Separation Science and Technology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713708471

The Effect of Mutual Solubility on the Distribution of the Methylene Group between Different Organic Solvents and Water

S. S. Davis[a]
[a] PHARMACEUTICS RESEARCH GROUP PHARMACY DEPARTMENT, UNIVERSITY OF ASTON IN BIRMINGHAM GOSTA GREEN, BIRMINGHAM, UNITED KINGDOM

To cite this Article Davis, S. S.(1975) 'The Effect of Mutual Solubility on the Distribution of the Methylene Group between Different Organic Solvents and Water', Separation Science and Technology, 10: 1, 1 — 20
To link to this Article: DOI: 10.1080/00372367508057064
URL: http://dx.doi.org/10.1080/00372367508057064

SEPARATION SCIENCE, 10(1), pp. 1–20, 1975

The Effect of Mutual Solubility on the Distribution of the Methylene Group between Different Organic Solvents and Water

S. S. DAVIS

PHARMACEUTICS RESEARCH GROUP
PHARMACY DEPARTMENT
UNIVERSITY OF ASTON IN BIRMINGHAM
GOSTA GREEN, BIRMINGHAM B4 7ET, UNITED KINGDOM

Abstract

The contribution of the methylene group to the distribution coefficient ($\Delta \log K_D/CH_2$) has been obtained for 38 different solvents. For nonpolar solvents $\Delta \log K_D/CH_2$ is in the range 0.60 to 0.64, whereas for polar solvents it is in the range 0.33 to 0.58. Attempts have been made to correlate group values with solvent polarity, and it is found that the solubility of water in the organic solvent phase has a profound effect. Equations are derived from the three-suffix Margules equation for a ternary system that relate $\Delta \log K_D/CH_2$ to mole fraction solubility of water. The agreement between theoretical and experimental values is good for the case of alcohol solvents. Correlations with the empirical solvent polarity parameter of Reichardt are also examined.

INTRODUCTION

The distribution behaviors of various organic functional groups have been studied in detail recently by Davis and others (*1–4*). It is now well established that the free energy of transfer of a solute between water and organic solvent is an additive function of the contributions from each of the constituent groups. Consequently, the distribution behavior of solutes can be predicted in an a priori fashion, and such data can be applied to a wide variety of studies; for example, solvent extraction (*5–8*), structure activity relations of medicinal compounds (*9*), protein structure (*10*), ionselective electrodes (*11*) and physical organic chemistry (*12*). A critical review of the group contribution approach to solution thermodynamics has been given recently by Davis et al. (*13*).

The methylene group provides a particularly interesting case since most investigations on the effect of chemical structure on physicochemical and biochemical properties, etc., consider a homologous series. Davis et al. (*1*) obtained values for the free energy of transfer of the CH_2 group from water to various organic solvents. Differences in group contribution were rationalized in terms of solvent polarity, and for nonpolar solvents group values could be predicted using an equation developed from the solubility parameter concept of Hildebrand and Scott (*14*, *15*). A similar equation has been presented by Tanaka et al. (*7*, *16*).

This paper considers the methylene group in further detail. Fifty-one new group contribution values have been abstracted from the literature, and we can now consider the distribution of the CH_2 group between water (or aqueous buffer) and 38 different organic solvents. Many of these solvents cannot be considered as being truly immiscible with water. Consequently the derived group contributions are affected by mutual solubility. It should be possible to determine from activity coefficient equations for ternary systems the extent to which mutual solubility influences the group contribution. In addition, correlation between group values and empirical solvent polarity parameters (*17*) is investigated.

GROUP CONTRIBUTION VALUES FOR THE DISTRIBUTION OF THE METHYLENE GROUP (Δ LOG K_D/CH_2)

Table 1 lists group contribution values ($\Delta \log K_D/CH_2$) for the CH_2 under 38 solvent headings ranging from nonpolar to polar solvents. The original partition data in the literature were examined critically for consistency and analytical accuracy. Where necessary, the data were corrected for solute association in the organic phase and ionization in the aqueous phase (*18*). By this procedure a list of preferred group values can be built up. For each solvent, mutual solubility values for water have been calculated in mole fraction units from literature data (*19*, *20*) or direct experimental measurement (Karl Fischer method for water in organic solvents). Solvent polarity has been characterized by the E_T parameter of Reichardt (*17*, *21*, *22*).

It is clear from Table 1 that the group contribution for the CH_2 group for nonpolar solvents is in the region of 0.60 to 0.64, but as the solvent becomes more polar the group contribution falls. The distribution coefficient K_D can be defined in terms of activity coefficients at infinite dilution

TABLE 1

Log K_D/CH_2 Values, Mutual Solubility Data (*19*, *20*), and Solvent Polarity Values (E_T) (*17*, *21*, *22*)

Solvent[a]	Solute	Group value Δ log K_D/CH_2[b]	Refs.
1. Hexane			
$x_B = 1.000$	Alkylaminobenzoates	0.66**[c]	*23*
$x_{B'} = 0.0053$	Alkyl compounds	0.62	
$E_T = 30.9$		0.64[d]	*24*
2. Heptane			
$x_B = 1.000$	Organophosphorous compounds	0.66[c]	*25*
$x_{B'} = 0.002$			
	Alkanols and alkylamines	0.64[c]	*25a*
	Alkanoic acid salts	0.62	*26*
	Alkanoic acid salts	0.62[c]	*27*
	Alkanoic acid salts	0.59[c]	*20*
		0.63	
3. Octane			
$x_B = 1.000$	Alkyl pyridines	0.67	*28*
$x_{B'} = 0.004$	Alkyl compounds	0.62	*24*
$E_T = 30.5$	Alkanoic acids and alkanols	0.57*	*29*, *30*
		0.62	
4. Dodecane			
$x_B = 1.000$	Alkanoic acids and alkanols	0.57*	*29*, *30*
$x_{B'} = 0.000$			
5. Hexadecane			
$x_B = 1.000$	Alkylpyridines	0.64	*28*
$x_{B'} = 0.000$	Alkanoic acids and alkanols	0.57*	*29*, *30*
		0.61	
6. Cyclohexane			
$x_B = 1.000$	Organophosphorous compounds	0.66[c]	*25*
$x_{B'} = 0.000$	Conjugated heterenoids and *n*-alkyl compounds	0.65	*31*, *32*
$E_T = 31.2$			
	Alkyl phenols and alkyl esters	0.64	*33*
	Dialkyl phenols	0.63[c]	*34*
	Alkyl amines	0.63[c]	*12*
	Alkanols	0.62[c]	*20*
		0.64	
7. Benzene			
$x_B = 0.9981$	Alkanoic acids	0.64	*1*
$x_{B'} = 0.0028$	Alkanoic acids	0.64[c]	*20*
$E_T = 34.5$	Alkanols	0.60	*35*
	Alkanoic acids	0.60[c]	*7*
	Alkanols	0.58[c]	*20*
		0.61	

(*continued*)

TABLE 1 (*continued*)

