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Correlation Analyses of Octanol/Water Partition Coefficient of Substituted Benzoguanamines

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The effects of various substituents in the phenyl moiety of *ortho*-, *meta*-, *para*-, and disubstituted benzoguanamines on the logarithmic 1-octanol/water partition coefficient, log *P*, were quantitatively examined by multiple regression analysis. The independent variables first used were empirical hydrophobic, electronic, and steric substituent parameters, π, σ, and E_s, respectively. Then, semi-empirical molecular orbital calculation was performed with the use of the AM1 Hamiltonian, and the calculated net charges on hydrogen-bondable atoms were used in place of the σ parameters in the analysis. With empirical σ as well as theoretically calculated electronic parameters, not only statistically but also physicochemically highly significant correlation equations were formulated for benzoguanamine derivatives including the multifunctional 2,6-diamino-1,3,5-triazine skeleton.

Key words log *P*; partition coefficient; triazine; correlation analysis; heteroaromatic molecule

The benzoguanamine derivatives 2,4-diamino-6-(substituted phenyl)-1,3,5-triazines were originally developed as antiulcer drugs,[1)] and were found to enhance intercellular communication.[2)] Our previous discriminant analysis revealed that a part of the potency variation is attributable to variations in the log *P* value,[3)] the logarithmic 1-octanol/water partition coefficient.

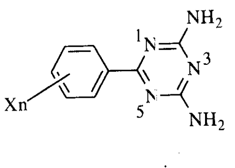
The log *P* value is widely used as a measure of hydrophobic character in quantitative structure–activity relationship (QSAR) studies.[3)] A number of drugs contain heteroaromatic moieties, and analysis and prediction of their log *P* values are required despite their complex physicochemical properties. Benzoguanamines represent a good model for such studies, because they are highly symmetrical and conformational analyses by molecular orbital computations are possible even for *ortho*-substituted derivatives. In this paper, we report analyses of the variations in the log *P* value of benzoguanamines with empirical Hammett type as well as theoretically calculated electronic parameters, along with the empirical hydrophobic and steric substituent parameters.

Experimental

Semi-empirical MO calculations were performed by using MOPAC 93[4)] with the AM1 model Hamiltonian[5)] run on a SPARC station 10. The keywords selected in calculations were AM1, PRECISE, and SYMMETRY when necessary.[6)] All bond lengths, bond angles, and dihedral angles were allowed to vary while the energy was minimized. The net charges of the most stable conformation were used in the analysis. Multiple regression analyses were performed with the StatView 4.0[7)] statistical program run on a Macintosh IIci.

Results and Discussion

Correlation with Empirical Parameters The log *P* values of *ortho*-, *meta*-, and *para*-disubstituted benzenes (X-C_6H_4-Y), where X represents a variable substituent and Y is a fixed functional group, are expressed by Eq. 1.[8,9)]



benzoguananines

Chart 1

$$\log P = a\pi + \rho\sigma^{\circ}(o, m, p) + \rho_{\mathrm{I}}\sigma_{\mathrm{I}}(o) + \delta E_s(o) + \text{const.} \tag{1}$$

In this equation, π is the hydrophobic substituent constant derived from the log *P* values of monosubstituted benzenes.[8-10)] σ° is a Hammett-type electronic parameter that applies when the resonance interaction of the functional groups with the benzene ring is insignificant.[11)] For *ortho* substituents, the σ° values for the corresponding *para* substituents were employed.[9,12)] σ_{I} is Charton's inductive parameter,[13)] and the $\sigma_{\mathrm{I}}(o)$ term reflects the proximity electronic effect of *ortho* substituents on the functional group. E_s is the Taft–Kutter–Hansch steric constant,[14)] and the $E_s(o)$ term primarily expresses the steric effect of the *ortho* substituent on the relative solvation of Y. The values of σ_{I} and E_s are necessarily zero for *meta* and *para* substituents.

