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Thermodynamics of distribution of para-substituted phenols between organic solvents and sodium chloride solution

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Summary

The distribution of para-substituted phenols between 8 organic solvents and 0.15 $\mathrm{mol \cdot dm^{-3}}$ NaCl solution has been determined at five different temperatures using the shake-flask technique and the thermodynamic parameters for the process (ΔH and ΔS) evaluated from the van't Hoff isochore. The free energy change for the transfer of the methylene group from water to organic solvent was entropically controlled. Logarithms of distribution constants of phenols for a given organic solvent–water system were linearly related to those for other solvent systems and also to the substituent constant of Hansch. The influence of the nature of the organic solvent upon the distribution constants of phenols and the incremental distribution constants per methylene group could be evaluated by the Regular Solution theory.

Introduction

The distribution behaviour of various solutes between different organic and aqueous phases has been studied widely by workers in the field of solvent extraction, analytical chemistry and medicinal chemistry (Collander, 1951; Fujita et al., 1964; Leo et al., 1971; Kojima et al., 1970; Davis et al., 1973, 1974; Davis, 1975; Hansch

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and Leo, 1979; Rogers and Wong, 1980). As a consequence, it is now well accepted that aspects of drug distribution and drug binding at receptors can be correlated with the hydrophobic properties of the drug molecule as measured by its oil–water partition coefficient (Davis et al., 1974). Hansch and others selected 1-octanol as the preferred solvent for use in structure–activity studies in drug design (Fujita et al., 1964; Hansch and Leo, 1979) and have proposed the use of linear free energy equations and substituent constants for predictive purposes.

The contribution made by the methylene group has been of special interest and values for the free energy of transfer of this group from water to organic solvent have been used to examine the hydrophobic effect and hydrophobic interactions (Davis et al., 1974; Tanford, 1973; Beezer and Hunter, 1983).

More recently, the thermodynamics of distribution of organic solutes between water and organic solvents have been studied to provide mechanistic information about the transfer process (Davis et al., 1976; Breslauer et al., 1980; Rogers and Davis, 1980; Beezer et al., 1980; Kinkel et al., 1981; Riebesehl and Tomlinson, 1983) and in some cases the free energy, enthalpy and entropy changes for the transfer of methylene group from aqueous solution to organic solvents have been considered (Rogers and Wong, 1980; Beezer et al., 1980, 1983; Anderson et al., 1983).

This paper examines the temperature dependency of the distribution constant of some *p*-substituted phenols between 0.15 mol · dm^{-3} NaCl solution and 8 organic solvents of differing polarity. The effect of the nature of the organic solvent on the distribution constant of the various phenolic compounds and on the increment provided by the methylene group to the distribution constant, have been considered in terms of solubility parameter theory and linear enthalpy–entropy compensation effects.

Materials and Methods

Apparatus

Phase equilibrium studies were conducted using a shaking water bath (Grant Instruments) thermostated at a given temperature (±0.1°C). A Beckman Model 25 spectrophotometer was used for the determination of phenol concentration in aqueous solution at their λ_{max} with 10 mm silica cells.

Chemicals

Water was distilled from an all-glass still. Phenol (99.99%), *p*-chloro- (99.5%), *p*-bromo-, *p*-methoxy- and *p*-hydroxyacetophenone from British Drug Houses and *p*-fluoro- (99%) and *p*-iodo-phenols from Aldrich Chemicals were used without purification. *p*-Cresol and *p*-ethylphenol (Koch-Light) were used after recrystallization. *p*-Propylphenol (99%) from Aldrich Chemicals was used after twice distillation. Aqueous solutions of *p*-substituted phenol (5×10^{-4} mol · dm^{-3} and/or 1×10^{-3} mol · dm^{-3}) were prepared by dissolving phenols in 0.15 mol · dm^{-3} NaCl solution containing a small amount of HCl (pH = 4). Perfluorohexane (Bristol Organics), *n*-hexane (special for spectroscopy), cyclohexane (Analar), methylene chloride

(Analar) and 2,2,4-trimethylpentane (Analar) (British Drug Houses). 1,2-dichloroethane (99%) and 1,2-dibromoethane (99%) (Aldrich Chemicals) and carbon tetrachloride (Hopkins and Williams) were washed successively with sodium hydroxide solution, distilled water, concentrated sulphuric acid and finally 5 times with distilled water. NaCl (Analar, British Drug Houses) was used without additional purification.

Procedure

An aliquot (20 or 40 ml) of phenol solution was shaken with an aliquot (10, 20 or 40 ml) of organic solvent (which had been equilibrated previously with 0.15 $mol \cdot dm^{-3}$ NaCl solution) in a 100 ml conical flask at a given temperature for about 24 h. After equilibration phase separation was achieved either by standing the system or, if necessary, by centrifugation. The absorbance of the aqueous phase was measured spectrophotometrically at its maximum wavelength of absorption in the range 270–290 nm and the concentration of phenol in the aqueous phase was calculated from a previously constructed calibration curve. The concentration of phenols in the organic phase was obtained by subtracting the phenol concentration in the aqueous phase from the initial concentration of phenol in the aqueous solution.

