



Models for liquid–liquid partition in the system propylene carbonate–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–propylene carbonate biphasic partition system where the organic solvent is *n*-heptane, isopentyl ether or 1-octanol. These partition coefficient databases are analyzed using the solvation parameter model facilitating a quantitative comparison of the propylene carbonate-based partition systems with other totally organic partition systems. Propylene carbonate is a weak to intermediate cohesive solvent, reasonably dipolar/polarizable and hydrogen-bond basic, and weak hydrogen-bond acidic. Propylene carbonate–organic solvent systems offer a complementary approach to other totally organic biphasic partition systems for sample preparation and descriptor measurements of compounds virtually insoluble or unstable in water.

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1. Introduction

A renewed interest in liquid–liquid partitioning as a sample preparation method stems from recent developments in miniaturized formats known as liquid-phase microextraction [1–3]. These methods have minimized many of the disadvantages of conventional liquid extraction methods, which were largely responsible for its replacement by solid-phase extraction methods over the previous decade [1–3]. Solvent-based methods are generally more tolerant of matrix burden and afford a wider selectivity range than is the case for commonly available sorbents. Solvent properties are more reproducible than sorbent properties and solvent-based methods compare favorably in terms of costs and equipment needs with sorbent-based methods [4,5]. 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 with 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 lim-

ited to volatile organic solvents because of the need to reduce the final volume of the solvent by evaporation to facilitate subsequent use in further sample preparation steps or to obtain suitable method detection limits using instrumental methods. For liquid-phase microextraction solvent evaporation is rarely required and this restriction on solvent selection is no longer a problem. This should allow a wider choice of solvents with different selectivity to be exploited. In a recent study formamide was identified as a useful solvent for liquid–liquid partition forming biphasic systems of different selectivity with *n*-heptane [8] or 1,2-dichloroethane, isopentyl ether, and 1-octanol [9] as counter solvents. As an extension of these studies we investigate the use of propylene carbonate as a base solvent for liquid–liquid extraction with different counter solvents in this report.

An important application of water-based biphasic systems is the determination of solute descriptors for use in the solvation parameter model [7,10]. The solvation parameter model finds many uses for characterizing distribution systems including chromatographic systems [10–15] and biopartitioning and environmental systems [16–18]. The use of aqueous biphasic systems for descriptor measurements with compounds of negligible water solubility, such as organosiloxanes, dialkyl phthalates, and polychlorinated biphenyls, 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 were recently used to determine solute descriptors for water insoluble and unstable organosiloxanes with a wide range of functional groups [19,20]. These studies demonstrated both the usefulness

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

Propylene carbonate has found many applications as a polar solvent in laboratory and chemical engineering applications [21,22]. It is essentially odourless, non-corrosive, non-toxic, biodegradable, nearly insoluble in water, of low viscosity (2.5 cP at 25 °C), moderate density (1.2 g/mL at 25 °C), high dielectric constant (65), and of low volatility (atmospheric boiling point 242 °C). In laboratory applications it is widely used as a polar, non-hydrogen-bond donor solvent in synthesis, spectroscopy, and electrochemistry [23,24]. Spectroscopic analysis of solvatochromic indicator compounds suggests that propylene carbonate is of intermediate polarity (Reichardt's dye $E_T^N = 0.472$) with significant dipolarity/polarizability and hydrogen-bond basicity but no hydrogen-bond acidity (Kamlet-Taft solvatochromic parameters $\pi^* = 0.87$, $\beta = 0.40$, and $\alpha = 0$) [22,24,25]. Hsu et al. used NMR and theoretical calculations to demonstrate the formation of hydrogen-bonds between the phosphorous hexafluoride anion and propylene carbonate [26] and Wang and Balbuena [27] provided evidence from theoretical calculations for the formation of propylene carbonate dimers in the gas phase stabilized by C–H...O interactions. These interactions are expected to be weak but call into question whether propylene carbonate should be classified as non-hydrogen bond donor solvent. Propylene carbonate was shown to be an effective solvent for the extraction of cationic dyes from water [28] and for the selective extraction of aromatic compounds from naphtha reformat [29].