Solvent[a]	Solute	Group value $\Delta \log K_D/CH_2$[b]	Refs.
8. Toluene			
$x_B=1.000$ $x_{B'}=0.00168$	Organosphosphorous compounds	0.66^c	*25*
$E_T=33.9$	Alkanoic acids	0.60	*1*
		0.63	
9. Xylene			
$x_B=1.000$	Alkanoic acids	0.55	*1*
$x_{B'}=0.0024$	Alkyl amines	0.54	*36*
$E_T=33.2$	Alkanoic acids	0.54^c	*20*
		0.54	
10. Methylene dichloride			
$x_B=0.9972$	Primary alkyl amines	0.63	*37*
$x_{B'}=0.0093$	Secondary alkyl amines	0.61	*37*
$E_T=41.1$	Alkylamines	0.58	*38*
		0.60	
11. Chloroform			
$x_B=0.9987$	Alkyl pyridines	0.66	*39*
$x_{B'}=0.0048$	Alkanoic acids	0.64	*40*
$E_T=39.1$	Alkyl sulfates	0.64	*41*
	Alkanoic acids	0.63^c	*20*
	Alkanoic acids	0.62	*1*
	Alkyl sulfates	0.61	*42*
	Barbituric acids	0.61	*43*
	Organophosphorous compounds	0.60^c	*25*
	Dialkyl phosphates	0.60^c	*44*
	Alkyl amines	0.60	*38*
		0.62	
12. Carbon tetrachloride			
$x_B=1.000$ $x_{B'}=0.0084$	Organophosphorous compounds	0.66^c	*25*
$E_T=32.5$	Alkyl pyridines	0.65	*28*
	Alkanols	0.65^c	*20*
	Alkanoic acids	0.62	*1*
	Alkanoic acids	0.57^c	*20*
		0.63	
13. 1, 2-Dichloroethane			
$x_B=0.9985$	Alkanoic acids	0.60^c	*7*
$x_{B'}=0.008$			
$E_T=42.3$			
14. Diethyl ether			
$x_B=0.9846$	Alkanols	0.60^c	*20*
$x_{B'}=0.0579$	Alkanols	0.57^c	*45*
$E_T=34.4$	Alkanoic acids	0.57	*1*

(*continued*)

TABLE 1 (*continued*)

Solvent[a]	Solute	Group value Δ log K_D/CH_2[b]	Refs.
	Alkyl amines	0.56	*46*
	Alkanoic acids	0.55	*47*
		0.57	
15. Isopropyl ether			
$x_B=0.9978$	Alkanoic acids	0.64[c]	*45*
$x_{B'}=0.0315$	Alkanoic acids	0.62	*48*
$E_T=34.0$	Alkanoic acids	0.60	*47*
	Dialkyl phosphates	0.57[c]	*44*
	Alkanoic acids	0.56	*7*
	Alkanoic acids	0.53	*20*
		0.59	
16. Dibutyl ether			
$x_B=1.000$	Alkylpyridines	0.64	*28*
$x_B'=0.0129$	Organophosphorous compounds	0.56[c]	*25*
$E_T=33.4$			
		0.60	
17. 1-Butanol			
$x_B=0.9808$	Alkanoic acids	0.44	*1*
$x_{B'}=0.5128$	Alkanoic acids	0.44	*47*
$E_T=50.2$	Alkanoic acids	0.44[c]	*20*
		0.44	
18. 2-Butanol			
$x_B=0.9664$	Alkanoic acids	0.44	*1*
$x_{B'}=0.7647$	Alkanoic acids	0.35	*47*
$E_T=48.5$	Alkanoic acids	0.33[c]	*20*
		0.37	
19. Isobutanol			
$x_B=0.9737$	Alkanoic acids	0.47[c]	*20*
$x_{B'}=0.4558$	Alkanoic acids and esters	0.45	*49*
$E_T=49.0$	Alkanoic acids	0.44	*1*
	Sulfonamides	0.41[c]	*50*
		0.44	
20. 1-Pentanol			
$x_B=0.9954$	Alkanoic acids	0.52[c]	*20*
$x_{B'}=0.2831$	Alkanoic acids	0.50	*47*
$E_T=46.5$		0.51	
21. 2-Pentanol			
$x_B=0.9905$	Alkanoic acids	0.43[c]	*20*
$x_{B'}=0.3957$	Dialkyl phosphates	0.47[c]	*44*
		0.45	
22. 2-Methyl-2-butanol			
$x_B=0.9753$	Alkanoic acids	0.43	*47*
$x_{B'}=0.6004$			

(*continued*)

TABLE 1 (*continued*)

	Solvent[a]	Solute	Group value Δ log K_D/CH_2[b]	Refs.
23.	4-Methyl-2-pentanol			
	$x_B=0.9970$	Alkanoic acids	0.54	*51*
	$x_{B'}=0.2779$	Dialkyl phosphates	0.47[c]	*44*
			0.50	
24.	1-Octanol			
	$x_B=0.9994$	Alkyl pyridines	0.59	*39*
	$x_{B'}=0.2680$	Alkanols	0.57[c]	*20*
	$E_T=43.5$	Alkanoic acids	0.54[c]	*20*
		Alkanoic acids	0.50	*52*
		Alkyl compounds	0.50	*53*
		Alkyl esters	0.50	*54*
		Alkanols, alkanones, and alkyl esters	0.50	*55*
			0.53	
25.	2-Ethyl hexyl alcohol			
	$x_B=0.9992$	Alkanoic acids	0.56[c]	*7*
	$x_{B'}=0.16$			
26.	6-Methyl heptanol	Alkanoic acids	0.61[c]	*56*
27.	Oleyl alcohol			
	$x_B=1.000$	Alkanoic acids	0.58[c]	*52*
	$x_{B'}=0.2218$	Tetracaine homologs	0.51[c]	*57*
			0.55	
28.	Ethyl acetate			
	$x_B=0.9823$	Alkanoic acids	0.48	*47*
	$x_{B'}=0.1307$	Alkanoic acids	0.45[c]	*20*
	$E_T=37.9$	Alkanoic acids	0.43[c]	*48*
			0.45	
29.	Pentyl acetate			
	$x_B=0.9997$	Aminobenzoate esters	0.62[c]	*58*
	$x_{B'}=0.0776$			
30.	2-Butanone			
	$x_B=0.9269$	Alkanoic acids	0.33	*47*
	$x_{B'}=0.3080$			
	$E_T=41.3$			
31.	3-Pentanone			
	$x_B=0.9920$	Alkanoic acids	0.33	*47*
	$x_{B'}=0.1130$			
32.	4-Methyl-2-pentanone			
	$x_B=0.9969$	Alkanoic acids	0.54	*51*[c]
	$x_{B'}=0.0973$	Dialkyl phosphates	0.51	*44*
		Organophosphorous compounds	0.50	*25*
			0.52	

(*continued*)

TABLE 1 (*continued*)

Solvent[a]	Solute	Group value $\Delta \log K_D/CH_2$[b]	Refs.
33. Methyl cyclohexanone			
$x_B=0.999$	Alkanoic acids	0.55	*48*
$x_{B'}=0.16$			
$E_T=40.8$			
34. Nitrobenzene			
$x_B=0.9998$	Alkanoic acids	0.54[c]	*7*
$x_{B'}=0.0121$	Alkanoic acids	0.51[c]	*20*
$E_T=42.0$	Dialkyl phosphates	0.50[c]	*44*
	Alkanoic acids	0.48	*1*
		0.51	
35. Nitrotoluene			
$x_B=1.000$	Alkanoic acids	0.52[c]	*20*
$x_{B'}=0.007$	Alkanoic acids	0.47[c]	*1*
$E_T=42.0$		0.50	
36. Silicone oil			
$x_B=1.000$	Alkylamino benzoates	0.54**,[c]	*23*
$x_{B'}=0.0047$			
37. Olive oil			
$x_{B'}=0.11$	Alkanols	0.53	*59*
38. Triolein			
$x_{B'}=0.19$	Alkanols	0.55[c]	*60*

[a] x_B is the quantity (mole fraction) of water in the aqueous phase, and $x_{B'}$ is the quantity (mole fraction) of water in the organic phase.

