[Chem. Pharm. Bull. 26(5)1353—1356(1978)]

UDC 615.322.011.5.074 : 547.673.1.08

Adsorption of Sulphonylureas by Carbon Black from Aqueous Solution[1,2]

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(Received July 7, 1977)

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

The adsorption isotherms obtained were well described with Langmuir equation. The adsorbed amount decreased with the increase in pH of buffer solution between 6 and 9, showing that pH had influence on the hydrophobic and hydrophilic balance of the molecule. The adsorbed amount increased with the increase in concentration of buffer solution at pH 7.0, showing that the concentration of buffer solution had influence on water molecules of carbon black surface. The decrease in adsorbed amount with addition of urea demonstrated that the adsorption of sulphonylureas proceeded on the hydrophobic interaction. The adsorbed amount of sulphonylureas by carbon black decreased with temperature, showing the entropy change of adsorption of sulphonylureas by carbon black from aqueous solution was apparently positive.

Keywords——sulphonylurea; adsorption from solution; carbon black; pH-dependence; effect of ionic strength; effect of urea; temperature-dependence; hydrophobic interaction

It has been demonstrated that oral hypoglycemic sulphonylureas are displaced by other drugs in human serum[4] and in solution of purified albumin.[5]

This phenomenon seems to have relation to the clinical effect, namely, the problem of drug interaction. Therefore, a detailed investigation of the association of sulphonylureas with serum albumin may give a helpful information for an understanding of this kind of drug interaction.

In this series of works,[6,7,8] it has been demonstrated that the adsorbability of several kinds of drugs by carbon black from solution is correlated to the protein binding, the gastrointestinal absorption, or the pharmacological effect. Following these previous works, this paper is concerned with the experiment of adsorption of sulphonylureas by carbon black from solution as an approach to understanding of the interaction of the sulphonylureas with albumin.

Experimental

Materials——Carbon black (CB) used was the same as that in a previous paper.[9] Highly purified compounds of sulphonylureas supplied by respective companies, which conformed the respective officially

1) This paper forms Part XXXI of "Physico-chemical Approach to Biopharmaceutical Phenomena." The preceding paper, Part XXX: J. Matsunaga, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **24**, 1169 (1976).
2) A part of this work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.
3) Location: *Ebra–2–4–41, Shinagawa-ku, Tokyo, 142, Japan.*
4) L.K. Christensen, J.M. Hansen, and M. Kristensen, *Lancet*, **2**, 1298 (1963).
5) J. Judis, *J. Pharm. Sci.*, **61**, 89 (1972).
6) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 176 (1969).
7) H. Nogami, T. Nagai, and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **18**, 348 (1970).
8) H. Nogami, T. Nagai, and N. Nambu, *Chem. Pharm. Bull.* (Tokyo), **18**, 1643 (1970).
9) H. Nogami, T. Nagai, E. Fukuoka, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2248 (1968).

registered descriptions, were as follows: Acetohexamide by Shionogi Pharmaceutical Co., Ltd., mp 188—190°; carbutamide by Sumitomo Chemical Co., Ltd., mp 144—145°; chlorpentazide by Kyorin Pharmaceutical Co., Ltd., mp 198°; chlorpropamide by Taito Pfizer Co., Ltd., mp 127—129°; tolbutamide by Hoechst Japan Co., Ltd., mp 128.5—129.5°; tolazamide by Nippon Upjohn Co., Ltd., mp 165—170°.

Procedure for Determination of the Adsorbed Amount by Batch Method——Ten milligrams of carbon black was added in 10 ml of 1/30 M phosphate buffer solution of each drug in a Nessler tube at 30° (unless otherwise stated), and then the procedure was carried out in the same way as described in the previous paper.[9]

Additionally, the effects of concentration and pH of the buffer solution were investigated in the same procedure in phosphate buffer solution of various concentrations and of various pH's.

Quantitative Determination of Sulphonylureas——The concentrations of sulphonylureas were determined according to ultraviolet absorption method, using a Hitachi 323 Spectrophotometer: acetohexamide at 249 nm; carbutamide at 256 nm; chlorpentazide at 229 nm; chlorpropamide at 230 nm; tolbutamide at 227 nm; tolazamide at 226 nm.

