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Binding of Phenothiazines to Bovine Serum Albumin and Related Phenomena[1,2]

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The binding of 13 kinds of phenothiazines (PZS) to bovine serum albumin (BSA) was studied as a series of physico-chemical studies of an approach to an understanding of the membrane action of PZS. The data obtained were analyzed by the usual method for non-specific binding of drug to protein reported by Klotz, *et al.*

The results obtained by two equilibrium dialysis methods correlated well, and also there was found a correlation between equilibrium dialysis methods and gel filtration method.

The binding increased with pH. The order of largeness of the effect of ion species was as follows: citrate>succinate>phosphate>acetate. The entropy change of binding was positive. The larger was the hydrophobicity of molecule of PZS with regard to structure, the more increased the amount bound to BSA. These results may suggest that a hydrophobic interaction takes part in the binding.

The binding to BSA correlated with the surface activity of PZS, and also increased with the partition coefficient in dodecan/water system, as may suggest that a hydrophobic interaction plays an important role for the binding. There was found no correlation between the binding to BSA and the adsorbability by carbon black, contrary to the case of barbiturates previously reported.

PZS of a similar chemical structure showed the correlations between the binding to BSA and the pharmacological activities, as might suggest that PZS of a similar chemical structure act on various interfaces and biological membranes in a similar way.

As a series of physico-chemical studies of an approach to an understanding of the membrane action of phenothiazines (PZS), adsorption from solution,[4] cellulose membrane permeation,[5,6] dissolution rate[5] were already studied, discussing the following things: the hydrophobic interaction in the adsorption of PZS by such hydrophobic substances as carbon black; the relation between the adsorbability or physico-chemical properties and pharmacological activities; the relation between the area occupied by a molecule upon the adsorption from solution by some adsorbents and that upon the permeation through cellulose membrane.

The present study was attempted to investigate the binding of 13 kinds of PZS to bovine serum albumin (BSA), discussing the difference among experimental methods, *i.e.*, equilibrium dialysis methods I and II, gel filtration method, the relation between the data and the adsorbability by carbon black, surface activity, partition coefficient or pharmacological activities, the effect of pH and ion species, and the thermodynamic properties.

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1) This paper forms Part XXIV of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part XXIII: H. Umeyama, T. Nagai, S. Wada, and H. Uchida, *Yakuzaigaku*, **31**, 194 (1971), (Article in English).

2) A part of this work was presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April 1972.

3) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo.*

4) H. Nogami, T. Nagai, and N. Nambu, *Chem. Pharm. Bull.* (Tokyo), **18**, 1643 (1970).

5) N. Nambu, T. Nagai, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **19**, 808 (1971).

6) N. Nambu, T. Nagai, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **19**, 1058 (1971).

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Although various studies have already been done concerning the protein binding of PZS,[7-15] the present study differs a little from them as to the variety of drugs, the experimental conditions and the other phenomena to relate the results with.

Experimental

Materials——13 kinds of phenothiazines used were the same as those in a previous paper.[4] Serum albumin fraction V, Armour Laboratories Co. of the molecular weight 69000[16] was used, making correction for the water content 3.4% determined by drying under reduced pressure.

Procedure for Determination of the Bound Amount——a) Equilibrium Dialysis Method I: A Visking cellulose tubing (Visking Co., Size 20/32) containing 10 ml of 2% BSA solution in 1/30M phosphate buffer solution (pH 7.00, unless otherwise stated) was immersed in 30 ml of 10^{-5}—10^{-3}M PZS in 1/30M phosphate buffer solution (pH 7.00, unless otherwise stated) in a Nessler tube, being kept for 3 days at 10°, and the concentration of PZS in the outside the Visking tubing was determined according to ultraviolet (UV) absorption method, making correction for the adsorption of drugs by Visking tubing according to blank test.

b) Equilibrium Dialysis Method II: A Visking cellulose tubing containing 10 ml of 10^{-5}—10^{-3}M PZS in 1/30M phosphate buffer solution containing 2% BSA (pH 7.00, unless otherwise stated) was immersed in 30 ml of 1/30M phosphate buffer (pH 7.00, unless otherwise stated) in a Nessler tube. Other procedures were the same as the method I mentioned above.

