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Models for liquid–liquid partition in the system dimethyl sulfoxide–organic solvent and their use for estimating descriptors for organic compounds

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ABSTRACT

Partition coefficients for varied compounds were determined for the organic solvent–dimethyl sulfoxide biphasic partition system where the organic solvent is n-heptane or isopentyl ether. These partition coefficient databases are analyzed using the solvation parameter model facilitating a quantitative comparison of the dimethyl sulfoxide-based partition systems with other totally organic partition systems. Dimethyl sulfoxide is a moderately cohesive solvent, reasonably dipolar/polarizable and strongly hydrogen-bond basic. Although generally considered to be non-hydrogen-bond acidic, analysis of the partition coefficient database strongly supports reclassification as a weak hydrogen-bond acid in agreement with recent literature. The system constants for the n-heptane–dimethyl sulfoxide biphasic system provide an explanation of the mechanism for the selective isolation of polycyclic aromatic compounds from mixtures containing low-polarity hydrocarbons based on the capability of the polar interactions (dipolarity/polarizability and hydrogen-bonding) to overcome the opposing cohesive forces in dimethyl sulfoxide that are absent for the interactions with hydrocarbons of low polarity. In addition, dimethyl sulfoxide–organic solvent systems afford a complementary approach to other totally organic biphasic partition systems for descriptor measurements of compounds virtually insoluble in water.

1. Introduction

Recent developments in liquid-phase microextraction have brought about a rebirth of interest in liquid–liquid partitioning as a sample preparation method [1–3]. The use of a miniaturized format compatible with chromatographic measurements and allowing the elimination of several sample processing steps makes the method competitive with solid-phase extraction, which had largely replaced conventional liquid–liquid partitioning as a sample preparation procedure for chromatographic analysis [1–3]. Solvent-based methods are generally more tolerant of matrix burden and afford a wider selectivity range than is the case for commonly used sorbents [4,5]. In addition, solvent properties are more reproducible between batches than sorbent properties.

Useful liquid–liquid partition systems require the formation of biphasic systems of low mutual solubility. For practical reasons most systems in common use consist of water as one phase and a low to moderately polar organic solvent as the other [4,6,7]. For compounds of low water solubility, and for compounds that are water unstable, predominantly aqueous biphasic systems are of limited use. Totally organic biphasic systems are an attractive alternative for these compounds but solvent selection is limited by the high mutual solubility of organic solvents. For conventional methods solvent selection is largely limited to volatile organic solvents because of the need to reduce the final volume of the solvent by evaporation to facilitate further sample preparation steps or to obtain suitable instrumental method detection limits. For liquid-phase microextraction solvent evaporation is rarely required allowing a wider choice of solvents with different selectivities to be exploited. In recent studies we have described the use of formamide [8,9], propylene carbonate [10], and ethylene glycol [11] as useful solvents for liquid–liquid partition forming biphasic systems of different selectivities with two or more of the counter solvents n-heptane, 1,2-dichloroethane, isopentyl ether, and 1-octanol. As an extension of these studies we investigate the use of dimethyl sulfoxide as a base solvent for liquid–liquid partition with n-heptane and isopenyl ether as counter solvents in this report.

An important application of water-based partition systems is the determination of solute descriptors for use in the solvation parameter model [7,12]. For compounds of negligible water solubility, such as organosiloxanes, dialkyl phthalates, and polychlorinated biphenyls, their use is limited by the problem of obtaining accurate partition coefficients, and of course, for compounds which react with water, is not applicable at all. Totally organic biphasic partition systems combined with retention measurements by gas chromatography were recently used to determine solute descriptors for water insoluble organosiloxanes [13,14].

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These studies demonstrated both the usefulness of this approach for difficult compounds, as well as the limited number and variety of well-characterized, totally organic biphasic systems then available. This provided further impetus for the studies described here.

Dimethyl sulfoxide has found many applications in synthesis, spectroscopy, and chemical engineering applications as a polar, non-hydrogen-bond acid solvent [15]. Over time it has become the *de facto* solvent of choice for solubilizing compounds for high throughput screening in the pharmaceutical industry on account of its ability to dissolve a wide range of chemical types, low volatility, relatively low toxicity, miscibility with water, and limited deleterious effects at low concentrations in bioassays [16,17]. Spectroscopic analysis of solvatochromic indicator compounds suggests that dimethyl sulfoxide is of intermediate polarity (Reichardt's dye $E_T^N = 0.444$) with significant dipolarity/polarizability and hydrogen-bond basicity but no hydrogen-bond acidity (Kamlet–Taft solvatochromic parameters $\pi^* = 1.00$, $\beta = 0.76$, and $\alpha = 0$) [15,18]. The biphasic system n-pentane–dimethyl sulfoxide can be used for the isolation of polycyclic aromatic compounds from complex matrices prior to chromatographic analysis [19–21]. Berthod et al. used dimethyl sulfoxide as a stationary phase for the separation of aromatic compounds by nonaqueous countercurrent chromatography with n-heptane as a mobile phase [22]. These authors also determined the mutual solubility of n-heptane in dimethyl sulfoxide (1.6 mol% or 11 g/L) and dimethyl sulfoxide in n-heptane (0.2 mol% or 2.2 g/L) as well as several partition coefficients for alkylbenzenes and polycyclic aromatic hydrocarbons. Geiser et al. employed dimethyl sulfoxide alone and solvent mixtures containing dimethyl sulfoxide for separations using nonaqueous capillary electrophoresis [23].

Although generally considered to be a non-hydrogen-bond acidic solvent Leggett used an indirect method to calculate the Kamlet–Taft α value for dimethyl sulfoxide suggesting a value of 0.25, typical of a weak hydrogen-bond acid [24]. Using molecular dynamics Vaisman and Berkowitz demonstrated the presence of weak C–H···O hydrogen bonds in water–dimethyl sulfoxide mixtures [25]. These observations were supported by more detailed computational studies of the water–dimethyl sulfoxide and methanol–dimethyl sulfoxide systems and confirmed by NMR and IR spectroscopic measurements [26–28]. Although most authors have attempted to explain the solvent properties of dimethyl sulfoxide with models that assume it to be a non-hydrogen-bond acid the above reports are of particularly interest since it was found necessary to conclude that dimethyl sulfoxide is a weak hydrogen-bond acid solvent to explain the observed partitioning of hydrogen-bond bases for the two totally organic biphasic systems described here.

As in earlier studies, the general method used to characterize the contribution of intermolecular interactions to the partitioning of solutes in biphasic organic solvent systems is based on the solvation parameter model in which the partition coefficient for neutral compounds, $\log K_p$, is described by a series of product terms made up of descriptors (solute properties) and system constants (complementary solvent properties) [7,12,29,30]

$$\log K_p = c + eE + sS + aA + bB + vV \quad (1)$$

The solute descriptors in Eq. (1) are represented by the capital letters and the system constants by the lower case letters. The E descriptor defines the solute's capacity for lone pair electron interactions ($cm^3/mol/10$), the S descriptor for interactions of a dipole-type, the A and B descriptors for hydrogen-bonding interactions with the solute acting as a hydrogen-bond acid or base, and the V descriptor is McGowan's characteristic volume ($cm^3/mol/100$). The system constants are calculated for the biphasic system from experimental partition coefficients for a group of varied compounds with known descriptor values by multiple linear regression analysis. The system constants provide a quantitative description of the intermolecular interactions responsible for the distribution of compounds between the two phases and facilitate a comparison with other biphasic solvent systems [7–12]. They are also required for the calculation of solute descriptors by liquid–liquid partition [7,12–14,31]. Mintz et al. [32] used the solvation parameter model to correlate the enthalpy of solvation for gaseous solutes in dimethyl sulfoxide. The model had good statistical properties but the system constants lack chemical significance when compared with models for free energy properties.

2. Experimental

2.1. Materials

Dimethyl sulfoxide containing <0.2% (w/w) water and a special anhydrous grade stored over molecular sieves containing <0.005% (w/w) water were obtained from Acros Organics (Morris Plains, NJ, USA). n-Heptane and isopentyl ether stored over molecular sieves were obtained from Sigma–Aldrich (Milwaukee, WI, USA). Common chemicals were of the highest purity available and obtained from several sources. The 30 m × 0.32 mm internal diameter HP-5 open-tubular column, 0.25 μm film thickness, was obtained from Agilent Technologies (Folsom, CA, USA).

