Thermochimica Acta, 116 (1987) 329–335
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SOLUTION THERMODYNAMICS FOR *o*-ALKOXYPHENOLS IN WATER AND IN WATER–ALCOHOL SYSTEMS

ANTHONY E. BEEZER, M. CONCEICAO P. LIMA [1], GARY G. FOX,
WILLIAM H. HUNTER and BRIAN V. SMITH [2]

Chemistry Department, Royal Holloway and Bedford New College, University of London, Egham Hill, Egham, Surrey TW20 0EX (Gt. Britain)
[1] *Departamento de Quimica, Universidade de Coimbra, Coimbra (Portugal)*
[2] *Chemistry Department, King's College (KQC), Campden Hill Road, London W8 (Gt. Britain)*

(Received 16 December 1986)

ABSTRACT

Solubilities have been measured for *o*-alkoxyphenols in water–alcohol mixtures. The alcohols ranged from the co-solvent methanol to the co-solute 1-octanol and each alcohol was present at the saturating concentration of 1-octanol in water viz. 0.00316 M. Plots of solubility vs. carbon number of the alcohols show discontinuities. Enthalpies of solution in these same solvent systems have also been measured. The data are compared with those for *m*-alkoxyphenols. The results and the comparison are discussed in terms of *H*-bonding, solvent–solute interactions and in terms of solute volumes.

INTRODUCTION

In a recent paper [1] we reported on the solution thermodynamics of *m*-alkoxy phenols in alcohol and in water–alcohol systems. The three component systems (phenol/water/alcohol) were of interest because of our previous studies [2] on the thermodynamic parameters of transfer of solutes of pharmaceutical interest between water and some non-aqueous solvents which were taken to represent the behaviour of the biological membrane [3]. Many partitioning experiments result in three component systems because of mutual solubility of the solvents. The alcohol present in each system studied was maintained at a concentration of 0.00316 M (the saturating concentration of octan-1-ol in water at 298 K). The alcohols from methanol to octan-1-ol were systematically investigated. When solubilities and enthalpies of solution were measured, discontinuities were observed in the plots of solubility vs. carbon number of the alcohols. The enthalpies of solution and the enthalpies of transfer (from water/alcohol to pure alcohol systems) were in agreement with the solubility measurements. The discontinuities were noted as occurring at the alcohol component of the solvent system whose molar volume was very close to that of the solute studied. The relationship between these observations on the solubilities of the *m*-alkoxyphenols and

0040-6031/87/$03.50

on the details of the solution process was not discussed in detail since three component systems are very complex but the explanation of the trends discovered must lie in the solute–solute and solute–solvent interactions.

The recently published discussions of linear solvation energy relationships [4], whilst illuminating as they do the factors that correlate a wide variety of solvent effects, have not included any discussion of the case of *mixed* solvent systems. The analysis of partitioning behaviour which is described in some of these publications draws attention to the correspondence between experimental values of the partition coefficient and those calculated using the LSER approach. The discussions do not, however, take account of the mutual solubility of the water/octan-1-ol system except in so far as the coefficients of the parameters of the terms of the LSER equation do indeed reflect properties of the solvent system under investigation. It remains to be seen whether the various coefficients correlate with chemically significant features of the solvents. The concentration of octan-1-ol in water at saturation is 0.00316 M at 298 K and of water in octan-1-ol is ca. 2.3 M at 298 K. Lee [5] has also described, for pure solvent systems, some of the factors which determine the solubilities of nonpolar solutes in water, this time in statistical–mechanical terms.

In an attempt to focus on some of the difficulties, and to provide some quantitative results for solution thermodynamics in these systems which may improve our understanding, we have extended our previous study to the *o*-alkoxyphenols in solution in the same water/alcohol systems by measurement of their solubilities and their enthalpies of solution. The interest here is in the behaviour of solutes whose enhanced possibilities of internal hydrogen bonding compared to their *m*-analogues may influence these properties.

There are insufficient data to allow the parameterisation of LSER equations and hence to evaluate the variation of the coefficients and their correlation with the varying properties of these solvent systems. It should be noted that the behaviour of the alcohols ranges from that of co-solvent, e.g, methanol to co-solute, e.g., octan-1-ol.

MATERIALS AND METHODS

The measurement of solubilities and of the enthalpies of solution were as previously reported [1,6]. The preparation and determination of purity of the alkoxyphenols have been described previously [3].

