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Adsorption of Sulfonamides from Aqueous Solution[1,2]

Hisashi Nogami, Tsuneji Nagai,[3a] and Sakae Wada[3b]

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

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The adsorption of sulfonamides by carbon black from solution was investigated in detail regarding the hydrophobic interaction.

The adsorption isotherms obtained were well described with Langmuir equation. pH and concentration of buffer solution had no distinct effect on the adsorption of sulfonamides near the neutral pH region.

From the following results, it was convinced that the adsorption of sulfonamides by carbon black from aqueous solution proceeds by the hydrophobic interaction: (1) adsorption of sulfonamides by carbon black from MeOH solution was correlated to that from aqueous solution; (2) adsorption of sulfonamides by graphite from aqueous solution was correlated to that by carbon black; (3) the entropy change of adsorption of sulfonamides by carbon black from aqueous solution was positive.

In the previous papers,[4,5] the adsorption of barbituric acid derivatives by carbon black from aqueous solution was related with the hydrophobicity of molecule, and eventually it was established that the adsorbability of such derivatives by carbon black in the above system had a good correlation to the biopharmaceutical data reported, *i.e.*, the gastric absorption, and the binding to bovine serum albumin.[5] Moreover, a fairly good correlation was observed between the above adsorbability and the existing pharmacological data.[5] These results suggested that the adsorption by carbon black could be a model giving useful informations for an understanding of biopharmaceutical phenomena.

Intending to ascertain whether the similar results would be obtainable for other homologous drugs, the adsorption of sulfonamides by carbon black from solution was investigated in detail, which will be necessary in discussing the correlation between the adsorbability and the biopharmaceutical data in the following paper.[6]

Experimental

Materials——Carbon black and graphite used were the same as those in the previous paper.[7] Sulfonamides used are listed in Table I, which were recrystallized from MeOH solution; samples No. 1—9 have NH_2– as R_1 and a six-membered ring as R_2, samples No. 10—14 NH_2– as R_1 and a five-membered ring as R_2, samples No. 15—18 NH_2– as R_1 and a straight chain as R_2, and samples No. 19—23 AcNH– as R_1 and a five- or six-membered ring as R_2. The rest of the materials were of the purest reagent grade.

Procedure for Determination of the Adsorbed Amount by Batch Method——1) Adsorption by Carbon Black from 1/30M Michaelis Buffer Solution (pH 7.4), or from MeOH Solution: 10 mg of carbon black

1) This paper forms Part VIII of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part VII: H. Nogami, T. Nagai, and H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 335 (1970).
2) A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
3) Location: *Hongo, Tokyo*; *a*) To whom communications should be directed; *b*) Fellow from *Research Laboratories, Chugai Pharmaceutical Co., Ltd., Takada, Toshima-ku, Tokyo.*
4) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 168 (1969).
5) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 176 (1969).
6) H. Nogami, T. Nagai, and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **18**, 348 (1970).
7) H. Nogami, T. Nagai, E. Fukuoka, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2248 (1968).

Table I. Sulfonamides used in This Study

R_1–⟨⟩SO_2NH–R_2

No.	Sulfonamides	No.	Sulfonamides
1	sulfamethoxypyridazine	13	sulfamethizole
2	sulfadimethoxine	14	sulfisomezole
3	sulfapyridine	15	sulfabutamide
4	sulfamethomidine	16	sulfanilamide
5	sulfamerazine	17	sulfaguanidine
6	sulfisomidine	18	sulfacetamide
7	sulfamonomethoxine	19	N^4–acetylsulfadimethoxine
8	6-sulfanilamido-2-methoxypyridazine	20	N^4–acetylsulfisomidine
9	sulfadiazine	21	N^4–acetylsulfamonomethoxine
10	sulfaphenazole	22	N^4–acetylsulfisomezole
11	sulfathiazole	23	N^4–acetylsulfadiazine
12	sulfaethidole		

was added in 10 ml of the solution, and then the procedure was carried out in the same way as described in the previous paper.[7] Additionally, the effects of concentration and pH of the buffer solution were investigated in the same procedure in Michaelis buffer solution of various concentration and of various pH.

