Determination of the Thermodynamic Parameters for Transfer of Alkoxyphenols from Aqueous Solution to SDS Micelles by a Taylor–Aris Diffusion Technique

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Using Taylor–Aris diffusion techniques, thermodynamic parameters have been measured for the transfer of a series of alkoxyphenols from water into SDS micelles. The results are compared with those for transfer to bulk organic solvents and to cells of *Escherichia coli*. The SDS micelles are found to be marginally more polar than *n*-octanol, but the results reveal significant differences between bulk solvents and the more ordered micellar pseudophase.

Micelles and liposomes are of major importance in both fundamental and applied chemistry.[1] Molecular diffusion, likewise, plays a central role in many chemical phenomena: in reaction kinetics, separation techniques and in countless biological processes. Diffusional behaviour in liquids may be modified by the presence of microparticulate pseudophases such as micelles or unilamellar vesicles (ULVS). In recent applications micellar systems have been used to modify chemical reactions,[2] in chromatography[3] and as model systems for the study of *e.g.* biological antioxidants.[4] A method[5] that depends upon measurement of diffusion coefficients *via* the Taylor–Aris[6] dispersion technique, has been described for determination of partition coefficients in micellar systems

$$P = a_o/a_w \approx c_o/c_w$$

where a_i are activities, c_i are concentrations and subscripts o and w refer to organic solvent and water, respectively. Extension to the analysis of the inhibition kinetics of chain-breaking phenolic antioxidants in micelles has also been described.[4]

Pratt and Wakeham[7,8] have given a detailed theoretical treatment of diffusion in liquids in Taylor–Aris dispersion systems. They noted the variation of the diffusion coefficient with dispersion time and analysed, in detail, the equilibrium (*i.e.* independent of dispersion time or flow rate) diffusion coefficient dependence on temperature (over the range 20–65 °C). More recently[9] convective–diffusive transport of chemically reactive solutes has been the subject of a detailed theoretical treatment.

The studies[4,5] on partition coefficients have relied upon the establishment of equilibrium conditions in the Taylor–Aris flowing system, moreover the partition coefficients reported were determined[4,5] for series of unrelated compounds at only one temperature in each study (298.15 and 313 K, respectively). Thus no thermodynamic data are available from these studies except the value of $\Delta_{trans} G$ (free-energy change associated with solute transfer from aqueous buffer to micelles) for each solute at the temperature of the experiment. A simple extension of this procedure to the study of solute transfer as a function of temperature should allow derivation (*via* the van't Hoff isochore, noting the limitations of this treatment[10]) of $\Delta_{trans} H$ and $\Delta_{trans} S$. Such data are of great

interest in medicinal chemistry, where thermodynamic foundations for the establishment of a relationship between drug structure and activity are commonly sought (quantitative structure activity relationships; QSAR).[11] Indeed, we have proposed[12] that thermodynamic parameters for transfer processes may be used to select solvent systems, including micellar and liposomal dispersions, that best mimic the properties of the biological membrane.

$\Delta_{trans} G$, $\Delta_{trans} H$ and $\Delta_{trans} S$ data for a homologous series of solutes may also be used to test for compensation, although we note here that data derived from van't Hoff treatments, and consequently subject[13] to error propagation, may yield spurious compensation in $\Delta H/\Delta S$ plots. The better plot to examine,[11,13] for 'chemical causality' is a plot of $\Delta G/\Delta H$ at the harmonic mean of the experimental temperature range.

The choice of solutes for study, a homologous series of 3-alkoxyphenols, was determined by their ready availability and by the existence of a body of thermodynamic data describing transfer of these same solutes from water to bulk solvents[14] (octan-1-ol, heptane and propylene carbonate) and for transfer from isotonic aqueous solution to non-metabolising *E. coli* cells.[15]

Experimental

Materials

Alkoxyphenols were prepared as described previously.[16] Sodium dodecyl sulphate was of AnalaR grade and anthracene was of AnalaR grade and was sublimed before use.

Apparatus

The apparatus was described previously.[4,5] The temperature was controlled by immersion of the tubing in a water bath maintained at the desired temperatures to ± 0.1 K. Flow rate was controlled *via* a Perkin-Elmer HPLC pump system.

Samples

Samples were prepared at 3 or 0.3 mmol dm^{-3} concentration in buffer (50 mmol dm^{-3} phosphate, pH 7.0). SDS concentration in the micellar systems was 15 mmol dm^{-3} (*i.e.* well

above the c.m.c.[17] for SDS). A function spikes (10^{-5} dm^3) of solute in buffer were introduced into the column and solute elution was monitored by UV absorption ($\lambda = 273$ nm).