Calculation of distribution constants

The distribution ratio of phenol between two immiscible solvents is given by:

$$D = \frac{C_{A,org}}{C_{A,aq}} = \frac{[HA]_{org} + n[(HA)_n]_{org}}{[HA]_{aq} + [A^-]_{aq}} \qquad (1)$$

where $C_{A,org}$ and $C_{A,aq}$ are the total phenol concentrations in the organic and aqueous phases, respectively, and HA denotes a phenolic molecule. When only a monomeric and unionized solute, HA, exist in both phases, and Eq. 1 is rewritten as:

$$D = K_d = \frac{[HA]_{org}}{[HA]_{aq}} \qquad (2)$$

$$= \frac{A_i - A}{A} \cdot \frac{v_{aq}}{v_{org}}$$

where K_d is the distribution constant of HA, in molar concentration units, A_i and A the absorbances of the aqueous phase before and after extraction, respectively, and v_{org} and v_{aq} the volumes of the organic and aqueous phases, respectively. Eqn. 2 was used to calculate the distribution constants of all solutes used. The reported values are mean values.

For $C_{A,org} \leq 5 \times 10^{-3}$ $mol \cdot dm^{-3}$ it was confirmed from preliminary experiments and other data (Johnson et al., 1965, 1976) that the phenols existed as monomers in the organic phase. The phenols existed in the non-ionized form in the aqueous phase, which contained ca. 10^{-4} mol · dm^{-3} acid. The distribution constant calculated from Eqn. 2 can be converted to the thermodynamic constant, K_d^x (mole fraction unit concentration) by using Eqn. 3.

$$K_d^x = K_d \cdot \frac{V_{org}}{V_{aq}} \tag{3}$$

where V_{org} and V_{aq} are the molar volumes of organic solvent and 0.15 mol · dm^{-3} NaCl solution (water), respectively. The molar volumes of organic solvents and water at different temperature were calculated from density values at the corresponding temperature (Landolt-Bornstein, 1960; Riddick and Bunger, 1970) from the knowledge that the density changes linearly with temperature.

Results and Discussion

As typical examples log K_d values obtained at 25 °C are given in Table 1 with the molar volume, solubility parameter of the organic solvent and the solubility of water in the solvent. As is evident from Table 1, the distribution constants increase with increase in solubility parameter of the solvent and the solubility of water in the solvent.

The thermodynamics of distribution of phenols are given by Eqns. 4 and 5.

$$\Delta G = -RT \ln K_d^x \tag{4}$$

$$\ln K_d^x = -\frac{\Delta H}{R} \cdot \frac{1}{T} + \frac{\Delta S}{R} \tag{5}$$

where ΔG, ΔH and ΔS are the partial free energy change, enthalpy change and entropy change of solute transfer and R and T are the gas constant and absolute temperature. By applying Eqn. 5 to the data for distribution constants obtained over a temperature range of 10–30 °C, ΔH and ΔS are calculated from the slope and the intercept of the plot of $\ln K_d^x$ against $1/T$, respectively, provided the enthalpy remains constant irrespective of the temperature range studied.

Figs. 1A–C show the van't Hoff plots obtained for *p*-methyl-, *p*-chloro- and *p*-methoxy-phenols. Figs. 2A–C show the same plots of alkyl phenols obtained for 3 different organic solvents as typical examples. Excellent linearity was obtained between $\ln K_d^x$ and $1/T$. This indicates that the enthalpy of transfer is constant over the temperature range studied in all cases. The distribution constant increases with increase in temperature for all of the solutes and solvents studied in the present work although it is known that for some solvents such as alcohols and esters (Korenman and Udalova, 1974), K_d decreases with increase in temperature.

In Tables 2 and 3, the values of ΔG, ΔH and ΔS obtained or calculated at 25 °C are summarized together with the correlation coefficient for the van't Hoff plots. As evident from Fig. 1, the greater the extent of extraction of the phenol into the

TABLE 1

DISTRIBUTION CONSTANTS OF *p*-SUBSTITUTED PHENOLS AT 25 ° C

Solute	log K_d								
	C_6F_{14}	iso-C_8H_{18}	*n*-C_6H_{14}	cy-C_6H_{12}	CCl_4	$ClCH_2CH_2Cl$	CH_2Cl_2	$BrCH_2CH_2Br$	1-$C_8H_{17}OH$ [e]
H	–	−1.006	−0.891	−0.776	−0.297	0.653	0.601	0.442	1.55
CH_3	−1.747	−0.403	−0.310	−0.203	0.309	1.191	1.153	1.014	2.10
C_2H_5	−1.330	0.144	0.249	0.377	0.889	1.683	1.656	1.517	2.59
C_3H_7	−0.877	–	0.889	1.031	1.517	–	–	–	3.21
F	–	–	−0.868	−0.787	−0.263	0.733	–	0.493	1.91
Cl	–	–	−0.347	−0.216	0.323	1.285	–	1.119	2.55
Br	–	–	−0.202	−0.040	0.508	1.488	–	1.383	2.59
I	–	–	0.072	0.276	0.826	1.836	–	1.819	2.82
OCH_3	–	–	−1.127	−1.032	−0.337	0.766	–	0.591	1.55
$COCH_3$	–	–	–	–	−1.296	0.293	–	−0.016	2.02
V_{org} [a]	205	166.1	131.7	108.8	97.1	79.4	64.5	86.6	1.58
δ_{org} [b]	5.6	6.85	7.3	8.2	8.6	9.9	9.7	10.2	10.3
log S_{H_2O} [c,d]	−3.24 [f]	−2.68	−2.49	−2.55	−2.08	−0.91	−0.84	−1.06	−0.56

[a] Weast (1974).

