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The Energy Aspect of Oil/Water Partition and Its Application to the Analysis of Quantitative Structure-Activity Relationships. Aliphatic Alcohols in the Liposome/Water Partition System

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The energy aspect of oil/water partition has been examined for several solutes in different partition systems by determining the thermodynamic parameters of the partition. The thermodynamic parameters changed systematically, depending on the polarity of the nonaqueous phase of the partition. To further investigate the partition system dependency of the QSAR (quantitative structure-activity relationships) treatments the thermodynamic properties have been determined for various aliphatic alcohols in a liposome/water system; the results are discussed with regard to the previous ones obtained in a 1-octanol/water system, while paying special attention to applicability in the QSAR analysis. The following trends were observed in common with the two partition systems of liposome/water and 1-octanol/water: 1. The enthalpy term (ΔH_p°) can well reproduce the toxicity data for halogenated and nonhalogenated alcohols collectively, whereas the conventional log P (partition coefficient) term can be applied only for the two types of alcohols separately; 2. The entropy term (ΔS_p°) adds a discernible contribution to the refinement of the regression analysis. A distinctive characteristic is also discussed from a statistical method of analysis for the thermodynamic properties obtained in the two partition systems.

Hitherto, oil/water partition coefficients have been studied extensively in relation to the quantitative structure-activity relationships (QSAR) for compounds with biological activity.[1,2] The coefficients reflect the Gibbs free energy change of solutes upon going from a water to an oil medium when the logarithm is taken. Hence, an energy consideration of the partition phenomena will be of great importance in discussing partition phenomena. Most frequently, the partition coefficients have been measured regarding a 1-octanol/water system.[2] It has, however, yet to be debated whether this system can well simulate the partition phenomena which occur in the biophase. Even though studies with a few different partition systems have proved that a linear relation is observed when a partition system is changed from one to another, there exist instances in which such a relation is not followed exactly, or even deviates extremely, for some of the solutes tested. As for the latter cases, dissimilar solute-solvent interactions, such as hydrogen bonding, can be pointed out as a cause. These facts indicate that different partition systems need to be tested before deducing a definite conclusion concerning characteristic aspects of partition for any solute. In a previous paper,[4] the authors attempted to separate the logarithm of the partition coefficient, which corresponds to the Gibbs free energy term, into its components of enthalpy and entropy. The results have disclosed the potential importance of the enthalpy term in the QSAR analysis for alcohol toxicities.

In the present study, different kinds of partition systems are first tested regarding the thermodynamic properties of partition using some typical solutes. The characteristic aspects of partition and its importance in QSAR analyses are then examined for aliphatic alcohols using a liposome/water partition system.

Experimental

Commercially available egg lecithin (Merck) and sodium dodecyl sulfate (Tokyo Kasei Co.) were used without further purification. The lecithin was ascertained to give only a single spot on a silica gel 60 plate in thin-layer chromatography. All other chemicals were distilled in a glass vessel.

Titration calorimetry was performed, following a previous study.[4] Liposome was prepared according to a reversed-phase evaporation method.[5] The concentration of lecithin in the suspension was determined by phosphorus colorimetry.[6] The concentration was typically around 10 mg ml^{-1}.

Determination of Partition Coefficients as Well as Enthalpies and Entropies of Partition. Measurement of partition coefficients was achieved as follows. Each alcohol was first dissolved in water; this aqueous phase was then mixed with a lecithin solution (5 ml) and shaken for 12—18 h in a constant-temperature bath. The bath temperature was regulated within an error of ±0.2 °C. The mixed solution was then separated by ultracentrifuge equipment (Beckman L8-80M). The supernatant aqueous solution was analyzed by gas chromatography using an internal reference, and the alcohol concentration was determined. The initial aqueous phase was also analyzed using the same method. The partition coefficient (K_p) was calculated according to

$$K_p=\left(\frac{A_0-A}{w/d}\right)\Big/\left(\frac{A}{V_s-w/d}\right), \quad (1)$$

