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Adsorption of Phenothiazines from Aqueous Solution. Approach to Understanding of Membrane Action[1,2]

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As an approach to an understanding of the membrane action of phenothiazines, the adsorption from solution was investigated using such adsorbents as carbon black (CB), graphite (GP), silica gel (SG) and polyethylene (PE), and relating the results with other physico-chemical properties and biological activities of the drugs.

The adsorption isotherms by CB and GP were in accordance with Langmuir equation. In the case of SG, the phenomenon looked like a multilayer adsorption. Phenothiazines were considered to be classified into three groups according to the adsorbability by PE.

The adsorbed amount was influenced by the molecular volume of $R_{10'}$ N at 9-position, sulfoxide group at 5-position, and the bulkiness of substituent at 2-position.

The adsorbed amount increased with pH of buffer solution between 5 and 8, and it was considered that pH had influence on the hydrophobic and hydrophilic balance of the molecule.

The decrease in adsorption with addition of urea demonstrated that the adsorption of phenothiazines proceeded on the hydrophobic interaction.

The adsorbability of phenothiazines by CB increased with the surface tension lowering of solution and also with the partition coefficient in $CHCl_3$–0.2N HCl.

It was shown that the adsorbability have relation to the neuroleptic and the haemolytic activities.

Phenothiazines have a great variety of pharmacological actions of much complicated mechanisms. However, it has been considered that their mechanisms are more or less based on the membrane action,[4,5] and it has been shown that phenothiazines are deposited on the biological membranes.[6–8] Therefore, their pharmacological activities seem to be related to the drug–membrane interaction, or to the adsorbability on the membrane.

In this series of works,[9,10] it has been demonstrated that the adsorbability of drug by carbon black gives a useful information for an understanding of biopharmaceutical phenomena. The present study was attempted to make an approach to an understanding of the membrane action mentioned above, carrying out the experiments of adsorption of phenothiazines from solution by various adsorbents such as carbon black (CB), graphite (GP), silica gel (SG) and polyethylene (PE), and relating the results with other physicochemical properties and biological activities of drugs. The adsorption studies of phenothiazines were reported by Sorby, *et al.* regarding the comparison in the adsorbing activity among adsorbents such as activated

1) This paper forms Part XII of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part XI: H. Nogami, T. Nagai, and A. Kondo, *Chem. Pharm. Bull.* (Tokyo), **18**, 1185 (1970).
2) A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
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4) G. Zografi, D.E. Auslander, and P.L. Lytell, *J. Pharm. Sci.*, **53**, 573 (1964).
5) G. Zografi and D.E. Auslander, *J. Pharm. Sci.*, **54**, 1313 (1965).
6) M.A. Spirtes and P.S. Guth, *Biochem. Pharmacol.*, **12**, 37 (1963).
7) A.R. Freeman and M.A. Spirtes, *Biochem. Pharmacol.*, **12**, 47 (1963).
8) A.R. Freeman and M.A. Spirtes, *Biochem. Pharmacol.*, **12**, 1237 (1963).
9) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 176 (1969).
10) H. Nogami, T. Nagai, and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **18**, 348 (1970).

carbon, talc and kaolin and also the correlation of the adsorbability with the surface tension of drugs,[11,12] but they were done, unlike the present study, from the view point of the effect of adsorption on the decrease in intestinal absorption of drugs.

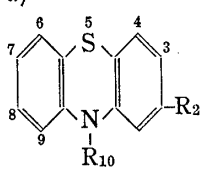
Experimental

Materials——Carbon black (CB), graphite (GP), and silica gel (SG) used were the same as those in the previous paper.[13] Polyethylene (PE) of density 0.919 g/cm^3 [14] and of specific surface area 0.5 m^2/g,[15]