Table 1 lists the benzoguanamines, their experimentally determined log *P* values,[1)] and empirical substituent parameters used in the analysis. For *meta*- and *para*-monosubstituted and unsubstituted compounds, Eq. 2 was formulated.

$$\log P = 1.012(\pm 0.059)\pi + 0.660(\pm 0.165)\sigma^{\circ} + 1.404(\pm 0.078) \tag{2}$$
$$n = 13, \quad s = 0.064, \quad r = 0.997, \quad F = 753.021$$

In Eq. 2 and the following equations, *n* is the number of compounds, *s* is the standard deviation, *r* is the correlation coefficient and *F* is the ratio of regression and residual variances. Figures in parentheses are the 95% confidence intervals.

When *ortho*- and disubstituted derivatives were included, Eq. 3 was obtained.

$$\log P = 0.941(\pm 0.064)\pi + 0.561(\pm 0.152)\sigma^{\circ} - 1.117(\pm 0.273)\sigma_{\mathrm{I}}^{ortho} + 0.608(\pm 0.119)E_s^{ortho} + 1.456(\pm 0.076) \tag{3}$$
$$n = 33, \quad s = 0.107, \quad r = 0.987, \quad F = 255.642$$

The regression coefficient of the π term in Eq. 3 is close

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Table 1. The Compounds, log P Values, and Physicochemical Substituent Parameters Used in Analyses

No.	Substituents	π[a]	σ°[a]	$\sigma_{\mathrm{I}}^{ortho}$[b]	E_{s}^{ortho}[c]	log P obsd.[d]	log P calcd.[e]
1	3-Cl	0.71	0.37	0.00	0.00	2.33	2.33
2	2-Cl-4-Cl	1.42	0.54	0.47	−0.97	2.07	1.98
3	2-Cl-5-Cl	1.42	0.64	0.47	−0.97	1.97	2.04
4	3-Br	0.86	0.38	0.00	0.00	2.44	2.48
5	2-Br-4-Cl	1.57	0.53	0.47	−1.16	2.09	2.00
6	2-F-5-Br	1.00	0.55	0.54	−0.46	1.94	1.82
7	2-F-5-Cl	0.85	0.54	0.54	−0.46	1.81	1.68
8	2-Br-5-Cl	1.57	0.63	0.47	−1.16	1.85	2.06
9	2-Cl-5-Br	1.57	0.65	0.47	−0.97	2.04	2.18
10	4-F	0.14	0.17	0.00	0.00	1.61	1.68
11	3-SCF_3	1.44	0.40	0.00	0.00	3.20	3.04
12	3-CF_3	0.88	0.47	0.00	0.00	2.67	2.55
13	3-NO_2	−0.28	0.70	0.00	0.00	1.57	1.59
14	4-Me	0.56	−0.12	0.00	0.00	1.92	1.92
15	4-Cl	0.71	0.27	0.00	0.00	2.33	2.28
16	4-NO_2	−0.28	0.82	0.00	0.00	1.60	1.65
17	3-SMe	0.61	0.13	0.00	0.00	2.16	2.10
18	2-Br-5-Br	1.72	0.64	0.47	−1.16	2.09	2.20
19	2-OMe-5-Br	0.84	0.22	0.30	−0.55	1.53	1.70
20	2-Cl-5-CF_3	1.59	0.74	0.47	−0.97	2.27	2.25
21	2-Cl-5-F	0.85	0.62	0.47	−0.97	1.38	1.49
22	2-Br-5-F	1.00	0.61	0.47	−1.16	1.45	1.51
23	3-F	0.14	0.35	0.00	0.00	1.73	1.78
24	H	0.00	0.00	0.00	0.00	1.36	1.46
25	2-Cl	0.71	0.27	0.47	−0.97	1.19	1.16
26	3-SO_2Me	−1.63	0.68	0.00	0.00	0.29	0.31
27	2-Br	0.86	0.26	0.47	−1.16	1.26	1.18
28	2-I	1.12	0.27	0.40	−1.40	1.41	1.36
29	2-Me	0.56	−0.12	−0.01	−1.24	1.26	1.17
30	2-Et	1.02	−0.13	−0.01	−1.31	1.65	1.56
31	2-OMe	−0.02	−0.16	0.30	−0.55	0.58	0.68
32	2-OEt	0.38	−0.14	0.28	−0.55	1.03	1.09
33	2-NO_2	−0.28	0.82	0.67	−1.01	0.49	0.29
34	2,6-Cl_2	1.42	0.54	0.94	−1.94	1.38[f]	0.87

