Determination of the Novel Quantitative Structure–Activity Relationships Descriptor σ_{S° for Di- and Trisubstituted Benzene Derivatives

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For di- and trisubstituted benzene derivatives, the novel quantitative structure–activity relationships descriptors σ_{S°, representing both dispersion and repulsion interaction energies, have been successfully determined from the linear relations of the observed absolute entropy S°_{298}(g) for the above series against those of monosubstituted benzene derivatives. Unknown values of S°_{298}(g) could be estimated statistically by inter- or extrapolation of the linear relations, and numerous kinds of descriptors, σ_{S° for *ortho*-, *meta*-, *para*-disubstituted benzene derivatives, together with those of the trisubstituted series, having the same kind of substituent, have been presented.

Their validities are supported by the results of evaluation of the gas liquid chromatography relative retention value $\log\gamma$ for disubstituted benzene derivatives.

Keywords substituent entropy constant σ_{S°; absolute entropy S°_{298}(g); disubstituted benzene derivative; trisubstituted benzene derivative; gas-liquid chromatography; relative retention value $\log\gamma$; regression analysis; substituent constant $\sigma_\pi^\pm$; descriptor μ^2/α

In our previous report[1] on the study of novel quantitative structure–activity relationships (QSAR) descriptors, the two kinds of descriptors σ_{s° and μ^2/α representing the dispersion and repulsion interaction energies, as well as those of the orientation and induction interactions, were shown to be effective for the evaluation of the gas liquid chromatography (GLC) relative retention value $\log\gamma$[2,3] and for QSAR analyses.[4]

Contrary to our expectation, S°_{298}(g) data[5] are not suitable to estimate the descriptor σ_{s°, especially for polysubstituted benzene derivatives.

In this work, for the purpose of QSAR studies, we have tried to estimate the descriptor σ_{s° for *ortho*-, *meta*- and *para*-disubstituted benzenes, as well as those of the trisubstituted series, where the unknown data of S°_{298}(g) for the above series have been determined by means of inter- or extrapolation of the linear relation between the observed values and those of the monosubstituted benzene derivatives, and their validities have been supported by measurement of the GLC relative retention value $\log\gamma$ of disubstituted benzene derivatives.

Experimental

Regression Analysis Regression analysis was carried out by using an NEC PC-9801 type personal computer utilizing the multi-regression analysis program MR compiled in the multivariate analysis program package MVA.[6] The standard deviation (s) is given by $s=[s_{se}/(n-k-1)]^{1/2}$, where n and k denote the numbers of observations and variables, and s_{se} denotes the sum of squares of the residuals. The values in parentheses in the regression equations denote the 95% confidence levels.

Method of Iteration In the first place, from Eqs. 1—3, values of S°_{298}(g) for substituted nitrobenzenes are estimated. Next, S°_{298}(g) of substituted fluorobenzenes could be determined from a similar linear relation. In the third step, the data for toluenes could be estimated from the values for nitro- and fluorobenzenes, and the observed three kinds of substituted toluenes ($n=5$). In order to estimate S°_{298}(g), the treatments were carried out for Br, Cl, Et, I, OH, NH_2, CN, OMe, COMe, CF_3, CO_2Me, COEt, OEt and CO_2Et series for *ortho*-, *meta*- and *para*-substituted benzene derivatives. Iterations were repeated until the correlation coefficient r for all series exceeded over 0.999, except for the Me- and F-series, where such a high value could not be attained.

Relative Retention Value $\log\gamma$ and Experimental Conditions of GLC The details are as given before.[2,3]

Results and Discussion

Estimation of S°_{298}(g) 1. Unsymmetrically Disubstituted Benzene Derivatives In the first place, the authors have found that the values of S°_{298}(g) observed for halogenonitrobenzene derivatives,[5a] as well as the estimated ones for *ortho*-, *meta*- and *para*-dinitrobenzene derivatives,[4] could

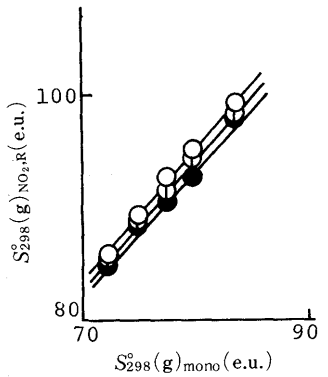

Fig. 1. Correlations between S°_{298}(g) of $NO_2C_6H_4R$ and Those of C_6H_5R

○ = *ortho*-, ① = *meta* and ● = *para*-series.

