Determination of the Chloroform / Water Distribution Coefficient of Weak Acids by a Stepwise Flow Ratiometry

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Abstract

The distribution coefficients, K_D, of phenol, benzoic acid and their derivatives were determined by a stepwise flow ratiometry. In a typical case, an aqueous solution of an analyte was delivered and merged with chloroform. The chloroform/aqueous flow ratio (R_f) was changed stepwise under a constant total flow rate. The duration time for each R_f was 2 min. The analyte was extracted to chloroform when both phases, segmented each other, passed through an extraction coil. One of the phases (*i.e.*, aqueous or organic phase) was separated from the segmented stream based mainly on the difference in specific gravities between them. The separated phase was led to an UV/Vis detector where the absorbance of the analyte (A) was monitored. The plots of A^{-1} *vs.* R_f, $(A\ R_f)^{-1}$ *vs.* R_f^{-1}, and $A\ R_f$ *vs.* A gave straight lines. The distribution ratio (D) of the analyte was calculated from their slopes and intersections. The present method was applied to the K_D determination of the weak aromatic acids, which have the log K_D values of -0.2 ~ 2.5. The log D values obtained were in good agreement with literature values of K_D when the determination was carried out at the pH that was low enough to prevent the acid dissociation of the analytes. The method was simple and efficient (< 10 min / determination) with satisfactory precision.

Keywords Stepwise flow ratiometry, distribution coefficient, partition coefficient, continuous flow extraction, weak acid.

1. Introduction

Distribution coefficient (K_D), also refereed as partition coefficient (P), is one of the most important physicochemical constants concerning the hydrophobicity (lipophilicity) of a substance. Thus, K_D is widely used as a parameter for the molecular design of drugs and for the toxicity estimation of environmental pollutants. Many experimental approaches, such as shake-flask method, stir-flask method, generator column method, reversed phase HPLC, counter-current chromatography, micellar electrokinetic chromatography and so forth, have been developed for determining K_D [1]. They each have inherent advantages and disadvantages. Shake-flask methods, for example, are accurate in principle but are laborious and tedious; chromatographic techniques are generally rapid but require suitable standards the K_D values of which are well established. Some papers on the determination of K_D by an FIA [2,3] and a segmental FIA (monosegmented continuous flow method) [4,5] have recently been published.

Flow ratiometry is a sophisticated variation of continuous flow analysis, where two independently delivered solutions (*e.g.*, reagent and sample solutions) are merged at various flow ratios R_f. Analytical signal is monitored at a downstream of the flow line. The concentration or some physicochemical property of an analyte is determined based on the relationship between the analytical signal and R_f. The origin of flow ratiometry can be traced back to a continuous titrimetry by Blaedel and Laessig [6,7]. Their method and succeeding analogue methods by many reserchers had limited efficiencies due to the lag time between the sample-reagent confluence point and its actual being registered by a recorder. Very recently, Dasgupta and his co-workers proposed a novel concept for continuous

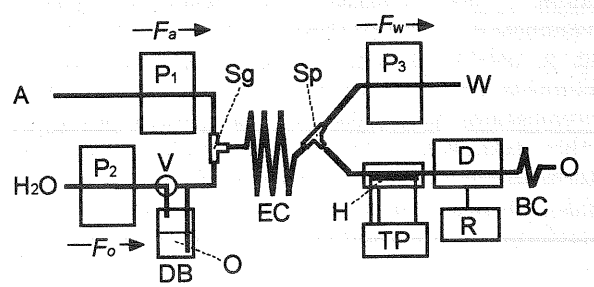

Fig. 1 Schematic diagram of a flow system. A, aqueous phase (buffer solution); H_2O, deionized water; O, organic phase (chloroform); P_1 and P_2, double plunger pumps; P_3, peristaltic pump (Rainin Dynamax RP-1); V, 3-ways valve; DB. displacement bottle (500 cm^3); Sg, T-segmentor; EC, extraction coil (knotted PTFE tubing); Sp, separator (see Fig. 2A); H, heater, TP, temperature controller (Toho electronic BX-303-104-OP) with thermocouple temperature sensor; D, UV/Vis detector (Shimadzu SPD-6AV); R, recorder (Shimadzu Chromatopac C-R6A), BC, back pressure coil (0.25 mm i.d., 1 m long); W, waste (mainly aqueous phase).

