

# Determination of the thermodynamics of hydroxyl and carboxyl groups in solutions of drug molecules

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The contributions of hydroxyl and carboxyl groups to solute activity and partition coefficients have been investigated using literature data. Both polar functions give rise to a reduced activity coefficient for aromatic solutes in water and differences exist between ring and  $\alpha$ -substitution. Partition coefficients are similarly affected but the magnitude of the group contribution to the free energy of transfer is dependent on the nature of the solute and the organic partition solvent. The contribution for the groups in the terminal position in aliphatic compounds can be obtained by an extrapolation procedure where the group value is a composite of the polar function and a term that takes into account the inequality of aliphatic  $\text{CH}_2$  and  $\text{CH}_3$  groupings ( $\text{H} \cdot \text{OH}$ ,  $\text{H} \cdot \text{COOH}$ ). For a range of solvents there is good correlation between hydroxyl and carboxyl group values. In addition an attempt has been made to correlate group values for  $\text{CH}_2$ ,  $\text{CH}_3$ ,  $\text{H} \cdot \text{OH}$ ,  $\text{H} \cdot \text{COOH}$ , with physico-chemical parameters that are characteristic of the partition system. The best correlations are obtained between group values and the solubility of water in the organic partition solvent. The  $\text{H} \cdot \text{OH}$  and  $\text{H} \cdot \text{COOH}$  group values can also be correlated with infrared spectroscopy data and self-association constants respectively.

Previously, Davis (1973a, c) and Davis, Higuchi & Rytting (1972) have described the determination of the thermodynamics of the methylene, methyl and halogen groups in solutions of drug molecules. This paper examines the effects of two polar groups, hydroxyl and carboxyl, and the correlation of group values derived from partition studies with the properties of the organic solvent.

## ACTIVITY COEFFICIENTS

The effect of a hydroxyl group on the activity coefficients of aromatic compounds has been considered by Tsouopoulos (1970), who concluded that the activity coefficient of a solute in water will be reduced considerably because the hydroxyl group can undergo hydrogen bond formation with water. If the OH group is attached directly to the ring, as in the phenols, the compound will be weakly acidic, whereas the aromatic alcohols that have the OH group in the side chain will be similar to the aliphatic alcohols which are weakly basic. Reported group contributions to the log of the activity coefficient of a solute at infinite dilution in water ( $\Delta \log \gamma_w^\infty$ ) for the hydroxyl group were  $-1.7 (\pm 0.1)$  for ring attachment and  $-1.9 (\pm 0.1)$  for side-chain attachment. Consequently, Tsouopoulos (1970) attributed the slight difference in the behaviour of isomeric phenols and aromatic alcohols in aqueous solution to small size differences.

The determination of the OH group contribution for an aliphatic solute is more difficult. The extrapolation of log activity coefficient data for a homologous series to zero carbon number does not provide a true group value since the aliphatic  $\text{CH}_2$  and the terminal  $\text{CH}_3$  have very different group contributions (Davis, 1973a). In some cases a  $\text{CH}_3$  correction term can be estimated and, using this approach, Davis (1973a) has reported an aliphatic OH contribution for  $\log \gamma_w^\infty$  of  $-1.46$ .

Substantial differences exist between the ring and  $\alpha$ -substituted COOH groups in aromatic compounds. Values quoted by Tsonopoulos (1970) for  $\Delta \log \gamma_w^\infty$  are  $-0.7$  for ring attachment and  $-1.74$  for side chain attachment. This is a surprisingly large difference that has yet to be adequately explained. Our calculations for the COOH group at the end of an aliphatic chain using the experimental data of Pierotti, Deal & Derr (1959), and correcting for the  $\text{CH}_2/\text{CH}_3$  difference, give a value of  $-0.75$ . This is close to the value for ring substitution.

#### PARTITION COEFFICIENTS

##### *Aromatic substituents*

Unlike the  $\text{CH}_3$  and halogen groups (Davis, 1973a, c) few reliable data have been published from which one can calculate group values for polar functions such as OH and COOH. Those that do exist are mainly for the partition system octanol-water that has been favoured by Hansch & co-workers (Hansch, 1971) (Table 1).

