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Biological Activities of Drugs. IX.[1] Structure-Activity Relationship of Sulfonamide Carbonic Anhydrase Inhibitors. (4)

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Hansch–Fujita's equation has been applied to an analysis of the natriuretic activity of sulfonamide carbonic anhydrase inhibitors using π and π_c as hydrophobic parameters, and σ, ΔpK_a, Δppm and Δf_r as electronic parameters. Sixteen benzenesulfonamide derivatives were satisfactorily applied to the structure–activity analysis of heterocyclic sulfonamides. It was concluded that a strong natriuretic activity was observed for sulfonamides which had an optimal hydrophobicity and low electronegativity at the sulfamoyl group or a strong inhibitory activity against carbonic anhydrase.

Recently, Hansch and Fujita have introduced a new method to rationalize the effect of substituents on the biological activity of an unsubstituted parent drug with the use of an electronic parameter σ and a hydrophobic parameter π.[3–9] They considered that drugs' biological response is generally subjected to two rate–limiting processes.

$$\text{Compound in extracellular phase} \xrightarrow{A} \text{Site of action in cellular phase} \xrightarrow{k}$$

$$\text{Interaction at the active-site} \longrightarrow \cdots\cdots \longrightarrow \text{Biological response}$$

where A is the permeation parameter of drugs to reach a site of action in cellular phase and k is a constant of reaction rate for drug–receptor interactions.

They formulated an equation assuming that an equivalent biological response to a series of drugs is related to rate–limiting reactions at the active site.

$$\text{Rate of biological response} = d\,(\text{response})/dt = A_X C_X k_X \qquad (1)$$

where C_X is the extracellular molar concentration of drug X being tested, k_X is the rate constant of X and A_X is the permeation parameter of X. The product $A_X C_X$ represents an effective concentration of X at the site of action.

Biological activities of drugs are mostly reported in terms of drug concentration with which a constant equivalent response is obtained under certain conditions. For these conditions, one can replace $d(\text{response})/dt$ with a constant.

Hansch, *et al.* introduced an equation for a structure–activity analysis using π and σ.

$$\log 1/C = -a\pi^2 + b\pi + \rho\sigma + c \qquad (2)$$

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where C is the equieffective concentration of a drug, and a, b, c and ρ are constants. π is defined by Eq. 3.

$$\pi = \log P_X - \log P_H \quad (3)$$

where P_X is the partition coefficient of a derivative X between n-octyl alcohol and water and P_H is that of a parent drug.

Previously, we have studied an inhibitory activity of sulfonamide derivatives against carbonic anhydrase and discussed the activity on the basis of drugs' physicochemical properties.[1] We concluded that the carbonic anhydrase inhibitory activity *in vitro* was markedly influenced by electronic properties of the sulfamoyl group in sulfonamides and hydrophobic properties of the substituted group.

Diuretic action of sulfonamide following an oral administration seems to be influenced by the following four processes resulting from a consecutive transportation of drug molecules to the active site in the living body.

1) Drug molecules administered orally permeate the membrane of the gastrointestinal tract; 2) molecules taken into the body fluid bind to protein and lipid and are frequently metabolized during circulation or transportation; 3) molecules transported to the active site interact with receptors at the site; 4) biological action or response such as diuresis is developed.

Intensity of biological response is proportional to the reaction rate of the third process, but it is also subjected to the first two processes. Specificity of biological response to a drug depends upon a specific interaction of the drug with receptors which maintain specific characteristics for living.

Thus, the diuretic activity of sulfonamide derivatives seems to be influenced by the first three processes which are closely correlated to the physicochemical properties of sulfonamides.

It has been well established that absorption of a drug through the gastrointestinal tract is markedly influenced by oil–water partitioning of the drug.[10–12]

Natriuretic and diuretic activity of sulfonamide carbonic anhydrase inhibitors seems to be influenced by a permeating ability through the gastrointestinal tract and a binding ability with the active site. Thus, Hansch and Fujita's method can be applicable for a structure–activity analysis for the natriuretic and diuretic activity of sulfonamides with the use of electronic and hydrophobic parameters.