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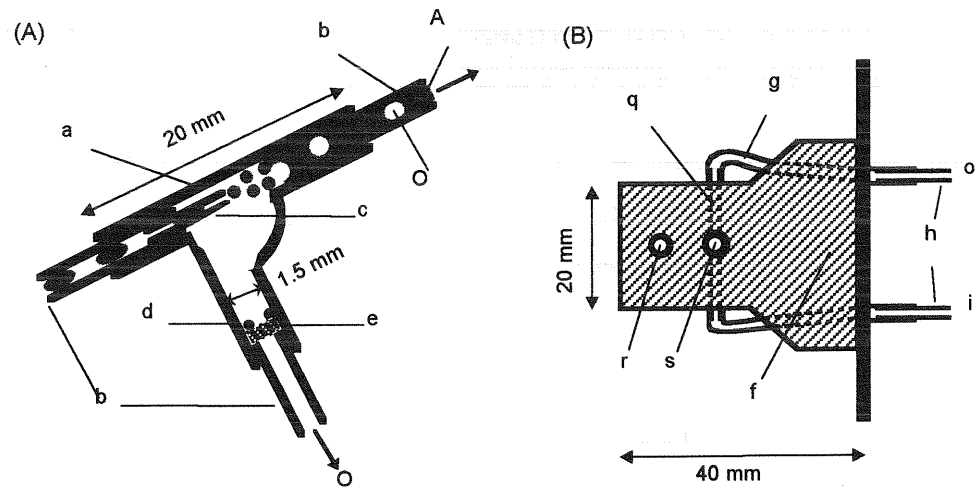

Fig. 2 (A) Separator and (B) flow cell units. A, aqueous phase; O, organic phase (to the detector); a, glass separator; b, PTFE tubing (0.8 mm i.d.); c: PTFE tubing (0.5 mm i.d.); d: PTFE O-ring; e, hydrophobic membrane (Advantec PF100); f: black rubber; g, PTFE tubing (2 mm i.d.); h, PTFE tubing (1 mm i.d.); i, inlet; o, outlet; q: quartz tubing (1 mm i.d., 2 mm o.d.); r, reference optical aperture (ϕ 1.5 mm); s: sample optical aperture (ϕ 1.5 mm).

titirimetry having very high throughput rate base on a feedback based flow ratiometry. They applied the concept to photometric [8] and potentiometric [9] titrations. By averaging rapid forward and backward titrations just vicinity of the neutralization point, the errors due to the lag time was compensated for.

We have been studying on the determination of K_D by experimental [10,11] and theoretical [12] approaches. In a previous study [10], we developed a system for the determination of K_D based on a continuous flow extraction and a flow ratiometry. Basic experimental conditions were optimized by using phenol as an analyte. The method was shown to possess advantages over conventional methods in the respect that it needed neither standard materials for K_D calibration nor information on the initial and final concentrations of analyte. In the present study, we further examined the method by applying it to the determination of K_D of various weak acids, namely, phenol, benzoic acid and their derivatives, in chloroform / aqueous systems.

2. Experimental

2.1 Flow system

Figure 1 shows the flow diagram of a representative configuration used in the present study. Two Shimadzu LC-10ADvp double plungers pumps (P_1 and P_2) were used for delivering buffer solutions (A) and deionized water (H_2O), respectively. A displacement bottle (DB) was used in order to deliver chloroform more steadily than chloroform being directly delivered. Other components of the system were almost the same as those in the previous study [10].