The solvation parameter model in a form suitable for modeling partition coefficients for neutral compounds, $\log K_p$, in biphasic propylene carbonate-containing system is set out below [7–10,19,20]

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

The capital letters are solute descriptors defining the capability of the solute to participate in interactions in the two phases and the lower case letters are the system constants defining the difference in the complementary interactions with the solutes in the two immiscible solvents. The E descriptor defines the solute's capacity for lone pair electron interactions ($\text{cm}^3/\text{mol}/10$), the S descriptor for interactions of a dipole-type, the A and B descriptor for hydrogen-bonding interactions with the solute acting as a hydrogen-bond acid or base, and the V descriptor is McGowan's characteristic volume ($\text{cm}^3/\text{mol}/100$). The system constants are calculated for the biphasic system from experimental partition coefficients for a varied group of compounds with known descriptor values by multiple linear regression analysis. The system constants and their ratios provide a quantitative description of system properties in terms of the intermolecular interactions responsible for solvation and facilitate a comparison of their properties to other biphasic solvent systems [7–9,30–32]. They are also required for the calculation of solute descriptors by liquid–liquid partition [7,10,19,20,33]. Mintz et al. [34] used the solvation parameter model to correlate the enthalpy of solvation for gaseous solutes in propylene carbonate. The model had good statistical properties but the system constants lack chemical significance compared with typical models for free energy properties. Abraham and Acree proposed models for the gas-propylene carbonate and water–propylene carbonate partition systems for both neutral and ionic compounds [35]. These models are suitable for predicting additional partition coefficients to about 0.18 log units for compounds contained in the same descriptor space.

2. Experimental

2.1. Materials

Propylene carbonate was obtained from Acros Organics (Morris Plains, NJ, USA) and dried over molecular sieves before use. Heptane, 1-octanol and isopentyl ether were obtained from Sigma–Aldrich (Milwaukee, WI, USA). Common chemicals were of the highest purity available and obtained from several sources. The $30 \text{ m} \times 0.32 \text{ mm}$ id HP-5 open-tubular column, $0.25 \mu\text{m}$ 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 one minute and then raised to 200 °C at 10 °C/min and then 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 [8,30–32]. The 2.0 mL screw-capped sample vials with PTFE-lined caps (Supelco, Bellefonte, PA, USA) were charged by syringe with 0.75 mL of propylene carbonate, 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 propylene carbonate (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.

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

where K_p is the partition coefficient for compound S , S_{cs} and S_{pc} the peak area for compound S in the counter solvent and propylene carbonate layer, respectively, I_{sc} and I_{pc} the peak area of the internal standard in the counter solvent and propylene carbonate layer, respectively, and K_p^{IS} the partition coefficient for the internal standard in the counter solvent–propylene carbonate system. The internal standard for the *n*-heptane–propylene carbonate system was biphenyl, $K_p = 0.857 \pm 0.010$ ($n = 10$), for isopentyl ether–propylene carbonate biphenyl, $K_p = 1.132 \pm 0.004$ ($n = 10$), and for 1-octanol–propylene carbonate acenaphthene, $K_p = 1.306 \pm 0.007$ ($n = 10$).

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 an in-house database [8–10,19,36] and are summarized in Table 1. The experimental

Table 1
Descriptor values for compounds used in the partition experiments.

