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SOLUTION THERMODYNAMICS OF 4-HYDROXYBENZOATES IN WATER, 95% ETHANOL–WATER, 1-OCTANOL AND HEXANE

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ABSTRACT

Solubilities have been measured for an homologous series of 4-hydroxybenzoates in water, 95% ethanol–water, 1-octanol and hexane. From solubility data over a range of temperatures, the values of ΔG_{soln}, ΔH_{soln} and ΔS_{soln} are determined. The ΔH_{soln} data are further used to determine the enthalpies of transfer of the solutes from water to the other solvents. In all the solvents studied the ΔG_{soln} data show two linear periods which exhibit breaks with between five and six carbon atoms in the alkyl chain. The data are discussed in terms of hydrophobic/hydrophilic interactions.

INTRODUCTION

In recent papers [1–3] we reported solubilities and enthalpies of solution for series of alkoxyphenols in water, 1-octanol, water–1-octanol (mutually saturated) and water–alcohol systems. The objective was to explore the relationships between structure and behaviour for some simple systems. Such data are of use in the development of quantitative structure–activity relationships (QSAR) for drug substances [4]. For the studies in the water–alcohol systems, the alcohols (from methanol to 1-octanol) were present in water at a concentration of 0.00316 mol dm^{-3} (the saturating concentration of 1-octanol in water at 298 K). Discontinuities in these and the other solvent systems were noted. Thus, plots of solubility versus carbon number in the alcohols showed breaks for both *m*- and *o*-alkoxyphenols [2,3]. In studies [1] where the solvent system was maintained constant and the solute

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varied, the solubilities (in water, and in water–1-octanol mutally saturated) revealed oscillations. In the light of these results and those reported by Yalkowsky et al. [5] for solutions of 4-aminobenzoates in a variety of solvents, where both discontinuities and oscillations were observed, we decided to extend our studies on solubilities and QSAR to the study of 4-hydroxybenzoates. These compounds are of some interest in their widespread use as preservatives (against microbial spoilage) in a variety of commercial products [6]. The discontinuities in the water–alcohol systems were noted as occurring at the point where the solute and alcohol molar volumes were approximately (within 10%) equal. The explanations offered for these observations were, obviously, related to H-bonding, to solute–solvent interactions and to molar volumes.

We have extended these studies to new solutes, the 4-hydroxybenzoates, and to the study of their solubilities in both pure and mixed solvent systems. We are interested in the extent to which physical properties are, generally, related to structure, in the role played by the solvent, and in discontinuities in physical properties as structures of solutes/solvents are changed.

MATERIALS AND METHODS

The measurements of solubilities were made as previously reported [1]. The 4-hydroxybenzoates were the gift of Apin Chemicals Ltd. (Abingdon, Great Britain) and were used as received (purity specified as > 99.5%). All solvents were of AnalaR grade. Absorbance measurements were made at $\lambda_{max} = 258$ nm.

RESULTS AND DISCUSSION

Table 1 describes the measured solubilities of the 4-hydroxybenzoates in the four solvent systems investigated, water, 95% ethanol–water, 1-octanol and hexane. Table 2 lists the values of the thermodynamic parameters for solution derived from the study of the variation of solubility with temperature. Table 3 describes the enthalpies of transfer of these solutes from water both to 95% ethanol–water and to hexane.

The noteworthy feature of the solubility data presented in Table 1 and in the form of ΔG_{soln} in Table 2 is the non-linear behaviour, with respect to carbon number in the alkyl chain, in all the solvents studied. In a study of the solubility of alkyl 4-aminobenzoates, Yalkowsky et al. [5] showed that the solubility of these solutes exhibited an unusual dependence upon alkyl chain length. The characteristic feature of the data reported by Yalkowsky et al. [5] was that the solubilities in water, silicone oil and hexane revealed a definite break in the alkyl chain length profile at about the butyl ester. Plots

TABLE 1

Solubilities (mol dm^{-3}) of 4-hydroxybenzoates in water, 95% ethanol–water, octanol and hexane at 288, 293 and 298 K