[b] All group values refer to 25 °C except those marked *, which are for 20 °C, and those marked **, which are for 37 °C.

[c] New value, not included in compilation of Davis et al. (1)

[d] Mean group value

(pure solute as standard state)

$$K_D = \gamma^\infty \text{ water}/\gamma^\infty \text{ oil} \tag{1a}$$

and

$$\Delta \log K_D/CH_2 = \Delta \log \gamma^\infty/CH_2/\text{water} - \Delta \log \gamma^\infty/CH_2/\text{oil} \tag{1b}$$

Davis et al. (*1*) have studied the methylene group contributions to the activity coefficient of solutes in water. They found that for 28 solutes

$$\Delta \log \gamma^\infty/CH_2/\text{water} = 0.62 \pm 0.03 \tag{2a}$$

Thus for inert solvents we have

$$\Delta \log \gamma^\infty/CH_2/\text{oil} = 0 \tag{2b}$$

and

$$\Delta \log K_D/\mathrm{CH}_2 = \Delta \log \gamma^\infty/\mathrm{CH}_2/\mathrm{water} \tag{2c}$$

The driving force for the transfer of the CH_2 group from water to nonpolar solvents can be attributed entirely to the interaction of the group with water (*5*). For polar-associated solvents such as the alkanols, we would expect that $\Delta \log \gamma^\infty/\mathrm{CH}_2/\mathrm{oil} > 0$ and $\Delta \log K_D/\mathrm{CH}_2$ will fall. Unfortunately, the available data on the activity coefficients of homologous solutes in the organic solvents listed in Table 1 are almost nonexistant and no reliable $\Delta \log \gamma^\infty/\mathrm{CH}_2/\mathrm{oil}$ values can be calculated.

Not only will the group contribution be affected by the nonideality of the CH_2 group in the oil, but also for many of the solvents the Nernst condition of solvent immiscibility is far from met. In a number of cases the organic solvent contains more water than oil when mutual solubility values are calculated on a mole fraction basis!

THE EFFECT OF SOLVENT MISCIBILITY ON GROUP CONTRIBUTIONS TO THE DISTRIBUTION COEFFICIENT

When the two solvents are miscible, one with the other, Eq. (1) is no longer valid. Instead, we must consider the ratio of the activity coefficients of the solute in the two phases as modified by the presence of the other phase. That is, we must consider "solvent rich" phases and activity coefficients at infinite dilution for ternary mixtures. A number of different equations are available whereby such activity coefficients can be calculated, but not all are suitable for the present purpose (*61–64*). We will employ the three-suffix Margules equation.

Let the solute to be distributed = A, and the two solvents B and C. x is the mole fraction solubility.

Three different cases will be considered.

1. The General Case

The activity coefficient of Solute A in the ternary system A, B, and C can be written as (*61*, *63*)

$$\begin{aligned}\log \gamma_{\mathrm{A}}^\infty = {} & x_{\mathrm{B}}^2 [\log \gamma_{\mathrm{AB}}^\infty + 2x_{\mathrm{A}}(\log \gamma_{\mathrm{BA}}^\infty - \log \gamma_{\mathrm{AB}}^\infty)] \\ & + x_{\mathrm{C}}^2[\log \gamma_{\mathrm{AC}}^\infty + 2x_{\mathrm{A}}(\log \gamma_{\mathrm{CA}}^\infty - \log \gamma_{\mathrm{AC}}^\infty)] \\ & + x_{\mathrm{B}}x_{\mathrm{C}}[\log \gamma_{\mathrm{BA}}^\infty + \log \gamma_{\mathrm{AC}}^\infty - \log \gamma_{\mathrm{CB}}^\infty] \\ & + 2x_{\mathrm{A}}(\log \gamma_{\mathrm{CA}}^\infty - \log \gamma_{\mathrm{AC}}^\infty) \\ & + 2x_{\mathrm{C}}(\log \gamma_{\mathrm{CB}}^\infty - \log \gamma_{\mathrm{BC}}^\infty) - T(1 - 2x_{\mathrm{A}})\end{aligned} \tag{3}$$

where T is a ternary constant. At low dilution $x_A \to 0$. Then

$$\begin{aligned}\log \gamma_A^\infty &= x_B^2(\log \gamma_{AB}^\infty) + x_C^2(\log \gamma_{AC}^\infty)\\ &\quad + x_B x_C[(\log \gamma_{BA}^\infty + \log \gamma_{AC}^\infty - \log \gamma_{CB}^\infty)\\ &\quad + 2x_C(\log \gamma_{CB}^\infty - \log \gamma_{BC}^\infty) - T]\end{aligned} \tag{4}$$

Consider two separate cases: (a) B-rich phase and (*b*) C-rich phase. Let x_B, x_C, be the mole fraction of the two solvents for (*a*) and $x_{B'}$, $x_{C'}$ the mole fractions for (*b*).

The distribution coefficient K_D can be defined as

$$K_D = \gamma_{AB}^\infty/\gamma_{AC}^\infty \tag{5}$$

Then

$$\begin{aligned}\log K_D &= \log \gamma_{AB}^\infty(x_B^2 - x_{B'}^2) + \log \gamma_{AC}^\infty(x_C^2 - x_{C'}^2)\\ &\quad + (\log \gamma_{BA}^\infty + \log \gamma_{AC}^\infty - \log \gamma_{CB}^\infty)(x_B x_C - x_{B'} x_{C'})\\ &\quad + (\log \gamma_{CB}^\infty - \log \gamma_{BC}^\infty)(2x_C^2 x_B - 2x_{C'}^2 x_{B'})\\ &\quad + T(x_{B'} x_{C'} - x_B x_C)\end{aligned} \tag{6}$$

The group contribution for a functional group X is defined as

$$\Delta \log K_{D/X} = \log K_{D/RX} - \log K_{D/RH} \tag{7}$$

Then if the presence of Solute A does not affect x_B, x_C; $x_{B'}$, $x_{C'}$; or γ_{BC}^∞ and γ_{CB}^∞, we can write

$$\begin{aligned}\Delta \log K_{D/X} &= (\Delta \log \gamma_{AB}^\infty)(x_B^2 - x_{B'}^2) + (\Delta \log \gamma_{AC}^\infty)(x_C^2 - x_{C'}^2)\\ &\quad + (x_B x_C - x_{B'} x_{C'})(\Delta \log \gamma_{BA}^\infty - \Delta \log \gamma_{AC}^\infty)\\ &\quad + \Delta T(x_{B'} x_{C'} - x_B x_C)\end{aligned} \tag{8}$$