In general, both groups give negative group contributions ( $\log F$ ) to the log of the partition coefficient, indicating that the solubility of the solute in the water phase has been increased by the presence of the group through a hydrogen bonding interaction mechanism. The group contributions are dependent on the nature of the solvent and the solute and the effect of a strong electron withdrawing group such as nitro is evident. The OH group values are smaller (less negative) for the octanol-water systems than for the cyclohexane-water system, because in the former system strong hydrogen bonding interactions can take place between the OH group attached to the solute and the OH group in solvent. This will result in an enhanced lipid solubility compared to an inert solvent such as cyclohexane. Polar solvent systems such as octanol have been advocated by many workers who have attempted to correlate biological activity with physico-chemical properties of drug molecules (Burton, Clarke & Gray, 1964; Pinney & Walters, 1969; Dearden & Weeks, 1971; Flynn, 1971; Hansch, 1971). In direct contrast, Beckett & Moffat (1969), Bickel & Weder (1969) and Nightingale, Tse & Stupak (1972) have found that the partition coefficients obtained with inert solvents (hexane; heptane) correlated biological data more satisfactorily. Rytting, Davis & Higuchi (1972) have shown that it is difficult to attempt estimation of thermodynamic properties of isolated functional groups from data on octanol-water partition. They suggested that an inert aliphatic hydrocarbon such as cyclohexane or isooctane should be adopted as the universal standard state for drug molecules.

Considering only the data for octanol-water partition studies and excluding the values obtained with nitrobenzene the OH group has a more negative  $\log F$  value (mean =  $-0.61$ ) than the COOH group (mean =  $-0.12$ ).

##### *Aliphatic substituents*

The group contribution for a polar substituent at the end of an aliphatic chain can be determined by extrapolating the linear log partition coefficient versus carbon

Table 1. *Log F values for OH and COOH attached to aromatic and other ring systems.*

Solvent	log F*	Position	Solute	Reference (1st author)	
Cyclohexane	-3.20	3-OH	} Conjugated heterenoids	Currie (1966)	
	-3.50	4-OH			
Diethyl ether	-0.30	16-OH	Steroids	Flynn (1971)	
1-Octanol	-0.54	2-OH	Phenylacetic acid	Fujita (1964)	
	-0.49		Phenoxyacetic acid		
	-0.52	3-OH	Phenylacetic acid		
	-0.38		Benzoic acid		
	-0.61		Benzyl alcohol		
	-0.66		Phenol		
	-0.73		Aniline		
	+0.15		Nitrobenzene		
	-0.61		4-OH		Phenoxyacetic acid
	-0.30				Benzoic acid
	-0.85		Benzyl alcohol		
	-0.87		Phenol		
	-0.86		Aniline		
	+0.11		Nitrobenzene		
	-0.36		Acetanilides		
-0.67	OH	Benzene			
-0.07	6-OH	Heterocyclics			
Isobutanol	-0.40	} OH various	Steroids	Scholtan (1968)	
	-0.59				
	-0.64				
1-Octanol	-0.15	3-COOH	Phenoxyacetic acid	Fujita (1964)	
	-0.27		Phenyl acetic acid	Leo (1971)	
	-0.19		Benzoic acid	Fujita (1964)	
	+0.04		Phenol		
	-0.02	4-COOH	Nitrobenzene		
	+0.12		Phenol		
	-0.03		Nitrobenzene		
	-0.605		Acetanilides	Dearden (1971)	
	-0.28		COOH	Benzene	Fujita (1964)

\* Log F = log partition coefficient substituted compound - log partition coefficient parent compound.

$$\Delta G_{\text{transfer}} = -2.303 RT \log F.$$

number plot to zero carbon number. The value so obtained will be a combination of the polar group value and the  $\text{CH}_3$  correction term that takes into account the fact that the  $\text{CH}_2$  and terminal  $\text{CH}_3$  groups are different (Davis, 1973a). Unfortunately, as yet we are only able to make approximate estimates for the  $\text{CH}_3$  correction term for partition data for just a few solvents (Davis, 1973a). One way of overcoming this problem is to determine and compare intercept values instead. These will be a measure of the group contribution for the species ( $\text{H} \cdot \text{OH}$  or  $\text{H} \cdot \text{COOH}$ ), that is, the polar function and the hydrogen atom of the terminal  $\text{CH}_3$ . But since the former will be dominant it is not too serious a mistake to neglect the hydrogen atom term in comparative studies (Krishnan & Friedman, 1971).