where A_0 and A are the relative peak intensities in the gas chromatogram for the brank (initial aqueous phase diluted with 5 ml water) and separated solutions, respectively; w and d are the weight and density of lecithin in the liposome solution, and V_s is the total volume of the solution. The density was cited from a reference.[7] These experiments were repeated several times and the obtained K_p values were averaged so as to give the means and standard deviations. The partition equilibrium was also achieved several times at temperatures near 25 or 40 °C; the resulting K_p values were used to derive

the enthalpy (ΔH_p°) and entropy (ΔS_p°) of the partition:[8]

$$\ln K_p = -\frac{\Delta H_p^\circ}{R}\cdot\frac{1}{T}+\frac{\Delta S_p^\circ}{R}. \quad (2)$$

Since the partition coefficient was defined as the ratio in mol dm^{-3}, the standard state of the derived thermodynamic properties corresponds to unit mol dm^{-3} at 25 °C in solution. Although the symbol K_p is used for the partition coefficient in Eq. 2, in the QSAR analysis below P is also used for this parameter, appearing as log P.

Results and Discussion

Partition System Dependency of the Partition Properties of Some Typical Solutes. The thermodynamic parameters of the partition change depending on the partition system adopted. Such a dependency has hitherto been studied in some different partition systems for the partition coefficient, the logarithm of which corresponds to the Gibbs free energy term, as evidenced by the equation $\Delta G_p^\circ = -RT\cdot\ln K_p$. However, a detailed discussion of the full dependency of the thermodynamic parameters, including the enthalpy and entropy terms, has been prevented because of the necessary extra work in experiments and the limited number of available experimental data. Such data are obtained from titration calorimetry for a few solutes in some partition systems, such as SDS micelle, 1-octanol, tetralin, and 2,2,4-trimethylpentane/water. The resulting data are compiled in Table 1 together with data from different sources. The free energy term (ΔG_p°) is seen to change monotonously, depending on the partition system: it decreases in the order of the nonaqueous phase of 2,2,4-trimethylpentane(saturated hydrocarbon), tetralin(aromatic hydrocarbon), 1-octanol(hydroxy compounds), and micelle(organic salt) or liposome (phospholipid). This order is consistent with the decreasing order in ΔH_p° and with the increasing order in the polarity of a nonaqueous medium. This fact supports the idea that solute–nonaqueous solvent interactions including electrostatic and hydrogen bonding parts stabilize the solutes in the nonaqueous phase, while decreasing the enthalpy (ΔH_p°) and increasing the partition coefficient. Since the entropy (ΔS_p°) changes parallel to the enthalpy (ΔH_p°), it contributes inversely to the free energy (ΔG_p°) as judged from a relation $\Delta G_p^\circ = \Delta H_p^\circ - T\cdot\Delta S_p^\circ$. It is, therefore, concluded that the enthalpy-entropy compensation relation holds and that the ΔH_p° term is the factor governing the partition system dependency regarding the thermodynamic properties. Since the enthalpy and entropy terms cancell each other, at least partly to yield the free energy, the partition system dependency becomes much larger when the free energy is separated into the two components of enthalpy and entropy. This is a merit of studying partition phenomena from a thermodynamic standpoint.

Model membrane (liposome) or micelle systems afford a lower ΔG_p° and a higher partition coefficient than does the widely used 1-octanol system. Since the former systems can better simulate the organized structure of a biophase medium, liposome or micelle systems may be recommended for the purpose of QSAR treat-

Table 1. Partition Properties of a Few Solute Molecules in Various Partition Systems[a]