The ternary constant T can be written as (*63, 65*)

$$\begin{aligned}T = \frac{1}{2}(&\log \gamma_{BA}^\infty - \log \gamma_{AB}^\infty + \log \gamma_{AC}^\infty\\ &- \log \gamma_{CA}^\infty + \log \gamma_{CB}^\infty - \log \gamma_{BC}^\infty)\end{aligned} \tag{9}$$

Therefore

$$\Delta T = \frac{1}{2}(\Delta \log \gamma_{BA}^\infty - \Delta \log \gamma_{AB}^\infty + \Delta \log \gamma_{AC}^\infty - \Delta \log \gamma_{CA}^\infty) \tag{10}$$

The true distribution coefficient in the absence of solvent miscibility is

$$\log K_{D\,\text{true}} = \log \gamma_{AB}^\infty - \log \gamma_{AC}^\infty \tag{11}$$

Hence we can substitute for log $\gamma^{\infty}_{\mathrm{AC}}$ in Eqs. (8) and (10) and solve for log $K_{D\,\mathrm{true}}$, knowing that $x_{\mathrm{C}} = (1 - x_{\mathrm{B}})$

$$\Delta \log K_{D\,\mathrm{true}} = \frac{[2\Delta \log K_{D\,\mathrm{app}} + (\Delta \log \gamma^{\infty}_{\mathrm{CA}} + \Delta \log \gamma^{\infty}_{\mathrm{BA}} - 6\Delta \log \gamma^{\infty}_{\mathrm{AB}})(x_{\mathrm{B}}^2 - x_{\mathrm{B'}}^2 - x_{\mathrm{B}} + x_{\mathrm{B'}})]}{(7x_{\mathrm{B}} - 7x_{\mathrm{B'}} - 5x_{\mathrm{B}}^2 + 5x_{\mathrm{B'}}^2)} \tag{12}$$

where $K_{D\,\mathrm{app}}$ is the observed distribution coefficient. Note for immiscible solvents

$$x_{\mathrm{B}} = 1, \qquad x_{\mathrm{B'}} = 0$$

and

$$\Delta \log K_{D\,\mathrm{true}} = \Delta \log K_{D\,\mathrm{app}} \tag{13}$$

Consider the methylene group. Davis et al. (*1*) have shown that

$$\Delta \log \gamma^{\infty}/\mathrm{CH_2}/\mathrm{water}\ (= \Delta \log \gamma^{\infty}_{\mathrm{AB}}) = 0.62$$

Values for $\Delta \log \gamma^{\infty}_{\mathrm{BA}}$ ($\Delta \log \gamma^{\infty}$/water/$\mathrm{CH_2}$) and $\Delta \log \gamma^{\infty}_{\mathrm{CA}}$ ($\Delta \log \gamma^{\infty}$/oil/$\mathrm{CH_2}$) have not been reported. Approximate estimates of these contributions can be made from published activity coefficient data (*24*, *66*) (Table 2). We find that $\Delta \log \gamma^{\infty}_{\mathrm{BA}} = 0.11$ and $\Delta \log \gamma^{\infty}_{\mathrm{CA}}$ ranges from $+0.12$ to -0.15. It is not possible to find values for all the solvents in Table 1 and, consequently, we have calculated a weighted mean of -0.05 for $\Delta \log \gamma^{\infty}_{\mathrm{CA}}$. This indicates that the activity coefficients for the solvents in Table 1, when present as solutes at infinite dilution in homologous solvents, are almost unaffected by an increase in the chain length of the solvent.

From Eq. (12) we can write:

$$\Delta \log K_{D\,\mathrm{true}} = \frac{2\Delta \log K_{D\,\mathrm{app}} - 3.66(x_{\mathrm{B}}^2 - x_{\mathrm{B'}}^2 - x_{\mathrm{B}} + x_{\mathrm{B'}})}{(7x_{\mathrm{B}} - 7x_{\mathrm{B'}} - 5x_{\mathrm{B}}^2 + 5x_{\mathrm{B'}}^2)} \tag{14}$$

2. The Symmetrical Case

If the system is symmetrical in terms of the activity coefficients contributions for both phases, i.e.,

$$\Delta \log \gamma^{\infty}_{\mathrm{BA}} = \Delta \log \gamma^{\infty}_{\mathrm{AB}}$$

$$\Delta \log \gamma^{\infty}_{\mathrm{AC}} = \Delta \log \gamma^{\infty}_{\mathrm{CA}}$$

or that the sum of the $\Delta \log \gamma^{\infty}$ values in Eq. (10) is zero, then $\Delta T = 0$,

TABLE 2

Group Contributions to Activity Coefficients for the Methylene Group (γ^∞/water/CH_2 and γ^∞/oil/CH_2)[a]

Solute	Solvent	log γ^∞
	Δ log γ^∞/water/CH_2	
Water	Alkanols (C_1–C_4)	0.11
Water	Alkanones (C_3–C_7)	0.11
	Δ log γ^∞/oil/CH_2	
Hexane	Alkanes (C_{12}–C_{17})	−0.02
Heptane	Alkanes (C_{16}–C_{18})	−0.03
Octane	Alkanes (C_{18}–C_{24})	−0.04
Hexadecane	Alkanes (C_6–C_7)	+0.02
Cyclohexane	Alkanes (C_6–C_7)	0.00
Benzene	Alkanes (C_5–C_6)	−0.01
	Alkanols (C_1–C_4)	−0.03
	Alkanones (C_3–C_4)	−0.15
Toluene	Alkanes (C_6–C_8)	0.00
	Alkanones (C_2–C_3)	0.00
Xylene	Alkyl esters (C_{14}–C_{16})	0.00
Chloroform	Alkanols (C_1–C_4)	−0.05
Carbon tetrachloride	Alkanes	+0.03
	Alkanols	+0.04
	Alkanones	+0.12
1-Butanol	Alkanes (C_7–C_{17})	+0.001
Isobutanol	Alkanes (C_7–C_{17})	−0.023
Ethyl acetate	Alkanols (C_1–C_3)	+0.02
2-Butanone	Alkanols (C_1–C_8)	0.00
	Alkanes (C_6–C_{16})	0.00
3-Pentanone	Alkanols (C_1–C_8)	−0.003
	Alkanes (C_7–C_{16})	−0.005
4-Methyl-2-pentanone	Alkanols (C_1–C_4)	−0.05

[a] Temperature range, 20 to 30°C.

and we can write

$$\Delta \log K_{D\mathit{true}} = \frac{\Delta \log K_{D\,\mathrm{app}} + (\Delta \log \gamma^\infty_{\mathrm{BA}} - 3\Delta \log \gamma^\infty_{\mathrm{AB}})(x_{\mathrm{B}}^2 - x_{\mathrm{B'}}^2 - x_{\mathrm{B}} + x_{\mathrm{B'}})]}{(3x_{\mathrm{B}} - 3x_{\mathrm{B'}} - 2x_{\mathrm{B}}^2 + 2x_{\mathrm{B'}}^2)} \qquad (15)$$