We have calculated  $\text{H} \cdot \text{OH}$  and  $\text{H} \cdot \text{COOH}$  group contributions (log F) from published compilations of partition data (Seidell, 1940; Landolt-Bornstein, 1960; Leo, Hansch & Elkins, 1971). The data used were examined for consistency and analytical accuracy and where necessary the effects of ionization in the aqueous

Table 2. Group contributions (*Log F*) and solvent parameters for various functional groups. I molar volume ( $\text{cm}^3 \text{mol}^{-1}$ ), II solubility parameter, III dielectric constant, IV dipole moment, V solubility of water in solvent (molar).

	Solvent	I	II	III	IV	V	log $F_x$			
							$\text{CH}_3$ (a)	$\text{CH}_3$ (b)	H..OH	H..COOH
1	Hexane	132	7.4	1.88	0	0.0039	0.62	—	-2.86	—
2	Heptane	147	7.5	1.92	0	0.0035	0.62	0.57	—	-3.13
3	Octane	164	7.6	1.95	0	0.0037	0.62	—	-2.12	-2.99
4	Dodecane	230	7.9	2.00	0	0.0036	0.58 (c)	—	-2.23	-2.98
5	Hexadecane	294	8.3 (l)	2.00 (l)	0	—	0.57 (c)	—	-2.28	-2.84
6	Cyclohexane	109	8.2	2.02	0	0.0044	0.64	0.60	-2.62	—
7	Benzene	89	9.2	2.37	0	0.030	0.62	—	-1.92	-2.63
8	Toluene	107	8.9	2.37	0.31	0.015	0.60	0.57	—	-2.38
9	Xylene	122	8.8	2.37	0.30 (e)	0.019 (e)	0.55 (d)	—	—	-2.12
10	Methylene dichloride	64	9.7	8.93	1.14	0.14	0.60	0.59	—	—
11	Carbon tetrachloride	97	8.6	2.24	0	0.0088	0.62	0.65	-2.21	-2.62
12	Chloroform	81	9.3	4.81	1.15	0.060	0.62	0.60	-1.36	-2.13
13	Diethyl ether	105	7.4	4.34	1.15	0.57	0.56	0.45	-0.95	-0.68
14	Isopropylether "Oils"	142 300 (l)	6.9 —	3.88 3.1 (f)	1.22 —	0.22 —	0.60 (d) 0.53	— 0.46	— -1.02 (-1.34) (g) (h)	— -0.85 -1.11 -1.34 (g) (h)
16	Nitrobenzene	103	10.0	34.2	4.03	0.15	0.48	—	—	-1.73
17	Nitrotoluene	114	—	23.0	—	—	0.47	—	—	-1.17
18	1-Butanol	91	11.4	17.51	1.75	9.2	0.44	0.30	—	-0.10
19	2-Butanol	92	11.1	16.56	—	19.6	0.40	—	—	0.12 0.21
20	Isobutanol	94	11.1	17.73	1.79	7.45	0.44	—	0 (h)	(-0.07) (h)
21	1-Pentanol	109	11.0	13.90	1.7	3.36	0.50	—	—	-0.29
22	2-Pentanol	109	—	13.82	1.66	6.60	0.46 (c)	0.38	—	-0.06
23	3-Methyl-1-butanol	109	11.1	14.7	1.82	4.32	..	0.40	—	—
24	2-Methyl-2-butanol	108	10.8	5.82	—	10.6	0.43	..	—	—
25	4-Methyl-2-pentanol	122	10.0	—	—	2.85	0.51 (d)	0.38	—	—
26	1-Octanol	124	10.3	10.34	1.7 (l)	2.3	0.51 (d)	0.50	-0.52	-0.50
27	Oleyl alcohol	316	—	—	—	0.71	0.58 (c)	—	-0.52	-0.58
28	Ethyl acetate	96	9.0	6.02	1.88	1.45	0.45	—	—	0.13
29	Isopentylacetate	149	8.5	4.60	1.82	0.77	—	0.45	—	—
30	2-Butanone	89	9.3	18.51	2.76	4.44	0.33	—	—	0.13
31	3-Pentanone	105	8.8	17.00	2.82	1.15	0.33	0.33	—	—
32	4-Methyl-2-pentanone	125	8.6	13.11	—	0.84	0.53 (d)	—	—	—
33	Cyclohexanone	107	10.4	18.3	3.01	3.59	—	0.28	—	—
34	Methyl cyclohexanone	123	9.3	18.3 (l)	—	—	0.55	—	—	—
35	o-Dichlorobenzene	113	10.0	9.93	1.27	0.22	—	0.53	—	—

(a) From Davis &amp; others (1972).

