

HYDROGEN BONDING. 39. THE PARTITION OF SOLUTES BETWEEN WATER AND VARIOUS ALCOHOLS

MICHAEL H. ABRAHAM, HARPREET S. CHADHA AND JULIAN P. DIXON

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

AND

ALBERT J. LEO

Medicinal Chemistry Project, Pomona College, Claremont, California 91711, USA

The general solvation equation

$$\log SP = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + \nu V_x$$

was applied to the partition of solutes between water and isobutanol, pentanol, hexanol, octanol, decanol and oleyl alcohol. It is shown that the two main factors that influence partitioning are solute hydrogen-bond basicity $\Sigma\beta_2^H$ and solute volume V_x . The b coefficient becomes steadily more negative along the above series of alcohols, showing that the alcoholic phases, which are all less acidic than water, become less and less acidic as the chain length increases, and the water content of the alcoholic phase decreases. The ν coefficient, on the other hand, becomes gradually more positive, indicating that as the chain length increases and the water content decreases, the alcoholic phase becomes more and more hydrophobic. Of great significance is that for all six alcohols, the a coefficient is effectively zero, so that all alcoholic phases have the same basicity as bulk water, no matter what their water content is. It is suggested that, contrary to results of solvatochromic measurements, the alcohols have similar hydrogen-bond basicity to water.

INTRODUCTION

Recently,^{1,2} we have constructed the general solvation equation

$$\log SP = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + \nu V_x \quad (1)$$

that has found considerable use in the correlation and understanding of physico-chemical and biochemical phenomena. These include solvent-water partition coefficients,^{3,4} HPLC capacity factors⁵⁻⁷ and the distribution of solutes between blood and brain.⁸ In equation (1) the dependent variable is $\log SP$, where SP is some property of a series of solutes in a given solvent system. The independent variables are solute properties or descriptors as follows:¹⁻³ R_2 is an excess molar refraction that can be determined simply from a knowledge of the compound refractive index or can easily be estimated; π_2^H is the solute dipolarity/polarizability, it being impossible to devise descriptors for these separately; $\Sigma\alpha_2^H$ is the solute overall or effective hydrogen-bond acidity; $\Sigma\beta_2^H$ is the solute overall or effective hydrogen-bond basicity; and V_x is the McGowan characteristic

volume, calculated from molecular structure. For certain particular classes of solute such as sulfoxides, anilines and alkyipyridines, the relative basicity appears to alter with the solvent system, and the basicity parameter $\Sigma\beta_2^H$ is replaced by the alternative descriptor $\Sigma\beta_2^0$ for partitions between water and organic solvents in which water is fairly soluble.³ These solvents include butyl acetate, diethyl ether, isobutanol and octanol.

One of the first applications of equation (1) was to hexadecane-water and octanol-water partition coefficients,⁴ $P(\text{hex})$ and $P(\text{octanol})$, respectively. For the former we found

$$\log P(\text{hex}) = 0.087 + 0.667R_2 - 1.617\pi_2^H - 3.587\Sigma\alpha_2^H - 4.869\Sigma\beta_2^H + 4.433V_x \quad (2)$$

$$n = 370, \rho = 0.9982, \text{ s.d.} = 0.124, F = 20\,235.5$$

where n is the number of data points (solutes), ρ is the correlation coefficient, s.d. is the standard deviation and F is the Fisher F -statistic. The coefficients in equation (1) are characteristic of the solvent system, and so we could deduce that hexadecane is more polarizable than

water ($r = 0.667$), is less dipolar than water ($s = -1.617$), is much less basic than water ($a = -3.587$) and is much less acidic than water ($b = -4.869$). These differences between water and hexadecane are all qualitatively as expected from the known properties of the two solvents, such as the refractive index η , and the Kamlet-Taft solvatochromic parameters π_1^* , α_1 and β_1 (see Table 1). As mentioned above, it has proved impossible to devise separate descriptors for solute polarizability and solute dipolarity that can be used successfully in LFER equations such as equation (1). The best we have been able to do is to remove part of the polarizability as the R_2 descriptor, but this still leaves the π_2^H descriptor as a blend of polarizability and dipolarity. Unless a solute set is specifically chosen, this usually results in R_2 and π_2^H being somewhat cross-correlated; for the hexadecane-water system the cross-correlation coefficient is 0.687 ($\rho^2 = 0.472$). The large positive ν coefficient ($\nu = 4.433$) is partly due to the greater difficulty of forming a cavity in the highly associated solvent water, as shown by the Hildebrand cohesive energy density (CDE) δ_H^2 , and partly due to the increased solute-solvent general dispersion interactions in the hexadecane phase. In the case of octanol-water partition coefficients, a somewhat different equation was obtained:

$$\log P(\text{octanol}) = 0.088 + 0.562R_2 - 1.054\pi_2^H + 0.034\Sigma\alpha_2^H - 3.460\Sigma\beta_2^H + 3.814V_x \quad (3)$$

$$n = 613, \rho = 0.9974, \text{s.d.} = 0.116, F = 23\,161.6$$

Note that in equation (3) the $\Sigma\beta_2^H$ descriptor is retained, because the solute data set did not include any of the