Substitution for Δ log γ^∞ values for the methylene group gives

$$\Delta \log K_{D\,\mathrm{true}} = \frac{\Delta \log K_{D\,\mathrm{app}} - 1.75(x_{\mathrm{B}}^2 - x_{\mathrm{B'}}^2 - x_{\mathrm{B}} + x_{\mathrm{B'}})}{(3x_{\mathrm{B}} - 3x_{\mathrm{B'}} - 2x_{\mathrm{B}}^2 + 2x_{\mathrm{B'}}^2)} \qquad (16)$$

3. Modified General Case

Wohl (*62*) has considered equations of the Margules type for ternary systems which are symmetrical and unambiguous with respect to the definition of the ternary constant. Then instead of Eq. (3) we can write (*62*, *64*)

$$\begin{aligned}\log \gamma_A = {} & x_B^2[\log \gamma_{AB}^\infty + 2x_A(\log \gamma_{BA}^\infty - \log \gamma_{AB}^\infty)] \\ & + x_C^2[\log \gamma_{AC}^\infty + 2x_A(\log \gamma_{CA}^\infty - \log \gamma_{AC}^\infty)] \\ & + x_B x_C[0.5(\log \gamma_{BA}^\infty + \log \gamma_{AB}^\infty + \log \gamma_{CA}^\infty \\ & + \log \gamma_{AC}^\infty - \log \gamma_{BC}^\infty - \log \gamma_{CB}^\infty) \\ & + x_A(\log \gamma_{BA}^\infty - \log \gamma_{AB}^\infty + \log \gamma_{CA}^\infty - \log \gamma_{AC}^\infty) \\ & + (x_B - x_C)(\log \gamma_{BC}^\infty - \log \gamma_{CB}^\infty) - (1 - 2x_A)E] \qquad (17)\end{aligned}$$

where E is a ternary constant. For low dilution of Solute A in both phases, $x_A \to 0$ and $E = 0$ (*64*), and

$$\begin{aligned}\log \gamma_A^\infty = {} & x_B^2(\log \gamma_{AB}^\infty) + x_C^2(\log \gamma_{AC}^\infty) \\ & + x_B x_C[0.5(\log \gamma_{BA}^\infty + \log \gamma_{AB}^\infty + \log \gamma_{CA}^\infty \\ & + \log \gamma_{AC}^\infty - \log \gamma_{BC}^\infty - \log \gamma_{CB}^\infty) \\ & + (x_B - x_C)(\log \gamma_{BC}^\infty - \log \gamma_{CB}^\infty)] \qquad (18)\end{aligned}$$

In a manner similar to the general case, we can consider solvent-rich phases and the group contribution to the distribution coefficient. We then obtain

$$\Delta \log K_{D\,\text{true}} = \frac{[2\Delta \log K_{D\,\text{app}} - (\Delta \log \gamma_{BA}^\infty + \Delta \log \gamma_{CA}^\infty - 2\Delta \log \gamma_{AB}^\infty)(x_{B'}^2 - x_B^2 + x_B - x_{B'})]}{(3x_B - 3x_{B'} - x_B^2 + x_{B'}^2)} \qquad (19)$$

and for the methylene group

$$\Delta \log K_{D\,\text{true}} = \frac{2\Delta \log K_{D\,\text{app}} - 1.15\,(x_B^2 - x_{B'}^2 - x_B + x_{B'})}{(3x_B - 3x_{B'} - x_B^2 + x_{B'}^2)} \qquad (20)$$

Attempts have been made to calculate $\Delta \log K_D/\text{CH}_{2\,\text{true}}$ values from Eqs. (15), (16), and (20). However, the results have been disappointing. In some cases the values exceed 0.65 for highly polar solvents, indicating incorrectly that the methylene group deviates from Raoults law in a negative way (i.e., solute-solvent interaction). The reasons for such anomolous results can be traced to the assumptions regarding symmetry, the difficulties in calculating Δ log γ^{∞} values from literature compilations, and the uncertainty in some of the reported mutual solubility data. In addition, the derived equations all contain subtraction terms that may result in a negative denominator. For example, considering a hypothetical case where Δ log K_D/CH_2 apparent = 0.40, x_B = 1.00, and $x_{B'}$ is changed from 0.0 to 0.9, we find that for Eqs. (15) and (16) the denominator has negative values at higher values of $x_{B'}$ (Fig. 1). It is concluded that before Eqs. (15), (16), and (20) can be applied to distribution data, considerable work has to be undertaken to obtain reliable activity coefficient and mutual solubility data. Moreover, it has been assumed that the presence of very small quantities of solute will not affect the mutual solubility of the solvents. This assumption may be unjustified (*67*). Equations (15), (16), and (20) can be utilized for examining the data in Table 1 if we make two approximations.

1st Approximation

Examination of the solubility data in Table 1 suggests that $x_B \simeq 1$ and therefore $x_B^2 \simeq 1$.

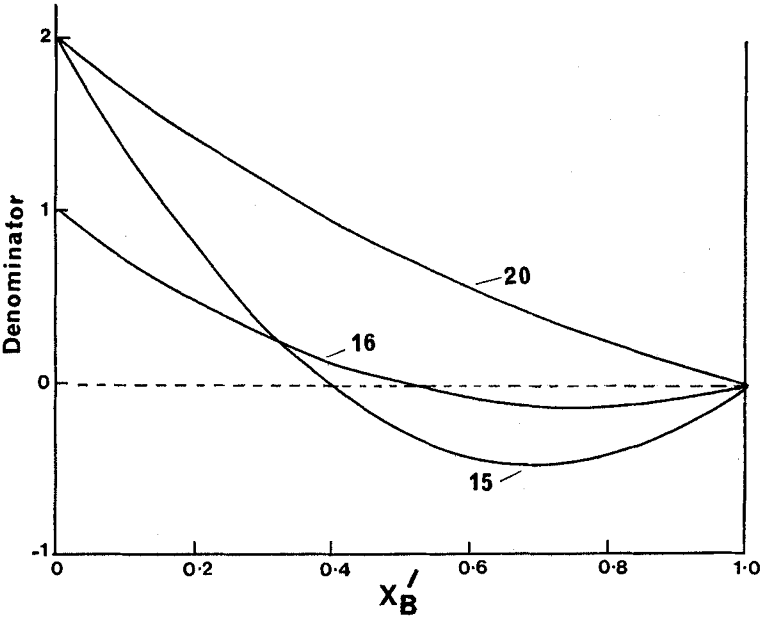

FIG. 1. The relation between the denominator in Eqs. (15), (16), and (20) and $x_{B'}$. Δ log $K_D/CH_{2\ \mathrm{app}} = 0.40$. $x_B = 1.00$.

2nd Approximation

The limited activity coefficient data available in the literature (*24*, *66*) suggests that $\Delta \log \gamma^{\infty}/\mathrm{CH_2}/\mathrm{oil} \simeq 0.0$ for most solvents. Rytting et al. have reached the same conclusion by examining distribution coefficient and solubility data (*68*). Thus we can substitute for $x_{\mathrm{B}} = x_{\mathrm{B}}^2 = 1$ and $\Delta \log K_D/\mathrm{CH}_{2\,\mathrm{true}} = 0.62$ in Eqs. (15), (16), and (20).