Compound	Descriptors				
	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>
Acenaphthene	1.604	1.050	0	0.220	1.2586
Acenaphthylene	1.557	1.119	0	0.200	1.2156
Acetanilide	0.960	1.144	0.538	0.708	1.1140
Acetophenone	0.806	1.026	0	0.503	1.0138
Benzamide	1.258	1.343	0.648	0.664	0.9728
Benzenesulfonamide	1.169	1.864	0.681	0.679	1.0971
1,4-Benzodioxan	0.884	1.054	0	0.354	1.0070
Benzophenone	1.224	1.330	0	0.576	1.4808
Benzyl benzoate	1.264	1.280	0	0.597	1.6804
Biphenyl	1.317	0.933	0	0.284	1.3242
Bis(trimethylsiloxy)methylsilane	-0.448	-0.148	0.032	0.375	1.9494
1-Bromohexane	0.349	0.400	0	0.120	1.1300
1-Bromonaphthalene	1.598	1.005	0	0.157	1.2604
1-Bromooctane	0.339	0.400	0	0.120	1.4108
3-Bromophenol	1.081	0.792	0.948	0.201	0.9500
4-Bromophenol	1.080	1.170	0.670	0.200	0.9500
<i>n</i> -Butyl benzoate	0.668	0.851	0	0.393	1.4953
Caffeine	1.518	1.726	0.039	1.232	1.3632
Carbazole	2.025	1.585	0.367	0.231	1.3154
4-Chloro-3-methylphenol	0.920	1.020	0.650	0.230	1.0384
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386
4-Chloroaniline	1.007	1.171	0.330	0.310	0.9386
Chlorobenzene	0.718	0.656	0	0.056	0.8388
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078
4-Chlorophenol	1.016	0.794	0.886	0.205	0.8975
Cinnamyl alcohol	1.067	0.959	0.490	0.600	1.1548
Coumarin	1.269	1.610	0	0.524	1.0619
Dibenzofuran	1.562	1.094	0	0.106	1.2087
Dibenzylamine	1.340	0.985	0.115	1.063	1.7058
3,4-Dichloroaniline	1.158	1.240	0.350	0.240	1.0610
2,4-Dichlorophenol	0.960	0.990	0.580	0.140	1.0200
Diethyl phthalate	0.729	1.465	0	0.869	1.7106
<i>N,N</i> -Dimethylaniline	0.957	0.840	0	0.410	1.0960
Dimethyl phthalate	0.780	1.410	0	0.880	1.4288
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.0569
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.0569
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648
Diphenylamine	1.599	1.077	0.341	0.549	1.4240
Dodecane	0	0	0	0	1.7994
Ethyl benzoate	0.694	0.886	0	0.444	1.2135
Fluoranthene	2.292	1.486	0	0.255	1.5846
Fluorene	1.664	1.120	0	0.252	1.3565
3-(Glycidoxypropyl)trimethoxysilane	0.133	1.090	0	0.970	1.8073
Heptane-2-one	0.123	0.662	0	0.496	1.1106
Hexanophenone	0.790	1.026	0	0.503	1.5775
Indole	1.018	1.184	0.390	0.240	0.9464
Iodobenzene	0.628	0.400	0	0.150	0.9304
Isocyanopropyltriethoxysilane	-0.049	0.634	0	0.832	2.0119
Methacryloxypropyltrimethoxysilane	0.046	0.869	0	1.024	1.9708
2-Methoxynaphthalene	1.449	1.140	0	0.359	1.2850
Methyl benzoate	0.738	0.923	0	0.439	1.0726
Methyl decanoate	0.057	0.564	0	0.456	1.7329
Methyl octanoate	0.069	0.564	0	0.456	1.4511
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263
2-Methylnaphthalene	1.304	0.880	0	0.154	1.2263
2-Methylphenol	0.774	0.745	0.621	0.357	0.9160
Naphthalene	1.240	0.906	0	0.193	1.0854
1-Naphthol	1.480	1.157	0.796	0.318	1.1441
2-Naphthol	1.457	1.181	0.807	0.345	1.1441
2-Nitroaniline	1.182	1.441	0.386	0.348	0.9904
3-Nitroaniline	1.248	1.602	0.466	0.415	0.9904
4-Nitroaniline	1.236	1.827	0.597	0.343	0.9904
Nitrobenzene	0.846	1.138	0	0.269	0.8906
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569
2-Nitrophenol	0.962	1.086	0.050	0.371	0.9493
2-Nitropropane	0.215	0.884	0.024	0.329	0.7055
2-Nitrotoluene	0.866	1.110	0	0.270	1.0315
3-Nitrotoluene	0.874	1.100	0	0.250	1.0315
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315
Nonan-1-ol	0.199	0.440	0.344	0.520	1.4354
Nonan-2-one	0.113	0.662	0	0.496	1.3924
Octadecane	0	0	0	0	2.6448
Octan-1-ol	0.198	0.440	0.344	0.520	1.2945
Octanophenone	0.779	1.026	0	0.503	1.8593

Table 1 (Continued)

Compound	Descriptors				
	E	S	A	B	V
<i>n</i> -Octyltriethoxysilane	-0.255	0.003	0	0.920	2.5030
Pentachlorophenol	1.217	0.860	0.610	0.090	1.3870
Phenanthrene	1.997	1.316	0	0.279	1.4544
Phenyl benzoate	1.330	1.420	0	0.470	1.5400
Phenyl ether	1.216	0.912	0	0.267	1.3829
2-Phenylacetamide	0.950	1.600	0.520	0.790	1.1140
1-Phenylethanol	0.823	0.793	0.393	0.681	1.0569
2-Phenylethanol	0.787	0.797	0.390	0.639	1.0569
4-Phenylphenol	1.510	1.178	0.853	0.437	1.3829
Phthalimide	1.219	1.729	0.214	0.622	1.0208
Phthalonitrile	0.804	1.934	0	0.365	1.0256
Pyrene	2.271	1.486	0	0.278	1.5846
Quinoline	1.268	1.090	0	0.562	1.0443
Resorcinol	1.175	0.935	1.252	0.578	0.8338
Tetrahydrofuran	0.295	0.540	0	0.469	0.6223
Tetrakis(trimethylsiloxy)silane	-0.989	-0.155	0	0.664	3.2627
2,4,6,8-Tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane	-0.095	0.215	0	0.670	2.7364
<i>p</i> -Tolualdehyde	0.862	1.000	0	0.420	1.0139
<i>o</i> -Toluidine	0.966	1.045	0.193	0.491	0.9571
<i>m</i> -Toluidine	0.946	1.128	0.112	0.516	0.9571
<i>p</i> -Toluidine	0.923	1.192	0.147	0.396	0.9571
Toluene	0.606	0.499	0	0.139	0.8573
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836
Tri- <i>n</i> -butyrin	0.035	1.193	0	1.578	2.4453
<i>n</i> -Undecane	0	0	0	0	1.6585
Valerophenone	0.795	1.026	0	0.503	1.4366

partition coefficients are given in Table 2. 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 [37].