a) Taken from reference 15. *b*) Taken from reference 13. *c*) Taken from reference 14. The reference point of the E_s value is shifted to that of H such that $E_s(H)=0$. *d*) Taken from reference 1. *e*) Calculated according to Eq. 3. *f*) Not included in Eq. 3.

to unity, indicating that the "non-perturbed" hydrophobic effect of aromatic substituents is satisfactorily separated from steric and electronic effects. The positive coefficient of the σ° term shows that electron-withdrawing substituents increase the log P values. Electron-withdrawing substituents make the functional groups on the diaminotriazine ring more electronically positive. Because 1-octanol is more basic than water, the diaminotriazine groups tend to be solvated preferentially with 1-octanol OH oxygen lone-pair electrons than with the corresponding oxygen of water, leading to an increased log P value.

The positive coefficient with E_{s}^{ortho} means that the bulkier the *ortho* substituents, the less favorable would be the overall solvation of the diaminotriazinyl moiety with bulkier 1-octanol relative to water, lowering the log P value. The negative coefficient with the $\sigma_{\mathrm{I}}^{ortho}$ term shows that overestimation of the electronic effect is made for *ortho* substituents with the use of the σ° term and that the inductive effect of *ortho* substituents generates some specific intramolecular interactions with the functional groups.

Table 2. The Compounds, log P Values, and Calculated Net Charges Used in Analyses

No.	Substituents	$\Delta q(N5)$[a]	$\Delta q(NH_2)$[b]	log P obsd.[c]	log P calcd.[d]
1	3-Cl	−0.004	0.072	2.33	2.28
2	2-Cl-4-Cl	0.187	0.132	2.07	1.97
3	2-Cl-5-Cl	0.182	0.138	1.97	2.00
4	3-Br	−0.001	0.084	2.44	2.45
6	2-F-5-Br	0.149	0.149	1.94	1.98
7	2-F-5-Cl	0.156	0.141	1.81	1.80
10	4-F	0.000	0.062	1.61	1.68
12	3-CF_3	−0.027	0.150	2.67	2.67
13	3-NO_2	0.018	0.227	1.57	1.51
14	4-Me	0.009	0.004	1.92	1.96
15	4-Cl	−0.032	0.073	2.33	2.37
16	4-NO_2	−0.003	0.235	1.60	1.59
17	3-SMe	−0.018	0.030	2.16	2.15
23	3-F	0.004	0.083	1.73	1.71
24	H	0.000	0.000	1.36	1.42
25	2-Cl	0.200	0.079	1.19	1.12
26	3-SO_2Me	−0.023	0.168	0.29	0.17
29	2-Me	0.051	0.023	1.26	1.19
30	2-Et	0.055	0.034	1.65	1.62
31	2-OMe	0.112	−0.062	0.58	0.63
33	2-NO_2	0.094	0.227	0.49	0.71

a) The net charge of the nitrogen atom on the riazine ring on the "same" side as the *ortho* substituents, as shown in Chart 2. *b*) The sum of the net charges of the two amino groups, *i.e.* 2 nitrogen and 4 hydrogen atoms. *c*) Taken from reference 1. *d*) Calculated according to Eq. 6.