2.2. Instrumentation

Gas chromatographic measurements were made with an Agilent Technologies (Palo Alto, CA, USA) HP 6890 gas chromatograph fitted with a split/splitless injector and flame ionization detector using ChemStation software (rev.B.04.01) for data acquisition. Nitrogen was used as carrier gas at a constant flow rate of 2.5 mL/min (velocity 47 cm/s). The split ratio was set to 30:1, septum purge 1 mL/min, inlet temperature 275 °C, and detector temperature 300 °C. Separations were performed using a temperature program with an initial temperature of 150 °C for 1 min and then raised to 280 °C at 25 °C/min. Occasionally, a slightly modified program was required to handle co-elution of solutes with the internal standard or solvent peaks.

2.3. Determination of partition coefficients

The method used to determine partition coefficients is described in detail elsewhere [8–10]. The 2.0 mL screw-capped sample vials with PTFE-lined caps (Supelco, Bellefontaine, PA, USA) were charged by syringe with 0.75 mL of dimethyl sulfoxide, 0.75 mL of counter solvent, 1–10 μL of liquid sample, and 1 μL internal standard. Solid samples were dissolved in either the counter solvent or dimethyl sulfoxide (depending on solubility) at a concentration of about 0.5–1.5 mg/mL and added to the vial as described for the pure solvent. Smaller sample sizes were used in some cases to avoid saturation in one of the phases. The vials were shaken for 30 s and allowed to stand for 1 h or overnight at room temperature (22 ± 2 °C). Sample volumes of 1 μL from each phase were taken for calculation of the partition coefficients using the relationship

$$K_p = \frac{S_{cs}}{S_{ds}} \frac{I_{ds}}{I_{cs}} K_p^{IS} \quad (2)$$

where K_p is the partition coefficient for compound S, S_{sc} and S_{ds} the peak area for compound S in the counter solvent and dimethyl sulfoxide layers, respectively, I_{sc} and I_{ds} the peak area of the internal standard in the counter solvent and dimethyl sulfoxide layers, respectively, and K_p^{IS} the partition coefficient for the internal standard in the counter solvent–dimethyl sulfoxide system. The internal standard was acenaphthene with values of $K_p = 1.022 \pm 0.020$ ($n = 10$) for n-heptane–dimethyl sulfoxide,

$K_p = 1.042 \pm 0.016$ ($n = 10$) for n-heptane–dimethyl sulfoxide with 1% (v/v) water added to the dimethyl sulfoxide, $K_p = 0.978 \pm 0.010$ ($n = 7$) for n-heptane–dimethyl sulfoxide containing <0.005% (w/w) water, and $K_p = 1.104 \pm 0.012$ (n = 10) for the isopentyl ether–dimethyl sulfoxide biphasic systems.

2.4. Calculations

Multiple linear regression analysis and statistical calculations were performed on a Dell Dimension 9200 computer (Austin, TX, USA) using the program PASW v18.0 (PASW, Chicago, IL, USA). The solute descriptors were taken from [12,33] and are summarized in Tables 1 and 2 together with the experimental partition coefficients. The uncertainty in the partition coefficients is indicated as a standard deviation for three independent measurements. The Kennard–Stone algorithm programmed in visual basic for use in Excel 2007 (Microsoft Corporation, Redmond, WA) was used to split the data set into training and test sets to estimate the predictive ability of the partition models [34].

3. Results and discussion

The solvation parameter model provides a suitable approach to identify the contribution of defined intermolecular interactions responsible for selectivity in biphasic liquid–liquid partition systems and for simulating the separation properties (partition coefficients) for compounds with known descriptors whose experimental partition coefficients are unavailable [7–13,31,35–37]. This requires calculation of the system constants for the partition systems.

3.1. n-Heptane–dimethyl sulfoxide partition system

Fitting the partition coefficients ($\log K_p$) in Table 1 to the solvation parameter model gave

$$\log K_p = 0.269(\pm0.100) + 0.055(\pm0.050)E - 1.775(\pm0.075)S - 3.096(\pm0.070)A - 1.126(\pm0.090)B + 1.185(\pm0.054)V \quad (3)$$

$$r = 0.994 \quad r^2_{ajd} = 0.988 \quad SE = 0.172 \quad F = 1562 \quad n = 97$$

where r is the multiple correlation coefficient, r^2_{ajd} the coefficient of determination adjusted for the number of degrees of freedom, SE the standard error of the estimate, F the Fisher statistic, and n the number of compounds with partition coefficients included in the model. The e system constant is not statistically significant and differences in electron lone pair interactions in the two phases make no contribution to the partition process. Setting the e system constant to zero (or using the stepwise entry criteria) results in the preferred model

$$\log K_p = 0.272(\pm0.100) - 1.715(\pm0.052)S - 3.085(\pm0.070)A - 1.177(\pm0.077)B + 1.191(\pm0.054)V \quad (4)$$

$$r = 0.994 \quad r^2_{ajd} = 0.988 \quad SE = 0.172 \quad F = 1948 \quad n = 97$$

The driving force for transfer of solutes to the n-heptane layer is indicated by the system constants with positive coefficients, in this case the v system constant only. Since n-heptane is a weak cohesive solvent the small v coefficient indicates that dimethyl sulfoxide is no more than a moderately cohesive solvent. Polar interactions characterized by the s, a, and b system constants favor transfer to the dimethyl sulfoxide layer from which we can infer that dimethyl sulfoxide is reasonably dipolar/polarizable, strongly hydrogen-bond basic and weakly hydrogen-bond acidic. Dimethyl sulfoxide is generally regarded to be a non-hydrogen-bond acidic solvent, although recent spectroscopic studies and theoretical calculations suggest some weak hydrogen-bond acidity [24–28].

To evaluate the predictive ability of the model the data set was split into a training set of 67 compounds and a test set of 30 compounds using the Kennard–Stone algorithm [34]. This approach ensures that the training set and the test set are selected to occupy a similar descriptor space. The model for the training set, Eq. (5), is similar to Eq. (4). Eq. (5) was then used to predict the partition coefficients ($\log K_p$) for the compounds in the test set and the average error, average absolute error, and root mean square error of the difference between the experimental and model predicted values used to assess the ability of Eq. (5) to estimate further values of $\log K_p$ within the same descriptor space. The average error is an indication of bias and at 0.036 indicates that this is not a concern for Eq. (5). The absolute average error (0.171) and root mean square error (0.189) are an indication of the likely error in predicting further partition coefficients based on Eq. (5). Since Eq. (5) is similar to Eq. (4), which is preferred because it is based on a larger number of compounds, it is reasonable to conclude that Eq. (4) should be able to predict partition coefficients to about ±0.18 log units for further compounds with known descriptors that lie within or close to the descriptor space ($E = -0.989$–2.305, $S = -0.155$–1.942, $A = 0$–0.931, $B = 0$–1.456, and $V = 0.706$–3.263) used to define the model.

$$\log K_p = 0.440(\pm0.145) - 1.794(\pm0.070)S - 3.256(\pm0.102)A - 1.100(\pm0.102)B + 1.104(\pm0.074)V \quad (5)$$

$$r = 0.993 \quad r^2_{ajd} = 0.986 \quad SE = 0.207 \quad F = 1172 \quad n = 67$$

3.2. Effect of water on the n-heptane–dimethyl sulfoxide partition system

Table 3 summarizes the system constants for other totally organic biphasic solvent systems and n-heptane–water [7–11,35–37] facilitating a comparison of the hydrogen-bond acidity of dimethyl sulfoxide with other organic solvents and water with low solubility in n-heptane. The b system constant for dimethyl sulfoxide is larger than the values for *N*,*N*-dimethylformamide, propylene carbonate, and acetonitrile (n-hexane as counter solvent). It is significantly larger than the value for methanol, although in this case the mutual solubility of methanol in n-heptane, and *vice versa*, is quite high compared with the above solvent systems. Ethylene glycol, 3,3,3-trifluoroethanol, formamide and water are stronger hydrogen-bond acids than dimethyl sulfoxide, as would be expected. In the case of water, which is the strongest hydrogen-bond acid in Table 3, it is about one-quarter as strong. Compared with the other organic solvents dimethyl sulfoxide saturated with n-heptane is positioned near the middle range for these solvent systems in terms of their hydrogen-bond acidity. Analysis of the dimethyl sulfoxide by gas chromatography with flame ionization detection failed to detect any organic impurities at a concentration greater than 0.1% (w/w), which might be considered sufficient to affect its solvation properties. The dimethyl sulfoxide used in this study is indicated to be 99.7% pure with the main contaminant water at <0.2% (w/w). Since water is a strong hydrogen-bond acid the effect of water on the n-heptane–dimethyl sulfoxide partition system was investigated. At the end of the experiments the water level of the dimethyl sulfoxide was determined to be 0.25% (w/w)

Table 1
Compounds and their partition coefficients and descriptor values used to characterize the n-heptane–dimethyl sulfoxide partition system.

