Partition of solutes into wet and dry ethers; an LFER analysis†

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Equations based on the Abraham solvation equations are presented for the partition of solutes between water and wet diethyl ether, wet diisopropyl ether, dry diethyl ether, dry diisopropyl ether, dry tetrahydrofuran and dry dioxane, and between the gas phase and wet diethyl ether, dry diethyl ether, dry tetrahydrofuran and dry dioxane. These equations can be used to predict further partition coefficients, and also provide information on the chemical features of the various systems. It is shown that wet diethyl ether is more basic and less hydrophobic than dry diethyl ether, although the differences are quite small. The hydrogen bond basicity of dry tetrahydrofuran and dry dioxane is about the same as that of wet diethyl ether and wet diisopropyl ether, and their hydrophobicity is between that of wet and dry diethyl ether.

Introduction

There are now numerous methods for the prediction of water–octan-1-ol partition coefficients, as log P_{oct}. Buchwald and Bodor[1] have surveyed the literature up to 1997; since then several other studies have been reported,[2–5] although the *C*log *P* method of Leo[6] is still the one most used. Other water–solvent systems have long attracted interest, with solvents such as olive oil,[7,8] or oleyl alcohol being used.[9] A number of workers have compared various water–solvent systems,[10–13] but only quite recently has there been any attempt to predict log *P* values in systems other than water–octan-1-ol. Marcus[14] analyzed data on a large number of water–solvent systems in which the solvent was suggested to be 'essentially dry'. However, these included ethyl acetate and diethyl ether that contain appreciable amounts of water when in equilibrium with water (1.44 and 0.58 mol dm^{-3} respectively).[15] Marcus[14] noted that a separate treatment might be necessary for such solvents. Rekker *et al.*[16] applied a fragmentation scheme to log *P* values for water–aliphatic hydrocarbons, taking all such solvents together, but more general methods have been put forward. Torrens[17] presented a scheme for the calculation of log *P* values between any two media; however, a comparison of calculated and observed values of logP_{oct} yielded a standard deviation, SD, of 1.44 log units. Much better results were obtained by Ruelle,[18] who used Mobile Order Theory (MOT) to calculate log *P* values for a large number of solutes in a wide range of water–solvent systems with an SD of 0.55 log units (reduced to 0.48 if results on five particular solutes were excluded). Interestingly, Ruelle[18] used properties of dry solvents, such as the molar volume, in his calculations. Presumably, his calculations would be the same for transfer from pure water to the pure, dry solvent. Meyer and Maurer[19] use a modified linear solvation energy relationship and correlate log *P* values for solutes in 20 water–solvent systems with an average absolute deviation (AAD) of 0.16 log unit, which corresponds to about 0.22 log unit in SD. In this system, solute parameters are used as surrogates for solvent parameters, there being no distinction between solvents that take up very little water, such as cyclohexane, and those that take up considerable quantities of water, such as diethyl ether and ethyl acetate. One reason for the apparent success of the methods of Marcus, of Ruelle, and of Meyer and Maurer over that of Torrens is that the three former methods deal with much simpler molecules than does Torrens.

In all four cases, however, parameters for pure 'dry' solvents are used to describe solvents in equilibrium with water. We have shown[20] for a number of water–alcohol systems that log *P* values for 'practical' partition between solvent-saturated water and water-saturated solvent are not the same as those for 'hypothetical' partition between water and the dry solvent. Hence different equations may be needed to describe partition of a series of solutes between water and a given 'wet' solvent, and partition between water and the 'dry' solvent. Recently,[21] we have extended our studies to partition between water and 'wet' and 'dry' di-n-butyl ether, and find that different equations are needed to correlate the log *P* values, even though the solubility of water in di-n-butyl ether is quite low (0.064 or 0.080 mol dm^{-3}).[21]

It seemed useful, therefore, to study partition between water and solvents, when the latter is capable of dissolving considerable quantities of water, in order to examine the effect of such dissolved water on partition. We chose ethers, especially diethyl ether (DEE), because DEE dissolves considerable quantities of water, and because we had already studied di-n-butyl ether (DBE).