In a typical case, an analyte was dissolved in an aqueous phase buffered at a pH. The organic / aqueous flow ratio R_f (= F_o/F_a) was automatically changed stepwise (each duration time: 2 min) while the total flow rate (F_o + F_a) was kept constant at 2 cm^3 min^{-1} by using a programming function equipped in the P_1 and P_2 pumps. Although such a stepwise strategy cannot be applied to the measurement of analyte whose concentration is continuously changing, it is useful for the determination of physicochemical constants such as K_D in the present study. Both the phases, almost immiscible with and segmented each other, passed through an extraction coil (EC; 0.5 mm i.d., 3 m long), which was sufficient for attaining the extraction equilibrium [10]. The organic phase was separated from the segmented stream based mainly on the difference in specific gravity between both the phases. The detail of a separator (Sp) used for this purpose was shown in Figure 2A. In order to prevent contamination of fine droplets of aqueous phase to the separated organic stream, the flow rate of a discharging pump (P_3) was held slightly higher than that of P_1. In addition, the separated phase was warmed up to 35℃ by using a heater (H), set between the separator and a detector, in order to maintain the solubility of water in chloroform. The relative absorbance of thus separated chloroform stream was monitored with an UV/Vis detector (D) at the absorption maximum wavelength of the analyte. An original flow cell equipped to the product had a cranked flow path to make an optical path length 1 cm. The cell could not remove severe noises, once droplets of the other phase and/or bubbles accidentally came into the cell. Therefore, a hand-made flow cell unit shown in Fig. 2B was introduced in the detector instead. A quartz tubing (1 mm i.d.), which was set perpendicular to the light path, was used as a sample flow cell. Its simple flow path made it possible, at the expense of sensitivity, to recover quickly from such noises. The analytical signals thus measured were recorded on a

Table 1. Three kinds of linear plot for obtaining distribution ratio

	A-type plot			B-type plot			C type-plot		
System*	Abscissa	Ordinate	D**	Abscissa	Ordinate	D**	Abscissa	Ordinate	D**
A/O	R_f	A_o^{-1}	$S\,I^{-1}$	R_f^{-1}	$(A_o\,R_f)^{-1}$	$I\,S^{-1}$	A_o	$A_o\,R_f$	$-S^{-1}$
A/A	R_f	A_a^{-1}	$S\,I^{-1}$	R_f^{-1}	$(A_a\,R_f)^{-1}$	$I\,S^{-1}$	A_a	$A_a\,R_f$	$-S^{-1}$
O/A	R_f^{-1}	A_a^{-1}	$I\,S^{-1}$	R_f	$R_f\,A_a^{-1}$	$S\,I^{-1}$	A_a	$A_a\,R_f^{-1}$	$-S$
O/O	R_f^{-1}	A_o^{-1}	$I\,S^{-1}$	R_f	$R_f\,A_o^{-1}$	$S\,I^{-1}$	A_o	$A_o\,R_f^{-1}$	$-S$

*: The phase in which an analyte is dissolved / the phase in which the analyte is measured. A, aqueous phase; O, organic phase.

**: S, slope obtained by the linear regression; I, intersection of the linear regression line at the ordinate.

recorder (R).

When an analyte was initially dissolved in chloroform, the solution was directly propelled by P_2 pump and led to the confluence point (Sg) without by way of DB.

2.2 Reagents

All the reagents used in the present study were purchased from Kanto Chemicals Co. Ltd. or Nacalai Tesque, and were used without further purification. Water is a Milli-Q SP deionized water. Solutions to be pumped by P_1 and P_2 were degassed by bubbling helium using a Shimadzu DGU-2A degas unit throughout the experiment. Buffer solutions used were 0.15 mol dm^{-3} acetate (pH 5.0), 0.15 mol dm^{-3} citrate (pH 2.25) and 0.05 mol dm^{-3} tetraborate-sodium carbonate (pH 9.7) buffers.