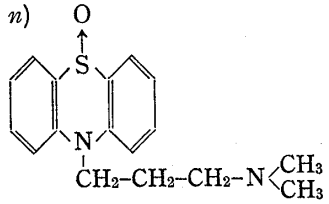
Table I. Phenotihazines in This Study

Compound	Structure[a] R_{10}	R_2
Anergen[b,c]	$-CH_2-CH_2-N(CH_3)_2$	H
Diethazine[b,d]	$-CH_2-CH_2-N(CH_2-CH_3)_2$	H
Promazine[b,e]	$-CH_2-CH_2-CH_2-N(CH_3)_2$	H
Chlorpromazine[b,d]	$-CH_2-CH_2-CH_2-N(CH_3)_2$	Cl
Trifluprомazine[b,f]	$-CH_2-CH_2-CH_2-N(CH_3)_2$	CF_3
Promethazine[b,d]	$-CH_2-CH(CH_3)-N(CH_3)_2$	H
Alimemazine[g,h]	$-CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	H
Levomepromazine[i,d]	$-CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	OCH_3
Methodilazine[b,j]	$-CH_2-HC(CH_2]N-CH_3)CH_2$	H
Perazine[d,k]	$-CH_2-CH_2-CH_2-N(CH_2-CH_2)_2N-CH_3$	H
Prochlorperazine[d,l]	$-CH_2-CH_2-CH_2-N(CH_2-CH_2)_2N-CH_3$	Cl
Trifluoperazine[c,m]	$-CH_2-CH_2-CH_2-N(CH_2-CH_2)_2N-CH_3$	CF_3
Chlorpromazine·sulfoxide[b,d,n]	$-CH_2-CH_2-CH_2-N(CH_3)_2$	Cl
Isothipendyl[b,c,o]	$-CH_2-CH_2-CH_2-N(CH_3)_2$	H

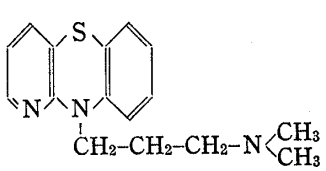
a)



n)



o)



b) hydrochloride c) Supported by Sumitomo Chemical Co., Ltd. d) Supported by Yoshitomi Pharmaceutical Co., Ltd. e) Supported by Banyu Pharmaceutical Co., Ltd. f) Supportdd by Nippon Squibb Co., Ltd. g) 1/2·tartarate h) Supported by Daiichi Pharmaceutical Co., Ltd. i) maleate j) Supported by Dainippon Pharmaceutical Co., Ltd. k) hydroxyphenylbenzoylbenzoate l) dimaleate m) dihydrochloride

11) D.L. Sorby and E.M. Plein, *J. Pharm. Sci.*, **50**, 355 (1961).
12) D.L. Sorby, E.M. Plein, and J.D. Benmaman, *J. Pharm. Sci.*, **55**, 785 (1966).
13) H. Nogami, T. Nagai, E. Fukuoka, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2248 (1968).
14) Determined with a Weld pycnometer replaced with alcohol.
15) Determined by BET method using nitrogen.

named "Hi-Zex-200", was supported by Mitsui Petrochemical Co., Ltd. Phenothiazines used are listed in Table I, which were recrystallized from isopropyl alcohol.

Procedure for Determination of the Adsorbed Amount by Batch Method——A given amount of adsorbent (10 mg, 40 mg, 250 mg, and 4000 mg of CB, GP, SG, and PE, respectively) was added in 20 ml of 1/30M phosphate buffer solution (pH 6.00)[16] of the respective drugs in red-brown vessels, and then the procedure was carried out in the same way as described in the previous paper.[13] Additionally, the effect of the addition of urea was investigated at the same pH as above and also the effect of pH was done at different pH's. It was examined preliminarily that the drugs were satisfactorily stable under the experimental conditions.

Quantitative Determination of Phenothiazines——After diluting the sample with the same buffer solution as used for the adsorption experiment, the concentration of the drug was determined according to ultraviolet (UV) absorption method: Anergen at 250 mμ; diethazine, 253; promazine, 253; chlorpromazine, 255; triflupromazine, 257; promethazine, 250; alimemazine, 253; levomepromazine, 253; methodilazine, 253; perazine, 254; prochlorperazine, 257; trifluoperazine, 258; chlorpromazinesulfoxide, 275; isothipendyl, 243.

Result and Discussion

Adsorption Isotherms of Phenothiazines

The adsorption isotherms by carbon black (CB) and graphite (GP) were well described with the following Langmuir equation (1), for example, as shown in Fig. 1.

$$M = \frac{abC}{1+bC} \qquad (1)$$

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.

The values of a and ab in the present case of CB were fairly different from those reported by Sorby, *et al.*[11,12] but there was found a correlation between the values of a in the case of CB and those in the case of GP, as shown in Fig. 2. It is well known that the surface of GP is more homogeneous and more hydrophobic than that of CB and thus the adsorption of pheno-

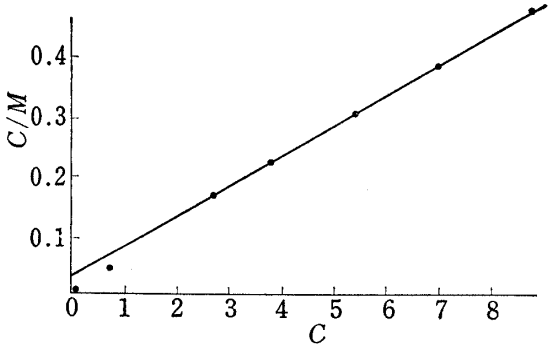


Fig. 1. Langmuir Plot of Adsorption of Diethazine by CB from 1/30M Phosphate Buffer Solution (pH 6.0) at 37°