RESULTS AND DISCUSSION

Table 1 and Fig. 1 report the solubilities of the homologues of *o*-alkoxy phenols as a function of the alcohol component of the water/alcohol solvent

TABLE 1

Solubilities (mM) of *o*-alkoxyphenols in water and in water/alcohol solvents (alcohol concentration, 0.00316 M) at 298.15 K

Solvent	*o*-Me	*o*-Et	*o*-Pr	*o*-Bu
Water	188 ± 3	60.9 ± 1	15.5 ± 0.3	3.92 ± 0.2
Water/methanol	190 ± 3	60.6 ± 1	15.8 ± 0.3	4.01 ± 0.2
Water/ethanol	191 ± 3	61.8 ± 1	16.3 ± 0.3	4.06 ± 0.2
Water/propanol	192 ± 3	60.3 ± 1	15.4 ± 0.3	3.98 ± 0.2
Water/butanol	193 ± 3	60.2 ± 1	15.5 ± 0.3	4.35 ± 0.2
Water/pentanol	192 ± 3	57.8 ± 1	15.1 ± 0.3	3.95 ± 0.2
Water/hexanol	184 ± 3	58.15 ± 1	16.0 ± 0.3	4.37 ± 0.2
Water/heptanol	175 ± 3	54.3 ± 1	14.0 ± 0.3	3.87 ± 0.2
Water/octanol	125 ± 3	52.0 ± 1	11.9 ± 0.3	3.73 ± 0.2

systems, each alcohol present at a concentration of 0.00316 M. Again, as with the *m*-alkoxyphenols the noteworthy feature of these results is the sharp break in solubility that occurs for each solute separating two linear sections. In contrast to the *m*-homologues, however, the break in the plot for the methoxy compound now occurs at the water/pentanol system not at the water/butanol system. The *o*-ethoxy compound shows a break at water/hexanol (cf. water/pentanol in the *m*-series) and interestingly the

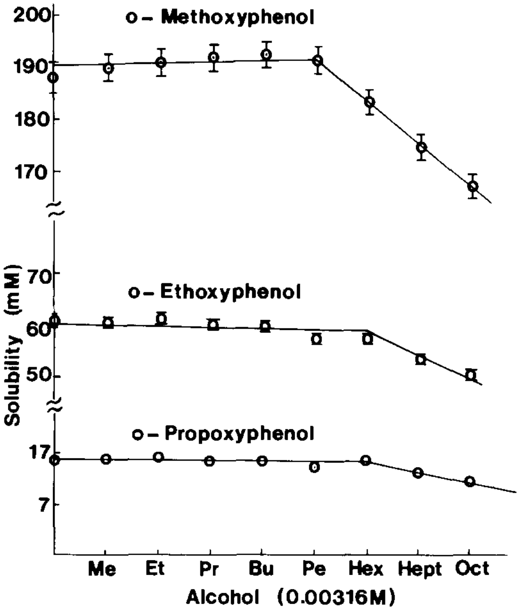

Fig. 1. Solubilities of *o*-alkoxyphenols in water/alcohol systems (alcohol concentration 0.00316 M).

break is still at the water/hexanol point for *o*-propoxy—the same break point as for the *m*-propoxy solute. The explanation for the breaks offered previously was that the volumes of the solute and the alcoholic component of the solvent were approximately the same and hence at this point we may regard the solute and the alcohol as co-solutes competing for the restricted non-aqueous cavities available in that solvent system. The fact that this simple relationship is disturbed somewhat in the *o*-series suggests a change in the " volume" of the *o*-homologues, at least up to the propoxy substituent. These data suggest therefore that some feature of the solute's structure is now contributing to this modified behaviour, perhaps internal hydrogen bonding. Reference was made in the earlier paper in this series to other results which lend some support to this proposal [7–13].

This conclusion, that the structure of the solute influences the solubility in a very dramatic manner is reinforced by the enthalpy of solution data presented in Table 2. Also presented in Table 2 are the enthalpies of solution of the *m*-methoxy and *m*-ethoxy compounds in some of the solvent systems. These data show that the enthalpies of solution of the *o*-analogues are very different from those of their *m*-counterparts. These differences lie not only in the absolute values of the enthalpies of solution but also in the trends revealed. For the *m*-compounds the trends showed increasingly

TABLE 2

Enthalpies of solution at infinite dilution (kJ mol^{-1}) for solution of *o*- and *m*-alkoxyphenols in water and in water/alcohol solvents (alcohol concentration, 0.00316 M) at 298.15 K