3. Principle

The principle of the present method was described before [10]. Its basis was on a strategy by Danielsson and Zhang [2,3], who had combined a flow injection extraction with a flow ratiometry. Briefly, when an aqueous solution of an analyte (concentration: C_{ai}) is fed at a flow rate F_a, and merged with an immiscible organic solvent having a flow rate F_o, the distribution ratio D of the analyte at equilibrium is expressed as Eq. (1);

$$D = C_o\,F_a\,(C_{ai}\,F_a - C_o\,F_o)^{-1}, \qquad (1)$$

where C_o is the concentration of the analyte in the organic phase. When the dissociation and association of the analyte in both the phases can be neglected, D corresponds to K_D. Equation (1) can be rewritten as Eq. (2) by assuming that the absorbance of the analyte in the organic phase (A_o) is proportional to C_o (the Beer's Law),

$$A_o = k_o\,D\,C_{ai}\,(1 + D\,R_f)^{-1} \qquad (2)$$

where k_o is the absorption constant of the analyte in the organic phase. From Eq. (2), the following three equations are derived for linear plots;

$$A_o^{-1} = R_f\,(k_o\,C_{ai})^{-1} + (k_o\,D\,C_{ai})^{-1} \qquad (3)$$

$$(A_o\,R_f)^{-1} = (k_o\,D\,C_{ai}\,R_f)^{-1} + (k_o\,C_{ai})^{-1} \qquad (4)$$

$$A_o\,R_f = k_o\,C_{ai} - A_o\,D^{-1} \qquad (5)$$

Therefore, by plotting A_o^{-1} against R_f, $(A_o\,R_f)^{-1}$ against R_f^{-1}, or $A_o\,R_f$ against A_o, D is calculated from each slope and intersection (Eqs. (3) and (4)) or only from the slope (Eq. (5)) without the information on C_{ai} and k_o values. It is possible to measure aqueous phase by exchanging the position of the components (P_3, D and so on) after the separator in Fig. 1. In this case, three equations for linear plots similar to Eqs. (3) - (5) are derived also by substituting A_a D and k_a for A_o and k_o in Eqs. (3) - (5),

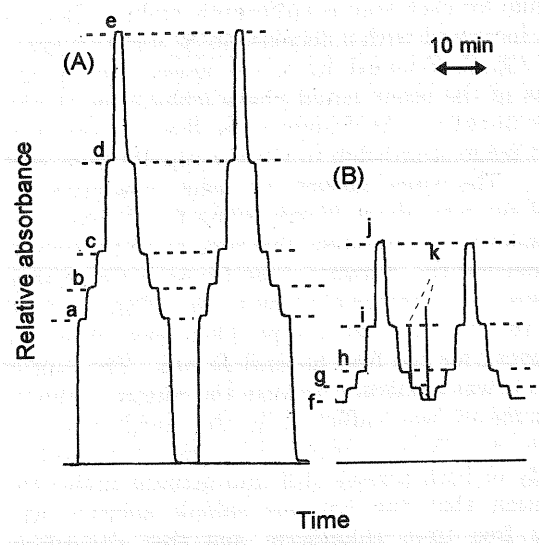

Fig. 3 Flow signal of A_o (A) and A_a (B) for *p*-chlorophenol. The aqueous solution of the analyte (buffered at pH 5.0) was used as a sample solution. R_f: a, 1.49; b, 1.21; c, 0.99; d, 0.66; e, 0.42; f, 0.66; g, 0.53; h, 0.42; i, 0.24; j, 0.10. The peaks denoted by k are noises.