C: equilibrium concentration ($\times 10^4$M)
M: amount adsorbed (mole/g)

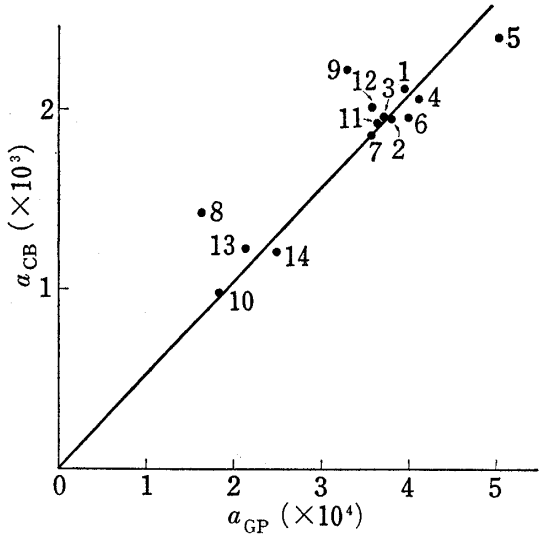


Fig. 2. Relationship between Adsorbability of Phenothiazines from Phosphate Buffer Solution (pH 6.0) by CB and that by GP at 37°

a_{CB}: value of a for CB in equation (1)
a_{GP}: value of a for GP in equation (1)

1: anergen	8: levomepromazine
2: diethazine	9: methodilazine
3: promazine	10: perazine
4: chlorpromazine	11: prochlorperazine
5: triflupromazine	12: trifluoperazine
6: promethazine	13: chlorpromazinesulfoxide
7: alimemazine	14: isothipendyl

16) Most of phenothiazines are in dissociate state at pH 6.00.

thiazines in the present cases was considered to proceed by the hydrophobic interaction. Comparing the values of b between the cases of CB and of GP, the latter was larger than the former, as shown in Table II, corresponding to the difference in hydrophobicity of the respective adsorbents.

Table II. Adsorption of Phenothiazines by Various Adsorbents

	CB		GP		SG		PS	
	$a\times10^{3}$	$b\times10^{-4}$	$a\times10^{4}$	$b\times10^{-4}$	$a\times10^{5}$	$b\times10^{-3}$	M_1	M_2
Anergen	2.12	0.893	3.98	2.09	4.16	2.17	0.78	1.53
Diethazine	1.96	1.46	3.73	3.35	5.62	1.79	1.04	2.08
Promazine	1.96	1.28	3.77	2.77	4.43	2.24	1.36	2.07
Chlorpromazine	2.06	3.46	4.14	2.52	6.18	2.61	4.48	6.24
Triflupromazine	2.41	0.500	5.06	0.79	7.14	1.67	6.10	7.66
Promethainze	1.96	1.245	4.00	3.13	2.77	4.31	0.78	1.52
Alimemazine	1.87	1.53	3.61	3.64	3.03	3.86	1.06	1.97
Levomepromazine	1.42	7.91	1.62					
Methodilazine	2.23	1.35	3.31	1.26	3.69	2.81	0.64	1.05
Perazine	0.987	1.99	1.86	9.61	28.6	0.707	1.18	
Prochlorperazine	1.93	3.06	3.65	4.57	50.0	1.07	5.00	
Trifluoperazine	2.01	1.78	3.57	6.22	83.3	0.935	7.42	
Chlorpromazine sulfoxide	1.24	1.41	2.16	6.61	6.33	1.89	0	0
Isothipendyl	1.21	4.84	2.51	6.14	2.56	2.72	0	0

a : The amount adsorbed when the entire surface is covered by a monolayer (mole/g).
b : the equilibrium constant of adsorption process (liter/mole)
M_1: the amount adsorbed at equilibrium concentration 5.0×10^{-4}M
M_2: the amount adsorbed at equilibrium concentration 1.0×10^{-3}M

In the case of silica gel (SG), the adsorption isotherms deviated to the upper part in the high equilibrium concentration, as shown in Fig. 3, being similar to a multilayer adsorption.

In this regard, the possibility of the multilayer adsorption by SG has been reported, for example, the adsorption of water vapour[17] and 2,4-dichlorophenoxy acetic acid through hydrogen bonding,[18] and moreover it has been suggested that large aromatic molecules are adsorbed on SG by chemisorption, in which SG plays a role as an electron-acceptor.[19] The values of a and b for SG in Table II were estimated from the Langmuir plots of the data obtained in the low equilibrium concentration. The values of a in this case were about 1/50 of those in the case of CB. This result could not be explained by considering the difference in surface area and was concluded to be due to the preferential adsorption of water because of the hydrophilic property of SG, as was supported by the result that the values of b were very small compared with the cases of GP and CB.