Solute	Partition System[b]	log K_p	ΔG_p°	ΔH_p°	$T\Delta S_p^\circ$	Ref.
Phenol	SDS micelle/W	1.89±0.05	−10.8 ±0.4	−5.9 ±0.3	5.0 ±0.3	This work
	SDS micelle/W	1.72	−11	−13	−2.3	10)
	1-Octanol/W	1.45±0.01	−8.27±0.05	−7.7 ±0.3	0.56±0.06	This work
	1-Octanol/W	1.54	−8.7	−8.3	0.42	11)
	Tetralin/W	0.27±0.03	−1.6 ±0.1	1.5 ±0.1	3.1 ±0.1	This work
	Isooctane/W	−0.91±0.05	5.2 ±1.0	19.4 ±1.7	14.2 ±0.1	This work
	Isooctane/W		5.48±0.04	19.4 ±0.4	13.92	12)
	Isooctane/W		−0.57	16.4	16.95	13)
4-Methylphenol	DMPC liposome/W		−13.51	−31.5	−18.01	14)
	Isooctane/W		−2.26±0.14	−18.85±0.17	−16.59	12)
1-Pentanol	Liposome/W	1.29±0.01	−7.35±0.06	4.46±1.47	11.81±1.44	This work
	SDS micelle/W	1.67±0.09	−9.6 ±0.2	4.83±0.03	14.3 ±0.2	This work
	1-Octanol/W	1.41±0.06	−8.1 ±0.2	8.4 ±0.1	16.5 ±0.2	This work
	Tetralin/W	0.76±0.01	−4.32±0.03	24.0 ±0.1	28.3 ±0.1	This work
	Isooctane/W		0.89	29.56	28.67	12)
Hexane	Lecithin/W		−27.8	−9.2	18.5	9)
	DOPC liposome/W		−25.9 ±0.2	−7.1	18.7	9)
	SDS micelle/W		−27.4	−8.8	18.7	9)
	1-Octanol/W		−22.7			9)
	Hexane/W		−32.4	0	32.4	9)

a) ΔG, ΔH, and $T\Delta S$ are given in the unit of kJ mol^{-1}. Experimenental values are obtained from the titration calorimetry under constant temperature (this work),[12] and from the temperature dependence of partition coefficient (van't Hoff plot).[9,11,13,14] b) SDS: Sodium dodecyl sulfate. DMPC: Dimyristoyl phosphatidylcholine. DOPC: Dioleoyl phosphatidylcholine. Lecithin: Liposome made from egg york lecithin. W: Water. Isooctane: 2,2,4-Trimethylpentane.

Table 2. Partition Properties of Alcohols in the Liposome/Water System[a)]

	Solute	K_p	ΔG_p°	ΔH_p°	ΔS_p°
1:	Methanol	0.211±0.008	3.86±0.10	17.9±2.1	47.2±7.0
2:	Ethanol	0.460±0.009	1.93±0.05	13.2±1.3	37.9±4.1
3:	1-Propanol	1.26 ±0.02	−0.57±0.05	9.4±1.2	33.5±4.0
4:	1-Butanol	4.25 ±0.09	−3.59±0.05	6.6±1.3	34.2±4.3
5:	1-Pentanol	19.43 ±0.48	−7.35±0.06	4.5±1.5	39.6±4.8
6:	1-Hexanol	47.52 ±1.20	−9.57±0.06	3.5±1.7	43.9±5.5
7:	1-Heptanol	171.4 ±4.5	−12.75±0.06	4.2±1.8	57.0±6.0
8:	2-Propanol	0.92 ±0.01	0.21±0.03	11.6±0.7	38.2±2.3
9:	2-Butanol	2.78 ±0.06	−2.54±0.06	10.5±1.4	43.8±4.6
10:	2-Pentanol	4.87 ±0.09	−3.93±0.05	7.8±1.2	39.5±4.1
11:	2-Hexanol	29.71 ±0.83	−8.41±0.07	3.7±1.9	40.4±6.4
12:	2-Heptanol	88.73 ±2.16	−11.12±0.06	5.2±1.5	54.7±5.0
13:	2-Methyl-1-propanol	3.38 ±0.06	−3.02±0.05	8.3±1.3	38.0±4.3
14:	2-Methyl-2-propanol	1.13 ±0.01	−0.30±0.02	8.7±0.8	30.3±2.7
15:	3-Methyl-1-butanol	5.88 ±0.11	−4.39±0.05	5.8±1.2	34.1±4.0
16:	2-Methyl-2-butanol	4.05 ±0.09	−3.47±0.05	6.6±1.2	33.8±4.0
17:	3-Methyl-2-butanol	17.77 ±0.41	−7.13±0.06	7.7±1.3	49.7±4.3
18:	2,2-Dimethyl-1-propanol	23.86 ±0.56	−7.86±0.06	6.0±1.5	46.6±4.8
19:	3,3-Dimethyl-2-butanol	27.36 ±0.54	−8.20±0.05	4.8±1.2	43.7±4.0
20:	2-Fluoroethanol	0.109±0.003	5.49±0.07	7.8±1.5	7.8±4.9
21:	2-Chloroethanol	0.61 ±0.01	1.24±0.05	6.5±1.2	17.6±4.0
22:	2,2-Dichloroethanol	2.94 ±0.07	−2.67±0.06	2.8±1.4	18.2±4.6
23:	2,2,2-Trichloroethanol	19.76 ±0.37	−7.40±0.05	1.4±1.2	29.5±3.9
24:	2-Bromoethanol	1.75 ±0.04	−1.39±0.06	2.6±1.5	13.4±5.0