Compounds	Solute descriptors					Partition coefficient		
	E	*S*	*A*	*B*	*V*	K_p	SD	Log K_p
Acenaphthylene	1.540	1.122	0.000	0.210	1.216	0.392	0.006	−0.407
Acetanilide	0.960	1.135	0.543	0.710	1.114	8.0E−04	8.0E−05	−3.076
Acetophenone	0.806	1.026	0.000	0.503	1.014	0.149	0.009	−0.827
Aniline	0.955	1.003	0.249	0.425	0.816	0.023	0.009	−1.646
Anisole	0.712	0.768	0.000	0.311	0.916	0.481	0.036	−0.318
Anthracene	1.942	1.301	0.000	0.260	1.454	0.347	0.024	−0.460
Benzaldehyde	0.813	1.025	0.000	0.394	0.873	0.127	1.2E−04	−0.898
Benzamide	1.260	1.325	0.684	0.663	0.973	1.2E−04	2.6E−05	−3.918
Benzensulfonamide	1.176	1.845	0.675	0.684	1.097	8.0E−05	2.0E−05	−4.119
1,4-Benzodioxan	0.884	1.060	0.000	0.296	1.007	0.148	0.001	−0.829
Benzonitrile	0.742	1.135	0.000	0.331	0.871	0.106	0.003	−0.974
Benzophenone	1.224	1.330	0.000	0.576	1.481	0.167	0.005	−0.778
Benzyl alcohol	0.803	0.882	0.400	0.557	0.916	0.007	6.9E−04	−2.186
Benzyl benzoate	1.248	1.304	0.000	0.584	1.680	0.216	0.007	−0.665
Biphenyl	1.319	0.952	0.000	0.279	1.324	0.669	0.008	−0.175
1-Bromohexane	0.349	0.400	0.000	0.120	1.130	6.135	0.501	0.788
1-Bromooctane	0.339	0.400	0.000	0.120	1.411	15.007	0.330	1.176
3-Bromophenol	1.081	0.777	0.931	0.208	0.950	2.1E−03	8.5E−05	−2.671
4-Bromophenol	1.080	1.170	0.670	0.200	0.950	1.1E−03	1.9E−04	−2.954
n-Butyl benzoate	0.668	0.845	0.000	0.401	1.495	1.704	0.075	0.232
Caffeine	1.606	1.705	0.055	1.245	1.363	2.8E−03	2.8E−04	−2.550
Carbazole	2.050	1.555	0.394	0.221	1.315	2.2E−03	1.5E−04	−2.660
4-Chloro-3-methylphenol	0.920	1.020	0.650	0.230	1.038	3.6E−03	1.2E−04	−2.444
1-Chloronaphthalene	1.410	0.939	0.000	0.138	1.208	0.816	0.022	−0.088
4-Chlorophenol	1.015	0.793	0.871	0.208	0.898	2.4E−03	1.5E−04	−2.619
Cinnamyl alcohol	1.081	0.987	0.481	0.594	1.155	5.7E−03	1.5E−04	−2.243
Coumarin	1.292	1.623	0.000	0.522	1.062	0.012	0.001	−1.935
m-Cresol	0.810	0.779	0.672	0.351	0.916	3.0E−03	1.2E−04	−2.525
o-Cresol	0.774	0.745	0.621	0.357	0.916	5.6E−03	2.0E−04	−2.256
Dibenzofuran	1.594	1.096	0.000	0.114	1.209	0.445	0.008	−0.352
Dibenzylamine	1.340	1.015	0.095	0.987	1.706	0.267	0.010	−0.574
3,4-Dichloroaniline	1.368	1.275	0.415	0.240	1.061	0.006	4.0E−05	−2.251
Diethyl phthalate	0.729	1.418	0.000	0.883	1.711	0.091	0.003	−1.043
Dimethyl phthalate	0.780	1.410	0.000	0.880	1.429	0.028	0.001	−1.557
2,6-Dimethylphenol	0.784	0.795	0.404	0.404	1.057	0.018	0.003	−1.756
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	4.8E−03	2.3E−04	−2.317
1,3-Dinitrobenzene	1.088	1.760	0.000	0.413	1.065	6.0E−03	1.1E−04	−2.225
Dodecane	0.000	0.000	0.000	0.000	1.799	508.745	0.152	2.707
Ethyl benzoate	0.694	0.890	0.000	0.450	1.214	0.672	0.031	−0.173
Fluoranthene	2.305	1.482	0.000	0.277	1.585	0.208	0.008	−0.683
Fluorene	1.670	1.104	0.000	0.257	1.357	0.570	0.012	−0.244
3-Glycidoxypropyltrimethoxysilane	0.067	1.105	0.000	0.987	1.807	0.217	0.093	−0.665
Hexanophenone	0.790	1.026	0.000	0.503	1.578	1.006	0.022	0.002
Iodobenzene	1.182	0.784	0.000	0.135	0.975	0.745	0.003	−0.128
Isocyanatopropyltriethoxysilane	0.045	0.652	0.000	0.833	2.012	2.339	0.121	0.369
Methacryloxypropyltrimethoxysilane	0.046	0.871	0.000	1.014	1.971	0.784	0.026	−0.106
2-Methoxynaphthalene	1.450	1.147	0.000	0.356	1.285	0.258	0.001	−0.588
Methyl benzoate	0.738	0.923	0.000	0.439	1.073	0.400	0.013	−0.398
Methyl deconoate	0.057	0.564	0.000	0.456	1.733	11.519	0.469	1.061
Methyl octanoate	0.069	0.564	0.000	0.456	1.451	4.501	0.890	0.653
1-Methylnaphthalene	1.337	0.909	0.000	0.201	1.226	1.003	0.034	0.001
2-Methylnaphthalene	1.304	0.895	0.000	0.189	1.226	1.049	0.024	0.021
N,*N*-Dimethylaniline	0.956	0.824	0.000	0.368	1.098	0.863	0.029	−0.064
Naphthalene	1.236	0.902	0.000	0.193	1.085	0.658	0.020	−0.182
1-Naphthol	1.442	1.127	0.757	0.329	1.144	6.0E−04	3.2E−05	−3.204