In the case of polyethylene (PE), the phenomenon was much complicated because the adsorbent does not sediment in water. However, the adsorbability in aqueous system had relation to those in the system containing MeOH or EtOH where PE sediment, as shown in Table III, though the adsorbed amount decreased as follows: water>MeOH>EtOH. As shown in Fig. 4, the saturated adsorbed amount was not observed under the present experimental conditions, but the results were useful enough in comparing the adsorbability among the drugs. It was considered that the adsorption of phenothiazines by PE was influenced

17) W. Hertl and M.L. Hair, *Nature*, **223**, 1150 (1969).
18) R. Haque and R. Sexton, *J. Colloid Interface Sci.*, **27**, 818 (1968).
19) *a*) E. Hunakubo, I. Moriya, N. Tojima, and T. Nagai, *Kogyo Kagaku Zasshi*, **66**, 237 (1963); *b*) A.V. Kiselev, *Doklady Akad. Nauk. S.S.S.R.*, **106**, 1046 (1956).

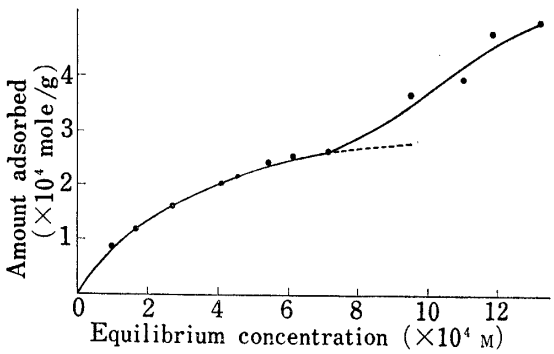


Fig. 3. Adsorption Isotherm of Promazine by SG from 1/30 M Phosphate Buffer Solution (pH 6.0) at 37°

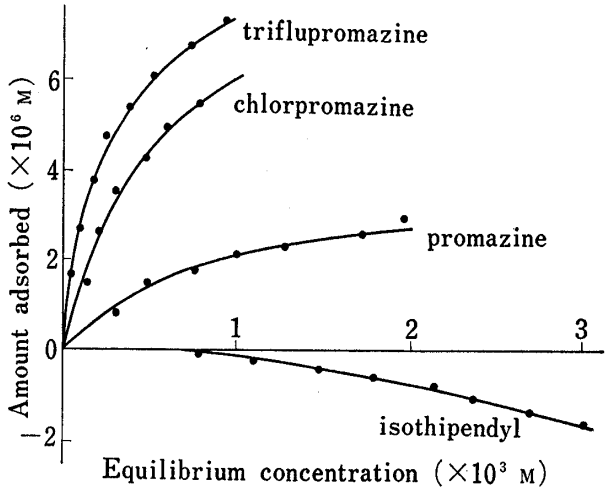


Fig. 4. Adsorption Isotherm of Phenothiazines by PE from 1/30M Phosphate Buffer Solution (pH 6.0) at 37°

Table III. Amount Adsorbed[a] by PE from Aqueous MeOH or EtOH Solution ($\times 10^7$ mole/g)

Solution	Promazine	Isothipendyl	Chlorpromazine	Chlorpromazine-sulfoxide
1/30M Phosphate buffer solution (pH 6.0)	9.2	0	33.7	0
50% MeOH	2.8	1.4	2.8	0
MeOH	0.37	0	0.6	−0.7
50% EtOH	1.5	0	1.5	0
EtOH	0	0.7	0	−1.6

a) at 3×10^{-4}M equilibrium concentration at 37°

by the adsorption of water or wetting on the adsorbent, as was well demonstrated by the plot for isothipendyl. Assuming that a constant amount of water was adsorbed on 4.0 g of PE in 20 ml of the solution (see Experimental), the higher the initial concentration of drug, the more it was concentrated after the adsorption of water. Therefore, the adsorbed amounts shown in Fig. 4 seemed to be apparent ones, being lower than intrinsic ones, and thus isothipendyl, which has a very low adsorbability, gave a nagative curve of adsorbed amount.

Phenothiazines may be classified into three groups accoding to the adsorbability by PE as: group I (very high), *i.e.*, chlorpromazine, trifluprazine, prochlorperazine, and trifluoperazine; group II (high), *i.e.*, anergen, diethazine, promazine, promethazine, methodilazine, and perazine; group III (low), *i.e.*, chlorpromazine sulfoxide, and isothipendyl.