The resultant expressions are:

Case 1

$$\Delta \log K_D/\mathrm{CH}_{2\ \mathrm{app}} = 0.62 - 0.34x_{\mathrm{B}'} - 0.28x_{\mathrm{B}'}^2 \tag{21}$$

Case 2

$$\Delta \log K_D/\mathrm{CH}_{2\ \mathrm{app}} = 0.62 - 0.11x_{\mathrm{B}'} - 0.51x_{\mathrm{B}'}^2 \tag{22}$$

Case 3

$$\Delta \log K_D/\mathrm{CH}_{2\ \mathrm{app}} = 0.62 - 0.36x_{\mathrm{B}'} - 0.27x_{\mathrm{B}'}^2 \tag{23}$$

It is interesting to note that Cases 1 and 3 give almost identical results whereas Case 2 is rather different. In the limit of $x_{\mathrm{B}'} = 0$, $\Delta \log K_D/\mathrm{CH_2} = 0.62$, whereas when $x_{\mathrm{B}'} = 1$, $\Delta \log K_D/\mathrm{CH_2} = 0.0$.

For the majority of solvents we would expect a reasonably simple relation between the group contribution for the methylene group and the solubility of water in the organic solvent phase (expressed in mole fraction units).

Figure 2 shows the experimental $\Delta \log K_D/\mathrm{CH_2}$ values plotted against $x_{\mathrm{B}'}$ together with the theoretical relations defined by Eqs. (21) and (23) and Eq. (22). One group of solvents, consisting mainly of the alcohols follows the theoretical line quite well until $x_{\mathrm{B}'}$ exceeds 0.4. Another group of solvents comprising the ethers, ketones, and esters follows a totally different relation.

Thus for some solvents the change in group contribution to the distribution coefficients with solvent polarity can be accounted for simply by the presence of dissolved water in the solvent. This is not the case with other solvents, and the experimental points lie well below the predicted line. For such systems the value of $\Delta \log \gamma^{\infty}/\mathrm{CH_2}/\mathrm{oil}$ may be very much greater than zero.

The alcohol solvents in particular provide an interesting linear relation between $\Delta \log K_D/\mathrm{CH_2}$ and $x_{\mathrm{B}'}$ (Fig. 3). The equation of the line is

$$\Delta \log K_D/\mathrm{CH_2} = 0.62 - 0.35x_{\mathrm{B}'} \tag{24}$$

for $x_{\mathrm{B}'}$ values up to 0.8

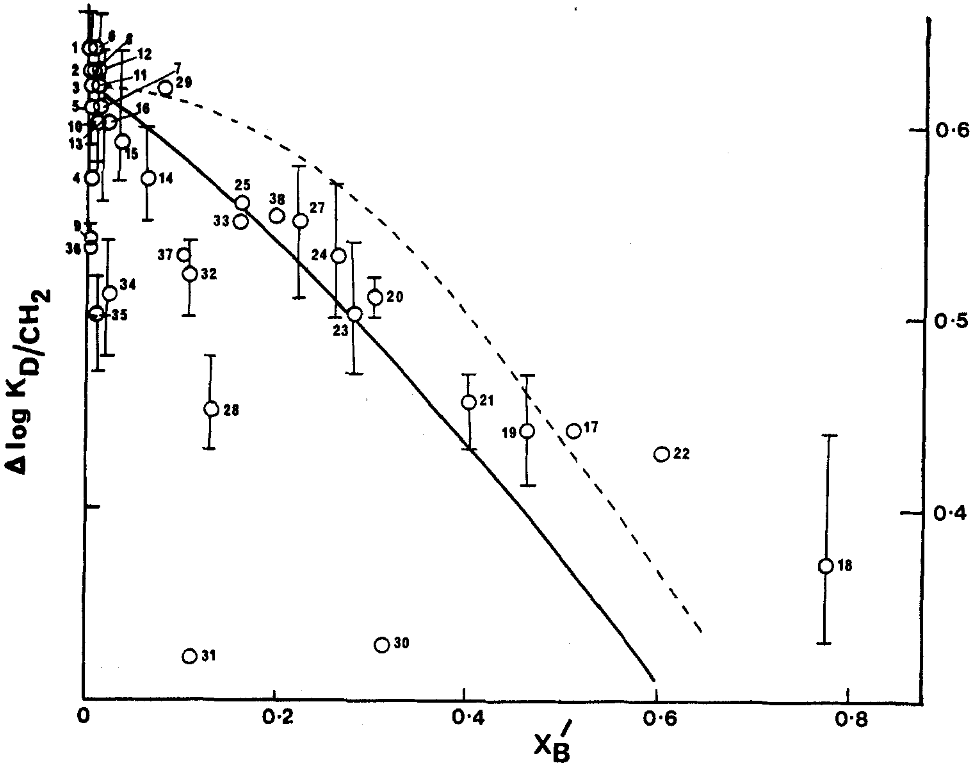

FIG. 2. The relation between $\Delta \log K_D/\mathrm{CH}_{2\,\mathrm{app}}$ and $x_{B'}$. Numbers refer to solvents listed in Table 1. Theoretical lines: (——) Eqs. (21) and (23); (- -) Eq. (22).

Many attempts have been made in the past to correlate distribution data with some physicochemical property of the organic phase. Dielectric constant, solubility parameter, and even interfacial tension data have been used; however, none has been particularly successful (*4*). The best correlations have usually been obtained between the distribution coefficient and the solubility of water in the solvent (*20*, *69*, *70*). It has been suggested that the ability of a solvent to accommodate water is a good measure of its polarity or acceptor tendency for hydrogen bonds. Polarity notwithstanding, the presence of water in the organic phase will result in the formation of a ternary system, and we would expect the distribution coefficient to change for this reason alone and not necessarily through

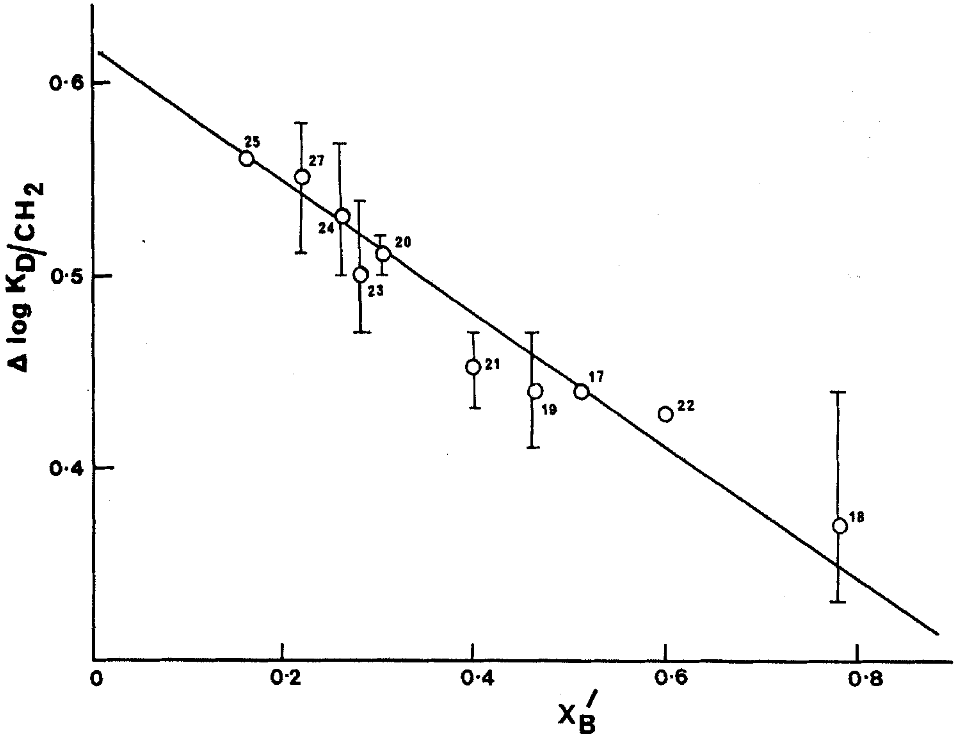

FIG. 3. The relation between $\Delta \log K_D/CH_{2\ \mathrm{app}}$ and $x_{B'}$ for alcohol solvents.

any specific solute–solvent interactions or preferred solute–solute interactions.