c) Gel Filtration Method: Following Clausen's method,[17] 2.8 g of Sephadex G-50 fine gel immersed beforehand in 1/30M phosphate buffer solution (pH 7.00, unless otherwise stated) containing a drug of a given concentration was put in 3.0 cm diameter brown glass column to make bed, which was kept at 10° by circulating water outside. After 10 ml of the solution of the same drug of the same concentration at the same pH as mentioned above, additionally containing 2% BSA, was let flow through the bed, the solution except BSA was let flow, and the concentrations of the drug and BSA of each 2.5 ml fraction was determined according to UV absorption method.

d) Calculation of the Bound Ratio β (%): This was done by dividing the amount of bound drug to BSA by the amount of the initial concentration of drug in 10 ml of the solution containing 2% BSA.

Result and Discussion

Effect of Various Factors on the Binding of PZS to Bovine Serum Albumin

The results obtained by the equilibrium dialysis methods were described with Langmuir equation, and thus the experimental data were analysed by usual method already reported for non-specific binding of drugs to protein.[18a,19] If binding sites are considered to be of the same kind, Klotz's equation (1) can be employed.[20]

7) *a*) J. Krieglstein and G. Kushinsky, *Arzneimittel-Forsch.*, **18**, 287 (1968); *b*) E. Jähnchen, J. Krieglstein, and G. Kushinsky, *Naunyn-Schmiedebergs Arch. Pharmak. Exp. Path.*, **260**, 147 (1968); *c*) *Idem*, *ibid.*, **263**, 375 (1969); *d*) J. Krieglstein and G. Kuschinsky, *ibid.*, **260**, 160 (1968); *e*) *Idem*, *ibid.*, **262**, 1 (1969); *f*) J. Krieglstein, J.W. Franz, and E. Jähnchen, *ibid.*, **264**, 261 (1969); *g*) *Idem*, *ibid.*, **264**, 463 (1969); *h*) H. Glasser and J. Krieglstein, *ibid.*, **265**, 321 (1970); *i*) E. Jähnchen, J. Krieglstein, F. Kunkel, and W.J. Samuels, *ibid.*, **266**, 363 (1970); *j*) E. Jähnchen, J. Krieglstein, F. Kunkel, W.J. Samuelis, and U. Wollert, *ibid.*, **269**, 67 (1971).

8) *a*) J. Krieglstein, W. Meiler, and J. Staab, *Biochem. Pharmac.*, **21**, 985 (1972); *b*) J. Krieglstein, F. Lier, and J. Michaelis, *Naunyn-Schmiedebergs Arch. Pharmak. Exp. Path.*, **272**, 121 (1972).

9) *a*) D.N. Teller, H.C.B. Denber, and M.J. Kopac, *Biochem. Pharmac.*, **16**, 1397 (1967); *b*) D.N. Teller, J.C. Levine, and H.C.B. Denber, *Agressologie*, **9**, 1 (1968); *c*) *Idem*, *Mol. Pharmacol.*, **40**, 435 (1968).

10) M.M. Tinao and F.G. Guiller, *Arch. Inst. Farmacol. Exptl.* (Madrid), **15**, 169 (1963).

11) P. Hele, *Biochem. Pharmac.*, **13**, 1261 (1964).

12) J. Jindrová, Z. Šípal, and A. Jindra, *Československ. Farm.*, **13**, 393 (1964).

13) L. Ahtee, M.J. Mattila, and H.I. Vapaatalo, *Biochem. Pharmac.*, **16**, 2432 (1967).

14) S.H. Curry, *J. Pharm. Pharmac.*, **22**, 193 (1970).

15) J.J. Noval and J.S.S. Mao, *Bull. Inst. Chem. Acad. Sinica*, No. **18**, 82 (1970).

16) I. Moriguchi, S. Wada, and H. Sano, *Chem. Pharm. Bull.* (Tokyo), **16**, 592 (1968).

17) J. Clausen, *J. Pharmac. Exp. Therap.*, **153**, 167 (1966)

18) *a*) I. Moriguchi, *Hyomen*, **6**, 141 (1968); *b*) K. Aoki, *Yushi*, **17**, 12 (1964).