Solvent	Me	Et	Pr	Bu
o-*Alkoxyphenols*				
Water	2.100 ± 0.040	0.122 ± 0.006	−0.284 ± 0.010	0.355 ± 0.008
Water/methanol	2.018 ± 0.016	0.125 ± 0.009	−0.286 ± 0.008	0.383 ± 0.011
Water/ethanol	2.110 ± 0.028	0.103 ± 0.003	−0.204 ± 0.011	0.383 ± 0.011
Water/propanol	2.002 ± 0.019	0.168 ± 0.006	−0.200 ± 0.006	0.352 ± 0.004
Water/butanol	2.098 ± 0.047	0.154 ± 0.008	−0.202 ± 0.005	0.383 ± 0.005
Water/pentanol	2.073 ± 0.032	0.156 ± 0.005	−0.205 ± 0.007	0.363 ± 0.002
Water/hexanol	2.107 ± 0.032	0.197 ± 0.007	−0.423 ± 0.005	0.339 ± 0.006
Water/heptanol	2.180 ± 0.028	0.189 ± 0.014	0.227 ± 0.005	0.566 ± 0.008
Water/octanol	2.115 ± 0.022	0.951 ± 0.028	0.898 ± 0.006	0.554 ± 0.008
Octanol saturated with water	0.674 ± 0.011	1.942 ± 0.017	1.742 ± 0.008	0.907 ± 0.005
Octanol	0.825 ± 0.009	1.528 ± 0.021	1.019 ± 0.008	0.240 ± 0.012
m-*Alkoxyphenols*				
Water	5.77 ± 0.18	5.48 ± 0.08		
Water/butanol	5.72 ± 0.11	5.21 ± 0.08		
Water/pentanol	5.74 ± 0.13	5.00 ± 0.06		
Water/hexanol	5.82 ± 0.10	5.14 ± 0.08		
Water/heptanol	6.26 ± 0.21	4.98 ± 0.13		
Water/octanol	5.51 ± 0.13	5.25 ± 0.11		

positive values in the enthalpies of solution (after the break point in the solubility data) whereas here, for the *o*-homologues the trend is increasingly *negative* up to the *o*-propoxy derivative and appears (there is only one datum after this compound) thereafter to become increasingly positive. For both *o*- and *m*-compounds their low solubility prevents study beyond the compounds reported here but further evidence for the profound influence of solute structure upon the solution process is seen in the decreased rates of solution noted for the *o*-series of compounds. This decrease in rate of solution (as observed microcalorimetrically) depends upon the homologue itself, the rate being slowest for the *o*-propoxy derivative. If, as seems likely, the *o*-compounds form intramolecular H-bonded structures these might not discourage the solution process to the same extent as might the intermolecular H-bonds that are the only possible type of such bond available in the *m*-series. Whatever the form of these internal H-bonding structures, it would appear that they dictate the rate at which these compounds dissolve in these mixed solvent systems and presumably the nature of the solvated species that exist in solution. For example, the *o*-propoxy compound, it would appear, forms more/stronger H-bonds with the solvent than it does internally (the enthalpy of solution is negative; compensating for the breaking of solute–solute associating forces).

Individually, each solute shows very little in the way of a trend in its enthalpy of solution in the solvent series studied, each value in the alcohol systems being rather similar to that in pure water. This statement is true up to the heptanol system for each of the four solutes studied. The data reveal large changes in the enthalpies of solution on solution in water/octan-1-ol. We can only suppose again that this profound effect is due to the particular effects of having octan-1-ol present in water at its saturating concentration thus highlighting the effects consequent upon attempting to place another solute into the solution.

Table 2 also shows the enthalpies of solution for the solutes on dissolution in octan-1-ol saturated with water and in pure octan-1-ol. As noted [1] in our earlier publication the interest in these solvent systems stems from our interest in transfer studies of solutes from water to some non-aqueous solvent which may mimic the properties of the biological membrane (i.e., these data are of use in quantitative structure activity relationships [14]; QSAR). Thus in Table 3 we show the derived thermodynamic parameters for transfer of these solutes from water saturated with octan-1-ol to octan-1-ol saturated with water (these are the solvent systems present in the partition experiment [6]; octan-1-ol has found most favour as the solvent which best represents biological lipid matrices (ref. 15 gives an account of a thermodynamic basis for the selection of solvent systems to represent biological membranes). The data for the enthalpies of transfer are, again, notably different from those for the *m*-homologues [6] which are all negative and of the order of 7 kJ mol^{-1}. The results for the *o*-compounds show a trend in

TABLE 3

Values of $\Delta_{trans}G$ (kJ mol^{-1}; calculated from values of partition coefficient at 298.15 K), $\Delta_{trans}H$ (kJ mol^{-1}) and $\Delta_{trans}S$ (J mol^{-1} K^{-1}) for transfer of *o*-alkoxyphenols from water saturated with octan-1-ol to octan-1-ol saturated with water