Methodology

Our method is based on two general linear free energy relationships, eqn. (1) and (2).[20–22] The former equation is used for processes in condensed systems, such as water–solvent

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† Electronic supplementary information (ESI) available: tables of solute descriptors and log *P* values. Values of log K_w and *L*. See http://www.rsc.org/suppdata/nj/b3/b303016d/

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partition, where SP will be log P. The partition coefficient here refers to the partition of unionized species.

$$SP = c + eE + sS + aA + bB + vV \tag{1}$$

$$SP = c + eE + sS + aA + bB + lL \tag{2}$$

The latter equation is used for gas-condensed phase processes, such as gas–water partition where SP will be log K. The gas–liquid partition coefficient, K, is equivalent to the Ostwald solubility coefficient. The independent variables in eqn. (1) and (2) are solute descriptors as follows.[20–23] E is the solute excess molar refractivity, in units of (cm^3 mol^{-1})/10, S is the solute dipolarity/polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, V is the McGowan characteristic volume in units of (cm^3 mol^{-1})/100, and L is the logarithm of the gas–hexadecane partition coefficient. The coefficients in eqn. (1) and (2) are evaluated through multiple linear regression analysis.

The log P data for water–wet solvent partition were all taken from the MedChem 2002 data base.[24] They can be converted into the corresponding gas phase–wet solvent partition coefficients, K^S, through eqn. (3) or (4), where K^W is the gas–water partition coefficient;[25] K^W and K^S are both dimensionless quantities.

$$K^S = K^W P \tag{3}$$

$$\text{Log } K^S = \log K^W + \log P \tag{4}$$

Log P values for hypothetical partition into dry solvents can be obtained through eqn. (4) in reverse, especially for the more volatile solutes. The gas–dry solvent partition can be obtained by a number of methods,[20,21,26] and then combined with log K^W values to yield the required log P values. For the less volatile solutes, log P values can be found through the ratio of solubilities in water and the dry solvent;[23] then the corresponding log K^S values are obtained through eqn. (4).

Results and discussion

Some years ago, Taylor *et al.*[13] found that the hydrogen bond basicity of certain specific solutes, as obtained from water–solvent partition systems, varied with the particular system. We dealt with this problem by defining[22] an alternative hydrogen bond basicity descriptor, B^0, for these specific solutes in water–solvent systems where the 'wet' solvent contained appreciable quantities of water. The solutes concerned are alkyl anilines, alkyl pyridines and sulfoxides, and typical 'wet' solvents are ethyl acetate and diethyl ether. For partition from water into wet DEE, analysis of log P values led to eqn. (5), with the alternative[22] B^0 parameter for the specific solutes. The solutes and descriptors are in the supplementary Table S1 (see ESI†). The log P values cover a range of no less than 8.8 log units, from −4.0 (erythritol) to 4.8 (phenanthrene) and the descriptors also cover very wide ranges, see Table S1.

$$\log P \text{ (wet DEE)} = 0.248 + 0.561E - 1.016S - 0.226A - 4.553B^0 + 4.075V \tag{5}$$

$$N = 239,\ R^2 = 0.939,\ \text{AAD} = 0.264,\ \text{SD} = 0.352,\ F = 721.8$$

The correlation coefficient is R, and F is the F-statistic. Our fit, with AAD = 0.264, and SD = 0.352, appears not to be as good as those of Marcus (SD = 0.14, N = 45)[14] or of Meyer and Maurer (AAD = 0.16, SD = 0.22 [estimated], N = 37),[19] but this is due to the very much larger data set we have used, with much more complicated compounds. We include, for example, compounds of the type of procaine, nicotine, cocaine, heroin, and steroids, none of which were in the previous data sets. The statistics of Ruelle (AAD = 0.54, SD = 0.78, N = 45)[18] cannot be compared with the above, because they refer to predicted log P values rather than to fitted values, and so AAD and SD are naturally much larger.

