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# Adsorption of Amino-acetamide Derivatives from 1-Octanol Solution by Silica Gel[1)]

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Adsorption of amino-acetamide derivatives by silica gel from 1-octanol solution, the 1-octanol/water partition coefficient and the capacity factor were investigated. The physico-chemical parameters obtained were well correlated with each other. On the other hand, there was no correlation between the Hammett constant and adsorption parameters. The results indicate that adsorbability measurement may provide useful information for quantitative structure–activity relationship (QSAR) studies.

**Keywords**——adsorption; amino-acetamide; silica gel; partition coefficient; dissociation constant; capacity factor; QSAR

The 1-octanol/water partition coefficient has been widely used as an index for the determination of hydrophobic character in quantitative structure–activity relationship (QSAR) studies of various materials having bioactivity. However, it is difficult to measure the oil/water partition coefficient for substances containing large hydrophobic groups by the usual methods such as the shaking flask method. Nagai *et al.*[2)] suggested that the adsorption of drugs by lipophilic powders from aqueous solutions may provide useful information on the hydrophobicity of drugs. In the present study we investigated the interactions of amino-acetamide derivatives (lipophilic, lightly soluble in water) and silica gel (hydrophilic powder) by measurement of the adsorption of the drugs from 1-octanol soltuions. The relationships among physico-chemical parameters in adsorption measurements, 1-octanol/water partition coefficient and capacity factor obtained by high performance liquid chromatography (HPLC) measurement, are discussed.

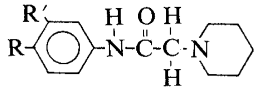
## Experimental

**Materials**——The amino-acetamide derivatives were synthesized in the manner previously reported[3)] and their ultraviolet (UV) absorption maxima are listed in Table I, together with the Hammett constant $\sigma$ and the hydrophobic constant $\pi$ from the literature.[4)] Silica gel (Wako gel C-300), 1-octanol, acetonitrile, sulfonic acid, sodium chloride, ammonium carbonate and *m*-nitrobenzene sulfonic acid were obtained from Wako Pure Chemical Ind., Ltd.

**Adsorption of the Amino-acetamide Derivatives (Batch Method)**——Silica gel adsorbent (2 g) was added to 50 ml of 1-octanol solution of an amino-acetamide of a given concentration, and the mixture was shaken continuously for 6 h, then allowed to stand for at least 16 h in an incubator maintained at a constant temperature of 25 °C. After removal of the supernatant solution with a pipette, the adsorbent and solution were seperated by centrifugation and filtration with a GC-25 glass filter having a pore size of 0.5 $\mu$m. The concentration of the amino-acetamide derivative in the filtrate was determined by UV absorption measurement using a Hitachi 139 UV-VS spectrophotometer. The amount of amino-acetamide derivative adsorbed was calculated from the difference between the initial and equilibrium concentrations.

**Determination of p$K_a$ by the Solubility Method**——An excess of the sample was dissolved in buffer solutions of various pHs. The ionic strength was adjusted to 0.1 by the addition of NaCl. Each solution was shaken for 3 d and the

TABLE I. Amino-acetamide Derivatives Used and Their Physicochemical Parameters Measured in This Study



| Sample No. | R | R' | $\sigma$ | $\pi$ | $\lambda_{max}$ (nm) | $a$ | $b$ | $pK_a$ | $\log P$ | $k'_0$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $-H$ | $-H$ | 0 | 0 | 241 | 14.47 | 6.06 | 7.89 | 3.949 | 0.192 |
| 2 | $-Cl$ | $-H$ | 0.23 | 0.71 | 249 | 18.68 | 4.52 | 8.00 | 4.446 | 0.176 |
| 3 | $-Cl$ | $-Cl$ | 0.52 | 1.25 | 251 | 18.77 | 3.14 | 7.93 | 4.562 | 0.164 |
| 4 | $-NO_2$ | $-H$ | 0.78 | $-0.28$ | 223 | 14.36 | 5.00 | 7.69 | 4.423 | 0.062 |
| 5 | $-CH_3$ | $-H$ | $-0.17$ | 0.56 | 246 | 15.57 | 6.06 | 8.02 | 4.211 | 0.430 |
| 6 | $-C_2H_5$ | $-H$ | $-0.15$ | 1.02 | 246 | 16.41 | 3.42 | 8.09 | 4.200 | 0.452 |
| 7 | $-OCH_3$ | $-H$ | $-0.27$ | $-0.02$ | 250 | 14.67 | 11.36 | 8.10 | 3.838 | 0.930 |
| 8 | $-OC_2H_5$ | $-H$ | $-0.24$ | 0.38 | 251 | 16.10 | 5.85 | 7.95 | 4.200 | 0.428 |