a) K_p and ΔG_p° are given at 25 °C. ΔG_p° and ΔH_p° are in the unit of kJ mol^{-1}, and ΔS_p° is in the unit of J K^{-1} mol^{-1}.

ment. In following sections of this paper, the partition properties of aliphatic alcohols (which the authors studied in the 1-octanol/water system[4]) are examined in the liposome/water system and compared with previous results.

Partition Properties of Aliphatic Alcohols in the Liposome/Water System. The data regarding K_p (at 25 °C), ΔH_p°, and ΔS_p° obtained in the present study are summarized in Table 2. The thermodynamic parameters (ΔG_p°, ΔH_p°, and ΔS_p°) change linearly with the molar volume (V_m) of alcohols (Figs. 1 to 3) when halogenated and nonhalogenated alcohols are veiwed separately. The molar volume dependency of ΔH_p° is parallel for the halogenated and nonhalogenated alcohols (Fig. 2); that of ΔS_p°, however, differs in

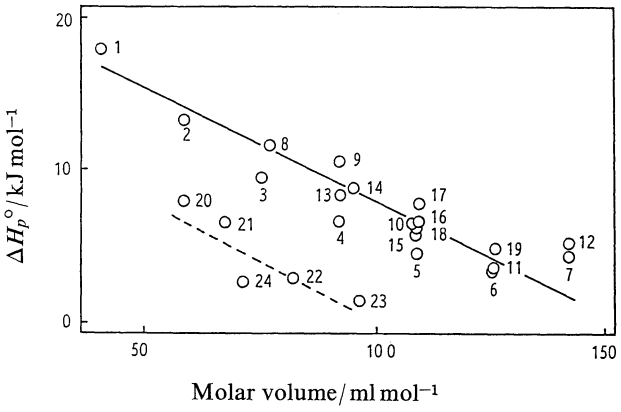

Fig. 2. Plots of ΔH_p° against the molar volume of solutes.

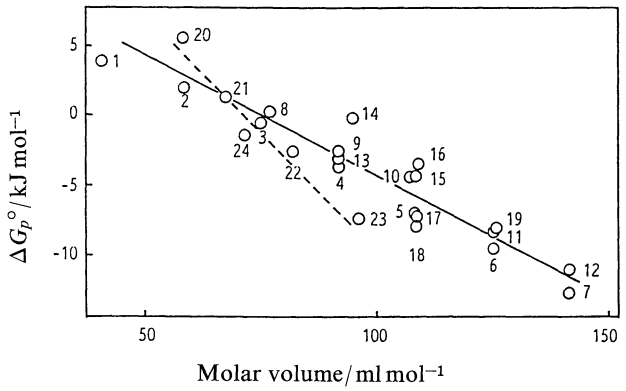

Fig. 1. Plots of ΔG_p° against the molar volume of solutes.