19) M. Nakagaki and H. Terada, *Yakugaku Zasshi*, **87**, 817 (1967).

20) *a*) I.M. Klotz, F.M. Walker, and R.B. Pivan, *J. Am. Chem. Soc.*, **68**, 1486 (1946); I.M. Klotz, "The Proteins," Vol. I, Academic Press, New York, 1953, p. 727; *b*) I. Moriguchi, S. Fushimi, and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **18**, 449 (1970).

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$$1/r = 1/nKC + 1/n \quad (1)$$

where r represents moles of bound drug per mole of protein, K intrinsic binding constant, C concentration of free drug, and n number of binding sites available on each protein molecule. Plotting $1/C$ against $1/r$ according to equation (1), n and K can be obtained from its slope and intercept, respectively.

If there is no interaction between bound drugs themselves or between bound and free drugs, the following relation exists between K and the first equilibrium constant K_1.[20]

$$K_1 = nK \quad (2)$$

Neglecting the electro-static energy change of binding, the free energy change of binding, ΔG_1, is given as follows:

$$\Delta G_1 = -RT \ln (nK) \quad (3)$$

Furthermore, the enthalpy change of binding, ΔH_1, and the entropy change of binding, ΔS_1 can be calculated from the data obtained at different temperatures.

Fig. 1 shows examples of plots of $1/r$ against $1/C$.

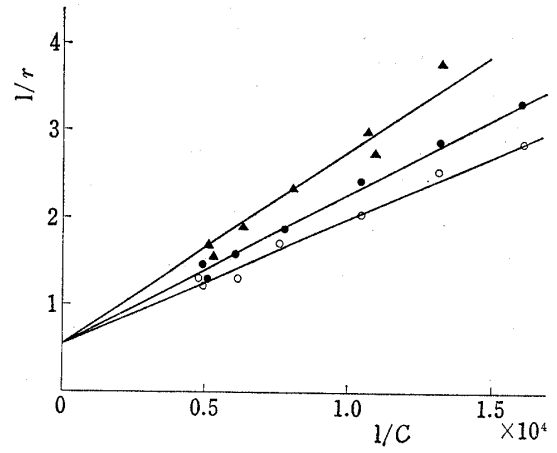

Fig. 1. Langmuir Plots of the Binding of PZS to BSA according to Equilibrium Dialysis Method II

○ : anergen; ▲ : diethazine; ● : promazine;
c : concentration of free drug at equilibrium (M);
r : moles of bound drug per mole of BSA

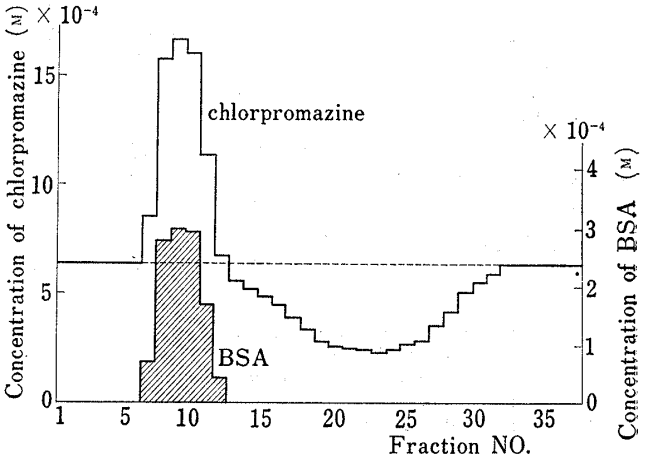

Fig. 2. Sephadex Gel Filtration Pattern of 5.96×10^{-4}M Chlorpromazine at pH 7.00 at 10°

Fig. 2 shows an example of elution pattern of gel filtration method. It was difficult to determine the equilibrium concentration in protein binding by gel filtration method, which is considered to be of a qualitative one.[18a] Therefore, only the bound ratio β (%) to initial concentration was calculated without making a detailed consideration.

Results of binding of PZS to BSA by equilibrium dialysis methods I and II are shown in Table I. In the case of isothipendyl, the amount bound to BSA was negative, no effective result being obtained. n was 2.0 except for perazine, prochlorperazine and trifluoperazine which have perazine ring at side chain R_{10}. For these three, n was 5.0. This result might suggest that ionic bonds by nitrogens in perazine ring take part in the binding.