2-Naphthol	1.461	1.188	0.785	0.345	1.144	1.1E−03	9.8E−05	−2.977
2-Nitroaniline	1.214	1.458	0.352	0.354	0.990	1.5E−03	3.3E−05	−2.817
3-Nitroaniline	1.286	1.660	0.412	0.415	0.990	1.2E−03	9.1E−05	−2.922
4-Nitroaniline	1.223	1.826	0.603	0.341	0.990	2.0E−04	7.2E−05	−3.800
Nitrobenzene	0.846	1.138	0.000	0.269	0.891	0.096	0.001	−1.017
4-Nitrobenzyl alcohol	0.996	1.289	0.491	0.602	1.090	2.4E−03	1.8E−04	−2.629
1-Nitronaphthalene	1.387	1.476	0.000	0.290	1.260	0.063	0.003	−1.204
1-Nitrohexane	0.209	0.927	0.047	0.269	1.128	0.546	0.040	−0.263
2-Nitropropane	0.215	0.892	0.016	0.328	0.706	0.178	0.012	−0.751
2-Nitrotoluene	0.866	1.110	0.000	0.270	1.032	0.159	2.4E−04	−0.799
3-Nitrotoluene	0.874	1.100	0.000	0.250	1.032	0.179	0.005	−0.746
4-Nitrotoluene	0.898	1.181	0.000	0.265	1.032	0.163	0.007	−0.787
Nonan-2-one	0.113	0.662	0.000	0.496	1.392	2.126	0.081	0.328
Octadecane	0.000	0.000	0.000	0.000	2.645	1905.02	2.040	3.280
Octan-1-ol	0.199	0.440	0.344	0.520	1.295	0.114	0.051	−0.943
Octan-2-ol	0.176	0.436	0.255	0.496	1.295	0.309	0.104	−0.511
Octanophenone	0.779	0.992	0.000	0.500	1.859	2.443	0.072	0.388
n-Octyltriethoxysilane	0.255	0.052	0.000	0.975	2.503	136.145	0.860	2.134
Pentachlorophenol	1.689	1.026	0.633	0.065	1.387	9.2E−03	3.9E−04	−2.035
Phenanthrene	1.996	1.312	0.000	0.280	1.454	0.311	0.013	−0.508
Phenyl acetate	0.648	1.051	0.000	0.522	1.073	0.110	0.007	−0.959
Phenyl benzoate	1.330	1.420	0.000	0.470	1.540	0.159	0.004	−0.798
1-Phenyl ethanol	0.823	0.770	0.408	0.671	1.057	0.010	5.8E−04	−1.997
2-Phenyl ethanol	0.787	0.814	0.411	0.630	1.057	0.010	0.002	−1.990
Phenyl ether	1.216	0.912	0.000	0.267	1.383	0.662	0.006	−0.179
4-Phenylphenol	1.524	1.220	0.794	0.440	1.383	6.0E−04	7.3E−06	−3.191
Phthalimide	1.179	1.681	0.263	0.585	1.021	9.0E−04	1.3E−05	−3.059
Phthalonitrile	0.729	1.942	0.000	0.387	1.026	2.3E−03	6.6E−04	−2.641
Pyrene	2.300	1.475	0.000	0.286	1.585	0.269	0.013	−0.570
Quinoline	1.268	1.090	0.000	0.562	1.044	0.171	0.002	−0.768
1,2,4,5-Tetrachlorobenzene	0.975	0.714	0.000	0.000	1.206	2.566	0.004	0.409
Tetradecane	0.000	0.000	0.000	0.000	2.081	1045.9	1.375	3.020
Tetrakis(trimethylsiloxy)silane	0.989	0.155	0.000	0.664	3.263	2092.7	1.402	3.321
2,4,6,8-Tetramethyl-2,4,6,8-tetravinycyclotetrasiloxane	0.095	0.215	0.000	0.670	2.736	183.36	0.0655	2.263
p-Tolualdehyde	0.862	1.000	0.000	0.420	1.014	0.142	0.063	−0.849
o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.013	2.3E−04	−1.886
p-Toluidine	0.923	1.192	0.147	0.396	0.957	0.014	0.007	−1.848
1,2,4-Trichlorobenzene	1.022	0.738	0.000	0.029	1.084	1.774	0.076	0.249
Tri-n-butyrin	0.064	1.189	0.000	1.456	2.445	0.362	0.018	−0.442
Undecane	0.000	0.000	0.000	0.000	1.659	146.18	0.9641	2.165
Valerophenone	0.795	0.984	0.000	0.513	1.437	0.6874	0.002	−0.163

Table 2
Compounds and their partition coefficients and descriptor values used to characterize the isopentyl ether–dimethyl sulfoxide partition system.

Compounds	Solute descriptors					Partition coefficient		
	E	*S*	*A*	*B*	*V*	K_p	SD	Log K_p
Acenaphthylene	1.540	1.122	0.000	0.210	1.216	0.494	0.002	−0.306
Acetanilide	0.960	1.135	0.543	0.710	1.114	0.012	0.002	−1.912
Acetophenone	0.806	1.026	0.000	0.503	1.014	0.258	0.020	−0.589
Anisole	0.712	0.768	0.000	0.311	0.916	0.758	0.018	−0.121
Anthracene	1.942	1.301	0.000	0.260	1.454	0.433	0.020	−0.364
Benzensulfonamide	1.176	1.845	0.675	0.684	1.097	5.1E−04	2.8E−05	−3.294
1,4-Benzodioxan	0.884	1.060	0.000	0.296	1.007	0.268	0.005	−0.572
Benzonitrile	0.742	1.135	0.000	0.331	0.871	0.074	0.007	−1.132
Benzophenone	1.224	1.330	0.000	0.576	1.481	0.289	0.005	−0.539
Benzyl alcohol	0.803	0.882	0.400	0.557	0.916	0.028	0.001	−1.560
Benzyl benzoate	1.248	1.304	0.000	0.584	1.680	0.347	0.010	−0.459
Biphenyl	1.319	0.952	0.000	0.279	1.324	0.795	0.006	−0.100
1-Bromohexane	0.349	0.400	0.000	0.120	1.130	5.490	0.566	0.740
1-Bromooctane	0.339	0.400	0.000	0.120	1.411	12.439	0.146	1.095
4-Bromophenol	1.080	1.170	0.670	0.200	0.950	0.011	3.7E−04	−1.957
n-Butyl benzoate	0.668	0.845	0.000	0.401	1.495	1.836	0.026	0.264
Caffeine	1.606	1.705	0.055	1.245	1.363	0.012	0.004	−1.903
Carbazole	2.050	1.555	0.394	0.221	1.315	0.021	0.001	−1.675
4-Chloro-3-methylphenol	0.920	1.020	0.650	0.230	1.038	0.025	0.002	−1.604
2-Chloroaniline	1.026	0.997	0.237	0.317	0.939	0.063	0.002	−1.198
4-Chloroaniline	1.006	1.169	0.345	0.308	0.939	0.014	2.7E−04	−1.860
1-Chloronaphthalene	1.410	0.939	0.000	0.138	1.208	0.921	0.019	−0.036
4-Chlorophenol	1.015	0.793	0.871	0.208	0.898	8.6E−03	1.8E−03	−2.066
Cinnamyl alcohol	1.081	0.987	0.481	0.594	1.155	0.016	4.4E−04	−1.785
Coumarin	1.292	1.623	0.000	0.522	1.062	0.031	8.4E−04	−1.506
m-Cresol	0.810	0.779	0.672	0.351	0.916	0.017	4.6E−04	−1.762
o-Cresol	0.774	0.745	0.621	0.357	0.916	0.027	0.009	−1.571
p-Cresol	0.793	0.769	0.664	0.353	0.916	0.019	0.062	−1.723
Dibenzofuran	1.594	1.096	0.000	0.114	1.209	0.639	0.040	−0.194
Dibenzylamine	1.340	1.015	0.095	0.987	1.706	0.425	0.001	−0.372
3,4-Dichloroaniline	1.368	1.275	0.415	0.240	1.061	0.013	0.001	−1.872
Diethyl phthalate	0.729	1.418	0.000	0.883	1.711	0.188	0.004	−0.727
Dimethyl phthalate	0.780	1.410	0.000	0.880	1.429	0.068	0.002	−1.167
2,6-Dimethylphenol	0.784	0.795	0.404	0.404	1.057	0.059	0.003	−1.232
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	0.036	0.002	−1.441
1,3-Dinitrobenzene	1.088	1.760	0.000	0.413	1.065	0.019	0.001	−1.715
Diphenylamine	1.583	1.277	0.170	0.495	1.424	0.104	0.002	−0.982
Dodecane	0.000	0.000	0.000	0.000	1.799	200.5	5.966	2.302
Ethyl benzoate	0.694	0.890	0.000	0.450	1.214	0.664	0.059	−0.178
Fluoranthene	2.305	1.482	0.000	0.277	1.585	0.309	0.019	−0.510
Fluorene	1.670	1.104	0.000	0.257	1.357	0.646	0.009	−0.190
3-Glycidoxypropyltrimethoxysilane	0.067	1.105	0.000	0.987	1.807	0.269	0.012	−0.571
Hexanophenone	0.790	1.026	0.000	0.503	1.578	1.264	0.017	0.102
Indole	1.028	1.202	0.394	0.236	0.946	0.017	0.001	−1.775
Iodobenzene	1.182	0.784	0.000	0.135	0.975	0.840	0.052	−0.076
Isocyanatopropyltriethoxysilane	−0.045	0.652	0.000	0.833	2.012	3.131	0.274	0.496
Methacryloxypropyltrimethoxysilane	0.046	0.871	0.000	1.014	1.971	1.056	0.036	0.024
2-Methoxynaphthalene	1.450	1.147	0.000	0.356	1.285	0.356	0.003	−0.448
Methyl benzoate	0.738	0.923	0.000	0.439	1.073	0.388	0.165	−0.411
Methyl deconoate	0.057	0.564	0.000	0.456	1.733	10.311	0.709	1.013
Methyl octanoate	0.069	0.564	0.000	0.456	1.451	4.591	0.224	0.662
1-Methylnaphthalene	1.337	0.909	0.000	0.201	1.226	1.036	0.032	0.015
2-Methylnaphthalene	1.304	0.895	0.000	0.189	1.226	1.104	0.023	0.043
N,*N*-Dimethylaniline	0.956	0.824	0.000	0.368	1.098	0.882	0.039	−0.054
Naphthalene	1.236	0.902	0.000	0.193	1.085	0.655	0.028	−0.184
1-Naphthol	1.442	1.127	0.757	0.329	1.144	0.012	8.0E−04	−1.930
2-Naphthol	1.461	1.188	0.785	0.345	1.144	6.3E−03	4.3E−04	−2.204
2-Nitroaniline	1.214	1.458	0.352	0.354	0.990	8.7E−03	0.013	−2.062
3-Nitroaniline	1.286	1.660	0.412	0.415	0.990	3.5E−03	2.5E−05	−2.454
4-Nitroaniline	1.223	1.826	0.603	0.341	0.990	7.4E−04	0.000	−3.129
Nitrobenzene	0.846	1.138	0.000	0.269	0.891	0.202	0.006	−0.694
4-Nitrobenzyl alcohol	0.980	1.362	0.547	0.571	1.090	3.1E−03	5.0E−04	−2.515
1-Nitronaphthalene	1.387	1.476	0.000	0.290	1.260	0.139	0.002	−0.857
2-Nitropropane	0.215	0.892	0.016	0.328	0.706	0.287	0.008	−0.542
2-Nitrotoluene	0.866	1.110	0.000	0.270	1.032	0.289	0.018	−0.539
3-Nitrotoluene	0.874	1.100	0.000	0.250	1.032	0.294	0.017	−0.531
4-Nitrotoluene	0.898	1.181	0.000	0.265	1.032	0.305	0.002	−0.516
Nonan-2-one	0.113	0.662	0.000	0.496	1.392	2.767	0.171	0.442
Octan-1-ol	0.199	0.440	0.344	0.520	1.295	0.547	0.047	−0.262
Octanophenone	0.779	0.992	0.000	0.500	1.859	2.753	0.153	0.440
n-Octyltriethoxysilane	−0.255	−0.052	0.000	0.975	2.503	92.300	0.813	1.965
Pentachlorophenol	1.689	1.026	0.633	0.065	1.387	0.074	0.008	−1.129
Phenanthrene	1.996	1.312	0.000	0.280	1.454	0.371	0.011	−0.431
Phenyl acetate	0.648	1.051	0.000	0.522	1.073	0.171	0.099	−0.767