TABLE I. Values of Correlation Coefficient r between Di- and Monosubstituted Benzene Series

	ortho	*meta*	*para*
NO_2	0.999	0.999	0.999
CN	1.000	1.000	1.000
COMe	1.000	1.000	1.000
COEt	1.000	1.000	1.000
CF_3	1.000	1.000	1.000
CO_2Me	1.000	1.000	1.000
CO_2Et	1.000	1.000	1.000
F	0.996	0.998	0.998
Cl	0.998	0.999	1.000
Br	0.998	1.000	0.999
I	1.000	1.000	1.000
Me	0.998	0.998	0.998
Et	0.999	0.999	0.999
OMe	1.000	1.000	1.000
OEt	1.000	1.000	1.000
OH	0.999	1.000	1.000
NH_2	0.999	1.000	1.000
NMe_2	1.000	1.000	1.000

be correlated successfully with those of the corresponding monosubstituted benzenes (*cf.* Fig. 1 and Eqs. 1—3).

$$S^\circ_{298}(g)(1,2) = 1.25(0.10)S^\circ_{298}(g)(mono) - 5.30(1.52) \quad (1)$$
$$n=5(NO_2, F, Cl, Br, I) \quad r=0.999 \quad F=1480 \quad s=0.28$$

$$S^\circ_{298}(g)(1,3) = 1.31(0.14)S^\circ_{298}(g)(mono) - 8.86(1.23) \quad (2)$$
$$n=5 \quad r=0.998 \quad F=884 \quad s=0.38$$

$$S^\circ_{298}(g)(1,4) = 1.23(0.28)S^\circ_{298}(g)(mono) - 5.02(4.36) \quad (3)$$
$$n=5 \quad r=0.992 \quad F=195 \quad s=0.77$$

Accordingly, using Eqs. 1—3, we are able to estimate the unknown values of $S^\circ_{298}(g)$ for *ortho*-, *meta*- and *para*-substituted nitrobenzene derivatives by means of inter- or extrapolation of the linear relations.