2) Adsorption by Graphite from Michaelis Buffer Solution (pH 7.4): 20 mg of graphite was added in 10 ml of the solution, and then the procedure was carried out in the same way as described in the previous paper.[7]

Procedure for Determination of the Solubilities of Sulfonamides——Excess amount of each sample was added in 10 ml of 1/30 M Michaelis buffer solution (pH 7.4), and then treated in the same way as described in the previous paper.[8]

Quantitative Determination of Sulfonamides——The Concentration of Sulfonamides were determined according to Ultraviolet (UV) Absorption Method: Sulfamethoxypyridazine at 255 mμ; sulfadimethoxine, 268; sulfapyridine, 262; sulfamethomidine, 262; sulfamerazine, 262; sulfisomidine, 262; sulfamonomethoxine, 262; 6-sulfanilamido-2-methoxypyridazine, 262; sulfadiazine, 255; sulfaphenazole, 250; sulfathiazole, 262; sulfaethidole, 260; sulfamethizole, 262; sulfisomezole, 262; sulfabutamide, 255; sulfanilamide, 262; sulfaguanidine, 262; sulfacetamide, 255; N^4-acetylsulfadimethoxine, 265; N^4-acetylsulfisomidine, 260; N^4-acetylsulfamonomethoxine, 260; N^4-acetylsulfisomezole, 260; N^4-acetylsulfadiazine, 255.

Measurement of Surface Tension——This was measured at room temperature with a Du-Noüy surface tensiometer (Rigosha Manufacturing Co.).

Results and Discussion

Adsorption Isotherms of Sulfonamides by Carbon Black from Solution

The adsorption isotherms obtained for all the samples of sulfonamides were well descrbed with Langmuir equation (1) in any experimental condition, as shown in Fig. 1,

$$M=\frac{abC}{1+bC} \tag{1}$$

where M is the amount adsorbed at the concentration C in solution at equilibrium, a the amount adsorbed when the entire surface is covered by a monolayer, and b the equilibrium constant of adsorption process.

In the figure, $1/M$ was plotted against $1/C$, while C/M was plotted against C in the previous paper,[4] but there was no trouble for obtaining a and b.

Influences of Concentration and pH of Buffer Solution on the Adsorption of Sulfonamides by Carbon Black

Solubilities of sulfonamides are sensitive to pH and most of them are slightly soluble in the lower pH region than the neutral (except in a strong acidic solution). Therefore, the

8) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2257 (1968).