Fig. 3 shows the relation of log K between equilibrium dialysis methods I and II. The correlation coefficient was 0.946, being significant by t-test at 1% level. In Fig. 3, only the datum for chlorpromazine-sulfoxide derivatives largely from the straight line, as might be due to the experimental error derived from the smallness of the bound amount. From the fact the results obtained by the two methods correlated well, the following discussion on the mechanism of the binding may be more reliable, as shown by Nakagaki, *et al.*[19]

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Table I. Binding of PZS to BSA in1/30M Phosphate Buffer Solution according to Equilibrium Dialysis Method I and II at pH 7.00 at 10°

Drugs	Method	n	$K\times10^{-3}$	log K	ΔG_1	r at $C=1\times10^{-4}$	r at $C=2\times10^{-4}$
Anergen	I	2.0	3.03	3.48	−4.90	0.465	0.758
	II	2.0	3.33	3.52	−4.95	0.500	0.800
Diethazine	I	2.0	2.22	3.35	−4.73	0.364	0.617
	II	2.0	2.21	3.34	−4.72	0.362	0.613
Promazine	I	2.0	3.03	3.48	−4.90	0.465	0.758
	II	2.0	2.81	3.45	−4.86	0.439	0.730
Chlorpromazine	I	2.0	7.81	3.89	−5.43	0.877	1.23
	II	2.0	6.17	3.79	−5.30	0.763	1.11
Triflupromazine	I	2.0	8.06	3.91	−5.45	0.901	1.25
	II	2.0	9.80	3.99	−5.56	1.00	1.32
Promethazine	I	2.0	1.82	3.26	−4.61	0.309	0.541
	II	2.0	1.94	3.29	−4.65	0.325	0.565
Alimemazine	I	2.0	2.53	3.40	−4.80	0.403	0.676
	II	2.0	2.66	3.42	−4.83	0.420	0.699
Methodilazine	I	2.0	1.65	3.22	−4.56	0.283	0.500
	II	2.0	1.71	3.23	−4.58	0.292	0.510
Perazine	I	5.0	1.68	3.23	−4.57	0.725	1.25
	II	5.0	2.13	3.33	−4.70	0.877	1.49
Prochlorperazine	I	5.0	4.94	3.69	−5.18	1.67	2.50
	II	5.0	5.04	3.70	−5.19	1.67	2.50
Trifluoperazine	I	5.0	5.31	3.73	−5.22	1.77	2.67
	II	5.0	6.38	3.80	−5.32	1.96	2.86
Chlorpromazinesulfoxide	I	2.0	0.617	2.79	−4.01	0.117	0.220
	II	2.0	2.17	3.34	−4.71	0.357	0.610
Isothipendyl	I	—	—	—	—	—	—
	II	—	—	—	—	—	—

n : number of binding sites available on each protein molecule (mole/mole)
K : intrinsic binding constant (1/M)
ΔG_1: free energy change of binding (kcal/mole)
r : moles of bound drug per mole of BSA (mole/mole)
C : free drug concentration (M)

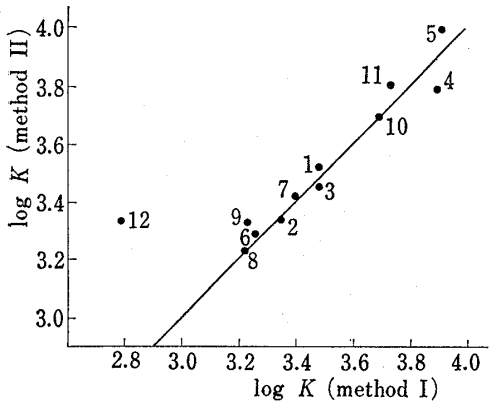

Fig. 3. Relation between the Binding Constant, K, by Equilibrium Dialysis Method I and that by Method II