pH of the solution was measured. After removal of the sample, the concentration was determined in the manner described above. The relationship between solubility $S$ and the concentration of hydronium ions is

$$S=[B](1+[H_3O]/K_a) \qquad (1)$$

where $[B]$ is the solubility of the undissociated bases and $K_a$ is the dissociation contant. The $pK_a$ values were obtained from the pH values at which the $S$ values were twice those of $[B]$ by a graphical method.

**Determination of Partition Coefficient**——A 20 ml aliquot of 1/30 M phosphate buffer solution (pH 7.4) saturated with 1-octanol was mixed with 20 ml of 1-octanol containing a suitable amount of amino-acetamide derivative and the mixture was shaken for 1 h, then allowed to stand for 1 d at 25 °C. The concentration of each layer was determined.

**Determination of the Capacity Factor by HPLC Measurement**——HPLC measurements were carried out using a UVIDEC-100-III (Japan Spectroscopic Co., Ltd.) which consisted of a pump operated at a flow rate of 1.0 ml/min, a 30 cm × 3.9 mm Fine Pak Sil $C_{18}$ column, and a photometric detector set at 240 nm. The eluent was 10—35% hydrated acetonitrile containing 0.1 g/l ammonium carbonate and $m$-nitrobenzene sulfonic acid as an internal standard.

The capacity factor ($k'$) was calculated by using equation (2):

$$k'=(t-t_0)/t_0 \qquad (2)$$

where $t_0$ and $t$ are the retention times of the internal standard and sample, respectively. The linear relation between $\log k'$ and water concentration is shown in Fig. 1. The values obtained by extrapolating the straight line to zero concentration ($k_0'$), were found to correspond to the capacity factor in the absence of acetonitrile in the mobile phase.

## Results and Discussion

### Adsorption from 1-Octanol Solution

The adsorption isotherms of all the samples appeared to be of the Langmuir type as shown in Fig. 2. The constants $a$ and $b$ were calculated from Langmuir plots (Fig. 3) and the values obtained are shown in Table I. No clear difference could be detected in the monolayer capacity, $a$, of the samples. On the other hand, there was a difference in the $b$ value, which is considered to be a measure of adsorbability or affinity between adsorbent and adsorbate.

### Relation between Partition Coefficient *P* and Parameter *b*

Figure 4 shows the relation between the logarithm of the partition coefficient $\log P$ and the inverse of the parameter $b$ in the Langmuir equation. The correlation coefficient was 0.939; this value is significant in the $t$-test at the 1% level.

### Relation between Capacity Factor *k'*₀ and *b*

A plot of the capacity factor $k'_0$, one of the hydrophobic parameters, against the inverse

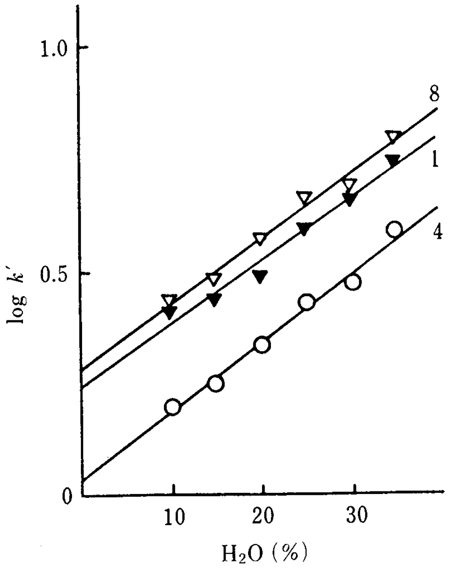


Fig. 1. Relationship between $\log k'$ and Water Content, $H_2O$ (%)

Numbering is the same as in Table I.