'variable basicity' compounds. Interpretation of the coefficients in equation (3) follows that for equation (2), except in the case of the a constant, which is statistically not significant. This implies that water and octanol have the same solvent hydrogen-bond basicity, or more correctly that octanol-saturated water and water-saturated octanol have the same basicity.⁴ There is a dilemma here, because the original Kamlet-Taft β_1 value for water (0.18) is considerably less than those for primary alcohols.⁹⁻¹¹ More recent results have led to higher values for water, mostly in the range 0.4-0.6 units^{12,13} (see Table 1), but these are still much less than the β_1 values for octanol (0.86-0.96) or for water-saturated octanol (0.79-0.95) obtained by Dallas and Carr.¹⁴

Dallas and Carr¹⁴ also measured the solubility of octanol in water as 9.3×10^{-4} mole fraction, confirming the earlier careful measurement of Dearden and Bresnen¹⁵ as 6.6×10^{-3} mol dm⁻³, and showing that the solubility is so small as to hardly affect the solubility properties of water. On the other hand, the solubility of water in octanol is fairly high, 0.27 mole fraction or 2.36 mol dm⁻³,¹⁵ and so water-saturated octanol may well have different properties to pure octanol. Both Dallas and Carr¹⁴ and Cabani *et al.*¹⁶ have noted small but significant values for the Gibbs free energy of transfer of solutes from octanol to water-saturated octanol, and water-saturated octanol is known to be more structured than is octanol itself.¹⁷

It is therefore possible that the presence of 2.36 mol dm⁻³ water in octanol modifies its solubility properties so that wet octanol is less basic than octanol (and hence of the same basicity as water), in spite of the solvato-

Table 1. Some solvent parameters^a

Solvent	η_D^{20}	π_1^*	α_1	β_1^b	δ_H^2	[H ₂ O] ^c	
Methanol	1.3288	0.60	1.09	0.79	0.66	205.2	—
Ethanol	1.3611	0.55	0.88	0.89	0.71	162.1	—
Propanol	1.3850	0.53	0.79	0.95	0.75	143.2	—
Butanol	1.3993	0.54	0.74	0.94	0.75	129.5	9.53
Isobutanol	1.3955	0.50	0.71	1.05	0.78	124.3	7.49
Pentanol	1.4101	0.50	0.73	0.97	0.80	119.7	3.36
Hexanol	1.4178					113.1	3.32
Heptanol	1.4249					108.5	2.45
Octanol	1.4295	0.50	0.70	0.86	0.96	103.3	2.36
Wet octanol		0.54	0.71	0.79	0.95		
Decanol	1.4578					98.6	1.65
Oleyl alcohol	1.4606					65.9	0.71
Water, Ref. 9	1.3333			0.14	0.47	549.0	
Water, Ref. 10				0.18			
Water, Ref. 12				0.42	0.57		
Water, Ref. 13		1.13	1.16	0.43	0.58		
Hexadecane	1.4345	0.08	0.00	0.00	0.00	64.1	0.002

^a Solvatochromic parameters for alcohols from Ref. 13, except for octanol and wet octanol from Ref. 14.

^b The first column shows values with 4-nitroaniline and the second column shows values with 4-nitrophenol as indicators.

^c Molar solubility of water in the alcohol.

chromic parameters given in Table 1. Alternatively, it is possible that water is just as basic as alcohols, and that the solvatochromic parameters do not reflect this. One approach is to obtain solvation equations on the lines of equation (3) for partitions in a series of water-alcohol systems, where the water content in the alcoholic phase varies widely. Examination of the a constant in the resulting equations will show whether or not the varied water content affects the alcohol basicity. To this end, we have set out equations for partitioning between water and alcohols where the latter range from isobutanol to decanol and to oleyl alcohol.

RESULTS AND DISCUSSION

For octanol-water partitions, the regression equation (3) was taken, all the $\log P$ values used to derive the equation have been given before.⁴ In all other cases, the required $\log P$ values were from the MedChem data base.¹⁸ A summary of the regression equations obtained is given in Table 2. The isobutanol-water equation, with 37 data points, is almost identical with the previously published equation with 35 data points. For the lower alcohols, which dissolve appreciable quantities of water, the alternative $\Sigma\beta_2^0$ descriptor was used. As mentioned above, the octanol-water equation was set up without any 'variable basicity' solutes, and by chance the equation for decanol-water contains no such solutes either. In these cases, the equation in $\Sigma\beta_2^0$ is identical with that in $\Sigma\beta_2^H$. Since oleyl alcohol dissolves very little water, we used the $\Sigma\beta_2^H$ descriptor, but the use of $\Sigma\beta_2^0$ results in an almost identical equation.