[b] Hildebrand and Scott (1964).

[c] Fujii et al. (1978).

[d] Kojima et al. (1970).

[e] Rogers and Wong (1980).

[f] Mak (1983).

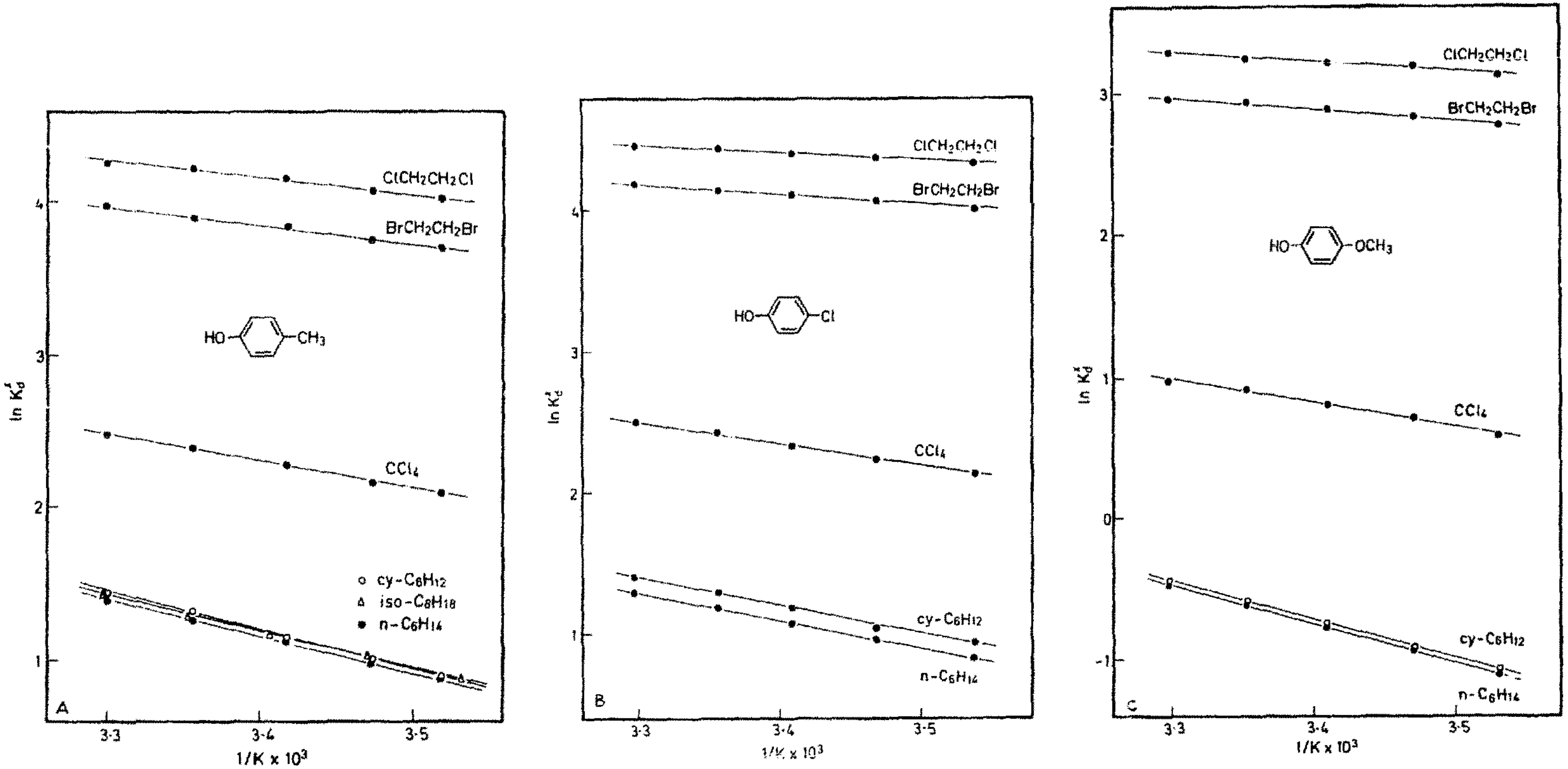

Fig. 1. A–C: van't Hoff plots for three phenols distributed between 0.15 mol·dm^{-3} aqueous NaCl solution and various organic solvents. A: *p*-cresol; B: *p*-chlorophenol; C: methoxyphenol.