3. Results and discussion

The solvation parameter model provides a suitable mechanism for studying liquid-liquid partition systems capable of revealing the contribution of intermolecular interactions responsible for selectivity differences between biphasic partitioning systems and for simulating the separation properties (partition coefficients) for compounds with known descriptor values whose experimental partition coefficients are unavailable [7–10]. This requires the calculation of the system constants of the solvation parameter models for the partition systems.

3.1. *n*-Heptane-propylene carbonate partition system

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

$$\log K_p = 0.502(\pm 0.074) + 0.455(\pm 0.036)E - 2.087(\pm 0.052)S - 2.646(\pm 0.046)A - 0.433(\pm 0.065)B + 0.807(\pm 0.043)V \quad (3)$$

$$r = 0.996 \quad r_{\text{adj}}^2 = 0.992 \quad SE = 0.115 \quad F = 2125 \quad n = 83$$

r is the multiple correlation coefficient, r_{adj}^2 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 driving force for transfer of solutes to the *n*-heptane layer is indicated by the system constants with positive coefficients, the v and e system constants. Since *n*-heptane is a solvent of low cohesion the small v coefficient suggests that propylene carbon-

ate possesses no more than weak to intermediate cohesion. The positive e system constant indicates that propylene carbonate is electron lone-pair repulsive, since by definition *n*-heptane has an E -value of zero. Polar interactions characterized by the s , a , and b system constants favor transfer to the propylene carbonate layer. These values support the assertion that propylene carbonate is reasonably dipolar/polarizable and strongly hydrogen-bond basic but weakly hydrogen-bond acidic. Propylene carbonate is generally assumed to be non-hydrogen-bond acidic solvent although NMR studies and theoretical calculations suggest some weak hydrogen-bond acidity [26,27]. Abraham and Acree [35] also observed weak hydrogen-bond acidity in models for the transfer of neutral compounds from the gas phase to propylene carbonate. The b system constant for propylene carbonate saturated with *n*-heptane, while small, is statistically significant at the 99% confidence level. Artificially setting the b system constant to zero results in the model

$$\log K_p = 0.628(\pm 0.069) + 0.571(\pm 0.039)E - 2.292(\pm 0.052)S - 2.708(\pm 0.056)A + 0.651(\pm 0.044)V \quad (4)$$

$$r = 0.994 \quad r_{\text{adj}}^2 = 0.988 \quad SE = 0.143 \quad F = 1708 \quad n = 83$$

which is almost as good as Eq. (3). It is necessary, therefore, to be cautious in addressing the question of the hydrogen-bond acidity of propylene carbonate. There is uncertainty in the experimental partition coefficients which might feed into the model resulting in a small but phantom value for the b system constant. Dividing the data set up into sub sets of different compounds (an example is shown below) favors models that include the b system constant in fitting the data and we believe that it is reasonable to conclude that propylene carbonate is a weakly hydrogen-bond acidic solvent in support of other recent indications [26,27,35].

To evaluate the predictive ability of the model the data set was split into a training set of 58 compounds and a test set of 25 compounds using the Kennard-Stone algorithm [37]. 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

Table 2
Experimental partition coefficients for the systems organic solvent–propylene carbonate.