(b) From Davis (1973a).

(c) New value obtained from further experimental data.

(d) Value modified from that previously quoted in light of further experimental data.

(e) Value for *m* derivative.

(f) 18°.

(g) Olive oil.

(h) Calculated from Diamond &amp; Wright (1969).

(l) Estimated from data from higher or lower homologues.

phase and/or association in the organic phase were corrected for by calculation of partition coefficients at infinite dilution (Moelwyn-Hughes, 1964). All partition coefficients were corrected to the mole fraction scale in accordance with the recommendations of Davis (1973b) who has concluded that log *F* values are more probably additive on the mole fraction (thermodynamic) scale than on the molar scale. The intercept values (Table 2) were determined by linear regression analysis.

The H..OH and H..COOH group values show a similar picture; for inert solvents, where specific hydrogen bonding interactions between functional groups and solvent molecules will be absent, the group values are large and negative. But as the solvent becomes more polar the log *F* values approach zero and eventually become positive indicating that the interactions between the polar function and the organic solvent are greater than for the polar function and water (remember that

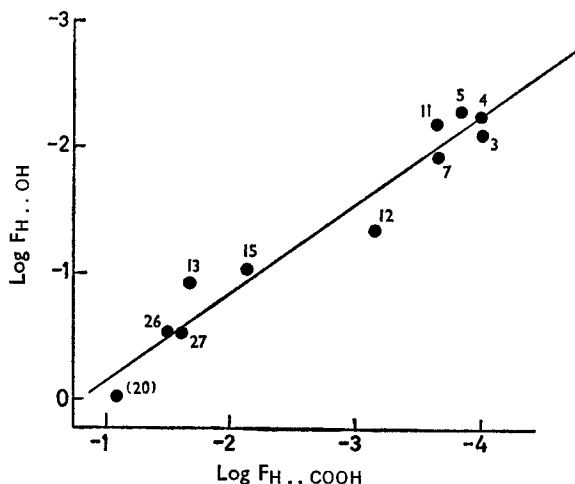


FIG. 1. Correlation between  $\log F_{H..COOH}$  and  $\log F_{H..OH}$ . In this and subsequent figures, numbers refer to solvents listed in Table 2.

the polar function "contains" a  $\text{CH}_3$  correction term and that the OH and COOH values would be about  $-1$  smaller than those in Table 2).

The  $H..COOH$  values are generally higher than the  $H..OH$  values and a plot of one set versus the other reveals a reasonable correlation (Fig. 1) that can be described by the regression equation:

$$\log F_{H..COOH} = 1.43 \log F_{H..OH} + 0.26 \quad \dots \quad (1)$$

(Correlation coefficient = 0.972, standard deviation = 0.26)  
(Number of points = 11)

Therefore, by knowing the value for one group in a given solvent the value for the other can be estimated.

Also listed in Table 2 are  $\log F$  values calculated from the data of Diamond & Wright (1969) who reported incremental free energies of transfer and solution for various aliphatic functional groups. The group values were found originally by subtracting the free energy value for the alkane from the free energy value for the substituted derivative. However, when group values are calculated in this way there is an overcompensation for the alkyl chain ( $2\text{CH}_3$  groups instead of 1) (Davis, 1973a). We have therefore corrected Diamond & Wright's values by subtracting a  $\text{CH}_3$  correction of  $1 \text{ kcal mol}^{-1}$ . This gives group values that are in reasonable accord with those determined by extrapolation. The slight difference can be rationalized by the fact that the  $\text{CH}_3$  correction term is only an approximation and will vary from solvent to solvent and that Diamond & Wright (1969) used only one alkanol or alkanolic acid datum for their calculations.