We have assembled a rather different data set for partition into dry DEE; details are in the supplementary material as Table S2 (see ESI†). Again, the range of log P is very large, that is 9.8 log units from −0.6 (trimethylamine) to 9.2 (octadecan-1-ol), and the descriptor ranges are also very large, see Table S2. The LFER equation for 49 compounds is:

$$\log P(\text{dry DEE}) = 0.330 + 0.401E - 0.814S - 0.457A - 4.959B + 4.320V \tag{6}$$

$$N = 49,\ R^2 = 0.995,\ \text{AAD} = 0\ 117,\ \text{SD} = 0.153,\ F = 1836.0$$

The statistics of eqn. (6) are very good, especially compared to those of eqn. (5). Both eqn. (5) and (6) show that bulk DEE (wet or dry) is less dipolar/polarizable than bulk water (s-coefficient is −ve), slightly less basic as a hydrogen bond species (a-coefficient −ve), very much less acidic as a hydrogen bond species (b-coefficient very −ve), and very much more hydrophobic (v-coefficient very +ve). Wet DEE is slightly less dipolar/polarizable, slightly more basic, slightly more acidic, and, slightly less hydrophobic than dry DEE. However, the SD values for the coefficients in eqn. (5) and (6) are about 0.10 unit, except for the v-coefficients (0.07 units), and so the differences in coefficients are only just significant.

Of the other dialkyl ethers, we were able to collect a reasonable amount data on log P values only for wet di-isopropyl ether, DIPE, the corresponding regression equation being:

$$\log P(\text{wet DIPE}) = 0.472 + 0.413E - 0.745S - 0.632A - 5.251B^0 + 4.059V \tag{7}$$

$$N = 46,\ R^2 = 0.977,\ \text{AAD} = 0.149,\ \text{SD} = 0.186,\ F = 347.3$$

Details of the log P values and compound descriptors are in the supplementary Table S3 (see ESI†). The statistics are not very good, but the coefficients are not too different to those for wet DEE, see Table 1.

A comparison with wet and dry DBE[21] is in Table 2; coefficients for partition into wet[27] and dry[20] alcohols are also given. The effect of the small amount of water in wet DBE is much larger than the effect of the large amount of water in wet DEE. It is possible that in DEE, the water simply acts as a co-solvent. In contrast, the water present in DBE has been suggested[21,28] to act as a complexing agent forming specific hydrogen bond complexes with solutes. Although the effect of water on partitions into the alcohols is quantitatively about the same as that on partition into DEE in absolute terms, the differences in the coefficients are often in opposite directions. Thus there is no general rule on the effect of water on partitions, and, at the moment, each system must be investigated individually.

Table 1 Coefficients in eqn. (1) for wet and dry ethers and wet and dry alcohols

Solvent	*c*	*e*	*s*	*a*	*b*	*v*	M[a]
Wet DEE	0.248	0.561	−1.016	−0.226	−4.553	4.075	0.58
Dry DEE	0.330	0.401	−0.814	−0.457	−4.949	4.320	
Wet DBE	0.252	0.677	−1.506	−0.807	−5.249	4.815	0.07
Dry DBE	0.203	0.369	−0.954	−1.488	−5.426	4.508	
Wet DIPE	0.472	0.413	−0.745	−0.632	−5.252	4.059	0.22
Dry THF	0.207	0.372	−0.392	−0.236	−4.934	4.447	
Dry dioxane	0.098	0.350	−0.083	−0.556	−4.826	4.172	
Wet pentan-1-ol	0.175	0.575	−0.787	0.020	−2.837	3.249	3.36
Dry pentan-1-ol	0.080	0.521	−1.294	0.208	−3.908	4.208	
Wet decan-1-ol	0.008	0.485	−0.974	0.015	−3.798	3.945	1.65
Dry decan-1-ol	−0.062	0.754	−1.461	0.063	−4.053	4.293	

[a] Molar concentration of water in the wet solvent.