Results and Discussion

Equilibrium

The diffusion coefficients were calculated from experimental data as described by Burkey et al.[5] for the systems (i) anthracene in micellar suspension, to act[4,5] as a tracer of micellar diffusion; (ii) alkoxyphenol in buffer; (iii) alkoxyphenol in micellar suspension. Partition coefficients were then evaluated for transfer of the alkoxyphenols from aqueous buffer to micelles.

The values of P, the partition coefficient, were derived by the method described by Burkey et al.[5] Essentially the method requires calculation of f, the fraction of the solute transferred from the aqueous, buffered phase to the micellar phase. P is therefore given as $f/(1-f)$. As always, provided the solutions are dilute (in the Henry's law region) and that saturation is not approached in either solvent system then the standard reference state is a property of the infinitely dilute solution.

As temperature was, necessarily, varied throughout this work the diffusion coefficients of the micelles themselves (using the anthracene tracer technique[5]) were measured at each experimental temperature. This procedure compensated for any effects upon the micelles of the variation in temperature.

As the calculation of fractionation (f) depends on the accurate determination of diffusion coefficients, our procedure was validated using the method of Burkey et al.[5] where the diffusion coefficient in a well defined system (diffusion of benzene in cyclohexane) was determined and found to compare favourably with the reported value.[5]

Variation in pump speed of buffer or micelles through a constant length tube allows control over the contact time. Previous publications[4,5] have relied upon (i) long tube length (10 m)[4] and (ii) such pump speeds that maintain laminar flow of liquid/suspension through the tube to ensure that equilibrium has been attained on passage of the solute through the detector.[7,8] It is clear that, in a tube of constant length, not all pump speeds will lead to laminar flow and moreover that trial and error will be required to confirm that equilibrium has been established (the partition coefficients, P, should be independent of pump speed at long contact times). Such a search procedure is unsatisfactory and a kinetic analysis of P_{app} (the apparent value of P at pseudo-equilibrium) should be capable of yielding values of P itself. This problem will be explored in a subsequent paper. Here we report only equilibrium values of P.

In Table 1 we report the derived values of the (equilibrium) partition coefficients for the solutes studied as a function of temperature and in Table 2 the values of $\Delta_{trans}H$. Table 3 summarises the thermodynamic data for the transfer process.

The notable features of the data displayed in Table 2 are, first, the excellent linearity of the ln P vs. $1/T$ plots and, secondly, the non-systematic variation in the derived values of $\Delta_{trans}H$. Unfortunately hexoxyphenol is insufficiently soluble in aqueous solutions to permit study in the partition experiment and is also precluded on this ground from study in the much more laborious shake-flask technique.[16] The values of $\Delta_{trans}G$ when plotted against carbon number in the alkyl chain do not produce a linear relationship. There is, however, a modest linear relationship between ΔH and ΔS (correlation coefficient 0.9814; compensation $T = 404$ K), and between ΔG and ΔH (correlation coefficient 0.9559). It is therefore just possible to show compensation behaviour and thus chemical

Table 1 Values of P^a as a function of temperature for transfer of m-alkoxyphenols from aqueous buffer to SDS micelles

solute	T/K	P
m-methoxyphenol	288	0.40
	293	0.37
	303	0.35
	313	0.27
m-ethoxyphenol	288	0.86
	293	0.90
	303	0.71
	313	0.65
m-propoxyphenol	288	4.11
	293	3.72
	303	2.64
	313	1.84
m-butoxyphenol	288	13.60
	293	12.53
	303	6.60
	313	5.33

^{a} Each value of P quoted is the average of a minimum of three replicates. The reproducibility in determination of f (the fraction of solute transferred to micelles[4,5]) is estimated as $\pm 3\%$.

causality[11,13,18] in the behaviour of these solutes in this micellar system.

Table 4 compares the values of $\Delta_{trans}H$ derived here with those for transfer[14] of these same solutes from water to heptane, octan-1-ol and propylene carbonate, and for transfer[15] from isotonic aqueous solution to non-metabolising E. coli cells. It is apparent from these data that no bulk solvent, or indeed micelles, represents as far as

Table 2 Values of $\Delta_{trans}H$ for transfer of the named solute from aqueous buffer to SDS micelles derived from plots of ln P vs. $1/T$

solute	$\Delta_{trans}H$/kJ mol^{-1} ^{a}	correlation coefficient
m-methoxyphenol	-11.6	0.9990
m-ethoxyphenol	-9.6	0.9986
m-propoxyphenol	-24.4	0.9954
m-butoxyphenol	-30.5	0.9743

^{a} The associated error is estimated to be $\pm 4\%$.