Laiken & Némethy (1970) have made estimates of OH (not  $H..OH$ ) group contribution to the thermodynamics of alcohols transferred between water and a hydrocarbon environment. At  $25^\circ$  the group parameters were  $\Delta(\Delta G)_{OH} = 5.1$  to  $4.7 \text{ kcal mol}^{-1}$ ,  $\Delta(\Delta H)_{OH} = 7.1 \text{ kcal mol}^{-1}$  and  $\Delta(\Delta S)_{OH} = 7.0$  to  $8.5 \text{ cal deg}^{-1} \text{ mol}^{-1}$ . Laiken & Némethy (1970) considered that these values served as rough guidelines because it was not possible to separate exactly the polar and non-polar contributions of the solute since some water molecules would be in contact with

both moieties. However, it is clear that the unfavourable free energy of transfer of the OH group from water to hydrocarbon is the result of an unfavourable enthalpy change. The excess entropy term is positive owing to the restrictions on the OH group in aqueous solution caused by hydrogen bond formation. The  $\log F_{\text{OH}}$  value calculated from a mean free energy increment is  $-3.66$ . This can be compared to the values in Table 2 by converting it to a  $\log F_{\text{H}\cdot\text{OH}}$  quantity by the addition of a  $\text{CH}_3$  correction factor. The resultant value of  $-2.29$  is in good agreement with the data for the alkane solvents.

Davies (1957) calculated additive group numbers for various functional groups for use in prediction of the hydrophilic-lipophilic balance of surface-active agents. These group numbers were obtained from data on the free energy of transfer of various solutes between water and non-polar oils. We can obtain  $\log F$  values from his data;  $\log F_{\text{H}\cdot\text{OH}} = -2.38$  and  $\log F_{\text{H}\cdot\text{COOH}} = -2.63$ . These also are in good agreement with the values for the alkane solvents in Table 2.

#### CORRELATION OF GROUP VALUES WITH PHYSICO-CHEMICAL PARAMETERS

It is apparent from the literature that in partition studies the nature of the organic phase has been extremely varied and attempts have often been made to correlate the partition coefficients for a given solute with physico-chemical parameters that describe solvent properties. Any method that will correlate partition coefficients may also correlate group contributions to the partition coefficient and we have therefore examined some of these previous investigations.

Sandell (1958) attempted to rationalize the effects of different solvents using Ewell, Harrison & Berg's (1944) classification scheme for hydrogen bonding properties of solvents and Davis & others (1972) found this a useful approach for the qualitative assessment of the  $\log F$  values of the  $\text{CH}_2$  group. The use of the solubility parameter concept of Hildebrand and Scatchard (Hildebrand & Scott, 1962) was proposed by Siekierski & Olszer (1963) and adapted by Wakahayashi and others (Omori, Wakahayashi & others, 1964; Oki, Omori & others, 1965; Wakahayashi, Oki & others, 1964; Wakahayashi, 1967; Suzuki, Akiba & others, 1968). Other correlations of partition data with solubility parameter have been presented by Buchowski (1962), Kemula, Buchowski & Lewandowski (1964) and Noel & Meloan (1972). Mottola & Frieser (1966, 1967) were rather disappointed with their attempts to utilize the solubility parameter equations for quantitative interpretation of partition data since it was apparent that the presence of many adjustable parameters permitted a variety of seemingly self-consistent results to be derived but Davis & others (1972) have achieved success for the prediction of the  $\log F_{\text{CH}_2}$  values for inert solvents.

Attempts have also been made to correlate partition coefficients obtained with different solvents with interfacial tension (Buchowski, 1962; Kemula & others, 1964; Vignes, 1960) and dielectric constant (Buchowski, 1962; Kemula & others, 1964; Mottola & Frieser, 1966; Johansson & Rydberg, 1969; Noel & Meloan, 1972) but none has been particularly successful. Recently, Noel & Meloan (1972) have attempted some empirical correlations of solvent extraction data with a multitude of solvent parameters that have included density, molar refractive index, parachor and the number of carbon atoms in the solvent.

In considering such correlations Leo & others (1971) have concluded that, although dipole moment, dielectric constant and solubility parameter had been useful in

establishing a scale of solvents in certain applications, none had been able to place partitioning solvents in a sensible order. However, a simple method that did work was to order solvents according to the amount of water they contained at saturation. They concluded that the inability of a particular solvent to accommodate water was a good measure of its lipophilic behaviour to a wide range of solutes. In addition the amount of water in some solvents employed in partition could be quite high and this might modify solvent character. Noel & Meloan (1972) also found that the solubility of water in the solvent was useful for correlation.