Table 2 Coefficients in eqn. (2) for wet and dry ethers and wet and dry alcohols

Solvent	*c*	*e*	*s*	*a*	*b*	*l*
Wet DEE	0.206	−0.169	0.873	3.402	0.000	0.882
Dry DEE	0.288	−0.347	0.775	2.985	0.000	0.973
Wet DBE	0.369	−0.216	0.026	2.626	−0.499	1.124
Dry DBE	0.165	−0.421	0.760	2.102	−0.664	1.002
Wet DIPE	0.114	−0.032	0.685	3.108	0.000	0.941
Dry THF	0.189	−0.347	1.238	3.289	0.000	0.982
Dry dioxane	−0.034	−0.354	1.674	3.021	0.000	0.919
Dry pentan-1-ol	−0.042	−0.277	0.526	3.779	0.983	0.932
Dry decan-1-ol	−0.136	−0.068	0.325	3.674	0.767	0.947

We have also examined partition into dry tetrahydrofuran (THF) and dry dioxane. Details of the solutes and the log *P* values we have obtained are in the supplementary Tables S4 and S5 (see ESI†). For THF the range of log *P* values is 7.5 from −0.9 (methanol) to 6.6 (nonane) and for dioxane the range is 7.2 from −1.2 (N,N-dimethylformamide) to 6.0 (nonane). The descriptors for the dry dioxane system cover the smallest range of all the systems: *E* (2.80), *S* (2.40), *A* (1.04), *B* (0.91) and *V* (1.57). The corresponding LFER equations are:

$$\log P(\text{dry THF}) = 0.207 + 0.372E - 0.392S - 0.236A - 4.934B + 4.447V \quad (8)$$

$$N = 86,\ R^2 = 0.992,\ \text{AAD} = 0\ 132,\ \text{SD} = 0.178,\ F = 2113.0$$

$$\log P(\text{dry dioxane}) = 0.098 + 0.350E - 0.083S - 0.556A - 4.826B + 4.172V \quad (9)$$

$$N = 105,\ R^2 = 0.992,\ \text{AAD} = 0\ 132,\ \text{SD} = 0.173,\ F = 2550.9$$

Equations for partition into dry solvents have found considerable use in the (indirect) determination of solubilities,[29–31] and in the assignment of physicochemical properties to solutes as different as stilbene,[32] ferrocene,[23] buckminsterfullerene[33] and diuron,[34] so the additional equations are of intrinsic value. Comparison of the equations for the dry ethers suggests that DBE is appreciably less hydrogen bond basic than the other ethers (the *a*-coefficient is very negative), and that dioxane is more dipolar/polarizable (the *s*-coefficient is the most positive). The latter might appear unreasonable, considering the zero dipole moment of dioxane, but as regards intermolecular interactions, dioxane seems to act as two separate ether functions.

We can use eqn. (4) to convert log *P* values into log K^S values, and then correlate the latter through eqn. (2), to give a number of equations that relate to partition from the gas phase to wet or dry ethers. Values of the *L*-descriptor that is required in eqn. (2) are collected in the supplementary Table S6 (see ESI†). The various equations are:

$$\log K\ (\text{wet DEE}) = 0.206 - 0.169E + 0.873S + 3.402A + 0.882L \quad (10)$$

$$N = 114,\ R^2 = 0.981,\ \text{AAD} = 0.193,\ \text{SD} = 0.262,\ F = 1474.0$$

$$\log K\ (\text{dry DEE}) = 0.288 - 0.347E + 0.775S + 2.985A + 0.973L \quad (11)$$

$$N = 49,\ R^2 = 0.999,\ \text{AAD} = 0.106,\ \text{SD} = 0.133,\ F = 7984.4$$

$$\log K\ (\text{wet DIPE}) = 0.114 - 0.032E + 0.685S + 3.108A + 0.940L \quad (12)$$

$$N = 38,\ R^2 = 0.979,\ \text{AAD} = 0.146,\ \text{SD} = 0.273,\ F = 381.2$$

$$\log K\ (\text{dry THF}) = 0.189 - 0.347E + 1.238S + 3.289A + 0.982L \quad (13)$$