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

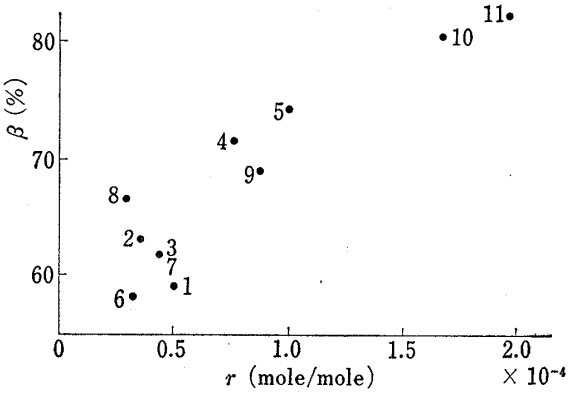

Fig. 4. Relation of PZS between r by Equilibrium Dialysis Method II in 1×10^{-4}M and β by Gel Filtration Method in 2×10^{-4}M

1: anergen; 2: diethazine; 3: promazine; 4: chlorpromazine; 5: triflupromazine; 6: promethazine; 7: alimemazine; 8: methodilazine; 9: perazine; 10: prochlorperazine; 11: trifluoperazine
r : moles of bound drug per mole of protein (mole/mole)
β : bound ratio

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Table II. Bindind of PZS to BSA in 1/30M Phosphate Buffer Solution at pH 7.00 at 10° according to Sephadex Gel Filtration Method

Drugs	Bound ratio β (%) $C_i=2\times10^{-4}$M	Bound ratio β (%) $C_i=6\times10^{-4}$M
Anergen	59.0	61.3
Diethazine	63.0	63.8
Promazine	61.8	62.9
Chlorpromazine	71.5	73.4
Trifupromazine	74.3	73.9
Promethazine	58.2	60.9
Alimemazine	61.8	62.8
Methodilazine	65.5	69.7
Perazine	69.0	72.7
Prochlorperazine	80.4	80.6
Trifluoperazine	82.3	87.3
Chlorpromazinesulfoxide	—	—
Isothipendyl	62.2	61.5

C_i: initial concentration of drugs

Results of the binding of PZS to BSA by gel filtration method are shown in Table II. It was unable to determine each concentration of chlorpromazine-sulfoxide and BSA according to UV absorption method and thus no datum is given regarding chlorpromazine-sulfoxide in Table II. The relation between bound ratio β (at initial drug concentration $C_i=2\times10^{-4}$M) and r shown in equation (1) (free drug concentration $C=1\times10^{-4}$M by equilibrium dialysis method II) is shown in Fig. 4. The value of β increases with that of r. The correlation coefficient was 0.743, being significant by t-test at 1% level. However, there was found no clear linearity between both the values. Therefore, the data obtained by the above two methods are considered to have different natures severally.

The effect of pH on the binding was remarkable, as shown in Table III. The fact that the binding increased with pH may indicate that undissociated drug molecules are more liable to bind to BSA, because the hydrophilic and hydrophobic balance is not considered to change remarkably in the present pH range.[18b)]

The effect of ion species on the binding and on the adsorbability by carbon black[4)] of PZS is shown in Table IV. The order of largeness of the effect was as follows: citrate>succinate>phosphate>acetate. This tendency was the same as the data regarding the effect

Table III. Effect of pH on the Binding of PZS to BSA in 1/30M Phosphate Buffer Solution at 10° according to Equilibrium Dialysis Method II

Drugs	pH	n	$K\times10^{-3}$	log K	ΔG_1	$r^{a)}$	$r^{b)}$
Promazine	7.0	2.0	2.81	3.45	−4.86	0.439	0.730
	6.0	2.0	1.96	3.29	−4.66	0.328	0.562
	5.2	2.0	1.16	3.06	−4.36	0.208	0.377
Chlorpromazine	7.0	2.0	6.17	3.79	−5.30	0.763	1.11
	6.0	2.0	4.39	3.64	−5.12	0.610	0.943
	5.2	2.0	2.17	3.34	−4.71	0.357	0.601

a) at $C=1\times10^{-4}$M
b) at $C=2\times10^{-4}$M
n : number of binding sites available on each protein molecule (mole/mole)
K : intrinsic binding constant (1/M)
ΔG_1: free energy change of binding (kcal/mole)
r : moles of bound drug per mole of protein (mole/mole)
C : free drug concentration (M)