We have examined correlations between group values for partition ( $\log F$ ) for  $\text{CH}_2$ ,  $\text{CH}_3$ ,  $\text{H}\dots\text{OH}$  and  $\text{H}\dots\text{COOH}$  and solvent properties as described by various physico-chemical parameters (Table 2). These are the solubility parameter squared ( $\delta^2$ ) (from the regular solution theory (Hildebrand & Scott, 1962)), the logarithm of the dielectric constant ( $\log \epsilon$ ) (after Mottola & Frieser, 1966), the square of the dipole moment as an estimate of polarizability ( $\mu^2$ ) (Krishan & Friedman, 1969) and the logarithm of the solubility of water in the solvent (molar) ( $\log S$ ) (Leo & others, 1971). Statistical analysis was conducted using single and multiple regression (2 independent variables) (Table 3). For each group the best correlations were obtained between  $\log F$  and the log of the solubility of water in the solvent. No improvement in correlation could be obtained by multiple regression.

The regression equations for  $\log F$  and  $\log S$  are

$$\log F_{\text{CH}_2} = -0.06 \log S + 0.47 \quad \dots \dots \dots (2)$$

$$\log F_{\text{CH}_3} = -0.09 \log S + 0.43 \quad \dots \dots \dots (3)$$

$$\log F_{\text{H}\dots\text{OH}} = 0.70 \log S - 0.75 \quad \dots \dots \dots (4)$$

$$\log F_{\text{H}\dots\text{COOH}} = 0.92 \log S - 0.75 \quad \dots \dots \dots (5)$$

Note that for  $\text{CH}_2$  and  $\text{CH}_3$  groups the coefficients of  $\log S$  have a negative sign. That is, as the organic solvent and water become more alike (increased miscibility),

Table 3. *Correlation of group parameters (Log F) with solvent properties.*

Group	Statistical parameters <sup>(a)</sup>	$\delta^2$	$\log \epsilon$	$\mu^2$	$\log S$
$\text{CH}_2$ n = 24	r	-0.56	-0.81	-0.60	-0.81
	s	0.080	0.059	0.077	0.057
	F	10**	42**	12**	42**
$\text{CH}_3$ n = 15	r	-0.53	-0.80	-0.76	-0.85
	s	0.10	0.075	0.081	0.065
	F	5.2*	23**	17**	35**
$\text{H}\dots\text{OH}$ n = 9	r	0.58	0.93	0.91	0.95
	s	0.67	0.29	0.34	0.26
	F	3.7	46**	34**	63**
$\text{H}\dots\text{COOH}$ n = 19	r	0.61	0.78	0.35	0.97
	s	1.01	0.80	1.18	0.30
	F	10.3**	27**	2.3	279**

(a) r = Correlation Coefficient. s = Standard deviation. F = F test value.

The correlation coefficient must always be assessed in relation to the number of data points being considered (n) (Tute, 1971). This is accomplished by the F test. F = (mean square deviation attributable to regression)/(mean square deviation from regression). The subscripts for F are 1, n-2 for single regression.

F values significant at the 5% level are given one asterisk. F values significant at the 1% level are given two asterisks (Snedecor & Cochran, 1967).

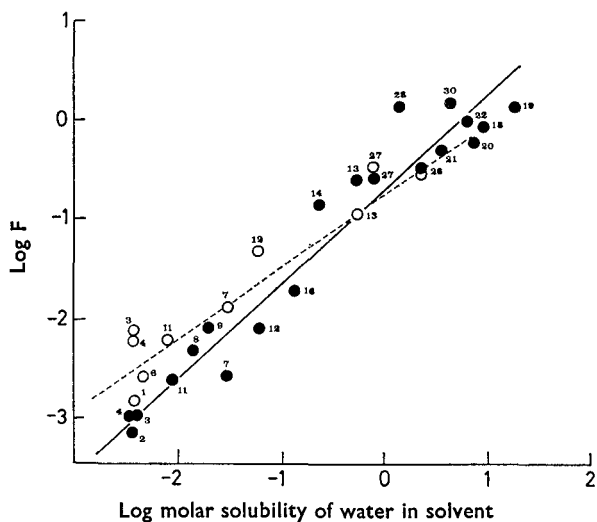


FIG. 2. Correlation between  $\log F_{H...OH}$  and  $\log F_{H...COOH}$  and the solubility of water (molar) in various organic solvents. —●—  $H...COOH$ . —○—  $H...OH$ .