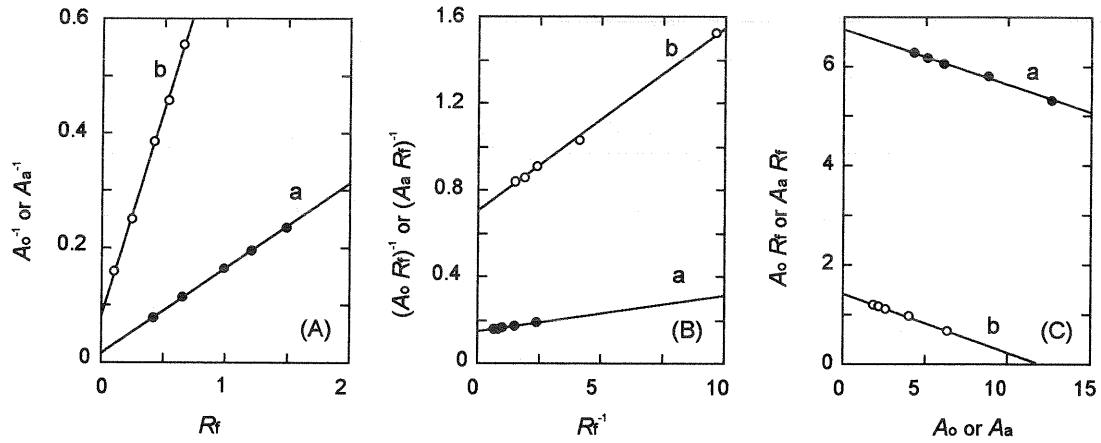

Fig. 4 Three kinds of linear plots (A-, B- and C-type plots) for the first upward run (from low R_f to high R_f) shown in Fig. 3. a, A/O system; b, A/A system

respectively. Likewise, such equations for linear plots can be derived for the systems in which an organic solution of analyte is used as a sample solution. Table 1 is the summary of the linear plots ("A-", "B-" and "C-" type plots) applicable to each system.

4. Results and Discussions

4.1 Analytical performance of the present system

Figure 3 shows an example of analytical signals, A_o and A_a, where 1 mmol dm^{-3} *p*-chlorophenol in 0.15 mol dm^{-3} acetate buffer (pH 5) was extracted to chloroform. The analytical wavelength was 281.4 nm. It shows the signal for each step is sufficiently stable. Both A_o and A_a increased with a decrease in R_f, and *vice versa*. Sharp signals denoted by k are noises due to fine droplets of the other liquid phase (chloroform in this case) or bubbles. As designed, the flow cell shown in Fig. 2B made it possible to recover rapidly from such noises. The time needed for each downward or upward run was about 10 min when five R_f steps-run was employed. Of course, this time could be reduced by decreasing the duration time for each step and/or decreasing the number of steps a run. Figures 4A-C shows the A-, B- and C-type plots (see Table 1), respectively, for the first upward R_f run. The unit of A_o and A_a was arbitrary because the relative value of the absorbance was sufficient for the calculation of D. The flow ratio R_f was corrected by taking the mutual solubility of both phases [13] into account under the assumption that the aqueous sample solution was initially free from chloroform and that chloroform phase was saturated with water. The effect of this correction was, however, not critical [11]. The linearity of the plots was extremely good. The squares of regression coefficients, r^2, were 1.0000, 0.9971 and 0.9960 for A_o, and 0.9995, 0.9981 and 0.9936 for A_a in Figs. 4A-C, respectively. The log D values obtained from these three plots were 0.939, 0.938 and 0.938 for A_o, and 0.947, 0.927 and 0.933, for A_a, respectively.

4.2 Application to diverse compounds

Table 2 is the summary of the experimental results obtained for the weak aromatic acids tested (mono-, di- and tri-substituted benzenes). The log D values that had been determined in our laboratory (a flow ratiometry [10] and a volume ratiometry [11,14]) ware also listed; literature values of log K_D [2,15] and pK_a [16,17] were footnoted. The experimental pH for each distribution equilibrium was lower than the pK_a of an analyte by 1.9 unit or more except for pH 9.70 for phenol. This means the dissociation of the analyte in aqueous phase is virtually negligible. As expected, the log D values obtained were in good agreement with the literature values of log K_D by taking into account that the difference up to 0.3 in log K_D is allowable [5]. By the same reason, the difference in log D among experimental setups (A/O, A/A, O/O or O/A systems; see the footnote in Table 2) seems to be in allowable range. However, as for *o*-nitrophenol, which has the highest K_D value among the compounds, its log D value was not measurable in the A/A system though we tried repeatedly. The error arising from the fact that the most of the molecules in aqueous phase move to chloroform phase may responsible for this result. The log D of phenol (0.094 ~ 0.132) at pH 9.7 was considerably lower than its log K_D (0.27~0.44) [2,15]. These values are, however, quite reasonable. That is, the theoretical value of log D at the pH, calculated from the well-known equation $D = K_D\ (1 + K_a / [H^+]_{aq})^{-1}$, is 0.130. As for the effect of plot type, the A-type plot was the best in linearity in most cases. However, log D values obtained were almost the same irrespective of differences in the types of plots.