Compound	Partition coefficients ^a					
	<i>n</i> -Heptane–propylene carbonate		isopentyl ether–propylene carbonate		1-octanol–propylene carbonate	
	<i>K_p</i>	SD	<i>K_p</i>	SD	<i>K_p</i>	SD
Acenaphthene	1.368	0.024	1.194	0.011	1.306	0.007
Acenaphthylene	0.590	0.021	0.615	0.020	0.774	0.007
Acetanilide					0.656	0.064
Acetophenone	0.222	0.071				
Benzamide	8.41×10^{-4}	4.02×10^{-5}			0.736	0.002
Benzenesulfonamide	1.04×10^{-4}	7.44×10^{-7}	0.008	0.001	0.121	0.003
1,4-Benzodioxan	0.199	0.003	0.320	0.008	0.551	0.010
Benzophenone	0.182	0.004	0.350	0.041	0.534	0.043
Benzyl benzoate	0.250	0.003	0.474	0.028	0.553	0.010
Biphenyl	0.857	0.010	1.132	0.001	0.874	0.002
Bis(trimethylsilyloxy)methylsilane	120.78	1.1	53.46	0.003	8.558	0.054
1-Bromohexane	5.082	0.38	4.111	0.006	2.581	0.030
1-Bromonaphthalene	1.227	0.029	1.365	0.058		
1-Bromooctane	11.38	1.47	8.831	0.013	3.993	0.032
3-Bromophenol	4.28×10^{-3}	<0.001	0.296	0.003	2.074	0.011
4-Bromophenol	2.14×10^{-3}	<0.001	0.149		0.017	
<i>n</i> -Butyl benzoate	1.245	0.020	1.710	0.011	1.304	0.022
Caffeine	0.011	0.003	0.067	0.009	0.317	0.018
Carbazole	9.27×10^{-3}	0.001	0.146	0.028	0.542	0.007
4-Chloro-3-methylphenol	8.49×10^{-3}	6.13×10^{-5}			0.846	0.015
2-Chloroaniline	0.066	0.001	0.244	0.002	0.518	0.014
4-Chloroaniline			0.107	0.002	0.361	0.006
Chlorobenzene	1.291	0.015	1.563	0.051	1.349	0.117
1-Chloronaphthalene	1.469	0.092	1.449	0.079	1.327	0.015
4-Chlorophenol	5.85×10^{-3}	0.001	0.244	0.013	1.717	0.048
Cinnamyl alcohol	0.015	0.001	0.201	0.018	1.196	0.028
Coumarin	0.023	0.008	0.067	0.005	0.280	0.005
Dibenzofuran	0.746	0.016	1.030	0.006	1.026	0.002
Dibenzylamine	0.536	0.022	0.861	0.035	1.404	0.011
3,4-Dichloroaniline	1.16×10^{-2}	0.005	0.119	0.005	0.404	0.004
2,4-Dichlorophenol			0.360	0.011		
Diethyl phthalate	8.79×10^{-2}	0.001	0.201	0.003	0.373	0.007
<i>N,N</i> -Dimethylaniline	0.745	0.001	1.047	0.091	0.898	0.015
Dimethyl phthalate	3.31×10^{-2}	0.001	0.091	0.001	0.194	0.001
2,6-Dimethylphenol	7.28×10^{-2}	0.006	0.498	0.048	1.575	0.064
3,5-Dimethylphenol	0.013	<0.001	0.356	0.010	1.519	0.082
1,3-Dinitrobenzene	1.03×10^{-2}	0.001	0.033	0.007	0.110	0.001
Diphenylamine	5.96×10^{-2}	0.003	0.289	0.002		
Dodecane					9.208	0.037
Ethyl benzoate	0.621	0.004	0.787	0.028		
Fluoranthene	0.479	0.015			0.823	0.026
Fluorene	0.873	0.010			0.953	0.007
3-(Glycidoxypropyl)trimethoxysilane	0.153	0.006	0.318	0.012	0.413	0.016
Heptane-2-one	0.767	0.017	1.191	0.036	1.547	0.061
Hexanophenone	0.887	0.028	1.315	0.012	1.298	0.006
Indole	9.71×10^{-3}	0.001	0.120	0.001	0.410	0.002
Iodobenzene			2.208	0.053	2.428	0.236
Isocyanopropyltriethoxysilane	2.046	0.105	2.624	0.101	2.264	0.414
Methacryloxypropyltrimethoxysilane	0.904	0.312	1.023	0.030	0.907	0.015
2-Methoxynaphthalene	0.369	0.009	0.598	0.004	0.584	0.002
Methyl benzoate	0.378	0.045	0.561	0.032	0.689	0.060
Methyl decanoate					3.754	0.078
Methyl octanoate					2.344	0.017
1-Methylnaphthalene	1.164	0.107	1.452	0.037	1.195	0.008
2-Methylnaphthalene	1.205	0.010	1.489	0.028	1.198	0.012
2-Methylphenol			0.308	0.044		
Naphthalene	0.818	0.007	1.074	0.045	0.909	0.013
1-Naphthol	3.75×10^{-3}	0.001	0.202	0.033	1.063	0.005
2-Naphthol	2.07×10^{-3}	0.001	0.134	0.009	1.106	0.009
2-Nitroaniline	5.73×10^{-3}	0.001	0.060	0.003	0.270	0.001
3-Nitroaniline			0.028	0.007		
4-Nitroaniline	1.51×10^{-4}	3.51×10^{-6}			0.204	0.004
Nitrobenzene	0.144	0.008	0.259	0.070	0.333	0.007
1-Nitronaphthalene	0.104	0.003	0.258	0.007	0.281	0.003
2-Nitrophenol	0.116	0.009	0.259	0.009	0.382	0.001
2-Nitropropane			0.311	0.021	0.320	0.010
2-Nitrotoluene	0.168	0.008	0.378	0.001	0.589	0.008
3-Nitrotoluene	0.170	0.006	0.396	0.001	0.444	0.008
4-Nitrotoluene	0.147	0.004	0.318	0.042	0.421	0.001
Nonan-1-ol	0.826	0.011				
Nonan-2-one			1.884	0.022		

Table 2 (Continued)