the two groups have less tendency to leave one phase in preference for the other. When the solubility of water in the solvent is high the Nernst partition law will no longer be valid (Davis & others, 1972). The square of the correlation coefficient for the correlation between  $\log F$  and  $\log S$  for the  $CH_2$  group indicates that only 65% of the variation in the data is accounted for by the regression model leaving 35% still to be explained. However, a much improved correlation can be obtained if a particular group of solvents is selected and the correlation between  $\log F$  and  $\log S$  investigated. This has been done for the alcohol solvents (Fig. 3). The regression equation is

$$\log F_{CH_2} = -0.13 \log S + 0.56 \quad \dots \quad (6)$$

(Correlation coefficient =  $-0.995$ , standard deviation =  $0.006$ )

These satisfactory correlations between  $\log F$  data and the solubility of water in the various partition solvents have yet to be explained in fundamental physico-chemical terms. Johnson (1966) has shown in investigations of the hydration of polar solutes that the solubility of water in the solvent is a good index to relative solvation ability. The molecular complexity of water as a solute in non-aqueous media has received some attention and more recent studies have indicated that in carbon tetrachloride, cyclohexane, benzene and toluene it is monomeric, whilst in 1,2-dichloroethane and 1,1,2,2-tetrachloroethane it can exist as higher species; trimers and tetramers (Hogfeldt & Bolander, 1963; Johnson, 1966). The presence of dissolved water in the organic solvent will alter the non-aqueous environment and will tend to reduce the differences between the two immiscible phases. Polar organic solvents will undergo specific solute-solvent interaction with dissolved water through a hydrogen bonding mechanism. For example 2-butanol contains more molecules of water (calculated as molar concentration) in the 2-butanol phase than 2-butanol. Water and 2-butanol are as much alike as two separate solvents can be (Leo & others, 1971). Notice that for the polar groups when the water solubility in the solvent is 1 molar the group contributions will be the same. This is shown graphically in Fig. 2.



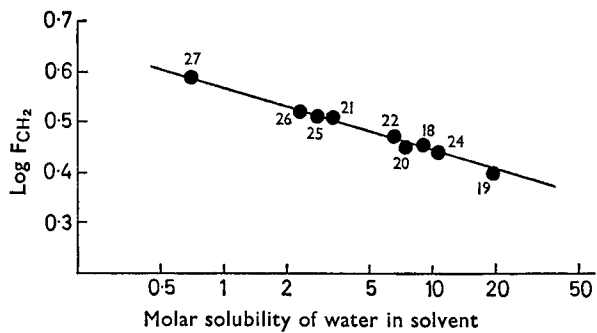


FIG. 3. Correlation between  $\log F_{CH_2}$  and the solubility of water (molar) in alcohol solvents.

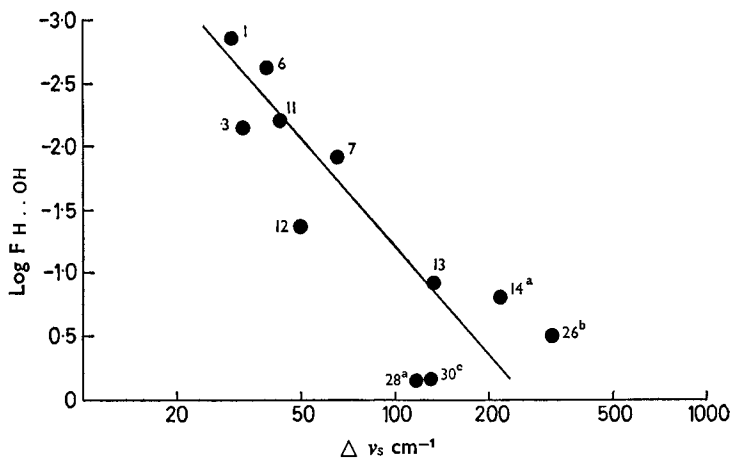


FIG. 4. Correlation between  $\log F_{H...OH}$  and  $\Delta \nu_s$  (the shift of OH stretching in the infrared spectra of solvent mixtures with methanol). (a)  $\log F_{H...OH}$  value calculated from  $\log F_{H...COOH}$  using equation (1). (b)  $\Delta \nu_s$  value for methanol. (c) As for (a) above,  $\Delta \nu_s$  value for acetone.