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Table IV. Effect of Ion Species on the Binding of PZS to BSA

Drugs	Ion species	log K[a]	$a\times10^3$[b]	$\Delta\gamma$[c]
Promazine	citrate	3.23[d]	1.83[d]	—
	succinate	3.20[e]	1.68[e]	—
	phosphate	3.06[f]	1.65[f]	—
	acetate	3.03[g]	1.59[g]	—
Chlorpromazine	citrate	3.61[d]	1.91[d]	4.6[h]
	succinate	3.50[e]	1.88[e]	2.5[i]
	phosphate	3.34[f]	1.86[f]	—
	acetate	3.32[g]	1.73[g]	1.5[j]

a) K: intrinsic binding constant of protein binding by equilibrium dialysis method II at pH 5.20 at 10° (1/M)
b) a: saturated adsorbed amount by carbon black at pH 5.20 at 37° (mole/g)[4]
c) $\Delta\gamma$: surface tension lowering at pH 5.00 at 25° at log (molar concentration) = −3.4, by Zografi[21]
d) 1/10M (monopotassium citrate+sodium hydroxide)
e) 1/20M (succinic acid+sodium borate)
f) 1/30M (potassium biphosphate+dibasic sodium phosphate)
g) 1/10M (acetic acid+sodium acetate)
h) 0.025M i) 0.10M j) 0.10M

of ion species on the surface activity reported by Zografi and Zarenda.[21] From the above results regarding the effects of pH and ion species, it might be considered that the hydrophobic interaction takes part in the present binding phenomena.

To investigate thermodynamic properties of binding, experiments were carried out at 10° and 30° for chlorpromazine. From these data and those at 10° shown in Table I, the results (at 30°) were obtained as follows: n=2.0 mole/mole; $K=9.43\times10^3$ /M; log K=3.97; $\Delta G_1=-5.54$ kcal/mole; $\Delta H_1=-1.93$ kcal/mole; $\Delta S_1=14.9$ e.u. Free energy change of binding may depend largely on the positive entropy term. The fact that the entropy change of binding was positive may suggest that the structure of water arround the hydrophobic moieties of protein and drug is destructed and also that a hydrophobic interaction takes part in the binding of PZS to BSA.

The data in Table I and II show the orders of the largeness of log K, r, and β, respectively, as follows: trifluprομazine>chlorpromazine>promazine; trifluoperazine>prochlorperazine>perazine; chlorpromazine>chlorpromazine-sulfoxide. The larger is the hydrophobicity of molecule with regard to structure, the more increases the amount bound to BSA. This result also may suggest that a hydrophobic interaction takes part in the binding of PZS to BSA.

Relation between Binding of PZS to Bovine Serum Albumin and Physico-chemical or Pharmacological Data

The relation between the binding to BSA and the surface activity represented by the surface tension lowering of 10^{-3}M solution of PZS in physiological salt solution[22] is shown in Fig. 5. The correlation coefficient was 0.862, being significant by t-test at 1% level.

The relation between the binding to BSA and the partition coefficient in dodecan/water system at 30° [23] is shown in Fig. 6. Although the data were few, it could be said the amount bound to BSA is larger, the larger the partition coefficient is. The results in Fig. 5 and 6 also may suggest that a hydrophobic interaction plays an important role for the binding of PZS to BSA.

There was found no correlation between the binding to BSA and the adsorbability by carbon black[4] of PZS, as shown in Fig. 7, contrary to the cases of barbiturates[24] and benzoic

21) G. Zografi and I. Zarenda, *Biochem. Pharmac.*, **15**, 591 (1966).
22) L. Ahtee, *Ann. Med. Exp. Biol. Fenn*, **44**, 453 (1966).
23) K.S. Murthy and G. Zografi, *J. Pharm. Sci.*, **59**, 1281 (1970).
24) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 176 (1969).