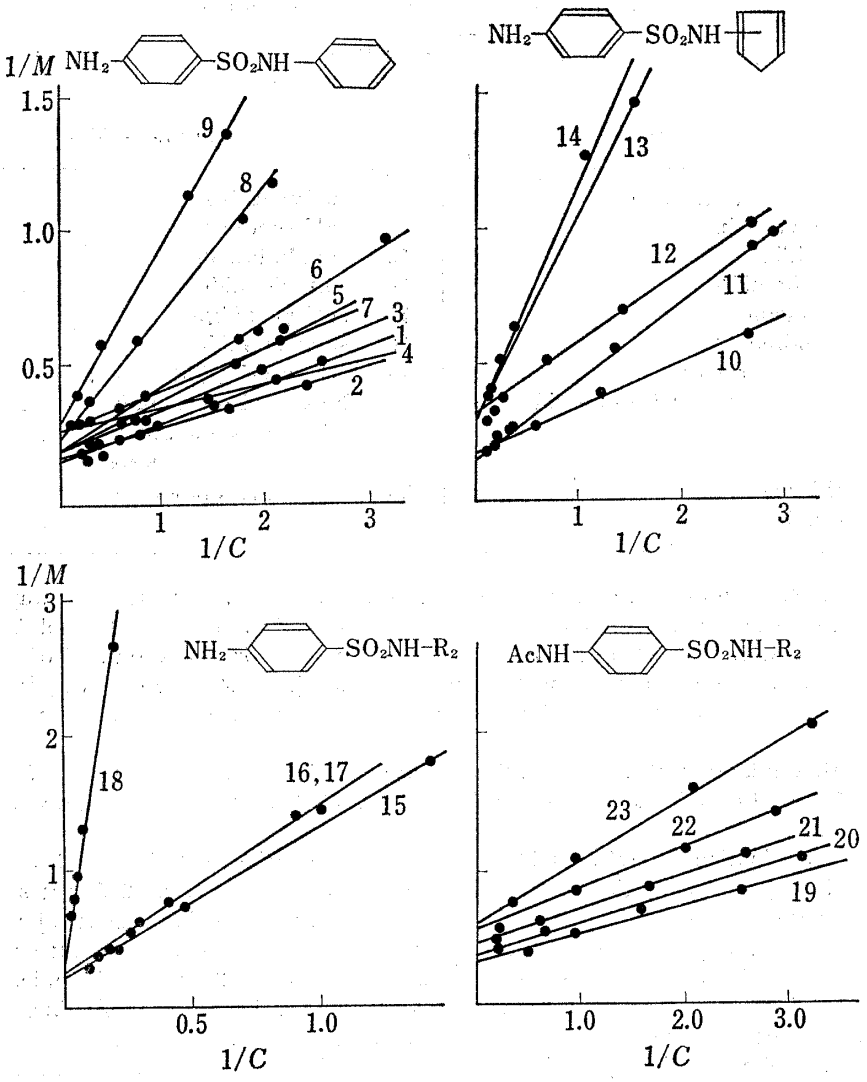

Fig. 1. Langmuir Plots of Adsorption of Sulfonamides by Carbon Black from Michaelis Buffer Solution (pH 7.4) at 40°

C: equilibrium concentration (10^5M) M: amount adsorbed (10^4 mole/g)

experiment should be carried out in a buffer solution, and the pH 7.4, employed in the experiment except the special cases, might be suitable from the pharmaceutical point of view.

In order to check the effect of concentration of buffer solution on the adsorption, the adsorptions of sulfadimethoxine and sulfanilamide by carbon black were measured in different concentrations of buffer solution. Both samples were chosen because the former showed a high adsorbability and the latter a low adsorbability among all the samples used. As shown in Fig. 2, the adsorbed amount seemed almost constant regardless of the concentration of buffer under the experimental conditions, though it actually decreased a little with the increase of the concentration of buffer solution.

The effect of pH of buffer solution on the adsorption by carbon black was checked using sulfisoxazole (pK_a=4.8) and sufanilamide (pK_a=10.1), as both samples have widely different pK_a values. Fig. 3 shows that pH had no distinct effect on the adsorption near the neutral pH region, while it decreased in strong alkaline region. This result was similar to the case of the adsorption of tryptophan by carbon black from aqueous solution in the previous paper,[7] as was considered due to the nonpolar property of carbon black surface.

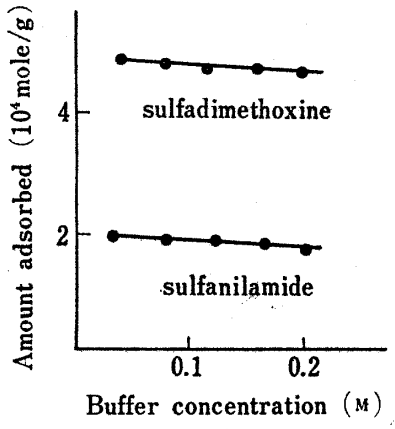

Fig. 2. Effect of Concentration of Michaelis Buffer Solution (pH 7.4) on the Adsorp tion by Carbon Black at 40°

equilibrium concentration: 4×10^{-4}M

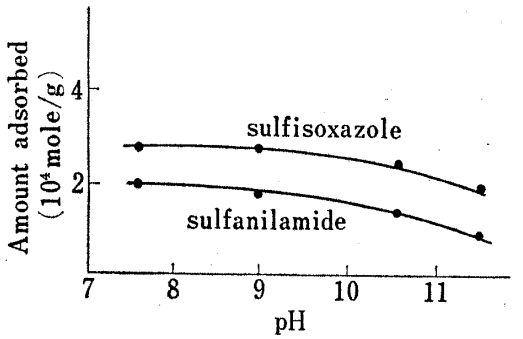

Fig. 3. Effect of pH of Michaelis Buffer Solution on the Adsorption by Carbon Black at 40°