Table 2 (*Continued*)

Compounds	Solute descriptors					Partition coefficient		
	E	*S*	*A*	*B*	*V*	K_p	SD	Log K_p
Phenyl benzoate	1.330	1.420	0.000	0.470	1.540	0.254	4.8E−04	−0.595
1-Phenyl ethanol	0.823	0.770	0.408	0.671	1.057	0.045	0.012	−1.348
2-Phenyl ethanol	0.787	0.814	0.411	0.630	1.057	0.036	0.008	−1.439
Phenyl ether	1.216	0.912	0.000	0.267	1.383	0.798	0.006	−0.098
2-Phenylacetamide	0.950	1.587	0.517	0.771	1.114	1.4E−03	9.7E−04	−2.845
4-Phenylphenol	1.524	1.220	0.794	0.440	1.383	6.9E−03	4.0E−05	−2.160
Phthalimide	1.227	1.688	0.284	0.581	1.021	2.5E−03	8.2E−05	−2.606
Phthalonitrile	0.729	1.942	0.000	0.387	1.026	0.016	0.004	−1.786
Pyrene	2.300	1.475	0.000	0.286	1.585	0.356	0.029	−0.448
1,2,4,5-Tetrachlorobenzene	0.975	0.714	0.000	0.000	1.206	2.458	0.042	0.391
Tetradecane	0.000	0.000	0.000	0.000	2.081	331.82	0.114	2.521
Tetrakis(trimethylsiloxy)silane	−0.989	−0.133	0.000	0.682	3.263	1159.3	1.564	3.064
2,4,6,8-Tetramethyl-2,4,6,8-tetravinycyclotetrasiloxane	−0.095	0.215	0.000	0.670	2.736	166.0	0.508	2.220
Thiophene	0.687	0.560	0.000	0.150	0.641	0.667	0.023	−0.176
p-Tolualdehyde	0.862	1.000	0.000	0.420	1.014	0.257	0.088	−0.591
Toluene	0.606	0.499	0.000	0.139	0.857	2.446	0.186	0.388
m-Toluidine	0.946	1.128	0.112	0.516	0.957	0.065	0.034	−1.187
o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.039	0.001	−1.414
p-Toluidine	0.923	1.192	0.147	0.396	0.957	0.031	0.0051	−1.502
1,2,4-Trichlorobenzene	1.022	0.738	0.000	0.029	1.084	1.693	0.045	0.229
Tri-n-butyrin	0.064	1.189	0.000	1.456	2.445	0.576	0.037	−0.240
Undecane	0.000	0.000	0.000	0.000	1.659	89.475	0.662	1.952
Valerophenone	0.795	0.984	0.000	0.513	1.437	0.906	0.009	−0.043

by Karl–Fisher titration, and had not been contaminated during laboratory operations due to its hygroscopicity. To ascertain what effect this concentration of water might have on the calculated hydrogen-bond acidity of the dimethyl sulfoxide the solvent was intentionally contaminated with a further 1% (v/v) water (corresponding to a total water concentration of about 1.17%, w/w). This solvent was then used to determine the partition coefficients for a representative group of compounds covering the same descriptor space as the original data set (determined using the Kennard–Stone method). The compounds and their partition coefficients are indicated in Table S-1. The partition coefficients for the two data sets, with and without the intentional addition of water, are plotted in Fig. 1. The regression model for the plot is

$$\log K_{ds+1\%} = 0.987(\pm 0.013)\log K_p + 0.067(\pm 0.018) \quad (6)$$

$$r^2 = 0.9954 \quad SE = 0.078 \quad F = 6038 \quad n = 30$$

where $\log K_{ds+1\%}$ is the partition coefficient for the n-heptane–dimethyl sulfoxide biphasic system to which 1% (v/v)

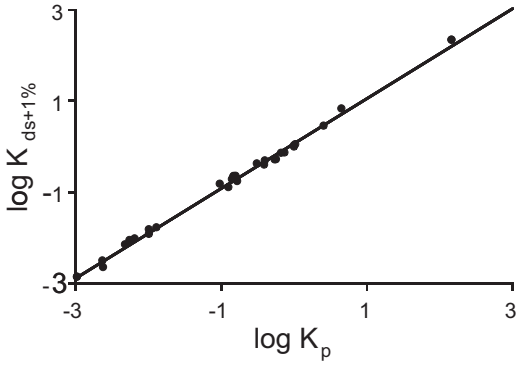

Fig. 1. Plot of the partition coefficients for a representative group of compounds in the n-heptane–dimethyl sulfoxide biphasic system containing intentionally added water (1%, v/v), $\log K_{ds+1\%}$, against the system without water addition, $\log K_p$. The purpose of this experiment was to confirm that the observed hydrogen-bond acidity of dimethyl sulfoxide could not be accounted for solelyt by the presence of water as a contaminant (0.25%, w/w) in the dimethyl sulfoxide solvent.

Table 3
System constants for totally organic biphasic partition systems and for n-heptane–water.