Compound	Partition coefficients ^a					
	<i>n</i> -Heptane–propylene carbonate		isopentyl ether–propylene carbonate		1-octanol–propylene carbonate	
	<i>K_p</i>	SD	<i>K_p</i>	SD	<i>K_p</i>	SD
Octadecane					20.70	0.687
Octan-1-ol			1.374	0.073		
Octanophenone	1.007	0.003	2.275	0.060	2.010	0.018
<i>n</i> -Octyltriethoxysilane	109.65	1.13	41.88	0.125	15.74	0.058
Pentachlorophenol	0.041	0.011				
Phenanthrene	0.537	0.006	0.785	0.012	0.814	0.001
Phenyl benzoate	0.206	0.001	0.370	0.001	0.440	0.008
Phenyl ether			1.279	0.013	0.868	0.007
2-Phenylacetamide	9.71 × 10 ⁻⁴	0.001				
1-Phenylethanol	0.067	<0.001	0.349	0.027		
2-Phenylethanol	0.033	0.001	0.224	0.011	1.199	0.011
4-Phenylphenol	1.87 × 10 ⁻³	0.001	0.150	<0.001	1.194	0.013
Phthalimide			0.032	0.003	0.114	0.015
Phthalonitrile	2.70 × 10 ⁻³	0.001	0.015	0.002	0.061	0.007
Pyrene	0.574	0.006	0.897	0.062	0.813	0.012
Quinoline	0.228	0.003	0.385	0.001		
Resorcinol	1.91 × 10 ⁻⁴	<0.001			1.199	0.042
Tetrahydrofuran					1.413	0.068
Tetrakis(trimethylsiloxy)silane	349.14	2.49	100.7	0.064	34.47	1.490
2,4,6,8-Tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane	55.59	0.93	38.19	0.062	6.238	0.063
<i>p</i> -Tolualdehyde	0.198	0.001	0.418	0.009	0.758	0.001
<i>o</i> -Toluidine			0.215	0.001	0.538	0.003
<i>m</i> -Toluidine	0.073	0.003	0.197	0.001	0.621	0.004
<i>p</i> -Toluidine					0.564	0.003
Toluene	1.718	0.079	1.667	0.038	1.339	0.093
1,2,4-Trichlorobenzene	2.564	0.240	2.897	0.030	2.045	0.039
Tri- <i>n</i> -butyrin	0.279	0.007	0.556	0.011	0.598	0.014
<i>n</i> -Undecane	72.44	0.930			5.288	0.410
Valerophenone	0.603	0.075	0.920	0.013	0.962	0.001

^a *K_p* = partition coefficient and SD = standard deviation in the partition coefficient measurement (*n* = 3).

very similar to Eq. (3). Eq. (5) was

$$\log K_p = 0.601(\pm 0.093) + 0.412(\pm 0.043)E - 2.076(\pm 0.058)S \\ - 2.687(\pm 0.057)A - 0.424(\pm 0.072)B + 0.753(\pm 0.051)V \quad (5)$$

$$r = 0.997 \quad r_{\text{adj}}^2 = 0.993 \quad SE = 0.119 \quad F = 1740 \quad n = 58$$

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 0.014 indicates that this is not a concern for Eq. (5). The absolute average error (0.100) and root mean square error (0.121) are an indication of the likely error in predicting further partition coefficients based on Eq. (5). Since Eq. (5) is similar to Eq. (3), which is preferred because it is based on a larger number of compounds, it is reasonable to conclude that Eq. (3) should be able to predict partition coefficients to about ± 0.12 log units for further compounds with known descriptor values that lie within or close to the descriptor space ($E = -0.989$ to 2.292 , $S = -0.155$ to 1.934 , $A = 0$ – 1.252 , $B = 0$ – 1.578 , and $V = 0.834$ – 3.263) used to define the model.

3.2. Isopentyl ether–propylene carbonate partition system

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

$$\log K_p = 0.264(\pm 0.065) + 0.298(\pm 0.035)E - 1.432(\pm 0.049)S \\ - 0.718(\pm 0.048)A - 0.472(\pm 0.062)B + 0.729(\pm 0.037)V \quad (6)$$

$$r = 0.990 \quad r_{\text{adj}}^2 = 0.979 \quad SE = 0.109 \quad F = 786 \quad n = 86$$