Presently, an analysis was made for possible correlations of natriuretic activity in rats[13] with drugs' physicochemical properties following the Hansch–Fujita's method. Presently, the σ term in Hansch–Fujita's equation was substituted with either of ΔpK_a, Δppm, Δf_r, Hammett's σ factor or carbonic anhydrase inhibitory constant (K_I), which were reported in the previous paper.[1] And the π term in the equation was replaced with π_c, the partition coefficient of unionized molecules between chloroform and water.

In the previous study,[13] we have observed a good correlationship ($r=0.999$) between diuretic activity of sulfonamides and their natriuretic activity. Thus, a structure–activity analysis was made for the natriuretic activity in the present study.

Results and Discussion

A structure–activity analysis of natriuretic activity (Table I) was made of 16 benzenesulfonamide derivatives (compd. No. 1—16) except for o-derivatives with the use of electronic and hydrophobic parameters. Equations were obtained with a least square analysis.

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11) L.S. Shanker, D.J. Tocco, B.B. Brodie and C.A.M. Hogben, *J. Pharmacol. Exp. Therap.*, **123**, 81 (1958).
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	r	s	
$\log 1/C=-0.392\pi_c^2-0.130\pi_c+0.470$	0.326	0.323	(4)
$\log 1/C=-0.171\pi^2+0.247\pi+0.338$	0.417	0.278	(5)
$\log 1/C=0.353\log 1/K_I+0.072$	0.644	0.260	(6)
$\log 1/C=-0.165\pi_c^2-0.020\pi_c+0.306\log 1/K_I+0.160$	0.692	0.224	(7)
$\log 1/C=-0.221\pi^2-0.197\pi+0.701\log 1/K_I+0.045$	0.878	0.163	(8)
$\log 1/C=0.598\sigma+0.177$	0.811	0.201	(9)
$\log 1/C=-0.597\Delta\,\mathrm{p}K_a+0.244$	0.898	0.148	(10)
$\log 1/C=1.164\Delta\,\mathrm{ppm}+0.188$	0.835	0.188	(11)
$\log 1/C=2.059\Delta f_r+0.320$	0.863	0.163	(12)
$\log 1/C=-0.198\pi_c^2-0.188\pi_c+0.470\sigma+0.292$	0.860	0.172	(13)
$\log 1/C=-0.186\pi_c^2-0.137\pi_c-0.561\Delta\,\mathrm{p}K_a+0.321$	0.928	0.126	(14)
$\log 1/C=-0.177\pi_c^2-0.169\pi_c+1.119\Delta\,\mathrm{ppm}+0.266$	0.886	0.156	(15)
$\log 1/C=-0.121\pi_c^2-0.078\pi_c+1.658\Delta f_r+0.369$	0.873	0.189	(16)
$\log 1/C=-0.175\pi^2-0.106\pi+0.668\sigma+0.317$	0.944	0.113	(17)
$\log 1/C=-0.143\pi^2-0.026\pi-0.674\Delta\,\mathrm{p}K_a+0.335$	0.965	0.089	(18)
$\log 1/C=-0.152\pi^2-0.091\pi+1.497\Delta\,\mathrm{ppm}+0.283$	0.939	0.116	(19)
$\log 1/C=-0.094\pi^2+0.016\pi+1.800\Delta f_r+0.376$	0.886	0.163	(20)

where r is the correlation coefficient and s is the standard deviation.

Equations 4 and 5 were derived on an assumption that the σ term in Eq. 3 is little by changes of substituent. Their correlation coefficients were very small. Similarly good correlation coefficients were not obtained in Eq. 6. An introduction of π_c into Eq. 6 did not improved the correlation coefficient (Eq. 7), but the introduction of π into Eq. 6 remarkably improved the correlation coefficient (Eq. 8). The value obtained with Eq. 8 is presented in Table I.

The optimal π value for the activity, $\log(1/C)$, was obtained by setting $\partial\log(1/C)/\partial\pi=0$ in Eq. 8, *i.e.* $\pi=-0.447$. The π value correspond to 0.704 of partition coefficient between *n*-octyl alcohol and water.

Monoparameter equations 9—12 revealed that the σ term in Hansch-Fujita's equation is a parameter of overwhelming significance against hydrophobic parameters, π_c and π, for the structure-activity relationship of natriuretic sulfonamide derivatives.