$$N = 87,\ R^2 = 0.997,\ \text{AAD} = 0.121,\ \text{SD} = 0.162,\ F = 6763.5$$

Table 3 Some observed and calculated values of log *P* for dry and wet DEE

Solute	Dry, obs	Dry, calc	Wet, obs	Wet, calc
Radon	1.76	1.99	1.72	1.81
Iodoethane	2.22	2.32	2.45	2.16
Diethyl ether	1.35	1.07	1.00	0.94
Propanone	−0.26	−0.25	−0.21	−0.38
Acetonitrile	−0.19	−0.18	−0.22	−0.36
Trimethylamine	−0.62	−0.37	−0.34	−0.36
Triethylamine	0.90	0.88	0.80	0.85
Methanol	−1.26	−1.11	−0.85	−1.03
Benzoic acid	1.83	1.66	1.30	1.59
3-Nitrobenzoic acid	1.76	1.70	1.31	1.68
2-Hydroxybenzoic acid	2.09	2.07	2.37	2.04
4-Hydroxybenzoic acid	1.17	1.10	1.42	1.16

$$\log K\ (\text{dry dioxane}) = -0.034 - 0.354E + 1.674S + 3.021A + 0.919L \quad (14)$$

$$N = 105,\ R^2 = 0.996,\ \text{AAD} = 0.134,\ \text{SD} = 0.172,\ F = 6711.5$$

It is rather easier to compare coefficients for gas to solvent transfer, because they relate to properties of the solvent itself. For water to solvent transfer the coefficients relate to differences in properties between water and the solvent. A summary of the equations for log *K* is in Table 2.

Examination of the coefficients in Table 2 generally confirms the conclusions reached from the coefficients in Table 1. The (dry) cyclic ethers are more dipolar/polarizable than the acyclic ethers, wet or dry. They are stronger hydrogen bond bases than the dry acyclic ethers but about the same hydrogen bond basicity as wet DEE or wet DIPE. The addition of water to DEE or DIPE has no effect on the solvent hydrogen bond acidity, which is zero in all cases. It is possible that the dissolved water is ineffective in interacting with basic solutes because it interacts preferentially with the large excess of ether, *e.g.* by R_2O:–H–O–H–:OR_2 type. As for the equations in log *P*, those in Table 2 indicate again the anomalous position of wet or dry DBE. We have no explanation for this, but note that DBE is the only solvent for which a ‘water-dragging’ effect has been confirmed and analyzed in terms of specific interactions.

For wet DEE and probably also for wet DIPE, the effect of water on partition is not very large—about the same quantitatively as for a long chain alcohol such as decan-1-ol, that dissolves rather more water than either DEE or DIPE. Thus in terms of predicting water–solvent or gas–solvent partitions, there is very little difference in the ‘wet’ or ‘dry’ equations. Values for solutes that are in both sets of data are in Table 3. The maximum difference between observed log *P* values in wet or dry DEE is no more than 0.53 log unit, and between the two calculated values is no more than 0.18 log unit.

For proton acids and proton bases that will be partially ionized in water, depending on the pH, all the log *P* and log *K* values and all the descriptors we have used are for the neutral species. Just as for the well-known case of partition from water to octanol, corrections for ionization have to be made when such compounds are extracted from aqueous solutions at pH values where they are partially ionized.

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References

1 P. Buchwald and N. Bodor, *Curr. Med. Chem.*, 1998, **5**, 353.
2 J. J. Huuskonen, D. J. Livingston and I. V. Tetko, *J. Chem. Inf. Comput. Sci.*, 2000, **40**, 947.