	$\Delta_{trans}G$	$\Delta_{trans}H$	$\Delta_{trans}S$
o-Me	−7.49	−1.44	20.3
o-Et	−9.88	0.99	36.5
o-Pr	−13.44	0.84	47.9
o-Bu	−16.25	0.35	55.7

enthalpy of transfer, being negative for the *o*-methoxy, becoming positive for the *o*-ethoxy and apparently becoming increasingly negative again for the *o*-propoxy and *o*-butoxy compounds. The values for the Gibbs function of transfer were derived from the appropriate partition coefficients. The values of the enthalpies of transfer and the entropies of transfer correlate [16,17] well with a compensation temperature [16] of 245 K (correlation coefficient of $\Delta H/\Delta S$ plot = 0.9793). There is no such compensation observed in the plots of $\Delta H/\Delta G$ which are [18,19], for data derived from van 't Hoff plots, a better test for chemical causality in related systems [19].

The data reported in this paper were obtained in an attempt to investigate the properties of mixed solvent systems where the co-solvent/co-solute ratio is systematically varied but whose concentration remained constant. It is apparent, however, that these results indicate not only the complexities of such solvent systems but also reveal the consequences of structural changes in the solutes studied. We noted in our previous publication [1] that discussion of such systems was not possible at any detailed level because of their complexity—the studies reported here reinforce that conclusion. They also, however, reinforce the view that any attempt to predict the behaviour of compounds in solvent systems or to calculate partition coefficients (as in QSAR) can lead not only to systematic errors but to gross errors in the case of a congeneric series.

REFERENCES

1 A.E. Beezer, P.L.O. Volpe, M.C.P. Lima and W.H. Hunter, J. Solution Chem., 15 (1986) 341.

2 A.E. Beezer, P.L.O. Volpe and W.H. Hunter, J. Chem. Soc., Faraday Trans. 1, 82 (1986) 2863.

3 A.E. Beezer, C.A. Gooch, W.H. Hunter, M.C.P. Lima and B.V. Smith, Int. J. Pharm., in press.

4 M.J. Kamlet, J-L.M. Abboud, M.H. Abraham and R.W. Taft, J. Org. Chem., 48 (1983) 2877; M.J. Kamlet, R.M. Doherty, R.W. Taft and M.H. Abraham, J. Am. Chem. Soc., 105 (1983) 6741; M.J. Kamlet, M.H. Abraham, R.M. Doherty and R.W. Taft, J. Am.

Chem. Soc., 106 (1984) 464; R.W. Taft, J-L.M. Abboud, M.J. Kamlet and M.H. Abraham, J. Solution Chem., 14 (1985) 153; R.W. Taft, M.H. Abraham, G.R. Famini, R.M. Doherty, J-L.M. Abboud and M.J. Kamlet, J. Pharm. Sci., 74 (1985) 807.
5 B. Lee, Biopolymers, 24 (1985) 813.
6 A.E. Beezer, W.H. Hunter and D.E. Storey, J. Pharm. Pharmacol., 32 (1980) 815.
7 R.B. Hermann, J. Phys. Chem., 76 (1972) 2754.
8 C.V. Krishnan and H.L. Friedman, J. Phys. Chem., 75 (1971) 3598.
9 J.N. Spencer, J.E. Gleim, C.H. Brevins, R.C. Garrett and F.J. Mayer, J. Phys. Chem., 83 (1979) 1249.
10 S.H. Yalkowsky, G.L. Flynn and T.G. Slunick, J. Pharm. Sci., 61 (1972) 852.
11 R.N. Smith, C. Hansch and M.W. Ames, J. Pharm. Sci., 64 (1975) 599.
12 A.H. Roux, D. Hetu, G. Perron and J.E. Desnoyers, J. Solution Chem., 13 (1984) 1.
13 J.E. Desnoyers, D. Hetu and G. Perron, J. Solution Chem., 12 (1983) 427.
14 A. Leo, C. Hansch and D. Elkins, Chem. Rev., 71 (1971) 525.
15 A.E. Beezer, C.A. Gooch, P.L.O. Volpe and W.H. Hunter, J. Pharm. Pharmacol. in press; in outline see A.E. Beezer, Gazz. Chim. Ital., 116 (1986) 271.
16 R. Lumry and S. Rajender, Biopolymers, 9 (1970) 1125.
17 E. Tomlinson, Int. J. Pharm., 13 (1983) 115.
18 R.R. Krug, W.G. Hunter and R.A. Grieger, J. Phys. Chem., 80 (1976) 2335.
19 R.R. Krug, W.G. Hunter and R.A. Grieger, J. Phys. Chem., 80 (1976) 2341.