The regression equations summarized in Table 2 are

all reasonably good, with correlation coefficients ranging from 0.9854 to 0.9974 and standard deviations from 0.109 to 0.167 log units. For the five new systems, the number of data points ranges from 37 to 74, so that the regression equations can be regarded as reasonably general.

Because the descriptors in the solvation equation (1) are chemically based, the coefficients in the regression equations will reflect the complementary properties of the system. In the case of partitions from water to organic phases, the coefficients will refer to the difference in the complementary properties of water and the phases. We can discuss the coefficients given in Table 2 on these lines.

Except for oleyl alcohol, the r coefficient is roughly constant along the series, indicating that the organic phases are more polarizable than water. The s coefficient becomes more negative from isobutanol to hexanol, and then levels off at about -1.00 unit (except, again, for oleyl alcohol). This indicates that the organic phases are less dipolar/polarizable than water, and since they are more polarizable, they must all be markedly less dipolar than water. The water content of the organic phase may play a part here, because as it decreases, so the dipolarity of the organic phase becomes less (from isobutanol to hexanol). Note that for the water-alcohol systems, the cross-correlation between R_2 and π_2^H for the different solute data sets is around $\rho = 0.80$ ($\rho^2 = 0.64$). From isobutanol to oleyl alcohol, the b coefficient steadily becomes more negative, showing that the organic phases become less and less acidic than water. The oleyl alcohol phase is the least acidic of all the alcohol phases, but even this C_{18} alcohol is still a hydrogen-

Table 2. Regression equations for alcohol-water partitions

Alcohol	c	r	s	a	b^a	v
Isobutanol	0.227	0.514	-0.693	0.020	-2.258	2.776
Pentanol	0.175	0.575	-0.787	0.020	-2.837	3.249
Hexanol	0.143	0.718	-0.980	0.145	-3.214	3.403
Octanol	0.088	0.562	-1.054	0.034	-3.460	3.814
Decanol	0.008	0.485	-0.974	0.015	-3.798	3.945
Oleyl alcohol	-0.359	-0.270	-0.528	-0.035	-4.042	4.204
Hexadecane	0.087	0.667	-1.617	-3.587	-4.869	4.433

	n	ρ	s.d.	F
Isobutanol	37	0.9911	0.119	344.5
Pentanol	40	0.9899	0.154	332.9
Hexanol	49	0.9854	0.167	288.9
Octanol	613	0.9974	0.116	23161.6
Decanol	51	0.9929	0.124	629.9
Oleyl alcohol	74	0.9929	0.109	944.9
Hexadecane	370	0.9982	0.124	20235.5

^a The b constant is for the $\Sigma\beta_2^0$ descriptor, except for octanol and decanol, where no 'variable basicity' solutes were included, and oleyl alcohol and hexadecane, where the $\Sigma\beta_2^H$ descriptor was used.

bond acid, as shown by the b coefficient of -4.04 compared with -4.87 for the non-acidic hexadecane phase (see Table 2).

In a similar vein, the v coefficient becomes larger as the alcohol becomes larger and the aqueous content becomes smaller. Indeed, the v coefficients begin to approach that for the hexadecane–water system (4.43), which is close to the maximum value yet found,³ 4.66, for the chlorobenzene–water system. The variation of v coefficients with the alcohol is as expected. As the chain length increases, the Hildebrand CED decreases and the easier it is to make a cavity in the solvent; in addition, the refractive index increases and the greater are the solute–solvent general dispersion interactions. Leahy *et al.*¹⁹ have noted that the methylene increment to $\log P$ for transfer from water to water-saturated alcohols increases as the water content of the organic phase decreases (expressed as mol dm^{-3}). The same is true for the v coefficient:

$$v = 4.22 - 0.210[\text{H}_2\text{O}] \quad (4)$$

$$n = 6, \rho = 0.9486, \text{ s.d.} = 0.185, F = 35.9$$

However, the difficulty here is that the variables such as $[\text{H}_2\text{O}]$, the refractive index function and the CED are related, so that reasonable correlations of the v coefficient against the refractive index function or the CED are also obtained. In any case, we can conclude that as the alcohol becomes larger, and the organic phase contains less water, so the phase becomes more hydrophobic.