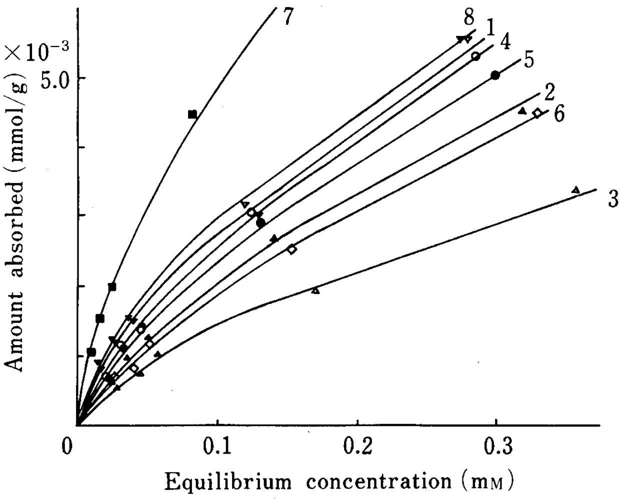


Fig. 2. Adsorption Isotherms

Numbering is the same as in Table I.

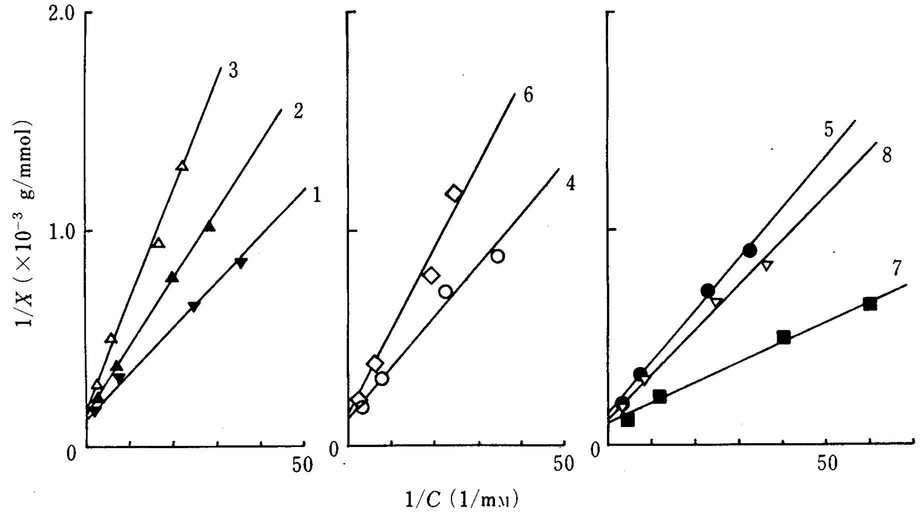


Fig. 3. Langmuir Plots

Numbering is the same as in Table I.

Langmuir equation $1/X = 1/ab \cdot 1/C + 1/a$.

$X$, amount adsorbed; $C$, equilibrium concentration; $a$, monolayer capacity; $b$, Langmuir constant.

of the parameter $b$ showed a very close correlation, as is evident from Fig. 5. The correlation coefficient was 0.898, a value significant in the $t$-test at the 1% level.

### Relation between Hydrophobic Substituent Constant $\pi$ and $b$

Figure 6 shows the relationship between the values of hydrophobic substituent constant $\pi$ given in the literature and $1/b$. The relationship is apparently linear. The correlation coefficient was 0.898, which is significant in the $t$-test at the 1% level. Only the datum for sample No. 4 deviated considerably from the straight line, possibly due to a difference between the affinity of this substance for water molecules and that for silanol groups on silica