Results and Discussion

The adsorption isotherms obtained for all the sulphonylureas were well described with Langmuir equation, as shown in Fig. 1.

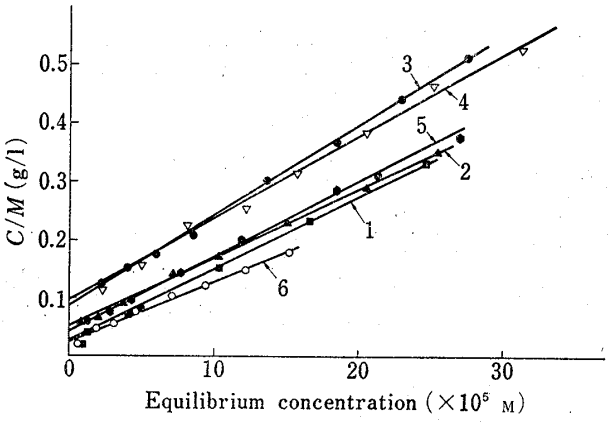

Fig. 1. Langmuir Plots of Adsorption of Sulphonylureas by Carbon Black from Phosphate Buffer Solution (pH 7.0) at 30°

C: equilibrium concentration (M), M: amount adsorbed (mol/g).

1: acetohexamide (■),
2: carbutamide (▲),
3: chlorpentazide (●),
4: chlorpropamide (▽),
5: tolbutamide (◐),
6: tolazamide (○).

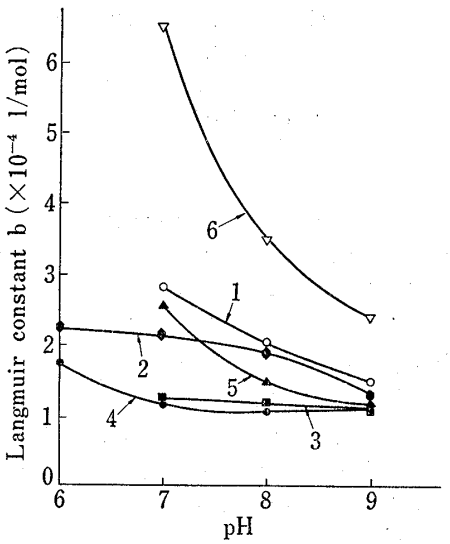

Fig. 2. Effect of pH of Phosphate Buffer on Adsorption at 30°

1: acetohexamide (○),
2: carbutamide (◐),
3: chlorpentazide (■),
4: chlorpropamide (●),
5: tolubutamide (▲),
6: tolazamide (▽).

The adsorbed amount of sulphonylureas by CB decreased with pH between 6 and 9, as shown in Fig. 2. This may be explained by considering that pK_a of the sulphonylureas is about 4.5 to 6.1 and thus the hydrophobic and hydrophilic balance of the molecule is very sensitive to the dissociation under the present experimental condition. In other words, the increase in the amount of dissociated molecule with an increase of pH may result in a distinct decrease in hydrophobicity of molecule, *i.e.*, the decrease in adsorption.

The adsorbed amount of sulphonylureas by CB increased with the concentration of buffer solution at pH 7.0, for example as shown in Fig. 3. This may be explained by considering that water molecules around the surface of CB are removed with the increase of the concentration of buffer solution and hence the molecules of sulphonylurea are adsorbed on

those sites, as was discussed in the case of phenothiazines.[10] In addition, salting out can be regarded as being important in this phenomenon.