We now consider the $a\Sigma\alpha_2^{\text{H}}$ term that was the main focus of the Introduction. For all the alcohol–water systems shown in Table 2, the a coefficient is statistically not significant, so that the hydrogen-bond basicity of water and the various phases must be the same. However, the water content of the alcoholic phase varies from 7.49 mol dm^{-3} in the case of isobutanol down to 1.65 for decanol and to 0.71 mol dm^{-3} for oleyl alcohol, but it should be noted that the variation in terms of mole fraction is much less, from 0.46 for isobutanol to 0.25 for decanol and 0.22 for oleyl alcohol. Even so, if the hydrogen-bond basicity of the organic phase was significantly influenced by the amount of water present, then the basicity would be expected to vary along the series of phases from water-saturated isobutanol to water-saturated oleyl alcohol. From the partition results, it seems clear that the alcohols themselves must have almost the same hydrogen-bond basicity as water. This is not the case with the solvatochromic measurements (Table 1). The original low values^{9,10} of 0.14 or 0.18 for β_1 for water now seem incorrect, but even the most recent values^{12,13} are not as high as those for the alcohols or for wet octanol; there is a large spread of results for the alcohols, but from butanol onwards the β_1 values lie between 0.7 and 1.0 , partly depending on the indicator

used in the determination. There is therefore a discrepancy between the partition results given in Table 2 and results of solvatochromic measurements.

Leahy *et al.*²⁰ have suggested that the anomaly of water having a lower solvatochromic β_1 value than alcohols, and yet having the same basicity as judged by partition equations, is due to a ‘mass law’ effect. They point out that the concentration of hydrogen-bond basic groups is 55.5 mol dm^{-3} in water, but only 7.9 mol dm^{-3} in wet octanol. However, the concentration of basic groups varies from 14 mol dm^{-3} in wet isobutanol down to only 4 mol dm^{-3} in wet oleyl alcohol, so that if this were a factor influencing the partitioning process, the a constant would be expected to vary from water–isobutanol to water–oleyl alcohol. Further, since the concentration of basic groups in the dry alcohols varies from 24.6 mol dm^{-3} in methanol and 17.0 mol dm^{-3} in ethanol down to 6.3 mol dm^{-3} in octanol, whereas the solvatochromic β_1 value varies randomly along the homologous series of alkan-1-ols, the ‘mass law’ effect cannot be a factor here, either.

The ‘mass law’ effect therefore does not explain the anomaly between the solvatochromic measurements and the partition equations. We feel that it is the solvatochromic results that present the difficulty rather than the results from the partition equations. There certainly seems to be considerable experimental error in the determination of β_1 for water by the solvatochromic method, and values of β_1 for the alcohols are clearly dependent on the indicator used,¹³ as shown in Table 1.

ACKNOWLEDGEMENT

This paper is dedicated to Professor W. Taft on the occasion of his 70th birthday.

REFERENCES

1. M. H. Abraham, *Chem. Soc. Rev.* **22**, 73 (1993).
2. M. H. Abraham, *Pure Appl. Chem.* **65**, 2503 (1993).
3. M. H. Abraham, *J. Phys. Org. Chem.* **6**, 660 (1993).
4. M. H. Abraham, H. S. Chadha, G. S. Whiting and R. C. Mitchell, *J. Pharm. Sci.*, **83**, 1085 (1994).
5. K. G. Millar and C. F. Poole, *J. High Resolut. Chromatogr.* **17**, 125 (1994).
6. M. H. Abraham and M. Roses, *J. Phys. Org. Chem.*, **7**, 672 (1994).
7. M. H. Abraham, H. S. Chadha and A. Leo, *J. Chromatogr.* in press.
8. M. H. Abraham, H. S. Chadha and R. C. Mitchell, *J. Pharm. Sci.* **83**, 1257 (1994).
9. M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.* **98**, 377 (1976).
10. T. Yokoyama, R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.* **98**, 3233 (1976).
11. M. J. Kamlet, J.-L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.* **48**, 2877 (1983).

12. Y. Marcus and Y. Migron, *J. Phys. Chem.* **95**, 400 (1991).
13. R. M. C. Goncalves, A. M. N. Simoes, L. M. P. C. Albuquerque, M. Roses, C. Rafols and E. Bosch, *J. Chem. Res. (M)* 1380 (1993); *(S)* 214 (1993).
14. A. J. Dallas and P. W. Carr, *J. Chem. Soc., Perkin Trans. 2* 2155 (1992).
15. J. C. Dearden and G. M. Bresnen, *Quant. Struct.-Act. Relat.* **7**, 133 (1988).
16. S. Cabani, G. Conti, V. Mollica and L. Bernazzani, *J. Chem. Soc., Faraday Trans.* **87**, 2433 (1991).
17. N. P. Franks, M. H. Abraham and W. R. Lieb, *J. Pharm. Sci.* **82**, 466 (1993).
18. The Pomona Medicinal Chemistry Project.
19. D. E. Leahy, J. J. Morris, P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2* 723 (1992).
20. D. E. Leahy, J. J. Morris, P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2* 705 (1992)fl