Adsorption of Phenothiazines in Relation to Molecular Structure

Relationship between the Adsorbed Amount and the Molecular Volume of Side Chain R_{10}——Comparing the adsorbed amount with the molecular volume of side chain R_{10} at the standard boiling point among the compounds which have H for R_2 and different groups for R_{10}, it decreased with the increase in the molecular volume of R_{10}, shown in Fig. 5, except for diethazine and methodilazine which have a little different kind of structures. The result suggests that the phenothiazine ring may hold an orientation on the surface of adsorbent and the side chain R_{10} may give a steric hindrance to such an orientation, *i.e.*, to the adsorption of the compound.

Considering that the analgesic activity of methadones was found to decrease with the increase in the size of side chain, *i.e.*, with the increase in the steric hindrance,[20] it may be supposed that such a steric hindrance regarding the adsorption on CB or GP as described above gives influence on the biological activity of phenothiazines, though the existing data are not enough to demonstrate this supposition.

In Relation to the Hydrophobic and Hydrophilic Balance of Molecule——It has been reported that not only the hydrophobic moiety but also the hydrophilic one gives influence on the interfacial and the biological activities of phenothiazines.[21-24] It is shown in Table II that promazine was adsorbed on CB, GP, and PE more than isothipendyl, the latter containing N at 9-position, and similarly chlorpromazine was adsorbed more than chlorpromazine sulfoxide, the latter containing sulfoxide. This is accepted by considering that promazine and chlorpromazine may be more hydrophobic than isothipendyl and chlorpromazine sulfoxide, respectively.

The adsorbed amount on SG of promazine was more than that of isothipendyl. This may demonstrate that the adsorption is predominated by the interaction between the hydro-

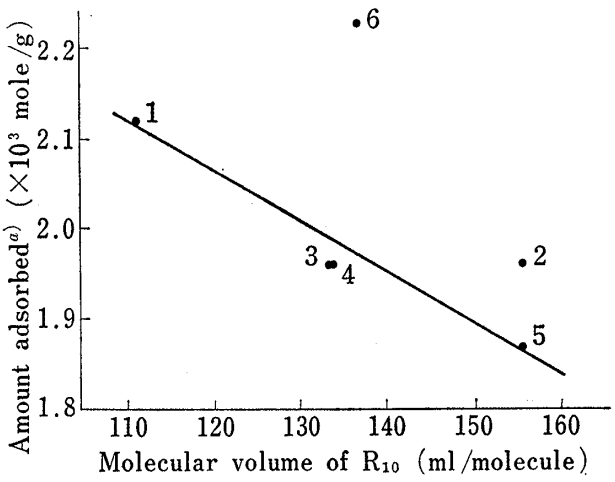


Fig. 5. Relationship between Adsorbability by CB and Molecular Volume of Side Chain R_{10}

a) Represented by Langmuir constant *a*.
1: anergen 4: promethazine
2: diethazine 5: alimemazine
3: promazine 6: methodilazine

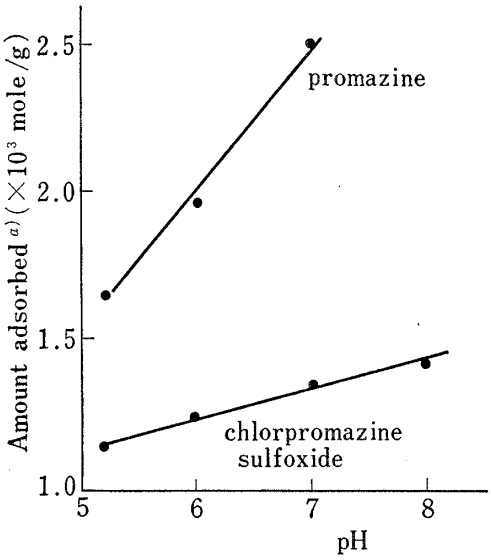


Fig. 6. Effect of pH of Phosphate Buffer on the Adsorbability by CB at 37°

a) Represented by Langmuir constant *a*.

Table IV. Influence of Side Chain R_2 on Various Factors

Compound	R_2	Molecular volume (ml/molecule)	Amount adsorbed ($\times 10^3$ mole/g)	$\pi^{a)}$	Surface activity[b] (dyne/cm)	Biological activity[c] (mg/day)
Promazine	H	3.7	1.96	0	1.7	79
Chlorpromazine	Cl	21.6	2.06	1.04	9.3	31
Triflupromazine	CF_3	40.9	2.41	1.49	16.5	18

a) parameter indicating hydrophobicity[25,26] *b*) in Ringer solution at 23°[12] *c*) average oral dose[22a]

20) S. Yamabe, "Iyakuhin Bunshiron," Asakura-shoten, Tokyo, 1968.
21) G. Zografi and I. Zarenda, *Biochem. Pharmacol.*, **15**, 591 (1966).
22) P.M. Seeman and H.S. Bialy, *Biochem. Pharmacol.*, **12**, 1181 (1963).
23) E.J. Ariëns and A.M. Simonis, *J. Pharm. Pharmacol.*, **16**, 137 (1964).
24) N.D. Weiner and G. Zografi, *J. Pharm. Sci.*, **54**, 436 (1965).