equilibrium concentration: 4×10^{-4}M

Adsorption of Sulfonamides by Carbon Black from MeOH Solution

Sulfonamides include the compounds of various pK_a values and thus the ratio of dissociated molecule to undissociated one at an appointed pH may vary with the sample. Therefore, in order to check the effect of pK_a, the adsorption of sulfonamides by carbon black from MeOH solution was compared with that from buffer solution (pH 7.4). Though MeOH is a relatively polar solvent among organic ones, it is most useful to this experiment because sulfonamides are very slightly soluble in the others. As shown in Fig. 4, both adsorption data were correlated with each other. There was not obtained a satisfactory correlation, as may be explained by considering that the hydrophobicities of both drug molecule and carbon black surface in MeOH are lower than those in water[9] and presumably a satisfactory correlation is not obtainable between the hydrophobicity of drug molecule in MeOH and that in water.

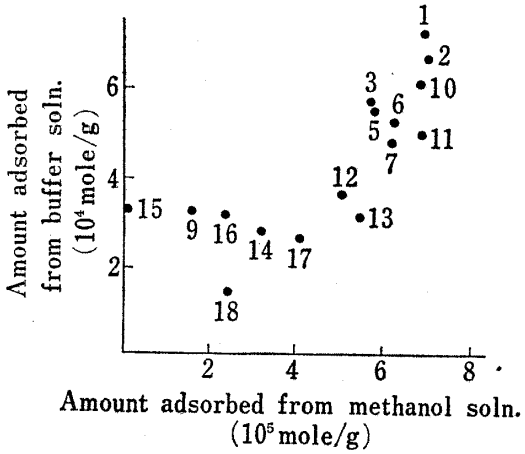

Fig. 4. Relationship between Adsorbability of Sulfonamides by Carbon Black from MeOH Solution and that from Michaelis Buffer Solution (pH 7.4)

from methanol soln: amount adsorbed at 10^{-4}M of equilibrium concentration (20°); from buffer soln: amount adsorbed at 2×10^{-4}M of equilibrium concentration (40°)

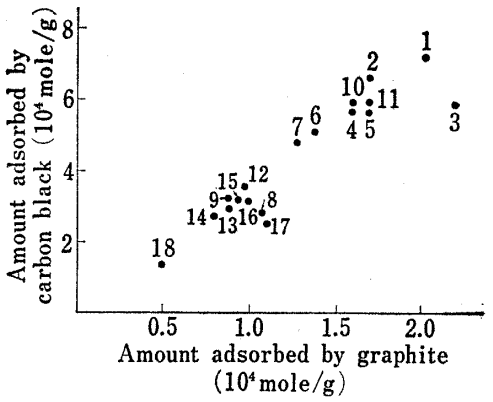

Fig. 5. Relationship between Adsorbability of Sulfonamides from Michaelis Buffer Solution (pH 7.4) by Graphite and that by Carbon Black at 40°

equilibrium concentration: 10^{-4}M

9) H. Nogami, T. Nagai, and H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 328 (1970).

In addition to the fact shown in Fig. 3 that pH had no distinct effect on the adsorption near the neutral pH region, the above result indicates that the hydrophobic moiety of sulfonamide molecule plays an important role on the adsorption on the surface of carbon black in the similar way to the cases of tryptophan[10] and barbituric acid derivatives[4] by carbon black from aqueous solution.

Adsorption of Sulfonamides by Graphite from Aqueous Solution

It is well known that the surface of graphite is more homogeneous and more hydrophobic than that of carbon black. Therefore, if the adsorption of sulfonamides by carbon black is correlated to that by graphite, it will be more convinced that the adsorption of sulfonamides proceeds on the hydrophobic interaction between the hydrophobic moiety of the adsorbate molecule and the carbon black surface. The result shown in Fig. 5 was considered to be a satisfactory proof of the above notion.