Addition of π_c to electron parameters except for Δf_r resulted in a considerable improvement of the correlation coefficients (Eq. 13—15). An introduction of π into eqs. 9—11 remarkably improved the correlation coefficients (Eq. 17—19). The values calculated with Eq. 17, 18 and 19 are presented in Table I.

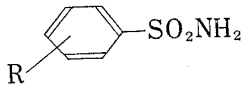
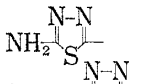
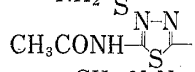
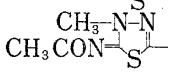
The optimal π values for the activity, $\log(1/C)$, were calculated by setting $\partial\log(1/C)/\partial\pi=0$ in Eq. 17—19, *i.e.* −0.303, −0.092 and −0.299, respectively. The π values correspond to 0.982, 1.60 and 0.993 of partition coefficient between *n*-octyl alcohol and water, respectively.

A positive sign of coefficients of σ and Δppm, and negative sign of coefficient of $\Delta\mathrm{p}K_a$ in Eq. 17, 18 and 19 suggest that a natriuretic activity increases with a decrease of electronic density at the sulfamoyl group in sulfonamide derivatives.

Calculated activity of *o*-derivatives with the use of Eq. 8, 17 and 18 was much larger than that of the experimentally obtained results (Table I). One of the reasons seems to be the intramolecular steric effect of *o*-substituted derivntives.

Natriuretic activity of 1,3,4-thiadiazole-5-sulfonamide derivatives is calculated with Eq. 8, 18 and 19 (Table I.) The calculated activity showed considerable correspondence with the experimental values. Thus, it may be considered that the equations derived presently for a structure-natriuretic activity analysis of benzenesulfonamides can be applicable to develop-

Taelb I. Comparison of Calculated and Observed Natriuretic Activities of Sulfonamide Derivatives

No.	R	log 1/C				
		Obsd.	Calcd.			
			Eq. 8	Eq. 17	Eq. 18	Eq. 19
						
1	*p*-CH_3NH	−0.301	−0.038	−0.229	−0.374	−0.213
2	*p*-NH_2	−0.200	−0.282	−0.229	−0.178	−0.214
3	*p*-CH_3O	0.238	0.256	0.116	0.179	0.100
4	*p*-CH_3	0.182	0.185	0.106	0.178	0.108
5	*m*-CH_3	0.176	0.086	0.162	0.218	0.115
6	H	0.155	0.203	0.317	0.335	0.283
7	*p*-Cl	0.301	0.384	0.363	0.328	0.401
8	*p*-Br	0.267	0.225	0.167	0.203	0.213
9	*m*-Cl	0.318	0.076	0.295	0.273	0.317
10	*p*-CH_3CO	0.462	0.742	0.661	0.526	0.627
11	*p*-CN	1.020	0.739	0.765	0.801	0.739
12	*m*-NO_2	0.699	0.611	0.755	0.678	0.836
13	*p*-NO_2	0.845	0.694	0.783	0.924	0.776
14	3,4-di-Cl	0.267	0.503	0.373	0.358	0.359
15	3-NO_2-4-Cl	0.324	0.364	0.325	0.337	0.316
16	3-NO_2-4-CF_3	0.602	0.591	0.622	0.556	0.596
17	*o*-CH_3	≪−0.301	−0.263	—	0.295	0.463
18	*o*-Cl	≪−0.301	0.268	—	0.246	0.621
19	*o*-NO_2	≪−0.301	0.270	—	1.197	0.983
		R-SO_2NH_2				
20		0.653	1.065	—	1.605	—
21		1.602	1.617	—	2.024	—
22		1.544	1.647	—	2.188	1.687

ment of new sulfonamide carbonic anhydrase inhibitors.

The structure–activity relationship of sulfonamide carbonic anhydrase inhibitors can be, thus, rationalized with the use of two permeability terms, π^2 and π, and carbonic anhydrase inhibitory constant, log $1/K_I$, or one of three electronic parameters such as σ, ΔpK_a, Δppm.

From the present study, the strongest natriuretic activity is expected for sulfonamides which have partition coefficient at about 0.7—1.6 and strong inhibitory activity for carbonic anhydrase of low electronic density at the sulfamoyl group. Similar results were obtained for the diuretic activity analysis.