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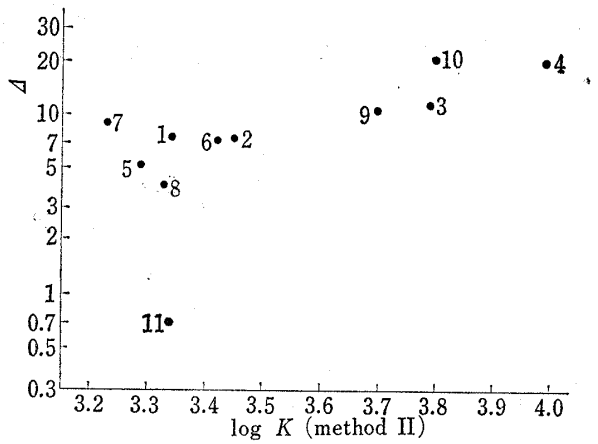

Fig. 5. Relation of PZS between the Binding Constant, K, and the Surface Tension Lowering of 10^{-3}M, Δ[22]

1: diethazine; 2: promazine; 3: chlorpromazine; 4: triflupromazine; 5: promethazine; 6: alimemazine; 7: methodilazine; 8: perazine; 9: prochlorperazine; 10: trifluoperazine; 11: chlorpromazine-sulfoxide

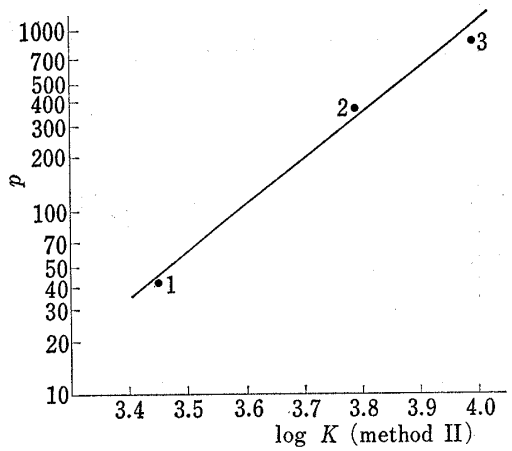

Fig. 6. Relation of PZS between the Binding Constant, K, and the Partition Coefficient in Dodecan/Water System at 30°, p[23]

1: promazine; 2: chlorpromazine; 3: triflupromazine

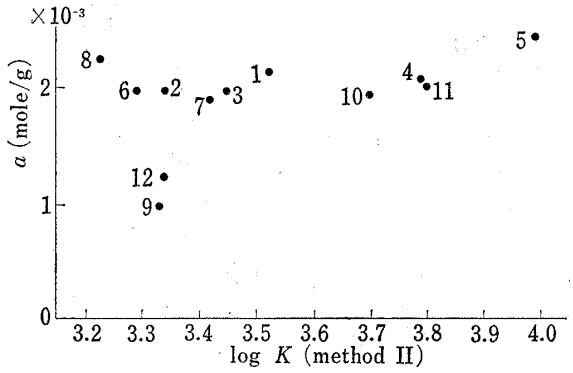

Fig. 7. Relation of PZS between the Binding Constant, K, and the Adsorbability by Carbon Black Represented by Saturated Adsorbed Amount, a[4]

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

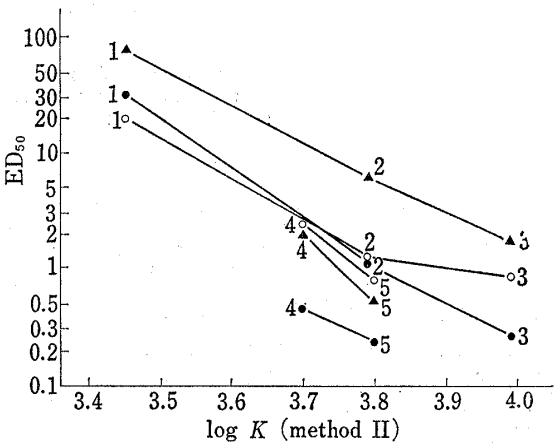

Fig. 8. Relation of PZS between the Binding Constant, K, and Pharmacological Activities, ED_{50} for Rat[27]

●: anti-amphetamine activity
▲: anti-apomorphine activity
○: anti-tryptamine activity

1: promazine
2: chlorpromazine
3: triflupromazine
4: prochlorperazine
5: trifluoperazine

acid derivatives.[25] This may be due to the complexity of the mechanism, as there was no correlation in the case of sulfonamides.[26]