Table 2 The log D determined by a flow ratiometry

Analyte	pH	System*	C_{ai} or C_{oi} / mmol dm^{-3}	n	A-type plot log D±$s.d.$	B-type plot log D±$s.d.$	C-type plot log D±$s.d.$	Log D** (our previous works)
Phenol	5.00	A/O	0.1-1.0	9	0.372±0.010	0.374±0.005	0.371±0.012	0.353[f], 0.387[b1]
	5.00	A/A	0.1	3	0..383±0.005	0.342±0.007	0.374±0.005	0.368[f], 0.390[b1]
	5.00	O/A	1.0	6	0.362±0.009	0.377±0.001	0.367±0.006	
	5.00	O/O	1.0	11	0.388±0.018	0.385±0.016	0.387±0.016	
	2.25	A/O	1.0	3	0.351±0.010	0.361±0.003	0.358±0.006	
	9.70	A/O	1.0	3	0.132±0.004	0.094±0.002	0.117±0.003	
o-Nitrophenol	5.00	A/O	0.5	3	2.63±0.82	2.04±0.26	2.07±0.28	2.07[b1], 2.56[b2]
	5.00	A/A	0.5		Not measurable	Not measurable	Not measurable	
p-Nitrophenol	5.00	A/O	0.1	8	0.168±0.015	0.162±0.008	0.164±0.009	0.087[f], 0.114[b1]
	5.00	A/A	0.1	15	0.255±0.011	0.255±0.007	0.253±0.010	0.361[b2]
o-Chlorophenol	5.00	A/O	0.1	10	1.47±0.06	1.45±0.06	1.45±0.06	1.51[b1]
	5.00	A/A	0.1	7	1.58±0.13	1.58±0.09	1.58±0.09	1.02[b2]
p-Chlorophenol	5.00	A/O	1.0	4	0.918±0.047	0.914±0.023	0.915±0.024	0.921[f], 1.01[b1]
	5.00	A/A	1.0	5	0.947±0.019	0.937±0.016	0.939±0.015	1.05[b2]
p-Hydroxybenzaldehyde	5.00	A/O	0.1	3	-0.205±0.009	-0.207±0.009	-0.206±0.009	-0.199[b1]
	5.00	A/A	0.1	8	-0.211±0.011	-0.214±0.012	-0.212±0.011	-0.112[b2]
Vanillin	5.00	A/O	0.1	8	1.35±0.17	1.31±0.14	1.31±0.14	1.23[b1]
	5.00	A/A	0.1-1.0	11	1.26±0.06	1.31±0.02	1.30±0.02	1.19[b2]
Benzoic acid	2.25	A/O	0.1	3	0.469±0.027	0.473±0.030	0.475±0.034	
p-Anisic acid	2.25	A/O	0.1	3	0.941±0.005	0.937±0.011	0.937±0.010	

*: the phase in which an analyte is dissolved / the phase in which the analyte is measured. A, Aqueous phase; O, organic phase.

**: mean of log D values obtained through the A-, B- and C-type plots. f, a flow ratiomaetry [10]; b1 and b2, a volume ratiometry [11,14].