CORRELATION OF GROUP CONTRIBUTION VALUES WITH SOLVENT PARAMETERS

Davis and others (*1*, *15*) and Tanaka and others (*7*, *16*) have attempted to predict group contribution values for the methylene group distributed between two solvents, using the solubility parameter concept of Hildebrand and Scott (*14*). This approach was successful only for nonpolar solvents. Other correlations with dipole moment and dielectric constant have been investigated by Davis (*4*).

The polarity of a solvent will be the result of a composite of factors that can include dispersion forces, dipole forces, and specific interactions such as hydrogen bonding. It is therefore perhaps asking too much to find a single physicochemical parameter that will describe polarity. For example, Marcus (*71*) considers that many solvents will probably need more than one parameter to describe the distribution equilibrium.

An alternative approach is to determine solvent polarity by experimental measurement, working backwards from the effect of solvent on a solvent-dependent standard process (*21*). In the field of gas–liquid chromatography, Novak (*72*, *73*) has suggested that a universal criterion of the

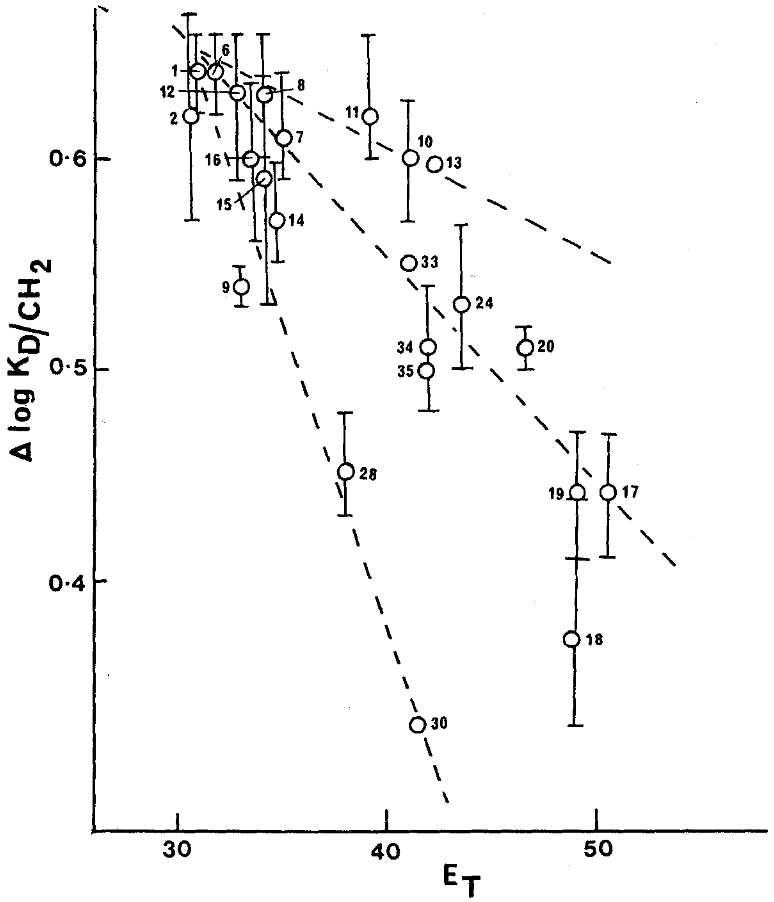

Fig. 4. The relation between Δ log $K_D/\mathrm{CH}_{2\ \mathrm{app}}$ and E_T.

polarity of sorbents is the partial excess Gibbs free energy of mixing per mole of CH_2 groups of solute. A similar polarity scale for distribution studies would therefore be the $\Delta \log K_D/CH_2$ values in Table 1! Alternatively, $\Delta \log K_D/CH_2$ values corrected for solvent immiscibility or $\Delta \log \gamma^{\infty}/CH_2/\text{oil}$ values would be suitable provided that the necessary experimental data were available.

We are thus faced with the dilemma that the best parameters for solvent polarity in distribution are probably the experimental values for $\Delta \log K_D/CH_2$ that we wish to correlate with solvent polarity!

Frolov et al. (*22*) have drawn attention to the correlation of distribution coefficients and the empirical parameters for the polarity of solvents (E_T) of Reichardt (*17*, *21*). This parameter is based on the absorption spectrum of pyridinium *N*-phenol betaine. The position of the charge transfer band (kcal/mole) is used to characterize the solvent. Such values can be used to correlate $\Delta \log K_D/CH_2$ values (Fig. 4). There is reasonably good agreement for different solvent groups. As expected from the work of Frolov et al. (*22*), the data for solvents that are strongly hydrogen bonded, the alcohols, fall on one line and, interestingly, data for the chlorinated compounds fall on another line.

It must be concluded that as yet there is no suitable single parameter to correlate and predict $\Delta \log K_D/CH_2$ values save for the $\Delta \log K_D/CH_2$ values themselves. Detailed studies on the activity coefficients of homologous solutes in various solvents should rectify the position.

REFERENCES

1. S. S. Davis, T. Higuchi, and J. H. Rytting, *J. Pharm. Pharmacol.*, *24*, 30P (1972).
2. S. S. Davis, *Ibid.*, *25*, 1 (1973).
3. S. S. Davis, *Ibid.*, *25*, 769 (1973).
4. S. S. Davis, *Ibid.*, *25*, 982 (1973).
5. D. Dryssen and D. Petkovic, *J. Inorg. Nucl. Chem.*, *27*, 1381 (1965).
6. C. Tsonopoulos and J. M. Prausnitz, *Ind. Eng. Chem. Fundam.*, *10*, 593 (1971).
7. I. Kojima, M. Yoshida, and M. Tanaka, *J. Inorg. Nucl. Chem.*, *32*, 987 (1970).
8. R. Modin and G. Schill, *Acta Pharm. Suecica*, *4*, 301 (1967).
9. C. Hansch, *Drug Design*, Vol. 1 (E. J. Ariens, ed.), Academic, New York, (1971), p. 271.
10. C. Tanford, *J. Mol. Biol.*, *67*, 59 (1972).
11. T. Higuchi, C. R. Illian, and J. L. Tossounian, *Anal. Chem.*, *42*, 1674 (1970).
12. I. H. Pitman, K. Uekama, T. Higuchi, and W. E. Hall, *J. Amer. Chem. Soc.*, *94*, 8147 (1972).
13. S. S. Davis, T. Higuchi, and J. H. Rytting, *Advan. Pharm. Sci.*, *4*, 73 (1974).
14. J. H. Hilderbrand and R. L. Scott, *Regular Solutions*, Prentice-Hall, Englewood Cliffs, New Jersey, 1962.
15. S. S. Davis, *Experientia*, *26*, 671 (1970).