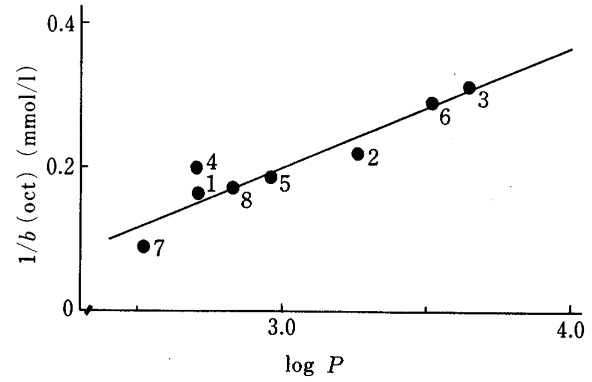


Fig. 4. Relationship between log $P$ and 1/$b$
Numbering is the same as in Table I.

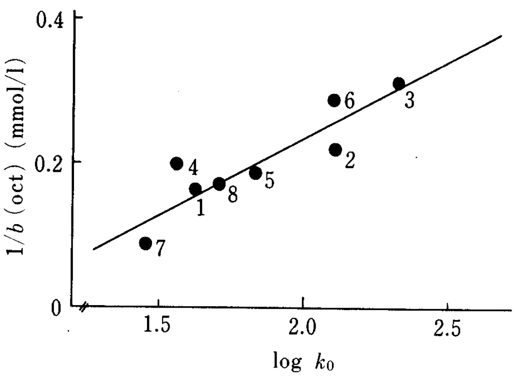


Fig. 5. Relationship between log$k_0'$ and 1/$b$
Numbering is the same as in Table I.

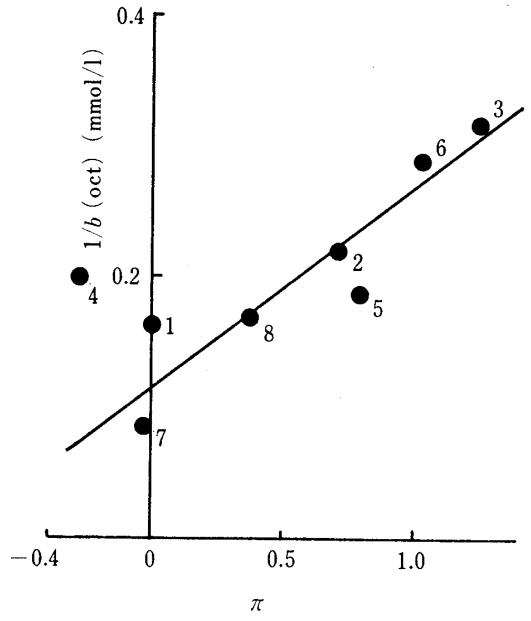


Fig. 6. Relationship between $\pi$ and 1/$b$
Numbering is the same as in Table I.

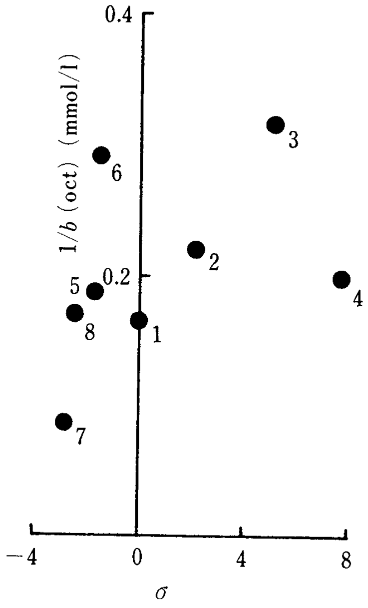


Fig. 7. Relationship between $\sigma$ and 1/$b$
Numbering is the same as in Table I.

gel.

### Relation between Hammett Constant $\sigma$ and Parameter $b$

The Hammett constant $\sigma$ generally used in QSAR studies is a measure of the electric effect. The relationship between $\sigma$ and 1/$b$ is shown in Fig. 7, and there is no apparent correlation between them.

It is difficult to measure the partition coefficient for extraneous nonpolar substances by conventional methods. Adsorbability of compounds by silica gel from 1-octanol solution may provide useful informations on the hydrophobicity of such substances.

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### References and Notes

1) This work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April

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