phobic moiety of the compound and the hydrophobic part on the surface of SG which is very small in the portion.[13] On the other hand, chlorpromazine sulfoxide was adsorbed on SG more than chlorpromazine. In this case, the hydrophilic property of sulfoxide group was considered to take an important role. In other words, the increase in hydrophilicity in the hydrophilic moiety with the introduction of sulfoxide group may cause an increase in the adsorption on such a hydrophilic adsorbent as SG, as is different from the case of isothipendyl mentioned above.

Effect of Substitution at 2-Position——Promazine, chlorpromazine and triflupromazine have the same side chain R_{10} but different substituents at 2-position. As shown in Tables II and IV, the adsorbed amount increased with the bulkiness of the substituents as follows: promazine<chlorpromazine<triflupromazine. This increasing tendency is similar to those of the parameter indicating hydrophobicity[25,26] and of the surface activity,[22] as shown in Table IV. Therefore, the result demonstrates that the substituent at 2-position also may adopt an orientation to the carbon black surface and may give influence on the hydrophobic interaction between the adsorbate and the adsorbent.

Effect of pH of Buffer Solution on the Adsorption of Phenothiazines

In the cases of tryptophan[13] and sulfonamides,[27] it was shown that pH had no distinct effect on the adsorption by CB near neutral pH region. However, the adsorption of phenothiazines by CB, GP, PE and SG increased with pH between 5 and 8, for example as shown in Fig. 6 and 7. This may be explained by considering that the hydrophobic and hydrophilic cbalance of molecule is very sensitive to the dissociation in the present experimental condition, as is understood from the facts mentioned above regarding the adsorption in relation to molecular structure. Accordingly the increase in the amount of undissociated molecule with pH may result in a distinct increase in the hydrophobicity of molecule, *i.e.*, the increase in adsorption.

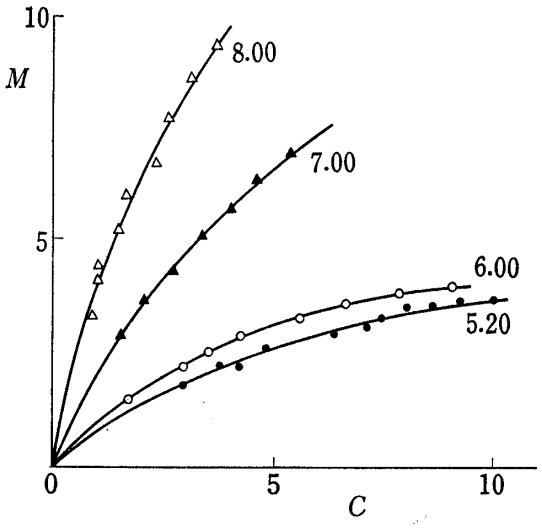


Fig. 7. Effect of pH of Phosphate Buffer on the Adsorption of Chlorpromazine-sulfoxide by SG at 37°

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

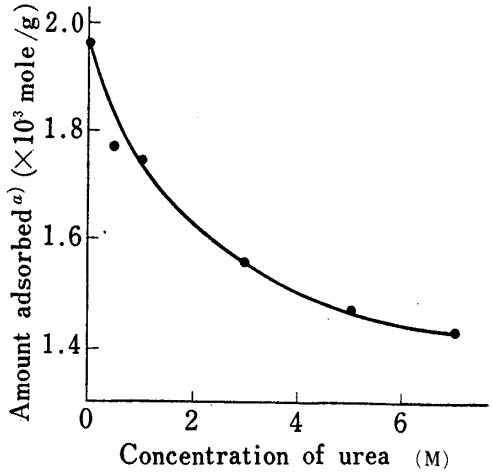


Fig. 8. Effect of Urea on Adsorption of Promazine from 1/30M Phosphate Buffer Solution (pH 6.0) by CB at 37°

a) Represented by Langmuir constant *a*.

25) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
26) C. Hansch, K. Kirks and G.L. Lawrence, *J. Am. Chem. Soc.*, **87**, 5770 (1968).
27) H. Nogami, T. Nagai and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **18**, 342 (1970).