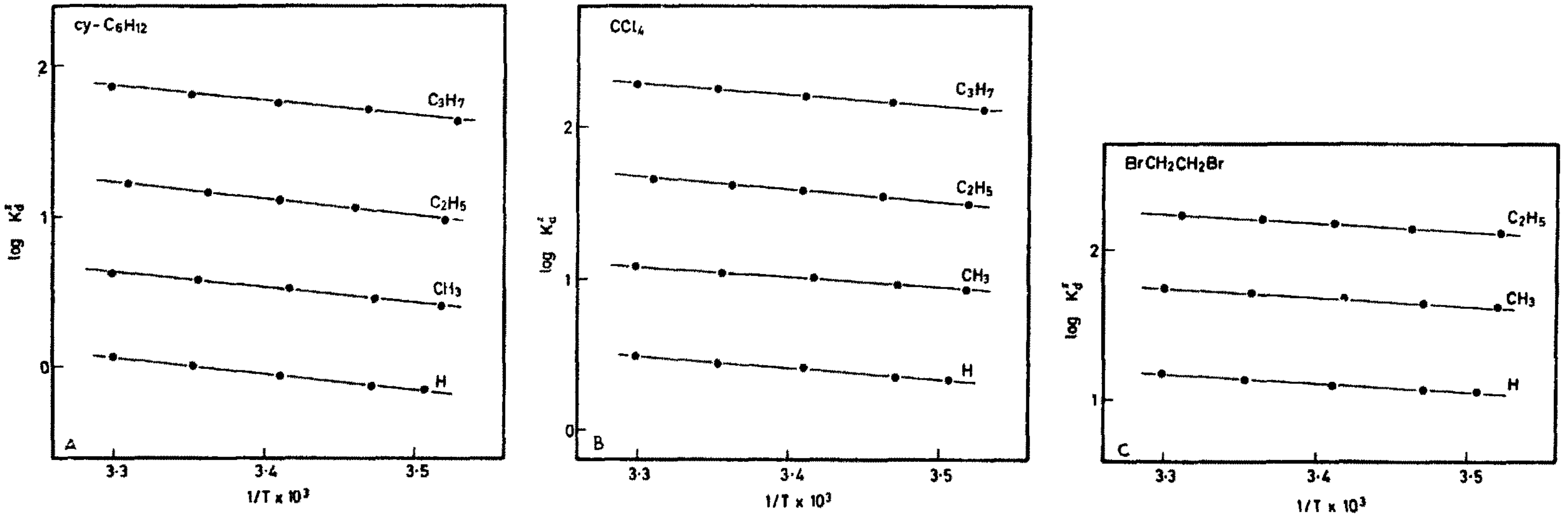

Fig. 2. A–C: van't Hoff plots for *p*-alkylphenols distributed between 0.15 mol·dm^{-3} aqueous NaCl solution and three organic solvents. A: cyclohexane; B: carbon tetrachloride; C: dibromoethane.

TABLE 2

THERMODYNAMIC CONSTANTS FOR DISTRIBUTION OF *p*-ALKYL-PHENOLS AT 25 °C

	Organic solvent	−X	Corr. coeff.	$-\Delta G^{x}$	ΔH^{x}	ΔS^{x}
1	C_6F_{14}	CH_3	1.000	−3.91	32.0	94
		C_2H_5	0.999	−1.46	34.6	111
		C_3H_7	1.000	1.07	32.1	111
2	iso-C_8H_{18}	H	0.998	−0.24	20.4	68
		CH_3	1.000	3.20	19.7	77
		C_2H_5	0.996	6.32	20.9	91
3	*n*-C_6H_{14}	H	0.999	−0.15	21.6	72
		CH_3	1.000	3.16	19.7	77
		C_2H_5	0.997	6.33	19.8	88
		C_3H_7	0.998	9.99	19.1	97
4	cy-C_6H_{12}	H	0.999	−0.03	21.2	71
		CH_3	0.999	3.29	21.5	83
		C_2H_5	0.996	6.59	21.0	93
		C_3H_7	0.997	10.34	20.0	102
5	CCl_4	H	0.999	2.48	15.6	61
		CH_3	0.999	5.92	14.8	70
		C_2H_5	0.998	9.22	16.2	85
		C_3H_7	0.996	12.83	14.8	93
6	$ClCH_2CH_2Cl$	H	0.991	7.40	8.0	52
		CH_3	0.990	10.46	9.1	66
		C_2H_5	0.985	13.24	9.0	75
7	CH_2Cl_2	H	0.994	6.58	8.0	49
		CH_3	0.996	9.73	7.2	57
		C_2H_5	0.994	12.61	7.1	66
8	$BrCH_2CH_2Br$	H	0.997	6.41	9.2	53
		CH_3	0.999	9.67	10.5	68
		C_2H_5	0.993	12.51	11.2	80

X = substituent in *p*-position of phenol; ΔG and ΔH are given in $kJ \cdot mol^{-1}$; ΔS is given in $J \cdot mol^{-1} \cdot K^{-1}$.

organic solvent, the smaller the negative slope of the van't Hoff plot. This tendency coincides fairly well with increase in the solubility parameter of the solvent and very well with increase in the solubility of water in the organic solvent. The enthalpy of transfer (ΔH) for all alkyl phenols studied is almost constant for a given solvent irrespective of the carbon number of the substituent in the *p*-position of the phenol (Table 2 and Fig. 2). On the other hand, the entropy of transfer increases with increasing carbon number of the substituent in the *p*-position. However, the increment in ΔS per methylene group is almost independent of the nature of the organic solvent. From these data, it may be concluded that the increment in free energy (ΔG) per methylene group does not arise from a change in ΔH but from ΔS.