Table 3 Values of $\Delta_{trans}G$ and $\Delta_{trans}H$ (kJ mol^{-1}) and $\Delta_{trans}S$ (kJ mol^{-1} K^{-1}) for transfer of m-alkoxyphenols from aqueous buffer to SDS micelles at 303.15 K

solute	$\Delta_{trans}G$	$\Delta_{trans}H$	$\Delta_{trans}S$
m-methoxyphenol	2.66	-11.56	-0.047
m-ethoxyphenol	0.85	-9.58	-0.031
m-propoxyphenol	-2.45	-24.44	-0.073
m-butoxyphenol	-4.76	-30.45	-0.085

Table 4 Values of $\Delta_{trans}H$ (kJ mol^{-1}) for transfer of m-alkoxyphenols from water to the specified non-aqueous solvent systems

solute	cells	SDS^a	octan-1-ol	heptane	propylene carbonate
m-methoxy	-0.22	-11.56	-8.03	20.9	23.2
m-ethoxy	-1.1	-8.58	-6.95	19.3	23.4
m-propoxy	-2.02	-24.44	-6.96	16.0	23.9
m-butoxy	-4.06	-30.45	—	13.9	23.4
m-pentoxy	-5.14	—	—	12.0	23.2

Cells means transfer[15] of the solutes from aqueous isotonic solution to non-metabolising E. coli. ^{a} At 303 K, all other entries refer to 298.15 K.

$\Delta_{trans} H$ is concerned, the properties of the selected biological cell. Moreover the data of Tables 2 and 4 show that for micelles the transfer process is enthalpically favourable.

The values of $\Delta_{trans} G$ shown in Table 3 reveal that for *m*-methoxyphenol and *m*-ethoxyphenol the transfer process is unfavourable whereas it may apparently become increasingly favoured as the alkyl chain extends beyond *m*-propoxyphenol. This favourability surprisingly derives mainly from the enthalpic advantage to be derived upon transfer of these increasingly hydrophobic solutes out of water into a lipophilic environment, the hydrocarbon core of the micelle.

The negative values recorded for $\Delta_{trans} H$ presumably implies that the removal of the solute from water results in a net increase of H-bonding following relaxation of the water structure back to that of bulk water upon removal of solute together with new solute/solvent–micelle association.

$\Delta_{trans} G$ itself can be factored into contributions from CH_2 groups (designated L) and from the parent group ($C_6H_4O_2H$; designated H) *via* the equation:[14]

$$\ln P = -\frac{n\Delta\mu_L^0}{RT} - \frac{\Delta\mu_H^0}{RT} \qquad (1)$$

where *n* is the number of methylene groups in the alkyl chain that contribute to the overall change in chemical potential upon transfer of $\Delta\mu_L^0$, and $\Delta\mu_H^0$ is the change in chemical potential associated with transfer of the parent fragment of the molecule. The results of this factoring for each experimental temperature are shown in Table 5.

These data indicate that there is an essentially constant contribution to $\Delta_{trans} G$ from transfer of the parent group. The transfer is affected, however, by the increasingly negative contribution made by the methylene groups to a favourable transfer process. It is notable that whereas there is no systematic dependence upon temperature for transfer of the parent group there is such a systematic dependence for the transfer process of methylene groups.

Treatment of the data in Table 5 *via* the van't Hoff isochore allows derivation of $\Delta_{trans} H$ for each group transferred from aqueous buffer to SDS micelles (Table 6). In Table 7 we show the assembled values of the thermodynamic parameters for these group transfer processes. In Table 8 are data reported[14] for transfer of these same groups from water to heptane to propylene carbonate and to octan-l-ol.

The value of $\Delta\mu_L^0$ reported here (Table 8) of -2.43 kJ mol^{-1} is close to, and consistent with, the mean of values (-1.72 to -2.9 kJ mol^{-1}) found[19] for transfer of a methylene group from water to micelles.