Positive system constant (ν and e) favor transfer to the isopentyl ether-rich layer while polar interactions have a negative sign (s , a and b) and favor solubility in the propylene carbonate-rich layer. The similar cohesion of isopentyl ether compared with propylene carbonate results in a small value for the ν system constant and the polar characteristics of isopentyl ether are reflected in the intermediate values for the s and a system constants. Isopentyl ether has no hydrogen bond acidity and small negative b system constant for the isopentyl ether–propylene carbonate system supports the assignment of weak hydrogen-bond acidity to propylene carbonate, as discussed for the *n*-heptane–propylene carbonate partition system (Section 3.1). The Kennard–Stone algorithm was used to split the data set into a training set of 60 compounds and a test set of 26 compounds. The model for the training set is given below

$$\log K_p = 0.277(\pm 0.080) + 0.313(\pm 0.042)E - 1.440(\pm 0.058)S \\ - 0.722(\pm 0.064)A - 0.485(\pm 0.070)B + 0.725(\pm 0.043)V \quad (7)$$

$$r = 0.991 \quad r_{\text{adj}}^2 = 0.981 \quad SE = 0.118 \quad F = 607 \quad n = 60$$

and is quite similar to Eq. (6). For the test set the average error was 0.063, the average absolute error 0.100 and the root mean square error 0.088. Thus, Eq. (6) should be able to predict further values of the partition coefficients to about 0.11 log units for compounds with descriptor values that lie within or close to the descriptor space ($E = -0.989$ to 2.165 , $S = -0.142$ to 1.942 , $A = 0$ – 0.948 , $B = 0$ – 1.507 , and $V = 0.830$ – 3.263) used to define the model.

Table 3
System constants for totally organic biphasic partition systems.

Partition system	System constants				
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
<i>n</i> -Heptane–formamide	0.561	–2.248	–3.250	–1.603	2.384
Formamide–1,2-dichloroethane	0.082	–0.399	–1.957	–1.298	1.705
1-Octanol–formamide	0.267	–1.053	–0.333	–0.929	1.314
Isopentyl ether–formamide	0.564	–1.715	–1.314	–1.407	2.005
<i>n</i> -Heptane–2,2,2-trifluoroethanol	0.882	–1.557	–1.312	–2.928	1.301
<i>n</i> -Heptane–Hexafluoroisopropanol	1.030	–1.712	–0.669	–1.746	1.121
<i>n</i> -Heptane– <i>N,N</i> -dimethylformamide	0.038	–1.391	–2.160	–0.593	0.486
<i>n</i> -Hexane–acetonitrile	0.349	–1.439	–1.611	–0.874	0.669
<i>n</i> -Heptane–methanol	0.186	–0.686	–1.098	–0.951	0.618
<i>n</i> -Heptane–ethylene glycol	0.374	–1.889	–4.072	–1.942	0.618
<i>n</i> -Heptane–propylene carbonate	0.455	–2.087	–2.646	–0.433	0.807
Isopentyl ether–propylene carbonate	0.298	–1.432	–0.718	–0.472	0.729
1-Octanol–propylene carbonate	0.256	–1.068	0.222	0	0.365

3.3. Octanol–propylene carbonate partition system

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

$$\log K_p = 0.282(\pm 0.064) + 0.256(\pm 0.033)E - 1.068(\pm 0.041)S - 0.222(\pm 0.047)A + 0.365(\pm 0.032)V \quad (8)$$

$$r = 0.971 \quad r_{\text{adj}}^2 = 0.941 \quad SE = 0.117 \quad F = 334 \quad n = 85$$

Positive system constant (v and e) favor transfer to the 1-octanol-rich layer while polar interactions have a negative sign (s , a) and favor transfer to the propylene carbonate-rich layer. The b system constant is statistically indistinguishable from zero. Since 1-octanol is a hydrogen-bond acid this observation is in keeping with earlier conclusions that propylene carbonate is weakly hydrogen-bond acidic. The modest mutual solubility of the solvent pair also needs to be taken into account in assigning interactions to the individual solvents. A notable feature of this system is the relatively large s system constant compared with the other system constants, highlighting the importance of dipole-type interactions in controlling selectivity. As before, the Kennard-Stone algorithm was used to split the data set into a training set of 59 compounds and a test set of 26 compounds. The model for the training set is given below

$$\log K_p = 0.377(\pm 0.078) + 0.266(\pm 0.040)E - 1.107(\pm 0.047)S - 0.190(\pm 0.056)A + 0.331(\pm 0.037)V \quad (9)$$

$$r = 0.977 \quad r_{\text{adj}}^2 = 0.951 \quad SE = 0.121 \quad F = 285 \quad n = 59$$

and is quite similar to Eq. (8). For the test set the average error was 0.012, the average absolute error 0.083 and the root mean square error 0.112. Thus, Eq. (8) should be able to predict further values of the partition coefficients to about 0.12 log units for compounds with descriptor values that lie within or close to the descriptor space ($E = -0.989$ to 2.292, $S = -0.155$ to 1.942, $A = 0$ –1.294, and $V = 0.622$ –3.263) used to define the model.