TABLE 3

THERMODYNAMIC CONSTANTS FOR DISTRIBUTION OF *p*-SUBSTITUTED PHENOLS AT 25 °C

Organic solvent	-X	Corr. coeff.	$-\Delta G^x$	ΔH^x	ΔS^x
n-C_6H_{14}	F	0.999	−0.03	22.3	75
	Cl	0.999	2.95	16.8	66
	Br	0.997	3.77	16.3	67
	I	0.991	5.34	13.9	65
	OCH_3	1.000	−1.51	23.1	72
cy-C_6H_{12}	F	0.998	−0.04	22.8	76
	Cl	1.000	3.23	17.2	68
	Br	0.999	4.23	17.4	73
	I	0.996	6.03	14.9	70
	OCH_3	1.000	−1.44	23.4	74
CCl_4	F	0.999	2.67	16.6	65
	Cl	0.999	6.02	13.5	65
	Br	0.999	7.07	12.6	66
	I	0.998	8.89	8.74	59
	OCH_3	0.998	2.25	14.6	56
	$COCH_3$	0.998	−3.23	24.3	71
$ClCH_2CH_2Cl$	F	0.994	7.86	8.25	54
	Cl	0.989	11.02	4.78	53
	Br	0.991	12.16	6.16	62
	I	0.975	14.16	3.70	60
	OCH_3	0.992	8.05	5.95	47
	$COCH_3$	0.999	5.35	7.79	45
$BrCH_2CH_2Br$	F	0.999	6.71	11.1	60
	Cl	0.989	10.29	6.57	57
	Br	0.988	11.78	7.36	64
	I	0.976	14.27	4.21	62
	OCH_3	0.998	7.26	7.18	48
	$COCH_3$	1.000	3.79	11.47	51

X = substituent of p-position of phenol; ΔG and ΔH are given in $kJ \cdot mol^{-1}$; ΔS is given in $J \cdot mol^{-1} \cdot K^{-1}$

It is to be expected that the solubility of water in the solvents studied may change slightly with change in temperature (Kinkel et al., 1981; Beezer et al., 1980). However, the derived functional group contributions are expected to be almost independent of this effect (Davis et al., 1974). The influence of the solubility of water in the organic phase on the distribution of solutes with hydrophobic functional groups will be discussed elsewhere (Davis and Kojima, in preparation).

It is well known that the distribution constant of an organic solute increases by a factor of about 4 for each methylene group added to the parent molecule (Davis et al., 1974). In the present study, an increment of 3.3 $kJ \cdot mol^{-1}$ for the free energy of transfer of the methylene group from aqueous to organic phases was found. As the change of ΔG of transfer per methylene group is almost entirely entropically controlled, the increment in ΔG corresponds to the increment in the entropy of transfer of the methylene group, i.e., $\Delta\Delta H \simeq 0$, $\Delta\Delta G \simeq (T\Delta S)$ and $\Delta S = 11.1\ J \cdot mol^{-1} \cdot K^{-1}$. This incremental value arises from the decrease in the entropy of solution of the methylene group in water, i.e. ca. $5.8\ J \cdot mol^{-1} \cdot K^{-1}$ for each incremental hydrogen atom (Tanford, 1973). This last value has also been found for the partitioning of *p*-alkoxyphenols between octanol and water (Beezer et al., 1980) and the solution of *p*-alkoxy-phenols in water and octanol-saturated water (Beezer et al., 1983).

For the case of halogen groups the distribution constant increases with increase in the volume of the substituent from fluorine to iodine (Table 3). Contrary to the results observed for the alkylphenols, ΔH decreases in going from F to I but ΔS is almost constant. Thus the change in ΔG of transfer for halo-phenols appears to be enthalpically controlled.

Linear enthalpy–entropy relationships

When thermodynamic data are obtained from the van't Hoff isochore, good correlations between ΔH and ΔS can often be obtained. However, these may arise from statistical artefacts rather than being of mechanistic significance. According to Leffler and Grunwald (1964), Krug et al. (1976a and b) and Kinkel et al. (1981), enthalpy–entropy compensation can be expressed correctly by:

$$\Delta H = \beta \Delta S + \Delta G\ (\text{at } T = \beta) \qquad (6)$$

where β is a proportionality factor. From the Gibbs equation, Eqn. 6 can be rewritten as:

$$\Delta G_T = \Delta H(1 - T/\beta) + T\Delta G/\beta \qquad (7)$$

In Figs. 3 and 4, the plots of ΔG versus ΔH are shown for some selected phenols and different organic solvents. These plots give different straight lines respective of the solutes and solvents used. This linear relationship can be expressed by Eqn. 8.

$$\Delta G^x = a\Delta H^x - b \qquad (8)$$

The values of the slope a and intercept b obtained are summarized in Tables 4 and 5. Figs. 3 and 4 suggest that all the solutes studied are distributed between an aqueous phase and the different solvents by the same mechanism, namely the hydrophobic effect. For the alkylphenols the value of b in Eqn. 8 is dependent on the size of the phenolic solute (Anderson et al., 1983); and increases with increase in the carbon number of alkyl group in the *p*-position of the phenol.