Next, the same operations were applied for another 17

TABLE II. Values σ_{s° for Disubstituted Benzene Derivatives

	NO_2	CN	COMe	COEt	CF_3	CO_2Me	CO_2Et	F	Cl	Br	I	Me	Et	OMe	OEt	OH	NH_2	NMe_2
ortho																		
NO_2	0.183																	
CN	0.152	0.123																
COMe	0.208	0.176	0.232															
COEt	0.248	0.214	0.272	0.313														
CF_3	0.208	0.176	0.232	0.272	0.232													
CO_2Me	0.251	0.217	0.275	0.316	0.274	0.318												
CO_2Et	0.283	0.247	0.306	0.348	0.306	0.351	0.385											
F	0.122[a]	0.103	0.155	0.191	0.154	0.194	0.223	0.078[a]										
Cl	0.139[a]	0.116	0.168	0.205	0.167	0.208	0.237	0.099[a]	0.103[a]									
Br	0.153[a]	0.128	0.180	0.218	0.180	0.220	0.250	0.114[a]	0.129[a]	0.128[a]								
I	0.166[a]	0.137	0.191	0.229	0.191	0.232	0.263	0.124[a]	0.129	0.142	0.151							
Me	0.152	0.123	0.176	0.214	0.176	0.217	0.247	0.103	0.116	0.128	0.137	0.117[a]						
Et	0.196	0.165	0.220	0.259	0.219	0.261	0.293	0.144	0.156	0.169	0.179	0.171[a]	0.208[a]					
OMe	0.195	0.164	0.220	0.259	0.219	0.262	0.293	0.143	0.156	0.169	0.179	0.164	0.207	0.207				
OEt	0.235	0.202	0.259	0.300	0.259	0.303	0.335	0.180	0.193	0.206	0.217	0.202	0.246	0.246	0.287			
OH	0.146	0.118	0.170	0.208	0.170	0.210	0.240	0.098	0.110	0.123	0.132	0.123[a]	0.159	0.158	0.196	0.113		
NH_2	0.150	0.122	0.174	0.212	0.174	0.214	0.244	0.110[a]	0.115	0.127	0.136	0.120	0.163	0.163	0.200	0.117	0.121	
NMe_2	0.201	0.170	0.225	0.265	0.225	0.268	0.299	0.148	0.161	0.174	0.184	0.170	0.213	0.213	0.252	0.164	0.168	0.218
meta																		
NO_2	0.187																	
CN	0.155	0.124																
COMe	0.212	0.180	0.236															
COEt	0.253	0.220	0.277	0.316														
CF_3	0.212	0.180	0.236	0.276	0.236													
CO_2Me	0.256	0.223	0.279	0.319	0.279	0.322												
CO_2Et	0.288	0.255	0.311	0.351	0.311	0.354	0.386											
F	0.125[a]	0.102	0.158	0.198	0.158	0.201	0.233	0.076[a]										
Cl	0.142[a]	0.116	0.171	0.211	0.171	0.214	0.245	0.100[a]	0.106[a]									
Br	0.159[a]	0.128	0.184	0.224	0.184	0.227	0.258	0.106	0.120	0.134[a]								
I	0.169[a]	0.139	0.195	0.235	0.195	0.238	0.269	0.117	0.130	0.143	0.154							
Me	0.155	0.124	0.180	0.220	0.180	0.223	0.255	0.102	0.116	0.128	0.139	0.123[a]						
Et	0.200	0.168	0.224	0.264	0.224	0.266	0.298	0.146	0.159	0.172	0.183	0.176[a]	0.213[a]					
OMe	0.199	0.168	0.224	0.264	0.224	0.267	0.298	0.146	0.159	0.172	0.182	0.168	0.211	0.211				
OEt	0.240	0.207	0.264	0.304	0.263	0.306	0.338	0.185	0.198	0.211	0.222	0.207	0.251	0.251	0.291			
OH	0.148	0.118	0.174	0.214	0.174	0.217	0.248	0.096	0.110	0.122	0.133	0.122[a]	0.162	0.161	0.201	0.112		
NH_2	0.152	0.122	0.178	0.218	0.178	0.221	0.252	0.098	0.113	0.126	0.137	0.122	0.166	0.165	0.205	0.116	0.120	
NMe_2	0.205	0.173	0.229	0.270	0.229	0.272	0.304	0.151	0.164	0.177	0.188	0.173	0.217	0.217	0.257	0.167	0.171	0.222
para																		
NO_2	0.180																	
CN	0.147	0.115																
COMe	0.206	0.173	0.231															
COEt	0.248	0.215	0.271	0.311														
CF_3	0.206	0.173	0.230	0.271	0.230													
CO_2Me	0.250	0.218	0.274	0.314	0.274	0.317												
CO_2Et	0.283	0.251	0.306	0.346	0.306	0.348	0.380											
F	0.119[a]	0.092	0.151	0.193	0.150	0.196	0.229	0.069[a]										
Cl	0.135[a]	0.105	0.164	0.206	0.164	0.209	0.242	0.077[a]	0.097[a]									
Br	0.148[a]	0.119	0.177	0.219	0.177	0.222	0.254	0.096	0.110	0.128[a]								
I	0.158[a]	0.130	0.188	0.230	0.188	0.232	0.265	0.107	0.120	0.134	0.145							
Me	0.148	0.116	0.174	0.215	0.173	0.218	0.250	0.101[a]	0.106	0.120	0.131	0.117[a]						
Et	0.193	0.161	0.218	0.258	0.218	0.261	0.293	0.139	0.152	0.165	0.176	0.171[a]	0.207[a]					
OMe	0.193	0.160	0.218	0.259	0.217	0.261	0.294	0.138	0.151	0.164	0.175	0.161	0.205	0.205				
OEt	0.234	0.202	0.258	0.298	0.258	0.301	0.333	0.179	0.193	0.205	0.216	0.202	0.245	0.245	0.285			
OH	0.141	0.109	0.167	0.209	0.167	0.212	0.244	0.086	0.099	0.113	0.124	0.111[a]	0.155	0.154	0.195	0.102		
NH_2	0.145	0.113	0.171	0.213	0.171	0.216	0.248	0.090	0.103	0.117	0.128	0.114	0.159	0.158	0.199	0.106	0.110	
NMe_2	0.199	0.166	0.223	0.264	0.223	0.267	0.299	0.144	0.157	0.170	0.181	0.167	0.211	0.211	0.251	0.160	0.164	0.216

a) Observed values.

kinds of *ortho*-, *meta*- and *para*-disubstituted benzene series. The regression analyses for the *ortho*-series all involve more than 5 congeners but the others are all less than 5. The iterations were repeated until the correlation coefficients r for all series exceeded over 0.999.