Regarding the correlations between the binding to BSA and the existing data of biological activities of PZS, anti-amphetamine, anti-apomorphine, and anti-tryptamine activities represented by ED_{50},[27] increased with the binding of PZS among those of a similar chemical structure, as shown in Fig. 8. The platelet 5HT releasing activity represented by 5HT release as % of total 5HT content[28] was correlated with the binding, as shown in Fig. 9, being

25) H. Umeyama, T. Nagai, H. Nogami, and T. Oguma, *Chem. Pharm. Bull.* (Tokyo), **19**, 412 (1971).
26) H. Umeyama, T. Nagai, S. Wada, and H. Uchida, *Yakuzaigaku*, **31**, 194 (1971), (Article in English).
27) K. Nakamura, G. Zbinden, and L.O. Randall, "Ko-Seishinyakuno-Yakuri," Asakura-Shoten, Tokyo, 1971, p. 23.
28) L. Ahtee, *Ann. Med. Exp. Biol. Fenn.*, **44**, 431 (1966).

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significant at 1% level. The haemolytic activity represented by haemolysis as % of total haemolysis[28] also was correlated with the binding, as shown in Fig. 10, being significant at 5% level.

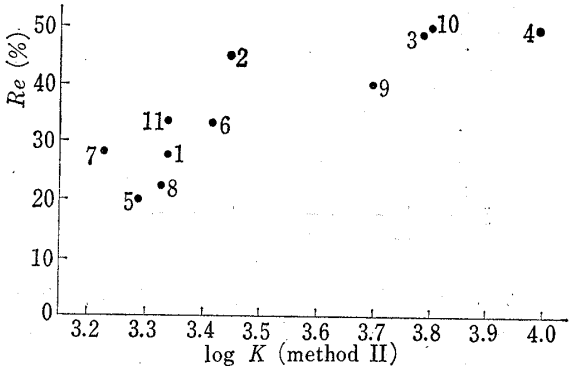

Fig. 9. Relation of PZS between the Binding Constant, K, and Platelet 5HT Releasing Activity Represented by 5HT Release (Re) as % of Total 5HT Content with 3×10^{-4}M Drugs[28]

1: diethazine; 2: promazine; 3: chlorpromazine; 4: triflupromazine; 5: promethazine; 6: alimemazine; 7: methodilazine; 8: perazine; 9: prochlorperazine; 10: trifluoperazine; 11: chlorpromazine-sulfoxide

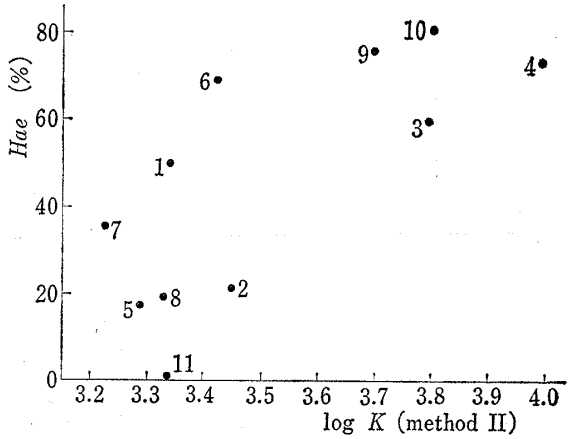

Fig. 10. Relation of PZS between the Binding Constant, K, and the Haemolytic Activity Represented by Haemolysis (Hae) as % of Total Haemolysis with 10^{-3}M Drugs[28]

1: diethazine; 2: promazine; 3: chlorpromazine; 4: triflupromazine; 5: promethazine; 6: alimemazine; 7: methodilazine; 8: perazine; 9: prochlorperazine; 10: trifluoperazine; 11: chlorpromazine-sulfoxide

PZS have a great variety of pharmacological actions of much complicated mechanism. However, the drugs of a similar chemical structure, the group of promazine, chlorpromazine and triflupromazine, and the group of perazine, prochlorperazine and trifluoperazine, showed the correlations between the binding to BSA and the pharmacological activities. These results might suggest that PZS of a similar chemical structure act on various interfaces and biological membranes in a similar way, and the characteristic action involving hydrophobic interaction mentioned above is considered to take part in the onset of pharmacological actions of PZS.

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