Ester	Temperature		
	288 K	293 K	298 K
Water			
Me	8.31×10^{-3}	9.97×10^{-3}	1.14×10^{-2}
Et	2.75×10^{-3}	3.37×10^{-3}	4.09×10^{-3}
Pr	2.05×10^{-3}	2.41×10^{-3}	2.57×10^{-3}
Bu	7.04×10^{-4}	8.35×10^{-4}	1.05×10^{-4}
Hex	3.68×10^{-4}	3.81×10^{-4}	6.19×10^{-4}
Hep	2.01×10^{-4}	2.52×10^{-4}	2.63×10^{-4}
Oct	1.47×10^{-5}	2.30×10^{-4}	4.65×10^{-4}
Dec	3.20×10^{-5}	3.71×10^{-5}	8.80×10^{-5}
95% Ethanol–water			
Me	1.54	1.90	2.80
Et	1.93	2.19	2.87
Pr	2.23	2.22	3.31
Bu	3.21	3.36	3.92
i-Bu	3.10	3.29	4.30
Hex	3.16	3.50	3.95
Hep	3.29	3.79	4.14
Oct	3.00	3.07	3.16
Dec	1.66	1.66	2.15
Dodec	2.30	2.40	2.49
Benzyl	1.41	1.79	2.39
1-Octanol			
Me			0.71
Et			–
Pr			2.16
Bu			2.39
i-Bu			2.81
Pen			3.96
Hex			6.35
Hep			4.52
Oct			3.67
Dec			1.96
Benzyl			9.76
Hexane			
Me	1.09×10^{-3}	2.50×10^{-3}	2.21×10^{-3}
Et	2.56×10^{-4}	4.38×10^{-4}	5.33×10^{-4}
Pr	6.67×10^{-4}	8.67×10^{-4}	1.28×10^{-3}
Bu	1.39×10^{-3}	2.23×10^{-3}	2.54×10^{-3}
Hex	1.90×10^{-2}	3.00×10^{-2}	3.90×10^{-2}
Hep	$1.0\ \times10^{-2}$	2.80×10^{-2}	3.20×10^{-2}
Oct	6.78×10^{-3}	1.10×10^{-2}	1.80×10^{-2}
Dec	3.08×10^{-3}	4.67×10^{-3}	7.16×10^{-3}

TABLE 2

Thermodynamic parameters (kJ mol^{-1}) at 298 K for solution of 4-hydroxybenzoates in water, 95% ethanol–water, 1-octanol and hexane. ΔG_{soln} calculated as $\Delta G_{\text{soln}} = -RT \ln x$, where x is the mole fraction of the solute at equilibrium

Ester	ΔG	ΔH[a]	ΔS
Water			
Me	11.09	22.64	0.04
Et	13.62	28.43	0.05
Pr	14.78	16.18	0.005
Bu	16.99	28.60	0.04
Hex	18.30	37.09	0.06
Hep	20.42	19.24	0.004
Oct	19.01	82.69	0.21
Dec	23.14	72.47	0.17
95% Ethanol–water			
Me	5.54	39.23	0.113
Et	5.49	25.68	0.66_8
Pr	5.33	20.62	0.005
Bu	4.81	12.38	0.025
i-Bu	4.62	26.15	0.05
Pen	4.32	7.49	0.01
Hex	4.80	13.88	0.03
Hep	4.70	14.51	0.03
Oct	5.28	3.25	-0.00_7
Dec	6.13	36.49	0.10
Dodec	5.80	5.15	-0.00_2
Benzyl	5.90	34.66	0.10
1-Octanol			
Me	5.69		
Et	–		
Pr	3.47		
Bu	3.20		
Pen	2.36		
Hex	1.71		
Hep	2.17		
Oct	2.48		
Dec	3.57		
Hexane			
Me	15.15	51.09	0.12
Et	18.67	52.78	0.11
Pr	16.50	46.71	0.10
Bu	14.80	43.37	0.10
Hex	8.04	83.70	0.25
Hep	8.53	83.35	0.25
Oct	9.95	69.99	0.20
Dec	12.24	60.49	0.16

[a] For most of the systems studied the correlation coefficients for plots of $\ln x$ vs. $1/T$ were > 0.98.

TABLE 3

Enthalpies of transfer (kJ mol^{-1}) of 4-hydroxybenzoates from water to 95% ethanol–water and from water to hexane

Ester	ΔH_{trs}
Water → 95% ethanol–water	
Me	16.59
Et	−2.75
Pr	−4.44
Bu	−16.22
Hex	−23.21
Hep	−4.73
Oct	−79.44
Dec	−35.98
Water → hexane	
Me	28.45
Et	24.35
Pr	30.53
Bu	14.77
Hex	46.61
Oct	−12.7
Dec	−11.98

of the ΔG_{soln} data ($\equiv -\ln \text{Sol}/RT$) as a function of chain length are shown in Fig. 1. The striking feature of these data is again that breaks are shown, in these cases at alkyl chain lengths (n) between 5 and 6. Solubility data referring to variation in solute solubility as a function of co-solvent chain length (alcohols, methanol to octanol, present in water at the same concentration, 0.00316 mol dm^{-3}) has indicated [1,2] that solvent properties,