For example, the substituted nitrobenzenes afford Eqs. 4—6 as below;

$$S^\circ_{298}(g)(1,2) = 1.05(0.02)S^\circ_{298}(g)(mono) + 10.37(0.18) \quad (4)$$
$$n=18 \quad r=0.999 \quad F=10331 \quad s=0.43$$

$$S^\circ_{298}(g)(1,3) = 1.07(0.20)S^\circ_{298}(g)(mono) + 9.16(0.19) \quad (5)$$
$$n=18 \quad r=0.999 \quad F=13200 \quad s=0.39$$

$$S^\circ_{298}(g)(1,4) = 1.07(0.029)S^\circ_{298}(g)(mono) + 7.65(0.22) \quad (6)$$
$$n=18 \quad r=0.999 \quad F=13841 \quad s=0.38$$

The r values after the iteration are summarized in Table I. These estimated data were all transformed finally to σ_{s° by using Eq. 7,[1] and the results are presented in Table II.

$$\sigma_{s^\circ} \equiv \log[S^\circ_{298}(g)B/S^\circ_{298}(g)A] \quad (7)$$

where the subscripts A and B denote benzene as the reference and the disubstituted benzene derivatives, respectively.

The data of σ_{s° determined from the observed $S^\circ_{298}(g)$ for 40 congeners gave an excellent correlation (Eq. 8) with those of the calculation given in Table II.

$$\sigma_{s^\circ obs} = 1.019(0.042)\sigma_{s^\circ cal} \quad (8)$$
$$n=40 \quad r=0.991 \quad F=2376.2 \quad s=0.004$$

2. Trisubstituted Benzene Derivatives In the same way, the correlations of the observed $S^\circ_{298}(g)$ for trisubstituted benzene derivatives,[5b,c] having the same kind of substituent against those of monosubstituted benzene series are expressed by Eqs. 9—11 (*cf.* Fig. 2).

$$S^\circ_{298}(g)(1,2,3) = 2.97(0.33)S^\circ_{298}(g)(mono) - 134.72(0.19) \quad (9)$$
$$n=4(F, Cl, Me, Et) \quad r=1.000 \quad F=1471.0 \quad s=0.81$$

$$S^\circ_{298}(g)(1,2,4) = 3.00(0.21)S^\circ_{298}(g)(mono) - 134.77(0.12) \quad (10)$$
$$n=4 \quad r=1.000 \quad F=3978.1 \quad s=0.50$$

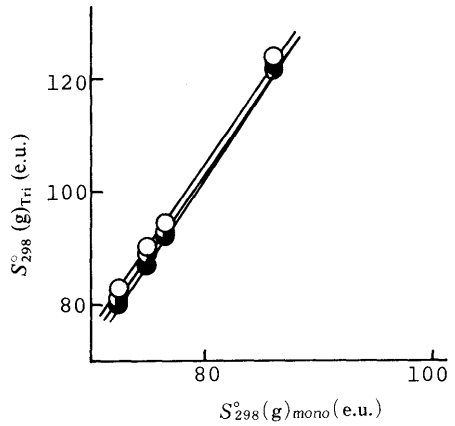

Fig. 2. Correlations between $S^\circ_{298}(g)$ of $C_6H_3R_3$ and Those of C_6H_5R
○ = 1,2,3-, ◑ = 1,2,4- and ● = 1,3,5-series.

TABLE III. Values of σ_{s° for Trisubstituted Benzene Derivatives

R	123—	124—	135—	R	123—	124—	135—
NO_2	0.250	0.259	0.250	Br	0.172	0.182	0.171[a]
CN	0.161	0.171	0.157	I	0.203	0.213	0.202
COMe	0.309	0.318	0.312	Me	0.155[a]	0.167[a]	0.156[a]
COEt	0.399	0.407	0.405	Et	0.275[a]	0.284[a]	0.276[a]
CF_3	0.309	0.317	0.311	OMe	0.279	0.288	0.280
CO_2Me	0.405	0.413	0.410	OEt	0.372	0.380	0.376
CO_2Et	0.470	0.477	0.477	OH	0.142	0.153	0.137
F	0.095[a]	0.109[a]	0.088[a]	NH_2	0.154	0.165	0.151
Cl	0.138[a]	0.145[a]	0.129[a]	NMe_2	0.293	0.302	0.295

a) Observed values.