3.4. General extraction properties of propylene carbonate–organic solvent systems

Principal component analysis with the system constants as variables using oblimin rotation and Kaiser normalization can be used to compare the extraction properties of the totally organic biphasic systems described for descriptor measurements, (Table 3) [8–10,19,20,30–32]. The first two principal components describe 73% of the variance and the two dimensional score plots afford only a poor classification of the partition systems, (Table 4). The

Table 4

Results from principal component analysis with oblimin rotation and Kaiser normalization for the biphasic partition systems indicated here.

Principal	Percent	Cumulative percent	
(i) Extraction of principal components			
Component	Variance	Variance	
PC-1	51.12		
PC-2	22.34	73.46	
PC-3	17.50	90.96	
System constant	PC-1	PC-2	PC-3
(ii) Loading on variables on the principal components			
<i>e</i>	–0.580	0.489	–0.769
<i>s</i>	0.293	0.283	0.947
<i>a</i>	0.379	0.885	0.407
<i>b</i>	0.918	–0.102	0.417
<i>v</i>	–0.859	–0.298	–0.239

first three principal components explain 91% of the variance and provide a more useful classification, (Fig. 1). Principal component 1 (PC-1) mainly expresses information about the b and v system constants, principal component 2 (PC-2) the a system constant, and principal component 3 (PC-3) the s system constant, (Table 4). The e system constant is loaded almost evenly on all three components. Fig. 1 demonstrates that the 13 totally organic biphasic systems have different selectivity with little clustering. Of the propylene carbonate systems, isopentyl ether–propylene carbonate is close to *n*-hexane–acetonitrile (but these are not selectivity equivalent) while the other propylene carbonate systems have no near neighbors in the selectivity space. A useful feature of the totally organic biphasic systems is that within the selectivity space defined by the system constants, Table 4, they afford reasonable coverage and allow some flexibility in the identification of suitable systems for separations.

For the determination of descriptors biphasic systems with large system constants to minimize errors in descriptor estimates as well as systems dominated by a single relatively large system constant are preferred. 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 1-octanol–propylene carbonate (for S) are the most suitable systems. The other biphasic systems with a non-alkane counter solvent are useful for compounds of low *n*-heptane solubility if water-based biphasic systems are also problematic.

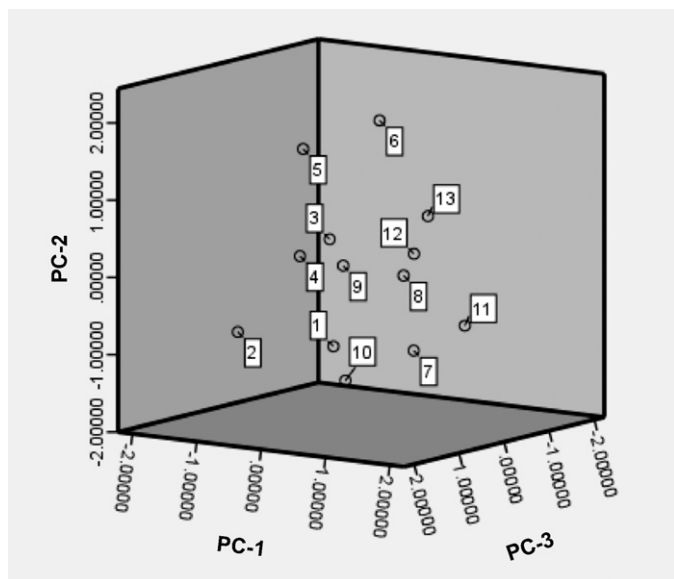


Fig. 1. Score plot of the first three principle components with the system constants as variables for 13 biphasic totally organic partition systems. Identification: 1: *n*-heptane–formamide; 2: formamide–1,2-dichloroethane; 3: 1-octanol–formamide; 4: isopentyl ether–formamide; 5: *n*-heptane–2,2,2-trifluoroethanol; 6: *n*-heptane–hexafluoroisopropanol; 7: *n*-heptane–*N,N*-dimethylformamide; 8: *n*-hexane–acetonitrile; 9: *n*-heptane–methanol; 10: *n*-heptane–ethylene glycol; 11: *n*-heptane–propylene carbonate; 12: isopentyl ether–propylene carbonate; and 13 = 1-octanol–propylene carbonate.

4. Conclusions

Propylene carbonate is demonstrated to be a useful solvent for liquid–liquid partition forming several complementary biphasic systems with organic counter solvents suitable for sample preparation and descriptor measurements. Propylene carbonate is a weak to moderately cohesive solvent, strongly dipolar and hydrogen-bond basic, and weakly hydrogen-bond acidic. For compounds that are virtually insoluble in water it provides a series of biphasic partition systems with complimentary properties to the totally organic biphasic systems used previously for the experimental determina-

tion of the *S*, *A* and *B* descriptors used in the solvation parameter model. For robust descriptor values it is recommended to use several experimental techniques that include chromatographic and solubility methods together with liquid–liquid partition when practical [7,10].

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