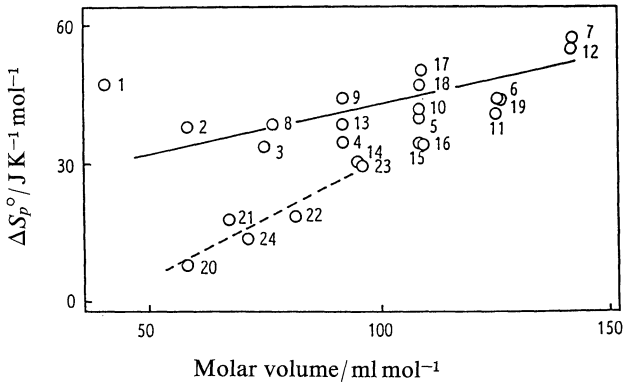

Fig. 3. Plots of ΔS_p° against the molar volume of solutes.

its slope between the two types of alcohols (Fig. 3). The latter difference is responsible for the difference in the slope shown in Fig. 1 for the halogenated and nonhalogenated alcohols. This result offers a rather clear contrast with that reached in the 1-octanol/water partition system:[4] in the latter system, the enthalpy (ΔH_p°; not the entropy) is responsible for the different slope of the molar volume dependency in ΔG_p°. When ΔG_p° and $\log K_p$ at 25 °C, as well as ΔH_p° and ΔS_p°, are interrelated between the partition systems of 1-octanol/water and liposome/water, linear relations are successfully obtained in regression analyses (Table 3). It is seen from the regression coefficients (smaller than 1.0 in Table 3) that the variations in the values of $\log K_p$, ΔG_p°, ΔH_p°, and ΔS_p° are smaller in the liposome/water system than those in the 1-octanol/water system when the solute alcohols are changed. The results listed in Tables 1 and 3 show a trend in that ΔH_p° and ΔS_p° are larger when observed using a more polar (ionic) nonaqueous phase. This trend, however, is inversed with respect to the free energy term. That is, ΔG_p° is increased, being decreased in absolute value, for the aliphatic alcohols in the liposome/water system, compared to that in the 1-octanol/water system (see 1-pentanol in Table 1 and also Table 3). This means that, for the aliphatic alcohols, ΔH_p° does not decrease very much in the liposome system compared to the data observed in other systems; this situation is reversed for ΔS_p°. This is equivalent to saying that the ratio of the enthalpy/entropy changes and the contribution of the enthalpy term is increased in the liposome/water system.

QSAR Analyses of the Biological Activities of Alcohols. Among the alcohols treated in the present study the biological activities are reported for twelve nonhalogenated alcohols,[15] as well as eight nonhalogenated and five halogenated alcohols.[16] The data concerning nonhalogenated alchohols,[15] which include LD_{50} (the concentration causing death in 50% of female white mice from i.v. injection), H (the concentration causing instantaneous hemolysis of erythrocytes), WI (the concentration causing inhibition of all the Tubifex worm movement within 2 min after immersion in a solution of alcohols), and FI (the dose that all fish assumed a side position or inverted position after 9—10 min of exposure to alcohols), were analyzed by means of the molecular connectivity index ($^1\chi$). The data, however, were also found to be quite successfully correlated with $\log P$ (Table 4).[17] Here, the $\log P$ data may be taken from either the liposome/water or the 1-octanol/water system, since the data from these two systems exhibit a high mutual colinearity, especially within the nonhalogenated alcohols (Table 2).