TABLE IV. Values of log γ for Disubstituted Benzene Derivatives and Their Descriptors

	log γ	σ_{s°	$\Sigma\sigma_\pi^\pm$	μ^2/α
ortho-Series				
1 H	0	0	0	0
2 Me_2	0.534	0.117	−0.156	0.018
3 Me, Et	0.729	0.171	−0.147	0.016
4 Et_2	0.928	0.208	−0.138	0.014
5 Me, OMe	0.740	0.164	−0.334	0.069
6 $(OMe)_2$	1.004	0.207	−0.562	0.111
7 OMe, OEt	1.121	0.246	−0.562	0.128
8 $(OEt)_2$	1.241	0.287	−0.562	0.149
9 Me, CN	0.835	0.123	0.148	1.007
10 Me, NO_2	1.056	0.152	0.191	0.903
11 Et, NO_2	1.240	0.196	0.167	0.801
12 Me, COMe	1.017	0.176	0.109	0.411
13 Me, CO_2Me	1.133	0.217	0.142	0.152
14 Me, CO_2Et	1.316	0.247	0.142	0.137
15 OMe, CO_2Me	1.415	0.262	−0.061	0.406
16 NO_2, OMe	1.407	0.195	0.028	1.498
17 NO_2, OEt	1.531	0.235	0.028	1.342
18 $(CO_2Me)_2$	1.653	0.318	0.337	0.402
19 $(CO_2Et)_2$	1.829	0.385	0.337	0.313
meta-Series				
20 Me, Et	0.666	0.176	−0.147	0
21 $(OMe)_2$	1.061	0.211	−0.562	0.095
22 OMe, OEt	1.252	0.251	−0.562	0.085
23 $(OEt)_2$	1.460	0.291	−0.562	0.078
24 Me, CN	0.835	0.124	0.148	0.900
25 Me, NO_2	1.133	0.155	0.254	0.709
26 OMe, COMe	1.341	0.224	−0.015	0.714
27 NO_2, CO_2Me	1.740	0.256	0.552	0.450
28 NO_2, COMe	1.642	0.212	0.598	0.535
29 $(NO_2)_2$	1.586	0.187	0.664	0.678
30 $(CO_2Me)_2$	1.817	0.322	0.440	0.139
31 $(CN)_2$	1.075	0.124	0.452	0.882
para-Series				
32 Me_2	0.469	0.117	−0.156	0
33 Me, Et	0.687	0.171	−0.147	0
34 Et_2	0.919	0.207	−0.138	0
35 $(OMe)_2$	1.062	0.205	−0.562	0
36 OMe, OEt	1.254	0.245	−0.562	0
37 $(OEt)_2$	1.425	0.285	−0.562	0
38 Me, NO_2	1.183	0.148	0.254	0.709
39 Et, NO_2	1.450	0.193	0.263	0.627
40 Me, COMe	1.146	0.174	0.188	0.458
41 Et, COMe	1.399	0.218	0.197	0.415
42 Me, CO_2Me	1.198	0.218	0.142	0.165
43 OMe, COMe	1.499	0.218	−0.015	0.913
44 OMe, CO_2Me	1.554	0.261	−0.061	0.473
45 NO_2, OMe	1.569	0.193	0.051	1.267
46 NO_2, OEt	1.759	0.234	0.051	1.143
47 Me, CN	0.888	0.116	0.148	0.900
48 NO_2, COMe	1.685	0.206	0.598	0.015
49 $(CN)_2$	1.127	0.115	0.452	0
50 $(COMe)_2$	1.718	0.231	0.532	0
51 NO_2, CO_2Me	1.740	0.250	0.552	0.142
52 NO_2, CO_2Et	1.931	0.283	0.552	0.128
53 $(NO_2)_2$	1.624	0.180	0.664	0

$$S^\circ_{298}(g)(1,3,5) = 3.08(0.09)S^\circ_{298}(g)(mono) - 144.20(0.05) \quad (11)$$
$$n=5(F, Cl, Br, Me, Et) \quad r=1.000 \quad F=13020.7 \quad s=0.28$$

The unknown values of $S^\circ_{298}(g)$ for the above three series could be estimated from the above Eqs. 9—11 by following the procedure in section 1.