Effect of Addition of Urea on the Adsorption of Phenothiazines

In the previous paper,[27,28] it was discussed that the hydrophobic interaction between the solute molecule and the surface of CB was weakened with the addition of urea, resulting in the decrease in adsorption. As shown in Fig. 8, the adsorption of promazine decreased with the addition of urea. In a similar way to the previous paper,[28] this decrease in adsorption may be explained on the consideration that, when urea comes in contact with the surface of adsorbent (and the solute) to result in a simultaneous structural change of iceberg around the surface of adsorbent (and the solute), the hydrophobicity of the surface of adsorbent (and the solute) becomes smaller than that in the solution without urea, causing a decrease in the escaping tendency of the solute from solution to the surface of adsorbent. Thus, it was demonstrated that the adsorption of phenothiazines proceeded on the hydrophobic interaction.

Adsorption of Phenothiazines in Relation to Surface Activity, Partition Coefficient, and Biological Activity

In Relation to Surface Activity——Sorby, *et. al*, showed by a statistical analysis that the correlation coefficient between the extent of adsorption of phenothiazines by activated carbon and the surface tension lowering of solution was —0.843, being significant by *t*-test at 5% level. However, Fig. 9 shows that the adsorbability of phenothiazines was positively correlated to logarithm of surface tension lowering of solution reported by Ahtee.[29] The case of barbituric acid deribatives also gave a positive correlation.[30] Therefore, the present result was understood to be reasonable by considering that the adsorption of phenothiazines may proceed by the hydrophobic interaction and thus the adsorption on such hydrophobic solid from solution may be correlated to the adsorption to air–solution interface because of a similarity in phenomenon, which is represented by the surface activity.

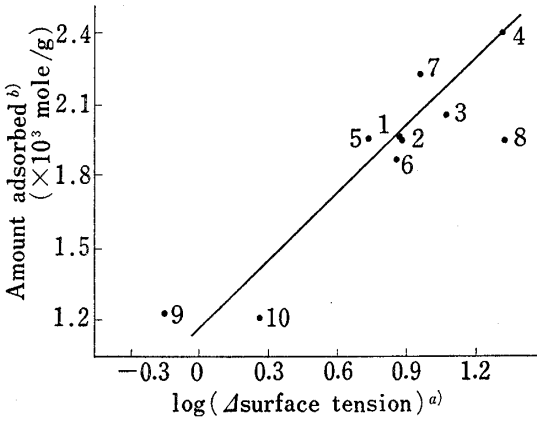


Fig. 9. Relationship between Surface Activity and Adsorbability by CB

a) log value of surface tension lowering of 10^{-3}M solution of phenothiazines in physiological salt solution[29]
b) Represented by Langmuir constant *a*.
1: diethazine
2: promazine
3: chlorpromazine
4: triflupromazine
5: promethazine
6: alimemazine
7: methodilazine
8: trifluoperazine
9: chlorpromazine sulfoxide
10: isothipendyl

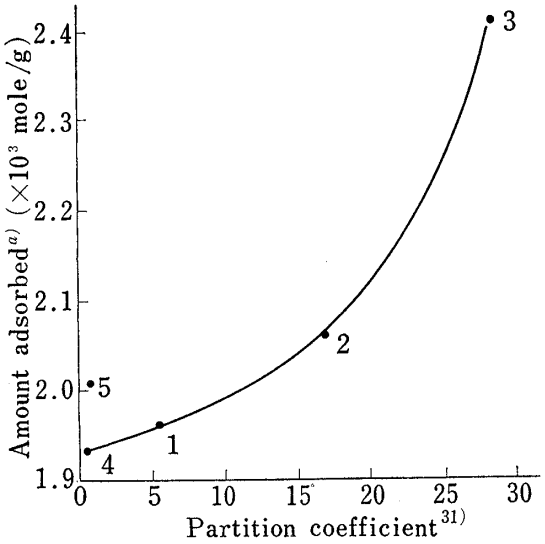


Fig. 10. Relationship between Adsorbability by CB and Partition Coefficient in $CHCl_3$/0.1N HCl

a) Represented by Langmuir constant *a*.
1: promazine
2: chlorpromazine
3: triflupromazine
4: prochlorperazine
5: trifluoperazine

28) H. Nogami, T. Nagai and H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 328 (1970).
29) L. Ahtee, *Ann. Med. Exp. Biol. Fenn.*, **44**, 453 (1966).
30) H. Nogami, T. Nagai and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 168 (1969).

In Relation to Partition Coefficient in $CHCl_3$–0.1N HCl System——In the previous paper,[27,30] it was discussed that the adsorbability of drug by CB may give a useful information for understanding of biological activity on the basis on the good correlation between the adsorbability by CB and the partition coefficient in butanol–water system. As shown in Fig. 10, the adsorbability of phenothiazines by CB increased with the partition coefficient in $CHCl_3$–0.1N HCl.[31] It is, therefore, demonstrated that the hydrophobic interaction plays an important role on the adsorption and there remains a high possibility of the correlation between such an adsorbability and the biological activity.