The toxicity data of alcohols, including halogenated ones,[16] are analyzed in Table 5. These data include the product of intrinsic toxicity, T_i (the slope of the dose-response curve in tissue culture), the tissue culture toxicity, ID_{50} (the concentration required to produce 50% inhibition of growth), the hemolytic activity, H_{50} (the concentration required to produce 50% hemolysis in saline at 37 °C), and the acute in vivo toxicity, LD_{50} (the single intraperitoneal dose required to kill 50% of the mice in 7 d). For the sake of a comparison the previous analyses using the partition properties in the 1-octanol/

Table 3. Interrelations of ΔG_p° (at 25 °C), $\log K_p$ (at 25 °C), ΔH_p°, and ΔS_p° Determined in the Partition Systems of Liposome/Water and 1-Octanol/Water[a]

Equations	r[b]	F[c]	SD[d]
$\log K_p$(liposome/W)=0.920(0.081)$\log K_p$(1-octanol/W)−0.132(0.095)	0.989	605	0.128
ΔG_p°(liposome/W)=0.918(0.026)ΔG_p°(1-octanol/W)+0.770(0.176)	0.989	600	0.736
ΔH_p°(liposome/W)=0.750(0.198)ΔH_p°(1-octanol/W)+0.227(1.870)	0.915	67	1.474
ΔS_p°(liposome/W)=0.813(0.163)ΔS_p°(1-octanol/W)−1.983(7.507)	0.948	116	4.493

a) Values in parentheses correspond to 95% confidence intervals. b) Multiple correlation coefficient. c) Variance ratio. d) Standard deviation.

Table 4. Linear Regression Analyses of the Biological Activities of Nonhalogenated Alcohols Based on $\log P$ in the Liposome/Water System and on the Molecular Connectivity Index $^1\chi$

Equations[a]	n[b]	r[c]	F[d]	SD[e]
$-\log LD_{50}$ =0.944(0.135)$\log P$−1.420(0.102)	12	0.980	244	0.132
−log H =0.885(0.155)$\log P$−0.166(0.117)	12	0.971	163	0.151
−log WI =1.180(0.135)$\log P$+0.274(0.102)	12	0.987	382	0.132
−log FI =1.380(0.152)$\log P$+0.458(0.089)	8	0.994	490	0.098
$-\log LD_{50}$ =0.922(0.132)$^1\chi$−3.030(0.309)	12	0.979	236	0.133
−log H =0.889(0.100)$^1\chi$−0.177(0.232)	12	0.987	389	0.100
−log WI =1.170(0.130)$^1\chi$−1.820(0.301)	12	0.987	400	0.129
−log FI =1.410(0.141)$^1\chi$−2.040(0.284)	8	0.995	601	0.089

a) 95% confidence intervals are depicted in parentheses. b) Number of the data. c) Correlation coefficient. d) Variance ratio. e) Standard deviation.

water system are also included in Table 5. The in vivo datum (LD_{50}) is excluded for 2-fluoroethanol in Table 5, since this alcohol is metabolized to a more active intermediate in vivo.[18] All other available data are included in Table 5.

Trends in the analysis of the toxicity data are summarized as follows:

1. All of the data can be correlated well with ΔH_p°.
2. The data exhibit no high correlation with ΔS_p°, but the regression analyses are improved when ΔS_p° is incorporated besides the ΔH_p° term.
3. The data can be correlated with log P only when the halogenated and the nonhalogenated alcohols are treated separately.
4. A slightly higher correlation is observed against ΔS_p° when in vivo toxicity data (LD_{50}) are concerned.