System	System constants					
	c	*e*	*s*	*a*	*b*	*v*
Ethylene glycol–1,2-dichloroethane	−0.639	0.096	0	2.468	0.991	−1.307
Formamide–1,2-dichloroethane	−0.207	−0.082	0.399	1.957	1.298	−1.705
n-Heptane–ethylene glycol	0.358	0.093	−1.553	−3.781	−1.548	2.133
n-Heptane–*N*,*N*-dimethylformamide	0.255	0.038	−1.391	−2.160	−0.593	0.486
n-Heptane–dimethyl sulfoxide	0.289	0	−1.781	−3.088	−1.167	1.180
n-Heptane–formamide	0.083	0.559	−2.244	−3.250	−1.614	2.387
n-Heptane–hexafluoroisopropanol	−0.490	1.030	−1.712	−0.669	−1.746	1.121
n-Heptane–methanol	−0.158	0.186	−0.686	−1.098	−0.951	0.618
n-Heptane–propylene carbonate	0.502	0.455	−2.087	−2.646	−0.433	0.807
n-Heptane–trifluoroethanol	0.013	0.882	−1.557	−1.312	−2.928	1.301
n-Heptane–water	0.325	0.670	−2.061	−3.317	−4.732	4.543
n-Hexane–acetonitrile	0.152	0.349	−1.439	−1.611	−0.874	0.669
Isopentyl ether–dimethyl sulsoxide	0.154	0	−1.452	−2.153	−0.972	1.116
Isopentyl ether–ethylene glycol	0.419	−0.090	−1.159	−1.530	−1.901	2.089
Isopentyl ether–formamide	0.130	0.564	−1.715	−1.314	−1.407	2.005
Isopentyl ether–propylene carbonate	0.264	0.298	−1.432	−0.718	−0.472	0.729
Octan1-ol–formamide	0.285	0.267	−1.053	−0.333	−0.929	1.314
Octan-1-ol–propylene carbonate	0.282	0.256	−1.068	0.222	0	0.365

water was added to the dimethyl sulfoxide. The 95% confidence interval for the slope of Eq. (6) includes 1 (0.960–1.013) so there is no obvious chemical difference for the two data sets. The 95% confidence interval for the intercept (0.104–0.030) does not include zero suggesting that the addition of water results in a small bias, which can probably be accounted for by the small difference in the cohesive energy of the two solvent systems resulting from the addition of water to the dimethyl sulfoxide. The distribution of the residuals for Eq. (6) is normal. For both data sets the solvation parameter model was used to assess whether the added water had a noticeable effect on the system constants. The models for the two n-heptane–dimethyl sulfoxide systems are

$$\log K_p = -0.142(\pm0.229) - 1.537(\pm0.135)S - 2.848(\pm0.125)A - 1.378(\pm0.214)B + 1.444(\pm0.1444)V \quad (7)$$

$r = 0.991 \quad r^2_{ajd} = 0.979 \quad SE = 0.165 \quad F = 338 \quad n = 30$

and

$$\log K_{ds+1\%} = -0.526(\pm0.268) - 1.430(\pm0.158)S - 2.582(\pm0.145)A - 1.414(\pm0.253)B + 1.737(\pm0.169)V \quad (8)$$

$r = 0.987 \quad r^2_{ajd} = 0.970 \quad SE = 0.195 \quad F = 235 \quad n = 30$

Both models are similar but not identical to either Eq. (4) or (5), which are based on a larger number of compounds. Since the partition coefficients used for Eq. (7) are a subset of those used in Eq. (4), Eq. (7) is likely a local model. Eq. (4) can explain both data sets with a root mean square error of prediction of about 0.17 log units supporting this hypothesis. At the 95% confidence level the differences in the c term and the v and a system constants for Eqs. (7) and (8) are significant while the s and b system constants are not. The differences in the system constants can probably be accounted for by the small difference in cohesion of the dimethyl sulfoxide as a result of the addition of water.

Dimethyl sulfoxide–water mixtures are known to form micro heterogeneous environments, albeit at water concentrations considerably higher than those in which water is present as a contaminant (<0.01 mole fraction) [38–41]. Compared with solvents such as methanol and acetonitrile the formation of solvent clusters containing water in dimethyl sulfoxide–water mixtures is only observed at relatively high water concentrations (mole fraction >0.8). For low mole fractions of water, solutes are preferentially solvated by dimethyl sulfoxide in dimethyl sulfoxide–water mixtures and from what is known of the structure of dimethyl sulfoxide–water mixtures there is little to suggest that trace amounts of water would have a significant effect on partition coefficients. Solvent effects employing binary mixtures are inherently non-linear, however, and so to confirm the hypothesis that trace amounts of water are unable to account for a significant fraction of the hydrogen-bond acidity assigned to dimethyl sulfoxide in this study the partition coefficients for the same thirty representative compounds identified above where determined using a thoroughly dried sample of dimethyl sulfoxide certified to contain less than 0.005% (w/w) water. The partition coefficients are summarized in Table S-2 and the regression model for the plot of the data set for dimethyl sulfoxide containing 0.25% (w/w) water and dry dimethyl sulfoxide ($\log K_{dry}$) is:

$$\log K_p = 1.004(\pm0.008)\log K_{dry} + 0.007(\pm0.011) \quad (9)$$

$r^2 = 0.9983 \quad SE = 0.048 \quad F = 16695 \quad n = 30$

The 95% confidence interval for the slope of Eq. (9) includes 1 (0.988–1.020) and the intercept includes zero (−0.016–0.030). Thus, there is no significant chemical difference between the two data sets. The average error for the two data sets (assuming the hypothesis that they should be identical) is 0.003 and the average absolute error 0.048. The average error is an indication of the lack of bias (takes the sign of the residuals into account) and the average absolute error is an indication of the typical difference between values in the two data sets independent of the sign of the residuals. Both values support the conclusion that the differences between the two data sets are no larger than could be explained by typical experimental error. The solvation parameter model for the dry dimethyl sulfoxide data set (Table S-2) is

$$\log K_{dry} = -0.394(\pm0.266) - 1.495(\pm0.145)S - 2.721(\pm0.135)A - 1.366(\pm0.231)B + 1.604(\pm0.169)V \quad (10)$$

$r = 0.989 \quad r^2_{ajd} = 0.975 \quad SE = 0.178 \quad F = 289 \quad n = 30$

The difference in the system constants for the n-heptane–dimethyl sulfoxide containing 0.25% (w/w) water model, Eq. (7), and the n-heptane–dry dimethyl sulfoxide model, Eq. (10), is not significant at the 95% confidence level. m-Toluidine is an extreme value in Eq. (10) but was retained so that the comparison could be made for the two models using exactly the same compounds.

In terms of why the above experiments were performed, there is no indication that low concentrations of water in dimethyl sulfoxide are solely or largely responsible for its observed hydrogen-bond acidity.

3.3. Mechanism for the isolation of polycyclic aromatic compounds by n-heptane–dimethyl sulfoxide partition

The success of dimethyl sulfoxide as a general solvent for different compound types is accounted for by the modest penalty paid to form a cavity in the solvent (moderate cohesive energy) combined with a significant capacity for dipole-type and hydrogen-bonding interactions. Its selectivity for the isolation of polycyclic aromatic compounds from aliphatic hydrocarbons and similar low-polarity compounds is due to the presence of a sufficient barrier to diminish the solubility of low-polarity compounds in the dimethyl sulfoxide layer aided by specific polar interactions with polycyclic aromatic compounds that provide for their transfer to the dimethyl sulfoxide layer. Some representative examples of the contribution of the different intermolecular interactions to the partition coefficient in the n-heptane–dimethyl sulfoxide biphasic system are summarized in Table 4. For the polycyclic aromatic hydrocarbons the driving force for transfer to the dimethyl sulfoxide layer is their dipolaity/polarizability (sS term) supplemented by their hydrogen-bond basicity (bB). These interactions exceed the opposing contribution from cavity formation (as well as differences in dispersion interactions in the two phases that are not cancelled when the solute is transferred) indicated as the vV contribution. Although polycyclic aromatic hydrocarbons have relatively large E descriptor values, electron lone pair interactions do not contribute to the selective extraction of these compounds because electron lone pair interactions are about the same in both phases ($e = 0$). For compounds which are less dipolar/polarizable than the polycyclic aromatic hydrocarbons but of a similar size, for example, bicyclohexyl and phenylcyclohexyl, the contribution of dipole-type interactions are unable to compensate for the difficulty of cavity formation in dimethyl sulfoxide and the partition coefficients for these compounds favor the n-heptane layer. The reason then that the n-heptane–dimethyl sulfoxide system is effective for the iso-

Table 4
The contribution of different intermolecular interactions to the transfer of polycyclic aromatic compounds to the dimethyl sulfoxide layer in the n-heptane–dimethyl sulfoxide partition system.