3 W. M. Meylan and P. H. Howard, *Perspect. Drug Discovery Des.*, 2000, **19**, 67.

4 W. Eisfeld and G. Maurer, *J. Phys. Chem. B*, 1999, **103**, 5716.

5 R. Mannhold and H. van de Waterbeemd, *J. Comput. Aided Mol. Des.*, 2001, **15**, 337.

6 A. J. Leo, *The Medicinal Chemistry Project*, Pomona College, Claremont, CA 91711, USA.

7 E. Overton, *Studien uber die Narkose*, Fischer, Jena, Germany, 1901.

8 H. Meyer, *Arch. Exp. Pathol. Pharmakol. (Naunyn-Schmiederbergs)*, 1899, **42**, 109–118; H. Meyer, *Arch. Exp. Pathol. Pharmakol. (Naunyn-Schmiederbergs)*, 1901, **46**, 338.

9 K. H. Meyer and H. Hemmi, *Biochem. Z.*, 1935, **277**, 39.

10 R. Collander, *Acta Chem. Scand.*, 1951, **5**, 774.

11 A. Leo and C. Hansch, *J. Org. Chem.*, 1971, **36**, 1539.

12 P. Seiler, *Eur. J. Med. Chem.*, 1974, **9**, 473.

13 D. Leahy, J. J. Morris, P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2*, 1992, 705.

14 Y. Marcus, *J. Phys. Chem.*, 1991, **95**, 8886.

15 J. A. Riddick and W. B. Bunger, *Organic Solvents*, Wiley-Interscience, New York, 1970.

16 R. F. Rekker, R. Mannhold, G. Bijloo, G. de Vries and K. Dross, *Quant. Struct. Act. Relat.*, 1998, **17**, 537.

17 F. Torrens, *J. Chem. Inf. Comput. Sci.*, 2000, **40**, 236.

18 P. Ruelle, *J. Chem. Inf. Comput. Sci.*, 2000, **40**, 681.

19 P. Meyer and G. Maurer, *I&EC Res.*, 1995, **34**, 373.

20 M. H. Abraham, J. Le and W. E. Acree, Jr., *Collect. Czech. Chem. Commun.*, 1998, **76**, 703.

21 M. H. Abraham, A. M. Zissimos and W. E. Acree, Jr., *Phys. Chem. Chem. Phys.*, 2001, **3**, 3732.

22 M. H. Abraham, *Chem. Soc. Rev.*, 1993, **22**, 73.

23 M. H. Abraham, N. Benjelloun-Dakhama, J . M. R. Gola, W. E. Acree, Jr., W. S. Cain and J. E. Cometto-Muniz, *New J. Chem.*, 2000, **24**, 825.

24 MedChem 2002, Daylight Chemical Information Systems, 27401 Los Altos, Suite 360, Mission Viejo, CA 92691, USA.

25 M. H. Abraham, J. Andonian-Haftvan, G. S. Whiting, A. Leo and R. W. Taft, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1777.

26 M. H. Abraham, J. Le, W. E. Acree, Jr. and P. W. Carr, *J. Phys. Org. Chem.*, 1999, **12**, 675.

27 M. H. Abraham, H. S. Chadha, J. P. Dixon and A. J. Leo, *J. Phys. Org. Chem.*, 1994, **7**, 712.

28 R.-S. Tsai, W. Fan, N. El Tayar, P.-A. Carrupt, B. Testa and L. B. Kier, *J. Am. Chem. Soc.*, 1993, **115**, 9632.

29 W. E. Acree, Jr. and M. H. Abraham, *Can. J. Chem.*, 2001, **79**, 1466.

30 W. E. Acree, Jr. and M. H. Abraham, *J. Solution Chem.*, 2002, **31**, 293.

31 W. E. Acree, Jr. and M. H. Abraham, *Fluid Phase Equilib.*, 2002, **201**, 245.

32 M. H. Abraham, C. E. Green, W. E. Acree, Jr., C. E. Hernandez and L. E. Roy, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2677.

33 M. H. Abraham, C. E. Green and W. E. Acree, Jr., *J. Chem. Soc., Perkin Trans. 2*, 2000, 281.

34 C. Green, M. H. Abraham, W. E. Acree, Jr., K. M. De Fina and T. L. Sharp, *Pest Manag. Sci.*, 2000, **56**, 1043.