Linear relationship between distribution constants

For solutes having the same functional group, the distribution constant of solutes in one organic solvent can be linearly related to those in other solvents. This

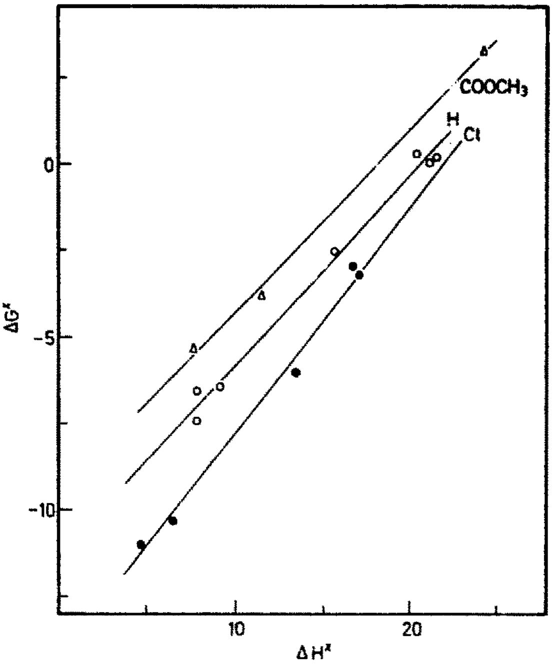

Fig. 3. Enthalpy-free energy compensation plots for three phenols distributed between 0.15 mol·dm^{-3} aqueous NaCl solution and different organic solvents. H = phenol; Cl = *p*-chlorophenol; $COOCH_3$ = *p*-hydroxyacetophenone.

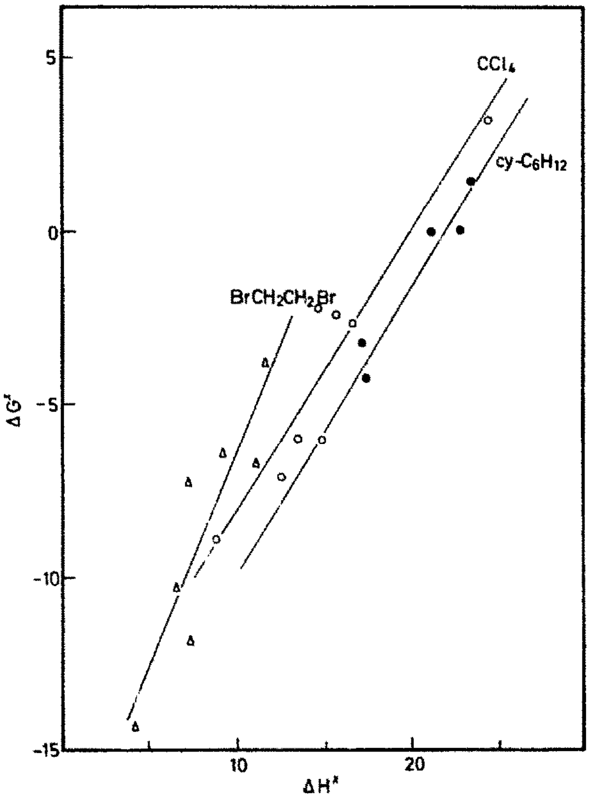

Fig. 4. Enthalpy-free energy compensation plots of different phenols distributed between 0.15 mol·dm^{-3} aqueous NaCl solution and three different organic solvents—cyclohexane, carbon tetrachloride and dibromoethane.

TABLE 4

ENTHALPY-ENTROPY COMPENSATION FOR PHENOLIC SOLUTES AND DIFFERENT SOLVENTS

	$\Delta G^x = a\Delta H^x - b$		
Substituent	a	b	corr. coeff.
H	0.546	11.33	0.995
CH_3	0.586	15.05	0.989
C_2H_5	0.550	17.74	0.990
C_3H_7	0.690	23.40	0.995
F	0.566	12.60	0.995
Cl	0.656	14.43	0.996
Br	0.781	17.15	0.991
I	0.801	17.05	0.980
OCH_3	0.546	11.03	0.995
$COCH_3$	0.527	9.62	0.999

TABLE 5

ENTHALPY-ENTROPY COMPENSATION FOR DIFFERENT SOLUTES AND THE SAME SOLVENT

	$\Delta G^x = a\Delta H^x - b$		
Solvent	a	b	corr. coeff.
n-Hexane	0.697	14.97	0.992
cy-Hexane	0.830	18.16	0.981
Carbon tetrachloride	0.808	15.96	0.962
Dichloroethane	1.504	19.02	0.844
Dibromoethane	1.239	18.75	0.889

relationship given in Eqn. 9 holds for a large number of solvents (Collander, 1951; Leo et al., 1971).

$$\log K_{d,S_1} = a \log K_{d,S_2} + b \tag{9}$$

The comparison of the distribution constants using cyclohexane for K_{d,S_1} and other solvents for K_{d,S_2} is shown in Tables 6 and 7. For non-polar and non-interactive solvents, a good linear correlation is obtained. The value of the slope, a, appears to be dependent on the properties of the solvent, e.g. the solubility parameter. With an increase or decrease in the solubility parameter from a value of 8.2, a, differs from unity. The intercept, b, is also dependent on the extractibility of the solvent. A positive intercept indicates that the solvent has a greater affinity for the solutes than does cyclohexane. By using the intercept, b, as a measure of the solvent lipophilicity, Leo et al. (1971) found a good correlation between the value, b, and the solubility of water in the organic solvents. This relation is also observed in the present study as

TABLE 6

LINEAR RELATIONSHIP OF DISTRIBUTION CONSTANT FOR PHENOLS

	$\log K_{d,solvent} = a \log K_{d,cyclohexane} + b$			
Solvent	a	b	corr. coeff.	$\Delta \log S_{H_2O}$
$n\text{-}C_6H_{14}$	0.965	−0.135	0.999	0.06
CCl_4	0.954	0.531	0.996	0.46
$ClCH_2CH_2Cl$	0.931	1.327	0.946	1.00
$BrCH_2CH_2Br$	0.843	1.457	0.964	1.49