Compound	Contribution to the partition coefficient ($\log K_p$)						Estimated partition coefficient (K_p)
	eE	*sS*	*aA*	*bB*	*vV*	*c*	
Anthracene	0	2.317	0	0.303	−1.716	−0.289	4.12
Biphenyl	0	1.696	0	0.326	−1.562	−0.289	1.48
Fluorene	0	1.966	0	0.300	−1.601	−0.289	2.38
Fluoranthene	0	2.639	0	0.323	−1.870	−0.289	6.35
Pyrene	0	2.627	0	0.334	−1.870	−0.289	6.33
Naphthalene	0	1.606	0	0.225	−1.280	−0.289	1.83
1-Acetonaphthone	0	2.486	0	0.644	−1.632	−0.289	16.2
1-Nitronaphthalene	0	2.629	0	0.338	−1.489	−0.289	15.5
1-Naphthol	0	2.007	2.338	0.384	−1.350	−0.289	1230
Bicyclohexyl	0	0.534	0	0	−1.867	−0.289	0.024
Phenylcyclohexyl	0	1.058	0	0.082	−1.715	−0.289	0.140

lation of polycyclic aromatic hydrocarbons is that the barrier to transfer to dimethyl sulfoxide represented by the cavity term (vV) is sufficiently high to minimize transfer of low-polarity hydrocarbons but not so high that it cannot be overcome by polar interactions possible for polycyclic aromatic hydrocarbons (sS and bB). For polycyclic aromatic compounds with polar functional groups transfer to dimethyl sulfoxide is favored by these additional polar interactions, especially for compounds which are strong hydrogen-bond acids, such as 1-naphthol, since dimethyl sulfoxide is a strong hydrogen-bond base. The n-heptane–dimethyl sulfoxide system cannot be expected to provide selectivity for the separation of polycyclic aromatic hydrocarbons and polycyclic aromatic compounds with polar functional groups since both types of compounds favor residence in the dimethyl sulfoxide layer and are only differentiated by the magnitude of their partition coefficients.

3.4. Isopentyl ether–dimethyl sulfoxide partition system

Fitting the partition coefficients ($\log K_p$) in Table 2 to the solvation parameter model gave

$$\log K_p = 0.154(\pm0.070) - 1.452(\pm0.037)S - 2.153(\pm0.053)A - 0.972(\pm0.059)B + 1.116(\pm0.041)V \quad (11)$$

$$r = 0.995 \quad r^2_{ajd} = 0.989 \quad SE = 0.125 \quad F = 2214 \quad n = 98$$

The higher cohesive energy of the dimethyl sulfoxide layer favors transfer of all compounds to the isopentyl ether layer (positive v system constant) while polar interactions favor transfer to the dimethyl sulfoxide layer (s, a and b). Since isopentyl ether is more dipolar/polarizable and hydrogen-bond basic than n-heptane it should complete more effectively with dimethyl sulfoxide for these interactions, which is reflected in the smaller values for the s and a system constants in Eq. (11) compared with Eq. (4). Isopentyl ether is a non-hydrogen-bond acid, and apart from differences in mutual solubility, the isopenyl ether–dimethyl sulfoxide biphasic system is expected to have a similar b system constant to the n-heptane–dimethyl sulfoxide biphasic system, which is indeed the case. Although the barrier represented by the difference in the cohesive energy for the two phases is similar the contribution of polar interactions to the transfer of polycyclic aromatic compounds to dimethyl sulfoxide is smaller and isopentyl ether–dimethyl sulfoxide is not expected to be as effective as the n-heptane–dimethyl sulfoxide system for the separation of polycyclic aromatic hydrocarbons from low-polarity hydrocarbons.

The Kennard–Stone algorithm was used to split the data set into a training set of 68 compounds and a test set of 30 compounds. The model for the training set is

$$\log K_p = 0.197(\pm0.085) - 1.458(\pm0.043)S - 2.173(\pm0.065)A - 0.948(\pm0.070) + 1.081(\pm0.048)V \quad (12)$$

$$r = 0.995 \quad r^2_{ajd} = 0.990 \quad SE = 0.131 \quad F = 1705 \quad n = 68$$

and is quite similar to Eq. (11). For the test set the average error was 0.087, the average absolute error 0.128 and the root mean square error 0.113. Thus, Eq. (11) should be able to predict further values of the partition coefficients to about 0.13 log units for compounds with descriptor values that lie within or close to the descriptor space (E = −0.989–2.305, S = −0.133–1.942, A = 0–0.871, and V = 0.7055–3.263) used to define the model.

3.5. General partition properties of dimethyl sulfoxide–organic solvent systems

With the models reported here, system constants have been calculated for seventeen totally organic biphasic systems (Table 3)

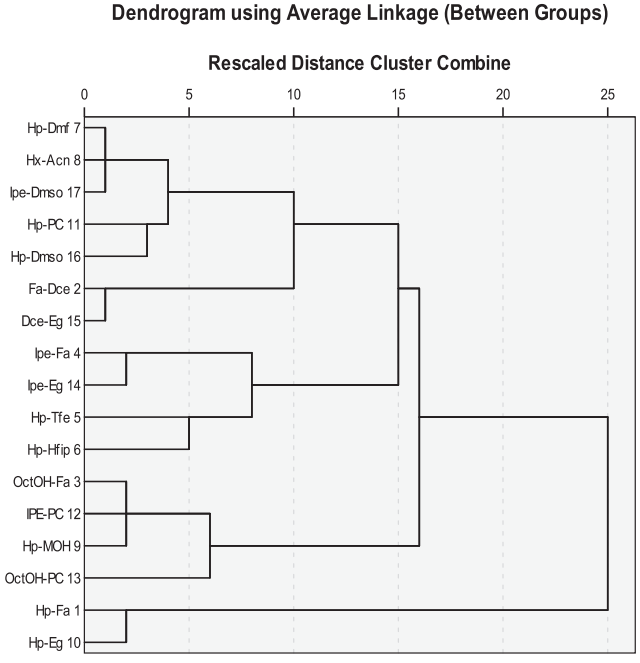

Fig. 2. Cluster dendrogram for the average linkage between groups agglomeration algorithm for the totally organic biphasic systems with the system constants of the solvation parameter models (Table 3) as variables.

Table 5
Determination of descriptors by chromatographic and totally organic liquid–liquid partition systems. (Total, sum of all data using different methods; GC, gas chromatography; LC, reversed-phase liquid chromatography; MEKC, micellar electrokinetic chromatography; LP, totally organic liquid–liquid partition.).

Compounds	Method	Descriptors						Statistics[a]	
		E	*S*	*A*	*B*	*L*	*V*	SD	*n*
Acetanilide	Total	0.960	1.149	0.541	0.707	5.920	1.1137	0.046	245
	GC	0.960	1.472	0.616		5.477		0.020	23
	LC	0.960	1.133	0.505	0.721		1.1137	0.038	168
	MEKC	0.960	1.205	0.506	0.691		1.1137	0.048	42
	LP	0.960	1.256	0.496	0.712		1.1137	0.045	6
Acetophenone	Total	0.806	1.055	0	0.497	4.491	1.0139	0.029	471
	GC	0.806	1.059	0		4.486		0.015	247
	LC	0.806	1.080	0	0.496		1.0139	0.030	146
	MEKC	0.806	1.124	0	0.473		1.0139	0.040	60
	LP	0.806	1.014	0	0.517		1.0139	0.071	13
Benzyl alcohol	Total	0.803	0.866	0.418	0.558	4.247	0.9160	0.039	375
	GC	0.803	0.869	0.410		4.251		0.026	213
	LC	0.803	0.860	0.363	0.569		0.9160	0.037	94
	MEKC	0.803	0.970	0.393	0.539		0.9160	0.031	44
	LP	0.803	0.893	0.486	0.452		0.9160	0.053	10
1-Bromonaphthalene	Total	1.594	1.008	0	0.157	6.574	1.2604	0.038	213
	GC	1.594	1.009	0		6.566		0.031	72
	LC	1.594	0.968	0	0.164		1.2604	0.034	126
	LP	1.594	0.997	0	0.205		1.2604	0.036	12
Caffeine	Total	1.572	1.680	0.045	1.249	7.666	1.3632	0.061	166
	GC	1.572	1.766	0.242		7.435		0.021	19
	LC	1.572	1.635	0.033	1.263		1.3632	0.051	124
	MEKC	1.572	1.368	0.121	1.340		1.3632	0.029	9
	LP	1.572	1.676	0.015	1.357		1.3632	0.116	10
4-Chlorophenol	Total	1.010	0.795	0.865	0.209	4.814	0.8975	0.040	298
	GC	1.010	0.827	0.963		4.726		0.023	118
	LC	1.010	0.728	0.886	0.220		0.8975	0.031	113
	MEKC	1.010	0.746	0.741	0.217		0.8975	0.033	21
	LP	1.010	0.798	0.837	0.224		0.8975	0.066	9
Coumarin	Total	1.286	1.620	0	0.522	6.016	1.0619	0.047	241
	GC	1.286	1.645	0		5.994		0.020	63
	LC	1.286	1.560	0	0.537		1.0619	0.043	161
	LP	1.286	1.580	0	0.621		1.0619	0.090	12
Nitrobenzene	Total	0.846	1.141	0	0.268	4.531	0.8906	0.038	412
	GC	0.846	1.130	0		4.548		0.030	144
	LC	0.846	1.158	0	0.261		0.8906	0.029	182
	MEKC	0.846	1.264	0	0.249		0.8906	0.037	57
	LP	0.846	1.163	0	0.239		0.8906	0.072	15
Phenol	Total	0.779	0.766	0.714	0.319	3.835	0.7751	0.033	471
	GC	0.779	0.746	0.730		3.853		0.026	216
	LC	0.779	0.823	0.622	0.326		0.7751	0.029	180
	MEKC	0.779	0.854	0.757	0.300		0.7751	0.030	57
	LP	0.779	0.754	0.743	0.320		0.7751	0.045	8