Adsorption of Sulfonamides by Carbon Black in Relation to Molecular Weight and Surface Tension

In the previous paper,[4] the adsorption of barbituric acid derivatives by carbon black increased with the molecular weight. However, in the present cases of sulfonamides, there was found no notable correlation between the adsorption and the molecular weight. This was considered due to the variety of the molecular structure, as the increase of the molecular weight is indifferent to the increase of hydrophobicity, contrary to barbituric acid derivatives.[4]

Considering that the adsorption of sulfonamides may proceed by the hydrophobic interaction with the carbon black surface, it is expected that the adsorption by carbon black is correlated with the adsorption to air-solution surface interface because of a similarity in phenomena, which is represented by the surface tension depressing activity. However, it was too difficult to obtain the above correlation because sulfonamides were too slightly soluble to determine the surface tension depressing activity, while it was possible in cases of barbituric acid derivatives.[4]

Temperature Dependence and Thermodynamic Functions of the Adsorption of Sulfonamides by Carbon Black from Aqueous Solution

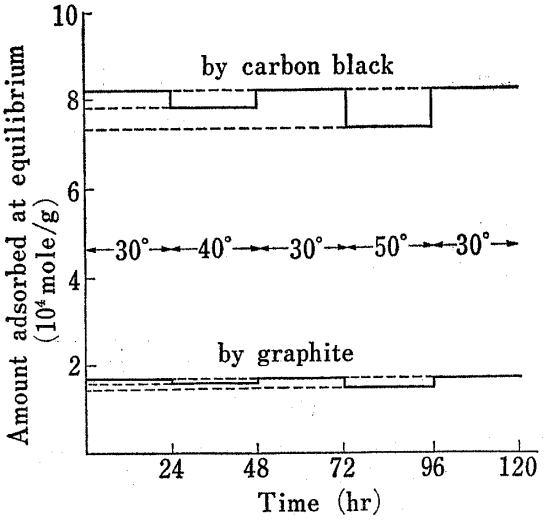

Fig. 6. Effect of Adsorption of Sulfadimethoxine upon Change of Temperature from Michaelis Buffer Solution (pH 7.4)

initial concentration of sulfonamides: by carbon black, 9×10^{-4}M; by graphite, 4×10^{-4}M

Upon change of temperature in the perturbed experiment, the adsorption was found to be reversible, as shown in Fig. 6. Therefore, it was reasonable to calculate the thermodynamic functions in the same way as described in the previous paper.[4]

The results obtained from the data at 30°, 40°, and 50°, are shown in Table II. The positive entropy change suggested that the structural change of iceberg around the adsorbate molecule took place through the adsorption process in the similar way to the cases of barbituric acid derivatives.[4] Then the above result also supported the view that adsorption proceeds by the hydrophobic interaction between the hydrophobic moiety of sulfonamide molecule and the carbon black surface.

10) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2263 (1968).

Table II. Thermodynamic Functions of Adsorption of Sulfonamides from Michaelis Buffer Solution (pH 7.4) by Carbon Black at 40°

No.	Sulfonamides	$-\Delta F$ kcal/mole	$-\Delta H$ kcal/mole	ΔS e.u.
1	sulfamethoxypyridazine	6.10	3.4	8.6
2	sulfadimethoxine	6.45	3.7	8.8
3	sulfapyridine	6.14	4.0	6.8
4	sulfamethomidine	6.19	4.0	7.0
5	sulfamerazine	6.10	5.0	3.5
6	sulfisomidine	5.91	4.0	6.1
7	sulfamonomethoxine	5.17	4.5	2.1
8	6-sulfanilamido-2-methoxypyrimidine	5.19	5.1	0.3
9	sulfadiazine	5.14	5.0	0.4
10	sulfaphenazole	6.07	3.9	6.9
11	sulfathiazole	5.70	4.4	4.2
12	sulfaethizole	5.43	3.8	5.2
13	sulfamethizole	5.16	4.6	1.8
14	sulfisomezole	5.16	4.3	2.0
15	sulfabutamide	5.01	4.4	2.0
16	sulfanilamide	4.72	3.8	2.9
17	sulfaguanidine	4.84	4.6	0.8
18	sulfacetamide	4.09	4.4	−1.0