These trends are all in common with the two partition systems of liposome/water and 1-octanol/water. In order to examine more closely the difference of using the data of the two partition systems, a bootstrap method[19] is applied for statistical tests of the regression co-

Table 5. Regression Analyses of the Biological Activities of Alcohols Based on the Partition Properties Obtained in the Liposome/Water and 1-Octanol/Water Systems

Equations[a]	n[b]	r[c]	F[d]	SD[e]
Liposome/water system				
$-\log H_{50} = 0.765(0.570)\log P + 0.250(0.504)$	10	0.736	9.5	0.529
$-\log H_{50} = 0.716(0.190)\log P + 0.005(0.175)$[f]	7	0.974	93.9	0.133
$-\log H_{50} = 1.180(4.690)\log P + 0.709(3.620)$[g]	3	0.955	10.3	0.405
$-\log H_{50} = -0.186(0.057)\Delta H_p^\circ + 2.010(0.455)$	10	0.936	56.4	0.276
$-\log H_{50} = -0.009(0.050)\Delta S_p^\circ + 0.984(1.840)$	10	0.139	0.2	0.775
$-\log H_{50} = -0.204(0.052)\Delta H_p^\circ + 0.015(0.016)\Delta S_p^\circ + 1.610(0.570)$	10	0.963	44.9	0.225
$-\log LD_{50} = 0.095(0.471)\log P + 2.460(0.388)$	12	0.140	0.20	0.451
$-\log LD_{50} = 0.114(0.219)\log P + 2.170(0.192)$[f]	8	0.460	1.61	0.162
$-\log LD_{50} = 0.313(0.317)\log P + 2.910(0.225)$[g]	4	0.949	18.0	0.081
$-\log LD_{50} = -0.102(0.039)\Delta H_p^\circ + 3.230(0.309)$	12	0.878	33.7	0.218
$-\log LD_{50} = -0.028(0.016)\Delta S_p^\circ + 3.450(0.582)$	12	0.770	14.5	0.291
$-\log LD_{50} = -0.076(0.029)\Delta H_p^\circ - 0.016(0.009)\Delta S_p^\circ + 3.590(0.288)$	12	0.957	48.9	0.139
$-\log(1/T_i) = 0.598(0.506)\log P + 3.310(0.422)$	13	0.617	6.77	0.593
$-\log(1/T_i) = 0.854(0.249)\log P + 2.790(0.218)$[f]	8	0.960	70.7	0.184
$-\log(1/T_i) = 0.744(0.884)\log P + 3.860(0.677)$[g]	5	0.840	7.17	0.464
$-\log(1/T_i) = -0.188(0.047)\Delta H_p^\circ + 4.900(0.374)$	13	0.935	76.7	0.267
$-\log(1/T_i) = -0.010(0.034)\Delta S_p^\circ + 3.870(1.190)$	13	0.181	0.37	0.741
$-\log(1/T_i) = -0.205(0.045)\Delta H_p^\circ + 0.012(0.012)\Delta S_p^\circ + 4.650(0.411)$	13	0.957	54.3	0.230
$-\log ID_{50} = 0.546(0.478)\log P + 1.580(0.399)$	13	0.604	6.32	0.560
$-\log ID_{50} = 0.760(0.255)\log P + 1.100(0.223)$[f]	8	0.948	53.4	0.189
$-\log ID_{50} = 0.733(0.640)\log P + 2.120(0.490)$[g]	5	0.903	13.3	0.336
$-\log ID_{50} = -0.180(0.035)\Delta H_p^\circ + 3.100(0.273)$	13	0.961	132	0.195
$-\log ID_{50} = -0.011(0.032)\Delta S_p^\circ + 2.160(1.110)$	13	0.217	0.54	0.686
$-\log ID_{50} = -0.194(0.031)\Delta H_p^\circ + 0.009(0.008)\Delta S_p^\circ + 2.900(0.286)$	13	0.976	102	0.159
1-Octanol/water system				
$-\log H_{50} = 1.010(0.721)\log P + 0.119(0.567)$	8	0.813	11.7	0.513
$-\log H_{50} = 0.814(0.193)\log P - 0.104(0.132)$[f]	5	0.992	179.9	0.073
$-\log H_{50} = 1.010(5.310)\log P + 0.622(4.960)$[g]	3	0.924	5.86	0.519
$-\log H_{50} = -0.155(0.081)\Delta H_p^\circ + 2.030(0.816)$	8	0.887	22.1	0.407
$-\log H_{50} = -0.016(0.057)\Delta S_p^\circ + 1.240(2.400)$	8	0.264	0.45	0.848
$-\log H_{50} = -0.212(0.064)\Delta H_p^\circ - 0.030(0.022)\Delta S_p^\circ + 1.330(0.700)$	8	0.970	39.5	0.235
$-\log LD_{50} = 0.333(0.612)\log P + 2.390(0.468)$	10	0.405	1.57	0.446
$-\log LD_{50} = 0.172(0.439)\log P + 2.140(0.296)$[f]	6	0.478	1.18	0.191
$-\log LD_{50} = 0.277(0.438)\log P + 2.890(0.387)$[g]	4	0.887	7.41	0.127
$-\log LD_{50} = -0.092(0.021)\Delta H_p^\circ + 3.380(0.212)$	10	0.963	102	0.134
$-\log LD_{50} = -0.025(0.017)\Delta S_p^\circ + 3.560(0.729)$	10	0.762	11.1	0.330
$-\log LD_{50} = -0.087(0.035)\Delta H_p^\circ - 0.003(0.012)\Delta S_p^\circ + 3.470(0.326)$	10	0.965	47.4	0.143

