, representing the induction and orientation or electrostatic interactions, occupies only minor weight.

Correction of Descriptor $\sum\sigma_\pi^\pm$ for *ortho* Effect According to the traditional viewpoint on *ortho*-disubstituted benzene derivatives, the vicinal substituent affords an out-of-plane mode of distortion entirely different from those of *meta*- and *para*-disubstituted series, and this effect is reflected in their physical and chemical specificities. This so-called "*ortho* effect" reduces the perturbation on the π-character, while promoting the σ-character. This hypothesis is commonly supported by the increased dipole moment of the *ortho*-disubstituted benzene series.

In order to prove the above concept, the present authors here tried to modify the substituent constant $\sum\sigma_\pi^\pm$ including a correction for the "*ortho* effect". For this purpose, they employed a drop of the intensity of p(^{1}La) band in the ultraviolet absorption spectra of *ortho*-disubstituted benzene derivatives. This came from the steric hindrance, and the drop of intensity was due mainly to the inhibition of π-electron charge delocalization. In this work, we examined the data[14] of the p(^{1}La) band for numerous kinds of *ortho*-disubstituted benzene series, and, after evaluating the intensity drop, the modified descriptor $\sum\sigma_\pi^\pm$ including the correction of the "*ortho* effect"[15] is presented (*cf.* Tables I and II) by estimating the value of $\varepsilon/\varepsilon^\circ\times\sigma_\pi^\pm$, where ε and ε° denote the Lennard-Jones parameters of the observed and reference compounds, respectively.

Relative Retention Value $\log\gamma$ for *ortho*-Substituted Halogenobenzene Derivatives The regression analyses for 11 congeners (Table I) and 17 ones (Table II), both including monohalogenobenzenes, gave Eqs. 3 and 4, respectively.

$$\begin{array}{llll} \log\gamma=18.14\sigma_{s^\circ} & +4.112\sum\sigma_\pi^+ & -0.400 & \\ \quad(\pm 2.36) & (\pm 1.135) & (\pm 0.296) & \\ \quad[0.842] & [0.397] & & \end{array} \tag{3}$$

$$n=11,\quad r=0.991,\quad s=0.092,\quad AIC=16.869$$

$$\begin{array}{llll} \log\gamma=17.08\sigma_{s^\circ} & +3.658\sum\sigma_\pi^+ & -9.739\sum\sigma_\pi^- & -0.404 \\ \quad(\pm 2.66) & (\pm 1.090) & (\pm 4.232) & (\pm 0.298) \\ \quad[1.035] & [0.581] & [-0.458] & \end{array} \tag{4}$$

$$n=17,\quad r=0.975,\quad s=0.138,\quad AIC=-13.769$$

where the descriptors $\sum\sigma_\pi^\pm$ are all corrected, except monohalogeno- and fluorobenzene derivatives. The results written above allow the following conclusions. (1) The correction of the descriptor $\sum\sigma_\pi^\pm$ is favorable. The statistical test by the bootstrap method[16] indicates that the multiple correlation coefficients for the regression equations using the corrected $\sum\sigma_\pi^\pm$ are better than the corresponding coefficients using the original $\sum\sigma_\pi^\pm$ (90% confidence level). (2) The regression equations rejected the entry of the term μ^2/α, as in the case of the nonhalogeno *ortho*-disubstituted benzene derivatives,[17] for which the nonplanarity of substrate is the most reasonable. (3) For nonhalogeno disubstituted benzene series, the entry of the term μ^2/α is significant only for the *para*-series, but for the halogenobenzene series, this term is significant for both the *meta*- and *para*-series when the participation of electrostatic and induction interactions between the polar substrate and stationary liquid Apiezon L is the most plausible.

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