TABLE 7

LINEAR RELATIONSHIP OF DISTRIBUTION CONSTANT FOR ALKYLPHENOLS

	$\log K_{d,solvent} = a \log K_{d,cyclohexane} + b$				
Solvent	a	b	corr. coeff.	$\Delta \log S_{H_2O}$	$\Delta \log S^{*}_{H_2O}$
$n\text{-}C_6H_{14}$	0.983	−0.121	1.000	0.06	0.14
CCl_4	1.003	0.497	1.000	0.46	0.41
$ClCH_2CH_2Cl$	0.893	1.355	1.000	1.00	0.97
$BrCH_2CH_2Br$	0.932	1.178	0.999	1.49	1.38
CH_2Cl_2	0.915	1.320	1.000	1.71	1.48
$iso\text{-}C_8H_{18}$	0.997	−0.222	1.000	−0.13	0.05
C_6F_{14}	0.705	−1.601	1.000	−0.46	−0.19
$1\text{-}C_8H_{17}OH$	0.912	2.264	1.000	2.79	2.95

can be seen from Tables 6 and 7. Indeed, the value of b obtained in the present study is very near to the difference in the logarithms of solubility of water in the pair of organic solvents ($\Delta \log S_{H_2O}$) ($\log S_{H_2O,cyclohexane} - \log S_{H_2O,solvent}$).

Functional group contribution

The hydrophobic or substituent constant, π_x, for various functional groups can be used to predict the distribution constants of compounds, based on the distribution constants obtained between a *n*-octanol and water (Fujita et al., 1964; Leo et al., 1971) or a diethyl ether–water system (Flynn, 1971). π_x values can be calculated from Eqn. 10:

$$\pi_x = \log K_{d,RX} - \log K_{d,RH} \tag{10}$$

where $K_{d,RX}$ and $K_{d,RH}$ are the distribution constants of the substituted and unsubstituted parent molecules, respectively. π_x is a free energy-related constant that will change with the nature of the organic solvent. In Table 8, the π_x values obtained from the present study are summarized with the π_x values previously reported (Hansch and Leo, 1979; Davis et al., 1974).

The π_x values for the non-alkyl substituents increase with increase in the solubility

TABLE 8

VALUES OF SUBSTITUENTS FOR DIFFERENT ORGANIC SOLVENTS

Substituent	π_x								
	n-C_6H_{14}	cy-C_6H_{12}	CCl_4	$ClCH_2CH_2Cl$	$BrCH_2CH_2Br$	Mean	a	b	c
H	0	0	0	0	0	0	0	0	0
CH_3	0.60	0.60	0.60	0.55	0.55	0.58	0.56	0.49	–
C_2H_5	1.20	1.20	1.20	1.10	1.10	1.16	1.02	–	–
C_3H_7	1.80	1.80	1.80	–	–	1.80	1.55	–	–
F	0.02	−0.02	0.04	0.07	0.07	0.04	0.14	0.31	0.07
Cl	0.60	0.56	0.60	0.64	0.69	0.62	0.71	0.93	0.56
Br	0.70	0.65	0.80	0.84	0.95	0.79	0.86	1.13	0.75
I	0.97	1.04	1.12	1.20	1.36	1.14	1.12	1.45	0.91
OCH_3	−0.22	−0.25	−0.03	0.08	0.14	−0.06	−0.02	−0.12	–
$COCH_3$	–	–	−1.00	−0.38	−0.48	−0.62	−0.55	–	–

a: $\log K_{d,C_6H_5\text{-}x} - \log K_{d,C_6H_6}$, from Hansch and Leo (1979).

b: $\log K_{d,x\text{-}C_6H_4\text{-}OH} - \log K_{d,C_6H_5\text{-}OH}$, from Davis et al. (1974).

c: value for non-polar solvents, from Davis et al. (1974).

parameter of the organic solvent corresponding to changes in the solute–solvent interaction of the different substituents.

For the halogenated phenols, the pK_a value of *p*-fluorophenol is higher than that for the other halo-phenols where the pK_a values are almost constant irrespective of the substituent group (Cl, Br and I) and for the halo-phenols the following equation holds well (Hansch and Leo, 1980).

$$\log K_{d,x} = \log K_{d,H} + \sigma^- \tag{12}$$

where σ^- is a substituent constant of the Hammett type that can be used to define the change of pK_a with molecular structure and for the F group is 0.2 lower than than for Cl, Br and I. When the data are corrected using Eqn. 12, a plot of $\log K_{d,x}$ against the increment of volume (Davis et al., 1974) due to the halo-substituent introduced to the *p*-position of phenol gives a good linear relationship.