Table 5. (Continued)

Equations[a]	n[b]	r[c]	F[d]	SD[e]
$-\log(1/T_i)=-0.679(0.680)\log P-1.810(0.515)$	11	0.599	5.04	0.631
$-\log(1/T_i)=0.876(0.241)\log P+2.670(0.163)$[f]	6	0.981	101	0.105
$-\log(1/T_i)=0.317(1.320)\log P+4.010(1.120)$[g]	5	0.402	0.58	0.711
$-\log(1/T_i)=-0.142(0.058)\Delta H_p^\circ-0.244(0.580)$	11	0.880	30.9	0.374
$-\log(1/T_i)=-0.019(0.034)\Delta S_p^\circ-0.790(1.380)$	11	0.396	1.67	0.724
$-\log(1/T_i)=-0.178(0.071)\Delta H_p^\circ+0.016(0.021)\Delta S_p^\circ-0.545(0.658)$	11	0.916	20.8	0.336
$-\log ID_{50}=0.677(0.615)\log P+1.475(0.466)$	11	0.639	6.20	0.571
$-\log ID_{50}=0.775(0.226)\log P+0.994(0.152)$[f]	6	0.979	90.5	0.099
$-\log ID_{50}=0.712(0.649)\log p+1.990(0.549)$[g]	5	0.896	12.2	0.348
$-\log ID_{50}=-0.137(0.048)\Delta H_p^\circ+3.000(0.482)$	11	0.908	42.2	0.311
$-\log ID_{50}=-0.018(0.032)\Delta S_p^\circ+2.440(1.300)$	11	0.391	1.63	0.683
$-\log ID_{50}=-0.176(0.060)\Delta H_p^\circ-0.017(0.018)\Delta S_p^\circ+2.680(0.558)$	11	0.951	38.0	0.243

a) 95% confidence intervals are depicted in parentheses. b) Number of the data. c) Multiple correlation coefficient. d) Variance ratio. e) Standard deviation. f) For only the nonhalogenated alcohols. f) For only the halogenated alcohols.

Table 6. The 95% Confidence Intervals of the Regression Coefficients Analyzed by the Bootstrap Method

	Liposome/water system	1-Octanol/water system
ΔH_p°	−0.080—−0.022	−0.103—0.006
ΔS_p°	−0.033—−0.012	−0.032—0.002
Constant	3.456— 4.167	3.334—4.175
r[a]	0.892— 0.984	0.763—0.989

a) Multiple regression coefficient.

efficients (Table 6). The results indicate that within the 95% confidence intervals the coefficients of ΔH_p° and ΔS_p° are not reduced to zero in the liposome/water system, whereas they are reduced in the 1-octanol/water system. This supports the superiority of data obtained in the liposome/water system for the QSAR analysis.

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