In Relation to Biological Activity——Various investigations have been done to obtain a correlationship between biological activity and physical chemical properties of phenothiazines,[22,32] but they have not always been successful because of a great variety of pharmacological actions. Regarding the neuroleptic drugs, Fig. 11 shows that the adsorbability by CB was correlated to the biological activity.[33] Similarly, the adsorbability had relation to the haemolytic activity, as shown in Fig. 12. Actually, usual average oral dose of promazine, chlorpromazine and trifluprometazine have relation to the adsorbability, as shown in Table IV.

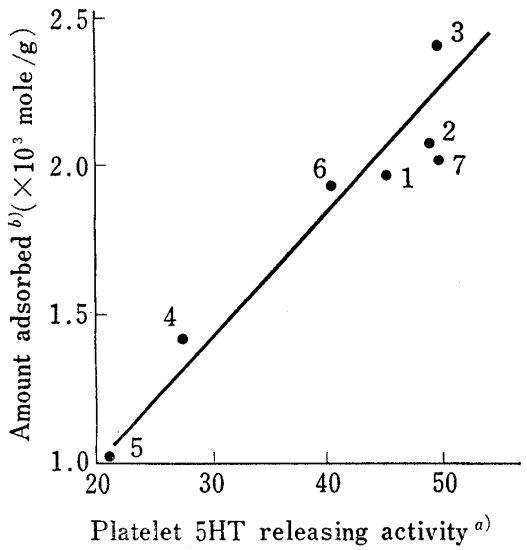


Fig. 11. Relationship between Adsorbability by CB and Platelet 5HT Releasing Activity

a) 5HT release as % of total 5HT content[33]
b) Represented by Langmuir constant *a*.
1: promazine
2: chlorpromazine
3: trifluprometazine
4: levomepromazine
5: perazine
6: prochlorperazine
7: trifluoperazine

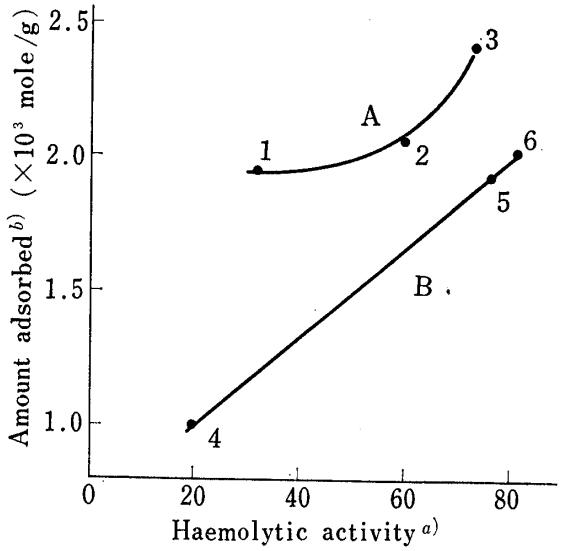


Fig. 12. Relationship between Adsorbability by CB and Haemolytic Activity of Phenothiazines

Groups A (1: promazine, 2: chlorpromazine, 3: trifluprometazine) and B (4: perazine, 5: prochlorperazine, 6: trifluoperazine) are classified according to the difference in R_{10}.
a) haemolysis as % of total haemolysis with 10^{-3}M of phenothiazines[33]
b) Represented by Langmuir constant *a*.

In the case of barbiturates[9] and sulfonamides,[10] there was found a correlation between the adsorbability by CB and the intestinal[10] absorption rate. However, in the present case, such a distinct correlation was not observed, comparing with the absorption data by Flaganan.[34] This result might have relation to the following differences of phenothiazines from

31) T.S. Mao and J.J. Noval, *Biochem. Pharmacol*, **15**, 501 (1966).
32) *a*) Y. Sasaki and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **16**, 958 (1968). *b*) A.L. Green, *J. Pharm. Pharmacol.*, **19**, 10 (1967). *c*) A. Fulton and L.E. Lyons, *Aust. J. Chem.*, **21**, 873 (1968).
33) L. Ahtee, *Ann. Med. Exp. Biol. Fenn.*, **44**, 431 (1966).
34) *a*) T.L. Flaganan, J.H. Newman, A.R. Maase and E.J. Van Loon, *J. Pharm. Sci.*, **51**, 996 (1962). *b*) E.J. Van Loon, T.L. Flaganan, W.J. Novick and A.R. Maase, *J. Pharm. Sci.*, **53**, 1211 (1964).

the above drugs: (a) strong tendency to entero-heptatic recirculation: (b) great variety of pharmacological actions: (c) pharmacological actions generally based on membrane action predominance.

From the results obtained, the adsorption studies are considered to have a high possibility of making an approach to an understanding of their behaviors in the biopharmaceutical system, for example, an interaction of another drug or additive which administered at the same time.

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