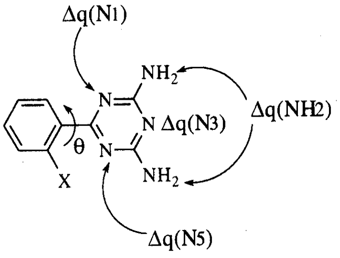

Chart 2

Correlation with Empirical and Theoretically Calculated Electronic Parameters We have reported the correlation of the Hammett σ constants with the net charges on hydrogen-bondable atoms of the carboxyl group of 27 substituted benzoic acids calculated by the AM1 semi-empirical molecular orbital method.[16]

$$\sigma=29.166(\pm 2.986)[q(=O)+q(\text{–}O\text{–})+q(H)]+12.681(\pm 1.283) \quad (4)$$

$$n=27, \quad s=0.083, \quad r=0.971, \quad F=404.7$$

In Eq. 4, $q(=O)$, $q(\text{–}O\text{–})$, and $q(H)$ are the net charges on carbonyl oxygen, hydroxyl oxygen, and hydroxyl hydrogen atoms of the carboxyl group, respectively.

Table 2 lists the compounds and net charges on hydrogen-bondable atoms in the optimized conformation of benzoguanamines according to the notations illustrated in Chart 2. The dihedral angle between the two rings, θ, was in the range of 30°—40° for *meta*- and *para*-substituted and unsubstituted compounds, and 40°—80° for *ortho*-substituted derivatives. To allow easier comparison with σ° and $\sigma_{\mathrm{I}}^{ortho}$, the net charges were multiplied by 10; their reference point was that of the unsubstituted benzoguanamine.

For *meta*- and *para*-monosubstituted and unsubstituted derivatives, Eq. 5 was obtained, where $\Delta q(\mathrm{NH_2})$ is the sum of the net charges on the two amino groups, *i.e.* those of the 2 nitrogen and 4 hydrogen atoms.

$$\log P = 0.979(\pm 0.079)\pi + 2.171(\pm 0.716)\Delta q(\mathrm{NH_2}) + 1.422(\pm 0.093)$$

$$n = 12,\quad s = 0.073,\quad r = 0.995,\quad F = 412.339 \qquad (5)$$

The positive coefficient of the $\Delta q(\mathrm{NH_2})$ term shows the increase in the $\log P$ values by electron-withdrawing substituents, which conforms with Eqs. 2 and 3. When *ortho*- and disubstituted derivatives were analyzed together, Eq. 6 was obtained.

$$\log P = 1.006(\pm 0.066)\pi + 1.866(\pm 0.520)\Delta q(\mathrm{NH_2}) \qquad (6)$$

$$+ 0.550(\pm 0.118)E_s^{ortho} - 3.146(\pm 0.770)\Delta q(\mathrm{N5}) + 1.422(\pm 0.075)$$

$$n = 21,\quad s = 0.083,\quad r = 0.993,\quad F = 291.745$$

The coefficients with π in Eqs. 5 and 6 were again very close to unity. $\Delta q(\mathrm{N5})$ represents the net charge on the ring nitrogen on the "same" side as *ortho* substituents, and accordingly $\Delta q(\mathrm{N5})$ expresses the "proximity" electronic effects of *ortho* substituents.

Equations 3 and 6 correspond with each other very well. The coefficients of π and E_s are practically equivalent in these two equations. The signs of the σ° and σ_I terms in Eq. 3, positive and negative, respectively, correspond with those of the $\Delta q(\mathrm{NH_2})$ and $\Delta q(\mathrm{N5})$ terms. The lone-pair electron density at the N5 position is very susceptible to the electronic properties of the *ortho* substituents. The mechanistic interpretation of the negative sign of the $\Delta q(\mathrm{N5})$ term has still to be explored, but the electronic effects expressed by the $\Delta q(\mathrm{NH_2})$ and $\Delta q(\mathrm{N5})$ terms are operative together for *ortho* substituents.

In conclusion, we formulated two correlation equations for the $\log P$ values with the use of the empirical substituent constants (σ° and σ_I) and theoretically calculated net charges ($\Delta q(\mathrm{NH_2})$ and $\Delta q(\mathrm{N5})$). Empirical parameters are more readily usable, but only when they are available. Although MO computation is time-consuming, it gives submolecular information by identifying the atoms primarily participating in the phenomena in question, in addition to the degrees of delocalization of electrons. With increasing availability of computer resources, extension of the present method is expected to be promising for analyzing and predicting $\log P$ values of a wide variety of heteroaromatic drug molecules.

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