16. M. Tanaka, in *Solvent Extraction. Proceedings of the International Solvent Extraction Conference, ISEC 71*, Vol. 1, SCI, London, 1971, p. 18.

17. C. Reichardt and K. Dimroth, *Fortschr. Chem. Forsch.*, *11*, 1 (1969).

18. E. A. Moelwyn-Hughes, *Physical Chemistry*, 2nd ed., Pergamon, Oxford, 1964.

19. J. A. Riddick and W. B. Bunger, *Techniques in Chemistry*, Vol. 2, *Organic Solvents Physical Properties and Methods of Purification*, 3rd ed., Wiley-Interscience, New York, 1970.

20. A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, *71*, 525 (1971).

21. C. Reichardt, *Angew. Chem.*, *77*, 30 (1965).

22. Yu. G. Frolov, A. A. Pushkov, and V. V. Sergievsky, in *Solvent Extraction. Proceedings of the International Solvent Extraction Conference, ISEC 71*, Vol. 2, SCI, London, 1971, p. 123.

23. S. H. Yalkowsky, G. L. Flynn, and T. G. Slunick, *J. Pharm. Sci.*, *61*, 852 (1972).

24. G. J. Pierotti, C. H. Deal, and E. L. Derr, *Ind. Eng. Chem.*, *51*, 95 (1959).

25. Z. Kolarik, N. V. Sistkoua, and J. Hejna, in *Solvent Extraction Research* (A. S. Kertes and Y. Marcus, eds.), Wiley-Interscience, New York, 1968, p. 59.

25a. L. P. Huston, Ph. D. Dissertation, University of Kansas, 1973.

26. D. S. Goodman, *J. Amer. Chem. Soc.*, *80*, 3887 (1958).

27. R. Smith and C. Tanford, *Proc. Nat. Acad. Sci.*, *70*, 289 (1973).

28. N. C. Yeh, Ph. D. Dissertation, University of Michigan, 1973.

29. R. Aveyard and R. W. Mitchell, *Trans. Faraday Soc.*, *65*, 2645 (1969).

30. R. Aveyard and R. W. Mitchell, *Ibid.*, *66*, 37 (1970).

31. D. J. Currie, C. E. Lough, R. F. Silver, and H. L. Holmes, *Can. J. Chem.*, *44*, 1035 (1966).

32. A. D. Delaney, D. J. Currie, and H. L. Holmes, *Ibid.*, *47*, 3273 (1969).

33. B. Krugman, M. Sc. Dissertation, University of Kansas, 1971.

34. C. K. Karr, P. A. Estep, and L. L. Hirst, *Anal. Chem.*, *32*, 463 (1960).

35. E. Hutchinson, *J. Phys. Chem.*, *52*, 897 (1948).

36. W. H. Smith, *Ibid.*, *26*, 256 (1922).

37. K. Gustavii, *Acta Pharm. Suecica*, *4*, 233 (1967).

38. G. J. Divatia and J. A. Biles, *J. Pharm. Sci.*, *50*, 916 (1961).

39. K. C. Yeh and W. I. Higuchi, *Ibid.*, *61*, 1648 (1972).

40. D. Weber, M. S. Dissertation, University of Kansas, 1969.

41. M. Mamtora, M. S. Dissertation, University of Kansas, 1969.

42. M. J. Harris, T. Higuchi, and J. H. Rytting, *J. Phys. Chem.*, *77*, 2694 (1973).

43. D. J. Lamb and L. E. Harris. *J. Amer. Pharm. Assoc* (*Sci. Ed.*), *49*, 583 (1960).

44. D. Dyrssen, S. Erberg, and D. H. Liem. *Acta Chem. Scand.*, *18*, 135 (1964).

45. E. Stockel, in *Ausgewahlte physikalische Methoden in der organischen Chemie*, Vol. 1 (G. Geiseler, ed.), Akademie-Verlag, Berlin, 1963.

46. R. Collander, *Acta Chem. Scand.*, *3*, 717 (1949).

47. R. C. Archibald, *J. Amer. Chem. Soc.*, *54*, 317 (1932).

48. A. Vignes, *J. Chem. Phys.*, *57*, 966 (1960).

49. R. Collander, *Acta Chem. Scand.*, *4*, 1085 (1950).

50. W. Scholtan, *Arzneim.-Forsch.*, *18*, 505 (1968).

51. D. E. Pearson and M. Levine, *J. Org. Chem.*, *17*, 1356 (1952).

52. R. Collander, *Acta Chem. Scand.*, *5*, 774 (1951).

53. C. Hansch and S. M. Anderson, *J. Org. Chem.*, *32*, 2583 (1967).

54. J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, *8*, 150 (1965).

55. C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, *33*, 347 (1968).
56. E. B. Hyman, *Biophys. J.*, *6*, 405 (1966).
57. J. Buchi, O. Meyer, and X. Perlia, *Arzneim.-Forsch.*, *17*, 1491 (1967).
58. R. Adams, E. Rideal, W. Brunett, R. Jenkins, and E. Dreger, *J. Amer. Chem. Soc.*, *48*, 1762 (1926).
59. R. Macy, *J. Ind. Hyg. Toxicol.*, *30*, 140 (1948).
60. B. A. Lindenberg, *J. Chem. Phys.*, *48*, 350 (1951).
61. K. Wohl, *Trans. Amer. Inst. Chem. Eng.*, *42*, 215 (1946).
62. K. Wohl, *Chem. Eng. Progr.*, *49*, 218, (1953).
63. E. Hala, J. Pick, V. Fried, and O. Vilim, *Vapour-Liquid Equilibrium*, 2nd ed., Pergamon, Oxford, 1968.
64. R. E. Treybal, *Liquid Extraction*, 2nd ed, McGraw-Hill, New York, 1963.
65. A. P. Colburn, *Chemical Engineers Handbook*, McGraw-Hill, New York, 1952, p. 523.
66. S. S. Davis, *Activity Coefficient Data*, University of Kansas, 1970 (unpublished literature compilation).
67. S. D. Christian, H. E. Affsprung, and S. A. Taylor, *J. Phys. Chem.*, *67*, 187 (1963).
68. J. H. Rytting, S. S. Davis, and T. Higuchi, *J. Pharm. Sci.*, *61*, 816 (1972).
69. D. E. Noel and C. E. Meloan, *Separ. Sci.*, *7*, 75 (1972).
70. D. Dyrssen and L. D. Hay, *Acta Chem. Scand.*, *14*, 1091 (1960).
71. Y. Marcus, in *Solvent Extraction. Proceedings of the International Solvent Extraction Conference, ISEC 71*, Vol. 1, SCI, London, 1971, p. D2.
72. J. Novak, *J. Chromatogr.*, *78*, 269 (1973).
73. J. Novak, J. Ruzickova, S. Wicar, and J. Janak, *Anal. Chem.*, *45*, 63 (1973).

Received by editor June 17, 1974