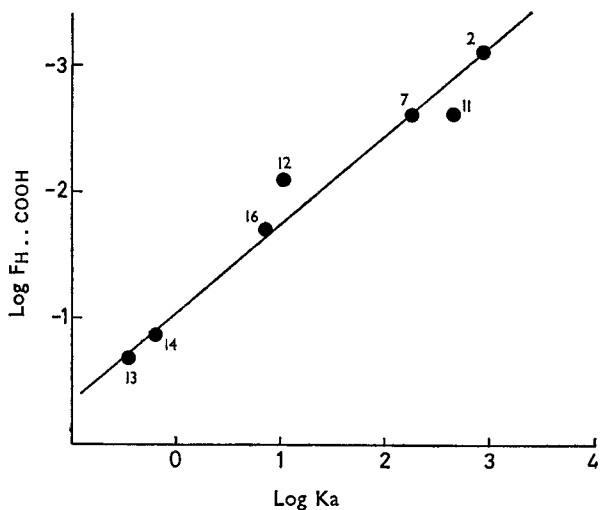


FIG. 5. Correlation between  $\log F_{H...COOH}$  and  $\log K_a$  (the self association constant for acetic acid in various solvents).

We conclude that the correlations between  $\log F$  and  $\log S$  are attributable to a composite of factors rather than to one physico-chemical mechanism.

Linberg (1958) suggested that the effect of specific groups in phenolic compounds on the free energy of distribution of solutes between water and diethyl ether could be related to their ability to form hydrogen bonds. And correlations between partition data and infrared spectra were presented. A similar idea was developed by Nakanishi, Ichinose & Shirai (1968) and Nakanishi (1969) who proposed that the infinitely dilute activity coefficient of various solvent-alcohol binaries could be correlated with the hydrogen bond shift of the hydroxyl group in infrared spectra for binary systems.

$$\log \gamma^\infty = a \log \Delta\nu_s + b \dots \dots \dots (7)$$

where  $a$  and  $b$  are constants and  $\Delta\nu_s$  is the hydrogen bond shift calculated as the difference in the frequency of the OH absorption peak of methanol in vapour phase minus the frequency of the OH absorption peak between methanol and the solvent. This is different from the conventional definition by which the frequency shift is measured by the deviation from the free OH absorption peak in dilute carbon tetrachloride solution.

We have investigated similar correlations using the infrared data of Cole, Little & Mitchell (1965) and Nakanishi (1969).

The derived regression equation is

$$\log F_{H..OH} = 2.29 \log \Delta\nu_s - 5.83 \dots \dots \dots (8)$$

(correlation coefficient = 0.884, standard deviation = 0.47).

This is shown diagrammatically in Fig. 4.

In a similar way the group values for the H..COOH function can be correlated with the properties of acetic acid in the different partition solvents. Christian, Johnson & others (1966) have shown that there is a good correlation between association constants and partition coefficients for the interaction between water and pyridine in various solvents. Thus we have investigated the relation between the self-association constant of acetic acid ( $K_a$ ) in various solvents (Pimentel & McClellan, 1960) and the  $\log F_{H..COOH}$  values (Fig. 5). If the solvent is inert (i.e. no hydrogen bonding interactions between the COOH group and the solvent molecules) the self-association constant is high. Conversely if the solvent can form hydrogen bonds the association constant is lower. The regression equation is

$$\log F_{H..COOH} = -0.63 \log K_a - 1.09 \dots \dots \dots (9)$$

(Correlation coefficient = 0.946, standard deviation = 0.31).

Equations 2 to 5, 8 and 9 will allow us to make reasonable estimates of group values from the physico-chemical properties of the organic solvent used in partition, or from its interaction with single alkanol and alcanoic acid solutes. These values can then be used for the prediction of the solution behaviour of drug molecules or can be employed in thermodynamically based structure-activity relations (Higuchi & Davis, 1970).

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