[a] SD, standard deviation of the Solver solution for *n* independent solvation parameter models.

[8–12,31–33]. Hierarchical cluster analysis using the average linkage between groups algorithm with the system constants as variables was used to compare extraction properties of these biphasic systems. The dendrogram (Fig. 2) demonstrates that the solvent systems encompass a wide selectivity range with little clustering. Although groups can be identified in the dendrogram these are generally composed of neighbors best described as the nearest equivalent system rather than selectivity equivalent system. The n-heptane–dimethyl sulfoxide system has n-heptane–propylene carbonate as its nearest neighbor and isopentyl ether–dimethyl sulfoxide the n-hexane–acetonitrile and n-heptane–*N*,*N*-dimethylformamide systems as the nearest neighbors. Within these solvent groups the individual solvent systems are sufficiently dissimilar in their solvation properties that one system could substitute for the other in only the broadest sense but none of the paired systems duplicate each other. A useful feature

Table 6
Calculation of revised descriptor values for organosiloxanes by gas chromatography and totally organic liquid–liquid partition.

Compounds	Descriptors						Statistics[a]	
	E	*S*	*A*	*B*	*V*	*L*	SD	*n*
3-Aminopropyltrimethoxysilane	−0.021	0.500	0.095	1.302	1.8983	5.550	0.050	79
Bis(trimethylsiloxy)methylsilane	−0.448	−0.159	0.037	0.372	1.9494	3.855	0.069	31
Glycidyloxypropyltrimethoxysilane	0.067	1.110	0	0.991	1.8073	6.209	0.063	94
Isocyanatopropyltrimethoxysilane	−0.049	0.672	0	0.854	2.0119	5.930	0.038	100
Methacryloxypropyltrimethoxysilane	0.046	0.873	0	1.016	1.9708	6.197	0.057	92
n-Octyltriethoxysilane	−0.255	−0.039	0	0.976	2.5030	7.026	0.077	39
Tetrakis(trimethoxy)silane	−0.989	−0.144	0	0.745	3.2627	5.427	0.099	46
2,4,6,8-Tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane	−0.095	0.223	0	0.700	2.7363	5.725	0.090	44

[a] SD, standard deviation of the Solver solution for *n* independent solvation parameter models.

Table 7
The prediction of octanol–water partition coefficients ($\log K_{OW}$) using descriptor values calculated solely from totally organic liquid–liquid partition systems for the compounds indicated in Table 5. Predictions of the octanol–water partition coefficients were made using the model $\log K_{OW} = 0.103 + 0.522E - 0.997S - 0.072A - 3.609B + 3.831V$ [12].

Compounds	Log K_{OW}	
	Predicted	Experimental
Acetanilide	1.01	1.16
Acetophenone	1.53	1.58
Benzyl alcohol	1.48	1.10
1-Bromonaphthalene	4.03	4.22
Caffeine	−0.42	−0.07
4-Chlorophenol	2.40	2.40
Coumarin	1.03	1.39
Nitrobenzene	1.93	1.85
Phenol	1.52	1.49

of the totally organic biphasic systems presented in Fig. 2 is that they afford reasonable coverage of the available selectivity space allowing some flexibility in the identification of systems for sample preparation.

3.6. Determination of descriptor values by liquid–liquid partition in totally organic systems

Biphasic systems with numerically large system constants are preferred for the calculation of solute descriptors because they afford descriptors with a lower uncertainty. The *V* descriptor is available by calculation and the *E* descriptor can be measured or estimated reasonably well for most compounds. Experimental methods are required to determine the *S*, *A* and *B* descriptors, and for these descriptors, totally organic biphasic systems are attractive for compounds of low water solubility (or compounds unstable in water). For this purpose n-heptane–formamide (for *A*, *B* and *S*), n-heptane–ethylene glycol (for *A* and *B*), n-heptane–propylene carbonate (for *A* and *S*), n-heptane–2,2,2-trifluoroethanol (for *B*) and isopentyl ether–ethylene glycol (for *B*) are the most suitable systems. The n-heptane–dimethyl sulfoxide system could be included in this list (for *A*) if an additional biphasic system was desired. The other biphasic systems with a non-alkane counter solvent could be useful for compounds with low n-heptane solubility when water-based biphasic systems are also inappropriate. For robust descriptor values it is recommended to use several experimental techniques, including chromatographic and solubility methods, together with liquid–liquid partition when practical [7,12]. This is illustrated by the results in Table 5 for a group of representative compounds whose descriptor values have been estimated using different separation techniques [12] as well as by totally organic liquid–liquid partition systems. The calculations were performed using the Solver method [12,42]. In Table 5, under method, the heading total contains all the data for the individual separation and totally organic liquid–liquid partition systems as well as additional values for aqueous liquid–liquid partition when suitable models and experimental data were available. These values are considered the best estimate of the true descriptor values. Gas chromatography is virtually indispensable for the determination of the *L* descriptor and useful for estimating the *A* and *S* descriptors, but cannot be used to estimate the *B* descriptor, since common stationary phases used for gas chromatography lack hydrogen-bond acidity [43]. Reversed-phase liquid chromatography and micellar electrokinetic chromatography are suitable for estimating the *B* descriptor, but are often less useful for estimating the *S* and *A* descriptors owing to the small system constants associated with these descriptor interactions. This is particularly so for strongly hydrophobic compounds that are excessively retained or require the use of predominantly organic mobile phases for their elution in reversed-phase liquid chromatography. For compounds of reasonable water solubility aqueous liquid–liquid partition is a useful method for estimating the *S*, *A* and *B* descriptors [7,31] but for compounds unstable or virtually insoluble in water an alternative approach is needed [13,14]. For these compounds, such as the organosiloxanes in Table 6, a combination of gas chromatography with totally organic liquid–liquid partition is the preferred approach. These compounds are either decomposed or virtually totally insoluble in aqueous systems and require non-aqueous systems for descriptor measurements.

As a test of the usefulness of totally organic liquid–liquid partition systems to estimate descriptor values the octanol–water partition coefficients are predicted for the compounds in Table 5 and summarized in Table 7. The estimated partition coefficients can be compared with their experimental values [44], also summarized in Table 7. The agreement is quite good with a relative absolute error of 0.18 log units, although for the prediction of physicochemical properties the descriptor values indicated as consensus values from different methods (total under heading method in Table 5) are preferred.

4. Conclusions

Dimethyl sulfoxide is shown to be a useful solvent for liquid–liquid partition forming complementary biphasic systems with n-heptane and isopentyl ether suitable for sample preparation and descriptor measurements. Dimethyl sulfoxide is a moderately cohesive solvent, reasonably dipolar/polarizable, strongly hydrogen-bond basic and weakly hydrogen-bond acidic. Its moderate cohesion and strong polar interactions make it suitable for the isolation of polar compounds in general, and the separation of polycyclic aromatic compounds from low-polarity hydrocarbons, in particular. For sample preparation and descriptor measurements the dimethyl sulfoxide biphasic systems provide complimentary properties to the totally organic biphasic systems used previously for descriptor measurements.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2011.05.023.

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