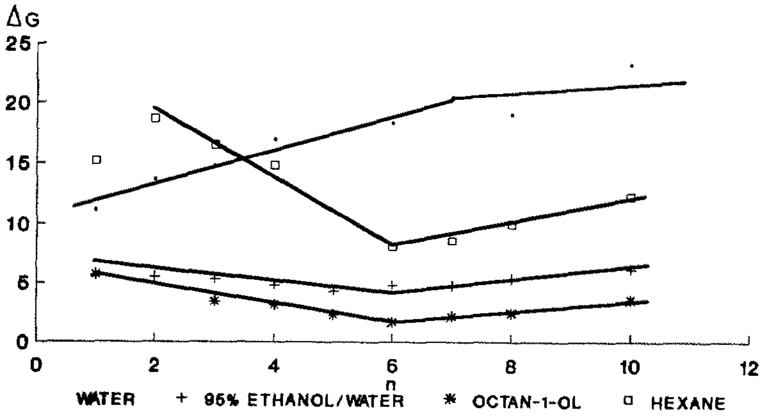

Fig. 1. Plot of ΔG_{soln} vs. n (the carbon number in the side chain) for solution of 4-hydroxybenzoates in water, 95% ethanol–water, 1-octanol and hexane.

particularly molar volume comparability between solute and the alcoholic component at which a break is seen, are important. The results reported here for solubility of homologous series of solutes in defined solvent systems indicate that other factors must be operating. Yalkowsky et al. [5] identified a change in the crystal lattice of the alkyl 4-aminobenzoates as being responsible for the characteristic solubility trends observed for these solutes. They also noted that, as here, partition coefficients increase systematically with alkyl chain length. The enthalpies of solution for the alkyl 4-hydroxybenzoates do not reveal any truly systematic patterns when examined in each separate solvent system. However, a pattern of a limited type does emerge when the enthalpies of transfer of these solutes from water to 95% ethanol–water and to hexane (the solubility of these alkyl 4-hydroxybenzoates was not measured as a function of temperature in octanol) are examined.

The enthalpy of transfer data again appear not to be correlated with alkyl chain length. Thus, again, a critical dependence of physico-chemical properties upon n appears to be established.

Inspection of the values of ΔG_{soln} in Table 2 and as displayed in Fig. 1 suggest the existence of two linear portions in plots of ΔG_{soln} vs. n. Table 4 shows the slope (i.e. the contribution to ΔG_{soln} per methylene group) and the square of the correlation coefficients for each solvent system at values of $n < 6$ and $n > 6$. The modest straight line relationships displayed by these data suggest that, for $n > 6$, the contribution to the Gibbs function of solution per methylene group for these solutes is not markedly dependent on the solvent system under study; the absolute values of ΔG_{soln} do, of course, depend upon the solvent. However, the contribution to the Gibbs function for solution per methylene group for $n < 6$ is very strikingly dependent on the solvent, being, for example, 1.43 kJ mol^{-1} in water and -2.66 kJ mol^{-1} in hexane. These values, of course, are confirmation of the unfavourable effects of increasing the hydrophobic moiety in water and the favourable effects of increasing hydrophobicity in hexane as solvent. The change in the slopes of ΔG_{soln} vs. n plots for $n < 6$ are, therefore, the compromise between

TABLE 4

Regression coefficients (slope and square of the correlation coefficient) for plots of ΔG_{soln} vs. n for all solvents investigated

Solvent	$n < 6$		$n > 6$	
	slope	r^2	slope	r^2
Water ($n < 7$)	1.43	0.9666	–	–
95% Ethanol–water	−0.40	0.9589	0.35	0.9374
1-Octanol	−0.61	0.9665	0.46	0.9900
Hexane	−2.66	0.9780	1.09	0.9818

the hydrophilic portions of the alkyl 4-hydroxybenzoates, i.e. the OH group and some H-bonding capacity of the –C=O in the benzoate group, and the hydrophobic aromatic ring and alkyl chain. The 95% ethanol–water system, like octanol, appears to possess properties which are intermediate between water and hexane with respect to trends in ΔG_{soln}. Thus the hydrophilic and hydrophobic portions of these solutes can find some reasonable and approximately similar accommodation in the two solvent systems. That there is a break at $n = 5$–6 is presumably due to the possible conformations of the alkyl chain at $n \geq 5$, and the impact of the hydrophobic hydration shell of the alkyl chain at $n \geq 5$ imposing a fairly uniform effect on the hydrophilic part of the solute molecule. These effects appear, therefore, to result in an almost uniform increment in the contribution to ΔG_{soln} per methylene group for $n > 6$.

These accounts are supported by data from Smith et al. [7], who have suggested (without detail being given) that breaks in log (partition coefficient) vs. n for partitioning into some lipoid solvents show breaks because of (i) hydrophobic interaction of the solute with dissolved non-aqueous solvent, (ii) folding of the solute molecule so as to present the smallest possible non-favourable "face" to the solvent, and (iii) some form of associative behaviour. It is unlikely that factor (iii) could have any role in these systems, whereas 95% ethanol–water and octanol clearly have some "dual", i.e. hydrophobic/hydrophilic character.

These data are, therefore, consistent with the view, expressed previously (see Ref 7. and references cited therein) that chain length has considerable influence on physico-chemical properties of solutes in solutions. They do, however, underline the need for careful investigations in attempts to relate chemical structure to behaviour (linear free energy relationships), and more particularly, in the study of such relationships in the pharmacy/biology field [4].

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