The results of regression analyses on the data using those of the $S^\circ_{298}(g)$ of monosubstituted benzenes as an independent variable are expressed by Eqs. 12—14, and the data of σ_{s° determined by Eq. 7 are summarized in Table III.

$$S^\circ_{298}(g)(1,2,3) = 3.07(0.02)S^\circ_{298}(g)(mono) - 142.35(0.01) \quad (12)$$
$$n=18 \quad r=1.000 \quad F=105934 \quad s=0.40$$

$$S^\circ_{298}(g)(1,2,4) = 3.10(0.02)S^\circ_{298}(g)(mono) - 142.47(0.01) \quad (13)$$
$$n=18 \quad r=1.000 \quad F=158320 \quad s=0.33$$

$$S^\circ_{298}(g)(1,3,5) = 3.19(0.02)S^\circ_{298}(g)(mono) - 152.19(0.01) \quad (14)$$
$$n=18 \quad r=1.000 \quad F=185074 \quad s=0.31$$

3. "*ortho* Effect" and σ_{s° The most important finding based on the above results is that the $S^\circ_{298}(g)$ of 1,2-di-, and 1,2,3- and 1,2,4-trisubstituted series having vicinal substituents could be expressed without exception as a subordinate variable to those of the monosubstituted series. Namely, contrary to our expectation, it may be concluded that the method of estimation by means of the linear relationships rejects the so-called "*ortho* effect", and, furthermore, the descriptor σ_{s°, representing the dispersion and repulsion interaction energies, excludes the so-called "*ortho* effect" customarily observed in the physico-chemical behavior of a substrate with a vicinal substituent group. In other words, the "*ortho* effect" seems to reflect the perturbation due to charge-transfer E_{CT}, electrostatic E_{es}, or induction E_{id}, in the energy contribution,[7] *i.e.*, it should be associated with the term represented by $\sigma_\pi^{\pm}$[8] or μ^2/α.

Disubstituted Benzene Derivatives and Their Relative Retention Values log γ in GLC In this work, in order to confirm the validity of the descriptor σ_{s° determined for disubstituted benzene derivatives, we have tried to express the relative retention value log γ of the above series, employing the three kinds of descriptors σ_{s°, $\Sigma\sigma_\pi^{\pm}$ and μ^2/α, where the revised descriptor based on the intensity drop[9,10] of the ultraviolet ^{1}La band due to the vicinal substituent group is used. The observed data of log γ and descriptors are summarized in Table IV, and the results of the regression analyses are expressed by Eqs. 15—17, where Eq. 15 suggests, as was expected, the prominent drop of the term $\Sigma\sigma_\pi^{\pm}$ and an increase of the μ^2/α terms for *ortho*-disubstituted benzene series.

$$\log\gamma(ortho) = 4.214\sigma_{s^\circ} + 0.150\mu^2/\alpha + 0.565\Sigma\sigma_\pi^- \quad (15)$$
$$(0.385) \quad (0.124) \quad (0.323)$$
$$n=19 \quad r=0.994 \quad F=395.3 \quad s=0.052$$

$$\log\gamma(meta) = 4.160\sigma_{s^\circ} - 0.460\Sigma\sigma_\pi^+ + 1.356\Sigma\sigma_\pi^- \quad (16)$$
$$(0.328) \quad (0.175) \quad (0.152)$$
$$n=16 \quad r=0.998 \quad F=799.7 \quad s=0.044$$

$$\log\gamma(para) = 4.024\sigma_{s^\circ} + 0.126\mu^2/\alpha - 0.531\Sigma\sigma_\pi^+ + 1.418\Sigma\sigma_\pi^- \quad (17)$$
$$(0.488) \quad (0.048) \quad (0.208) \quad (0.175)$$
$$n=23 \quad r=0.995 \quad F=438.2 \quad s=0.051$$

The charge-transfer contribution expressed by the term observed in the GLC should be ascribed to a sort of CH---π interaction[11] between the substrate and stationary liquid.

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