Effect of solubility parameter of organic solvent on the distribution constant of phenols

When the solute concentration is sufficiently low in both phases, the Regular Solution theory can be used to derive an equation for the distribution constant of solute A (Hildebrand et al., 1970; Shinoda, 1978).

$$\ln K_d^x = \frac{V_A}{RT}\left(\delta_{aq} - \delta_{org}\right)\left(\delta_{aq} + \delta_{org} - 2\delta_A\right) \tag{13}$$

where V_A and δ_A are the molar volume and the solubility parameter of solute A and δ_{aq} and δ_{org} the solubility parameters of the aqueous solution and the organic solvent, respectively. Thus a plot of $\ln K_d^x/(\delta_{aq} - \delta_{org})$ against δ_{org} should yield a straight line with a theoretical slope of V_A/RT. As evident from Fig. 5, this plot yields a straight

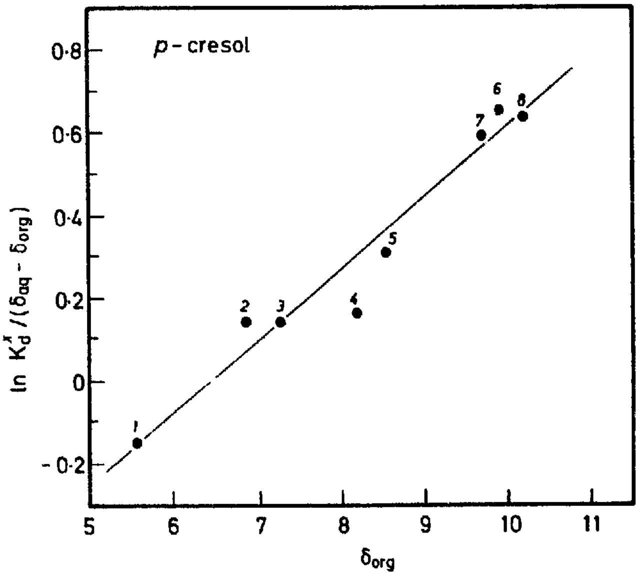

Fig. 5. Plot of $\ln K_d^x/(\delta_{aq} - \delta_{org})$ against δ_{org} for *p*-cresol. Numbers refer to solvents in Table 2.

line with a slope of 0.173, using *p*-cresol as an example. This is in good agreement with the theoretical value of 0.174 calculated using $V_A = 103$ cm^3. A value of δ_{aq} ranging between 15.0 and 16.5 gave good fits with the experimental data. Solubility parameter values for water in the same range have been preferred by previous workers who have studied alkane–water systems and distribution data (Wakahayashi et al., 1964; Davis et al., 1972). For the other phenols similar linear relationships were also obtained.

Effect of solvents on the incremental distribution constant of the methylene group

As evident from Eqn. 14, the distribution constant depends on δ_{org}, δ_A and V_A. The solubility parameter of a solute can be calculated from Eqn. 14.

$$\delta_A = \frac{Z_i}{V_i} \qquad (14)$$

where Z_i and V_i are the molar attraction constant and the molar volume of each group in the solute A, on a constitutive basis (Small, 1953; Rheineck and Lin, 1968). For the increment of one methylene group to log K_d^x, Eqn. 16 is obtained from Eqns. 13 and 14 (Davis et al., 1972).

$$2.303RT\,\Delta \log K_d^x = V_{CH_2}\left(\delta_{aq} - \frac{Z_{CH_2}}{V_{CH_2}}\right)^2 - V_{CH_2}\left(\delta_{org} - \frac{Z_{CH_2}}{V_{CH_2}}\right)^2 \qquad (15)$$

where Δ log K_d^x is the incremental distribution constant per methylene group. With values of Z_{CH_2} between 133 and 140 (cal · cm^{-3})$^{1/2}$ (Small, 1953; Rheineck and Lin, 1968) and $V_{CH_2} = 16.5$ cm^{-3} (Rheineck and Lin, 1968) a maximum value of Δ log K_d^x is found in the region of $\delta_{org} = 8.1$–8.5. A plot of Δ log K_d^x against δ_{org} is shown

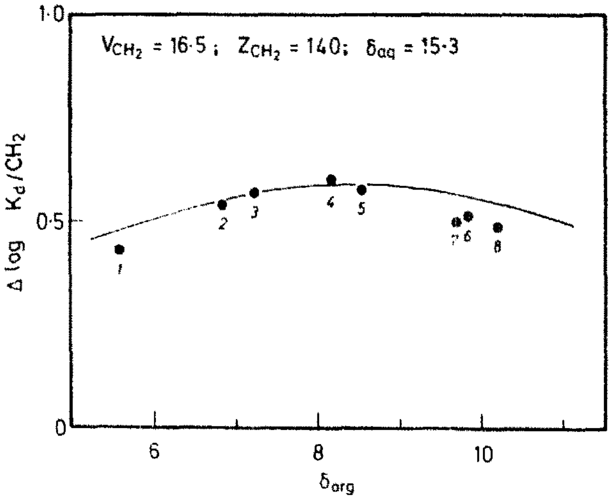

Fig. 6. Plot of Δ log K_d/CH_2 against δ_{org} according to Eqn. 15.

in Fig. 6. As evident from Fig. 6 and Eqn. 15, a maximum value of Δ log K_d^* is obtained at δ_{org} 8.3.

Conclusions

The distribution of various *p*-substituted phenols between water and various organic solvents is determined by the nature of the solute and solvent. For the case of the alkyl phenols the transfer process is entropically controlled while for other substituted phenols the process is enthalpically controlled. Linear enthalpy–entropy plots indicate that the same mechanism of transfer operates for all solutes and solvents studied. Data obtained with one solvent can be converted to those relevant to another solvent using simple linear free energy equations. The data for the transfer of the methylene group can be compared with the theoretical prediction of Regular Solution theory.

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