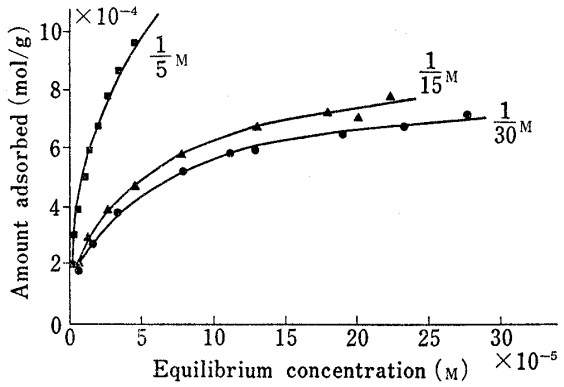

Fig. 3. Effect of Concentration of Buffer Solution on Adsorption of Tolbutamide by CB at 30°

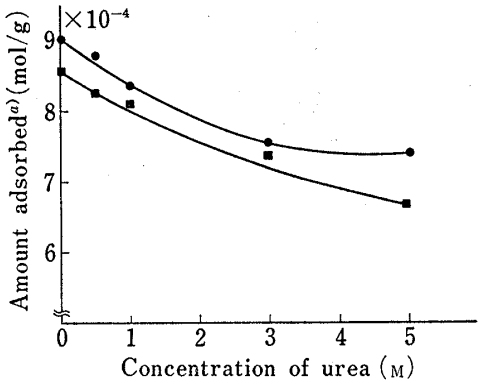

Fig. 4. Effect of Urea on Adsorption of Tolbutamide and Tolazamide from 1/30 M Phosphate Buffer Solution (pH 7.0) at 30°

a) Represented by Langmuir constant a.
●: tolbutamide,
■: tolazamide.

Urea is known to act as a chaotropic agent. In this connection, the effect of urea on adsorption by CB was checked using tolbutamide and tolazamide. Both of the drugs were chosen because the former was widely used for clinical treatments and the latter showed highest adsorbability among all the samples used in this study. As shown in Fig. 4, the adsorbed amount of tolbutamide and tolazamide decreased with the addition of urea. In a similar way to the previous paper,[11] this decrease in adsorption may be explained on the consideration that urea had influenced a structural change of iceberg around the surface of CB and the drugs, causing a decrease in the escaping tendency of solute from solution to the surface of adsorbent. Thus, it was demonstrated that the adsorption of sulphonylureas might proceed on the basis of hydrophobic interaction.

In order to discuss the mechanism of adsorption process of sulphonylureas by CB, adsorption isotherms were investigated at different temperatures and the thermodynamic functions were calculated in the same way as described in the previous paper.[6] The result obtained from the data at 10°, 20°, and 30° are shown in Table I.

Table I. Thermodynamic Functions of Adsorption of Sulphonylureas from Phosphate Buffer Solution (pH 7.0) by Carbon Black at 30°

No.	Sulphonylureas	$-\Delta F$ kcal/mol	$-\Delta H$ kcal/mol	ΔS e.u.
1	Acetohexamide	6.18	0.99	17.1
2	Carbutamide	6.02	3.58	8.1
3	Chlorpentazide	5.68	0.84	16.0
4	Chlorpropamide	5.66	2.69	9.8
5	Tolbutamide	6.12	1.26	16.0
6	Tolazamide	6.67	1.14	18.3

The low values of ΔS and the high values of ΔH of carbutamide and chlorpropamide compared with those of other drugs may be explained on the consideration that carbutamide is an amphoteric electrolyte having an aromatic amino group and chlorpropamide has *p*-chloro

10) N. Nambu, T. Nagai, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **19**, 1058 (1971).
11) H. Nogami, T. Nagai, and H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 328 (1970).

group and propyl group which makes the drug more water soluble than the other substituent groups of the other drugs. This positive entropy change suggested that the structural change of iceberg around the adsorbate molecule might take place through the adsorption process in the similar way to the cases of barbituric acid derivatives[6] and sulfonamides.[12] Then the above result also supported the view that adsorption proceeds by the hydrophobic interaction between the hydrophobic moiety of the molecule of sulphonylureas and the carbon black surface.

From these results, it may be suggested that a hydrophobic force in the addition to the electrostatic force[13] play an important role in the interaction of sulphonylureas with albumin.

12) H. Nogami, T. Nagai, and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **18**, 342 (1970).
13) M.J. Crooks and K.F. Brown, *J. Pharm. Pharmac.*, **26**, 304 (1974).