Literature values of log K_D: phenol, 0.27, 0.34, 0.36, 0.37, 0.38, 0.41, 0.44 [15], 0.367, 0.387, 0.396 [2]; *o*-nitrophenol, 2.35, 2.54 [15]; *p*-nitorophenol, 0.08, 0.20, 0.27 [15], 0.21, 0.22, 0.25 [2]; *o*-chlorophenol, 1.36 [15]; *p*-chlorophenol, 0.93, 1.01 [15]; *p*-hydroxybenzaldehyde, -0.15, -0.12 [15], -0.22, -0.19, -0.13 [2]; vanillin (= *p*-hydroxy-*m*-methoxybenzaldehyde), 1.42, 1.42 [15]; benzoic acid, 0.30, 0.46, 0.50, 0.54, 0.71 [15], 0.42, 0.62 [2]; *p*-anisic acid (= *p*-methoxybenzoic acid), 0.90, 1.48 [15]. The pK_a values of these compounds at 25℃are 9.82, 7.05, 6.90, 8.29, 9.14, 7.65 [16], 7.40 [17], 4.20 and 4.48 [16], respectively. Analytical wavelength used for these compounds were 270, 353, 308, 273, 281, 273, 274, 273 and 256 nm, respectively.

4.3 Effect of dimmer formation

It is known that benzoic acid easily forms dimmers in organic phase. The dimerization constants (K_d = [dimmer] / [monomer]^2) of benzoic acid in water-saturated chloroform are 120.5, 47.6 and 31.2 mol^{-1} dm^3 at 15, 35 and 45 ℃, respectively [18]. If the dissociation of an analyte in aqueous phase can be neglected and the polymerization of analyte in organic phase is limited to dimmer formation, the following equation is obtained instead of Eq. (2).

$$A_o = k_o R_f^{-1} \{C_{ai} + [1 + K_D R_f - ((R_f^2 + 8 K_D R_f C_{ai}) K_D^2 + 2 R_f K_D + 1)^{0.5}] (4 K_D^2 K_d R_f)^{-1}\} \quad (6)$$

A simulation was carried out for benzoic acid in A/O system in the R_f range of 0.3269～1.6584, where C_{ai}, k_o and log K_D were set at 0.1 mmol dm^{-3} (present experimental condition) and 1 cm^{-1} mol^{-1} dm^3 (= 1 m^2 dmol^{-1}) and 0.5 (the median of the literature values [2,15]), respectively. In the calculation, 84.35 mol^{-1} dm^3 was adopted for K_d at 25 ℃ (approximate experimental condition). This value was obtained through a linear interpolation between the above-mentioned K_d values. The values of log D obtained from the A-, B- and C-type plots were 0.5133, 0.5152 and 0.5147, respectively. The values were slightly higher than the log K_D (0.5) by *ca.* 3.0 %. When higher C_{ai} was adopted, the error arising from the dimmer formation became more significant beyond allowable range. The calculated values for C_{ai} = 1 and 10 mmol dm^{-3} were 0.6091 ～ 0.6228 and 0.9585 ～ 0.9958 (depending on the types of plots), respectively. Likewise, such the simulations were possible for other systems. The log D values obtained from the three linear plots deviated downward from log K_D for A/A system and did so upward for O/A and O/O systems with an increase in the initial concentration of analyte.

The dimerization constants of other compounds in water saturated chloroform are not available as far as we know, the effect of dimerization on log D at the present experimental conditions seemed not so critical for the compounds tested. That is, the obtained log D values of phenol at C_{ai} = 0.1, 0.5 and 1.0 mmol dm^{-3} in A/O system were 0.3766, 0.3770 and 0.3650 (the mean of the values obtained from three kinds of linear plots), respectively. These results indicate the insensitivity

of log D to C_{ai} so long as C_{ai} is sufficiently low as in the present study.

5. Conclusion

In conclusion, the present method is rather simple and rapid (< 10 min / determination) with satisfactory precision. The method has an advantage of requiring no information on the initial and final concentrations of analyte. The information needed is the flow ratios (R_f) and the absorbance of analyte in either of the phases, so long as the absorbance is proportional to the analyte concentration. The present method is useful to estimate the K_D of compounds having moderate K_D values.

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