Table 7 shows that transfer of the parent fragment is unfavourable whereas transfer of the methylene group is

Table 5 Values of $\Delta\mu_H^0$ and $\Delta\mu_H^0$ (kJ mol^{-1}) at each experimental temperature

T/K	$\Delta\mu_H^0$	$\Delta\mu_L^0$	correlation coefficient
288	5.50	−2.91	0.9925
293	5.51	−2.86	0.9961
303	5.19	−2.43	0.9944
313	5.65	−2.39	0.9989

Table 6 Values of $\Delta_{trans} H$ (kJ mol^{-1}) derived from transfer of methylene and parent groups (see text) from aqueous buffer to SDS micelles

group	$\Delta_{trans} H$
CH_2(L)	−7.4
parent, *i.e.* $C_6H_4O_2H$(H)	*ca.* 0

Table 7 Thermodynamic parameters (kJ mol^{-1}) for group transfer (L, H; see text) from aqueous buffer to SDS micelles

group	$\Delta\mu^0$	$\Delta_{trans} H$	$\Delta_{trans} S$
CH_2(L)	−2.43	−7.4	−0.02
parent, *i.e.* $C_6H_4O_2H$, (H)	5.19	*ca.* 0	−0.02

favoured. Eventually, of course, as the alkyl chain extends the effects of the contribution from methylene groups dominate overall behaviour (Table 3). The, apparently, near-zero enthalpy of the transfer of the parent group is surprisingly different from the data for transfer of this same group from water to other solvent systems. It was noted previously[14] that transfer of methylene groups to a variety of bulk solvents was accompanied by values of $\Delta_{trans} H$ of *ca.* 0. The values recorded here for transfer of alkoxyphenols to SDS micelles are presumably, therefore, a consequence of transfer of these solutes from a bulk solvent (water) to an organised solvent (the micelles).

We have proposed[14] that for QSAR purposes a reference transfer solvent system would be advantageous and, given its ubiquity, we have adopted[12] octan-l-ol. Consequently analysis[12] of the Collander equation

$$\ln P(I) = a + b \ln P(II) \qquad (2)$$

where $P(I)$ and $P(II)$ represent partition coefficients for the same solute partitioned between water and non-aqueous solvent I and between water and non-aqueous solvent II, can lead,[12] through expressions of the form of eqn. (1) and assignment of solvent system II as a reference system, to use of *b* in eqn. (2) as a solvent scaling factor. *b* is shown to be equal to $\Delta\mu_L^0(I)/\Delta\mu_L^0(II)$.

Table 9 lists values of *b* calculated on this basis and incorporates the value of *b* for the work reported here where (I) refers to W → SDS transfer and (II) to W → octan-l-ol transfer for the same solutes. The position of SDS in this listing implies that (with the general conclusions of our earlier work in which values of $b < 1$ are associated with solvent systems

Table 8 Thermodynamic data (kJ mol^{-1}; $\Delta_{trans} S$/kJ mol^{-1} K^{-1}) for transfer of CH_2(L) and parent group (H) from water (W) to heptane (h), propylene carbonate (pc), octan-l-ol (o) and to SDS micelles

system	$\Delta_{trans} H$	$\Delta_{trans} G$	$\Delta_{trans} S$	ref.
		parent group (H)		
W → h	23.5	2.92	0.069	14
W → pc	−22.1	−10.69	−0.038	14
W → o	−9.2	−9.75	0.002	14
W → SDS	0	5.19	−0.02	this work
		CH_2 group (L)		
W → h	0	−3.07	0.013	14
W → pc	0	−1.11	0.004	14
W → o	0	−2.96	0.01	14
W → SDS	−7.4	−2.43	−0.02	this work

Table 9 Values of *b* [eqn. (2)] calculated for transfer of *m*-alkoxyphenols from water to the specified solvent (I)

solvent (I)	*b*	ref.
propylene carbonate	0.36	14
SDS micelles	0.82	this work
octan-l-ol	1.0	14
heptane	1.04	14

Octan-l-ol is defined[12] as solvent (II).

which are wetter than octan-l-ol and $b > 1$ values are associated with essentially hydrophobic solvent systems) transfer of these solutes appears to result in a micelle which is wetter than octan-l-ol. This result is reasonably consistent with some data in the literature, for example, free-radical dynamics in organised solvent systems have been shown[20] to reflect solvent polarity. Reaction half-lives in methyl laurate were shown to be much shorter than those in dodecane but longer than those in butan-l-ol. However the sensitivity of b to variation in solvent polarity is, as yet, unknown.

Overall therefore, the equilibrium approach to the determination of P via Taylor–Aris diffusion techniques has been shown to be simple, rapid and capable of yielding thermodynamic data which are consistent with data derived for the sample solutes in other transfer systems. They are, however, apparently indicative of the differences between bulk solvent systems and of structure solvent systems.

We believe, therefore, that this simple, flowing, dispersion system should, under appropriately controlled conditions, be capable of yielding P values for solute (drug) transfer into SULVS, and, indeed, biological cells. This prospect, of a simple, rapid and effective determination of P in complex solvent systems is under systematic investigation in our laboratories.

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