

Gas to Olive Oil Partition Coefficients: A Linear Free Energy Analysis

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Literature values of gas to olive oil partition coefficients at 37 °C have been assembled for 218 compounds. Application of an Abraham linear free energy equation correlates 215 compounds with $R^2 = 0.981$ and a standard deviation, SD, of 0.196 log units. One hundred and eight compounds were then used as a training set, and the resulting equation was used to predict the remaining 107 compounds with an average error of 0.025, an absolute average error of 0.150, and a standard deviation of 0.224 log units. The linear free energy equation shows that as a solvent olive oil is not very polar but is reasonably basic, although with a weaker hydrogen bond base than ethyl acetate or acetone, and has no hydrogen bond acidity. The coefficients for partition from the gas phase to biological phases such as blood and brain lie between those for water and olive oil, which explains why gas to biological phase partition can be described in an empirical way by a combination of gas to olive oil and gas to saline coefficients

INTRODUCTION

The water to olive oil system was used by both Overton¹ and H. Meyer² as a qualitative model for the aqueous narcosis of tadpoles. Some years later K. H. Meyer and Gottlieb-Billroth³ established a mathematical relationship between narcotic concentration and the water to olive oil partition coefficient, Polive, in what was probably the first quantitative structure–activity relationship. K. H. Meyer and co-workers then showed^{4,5} that the gas to olive oil system could be used as a model for gaseous narcosis, or anesthesia, and measured a number of gas to olive oil partition coefficients, Kolive. Since then, gas to olive oil partition coefficients have traditionally been related to anesthetic properties and also used in empirical relationships for the prediction of gas to tissue partition coefficients.^{6,7} Not surprisingly, there have been numerous studies in which Kolive values have been determined. The defining equation is

$$\text{Kolive} = \frac{\text{concn of solute in olive oil}}{\text{concn of solute in the gas phase}} \quad (1)$$

If concentration units are the same in olive oil and in the gas phase, for example mol dm⁻³, then Kolive is dimensionless and is entirely equivalent to L , the Ostwald solubility coefficient. In this work all Kolive values are dimensionless and refer to a temperature of 37 °C.

There have been but few models for the correlation and prediction of Kolive values. Weathersby and Abraham⁸ constructed a model to correlate gas to olive oil distribution for a data set of 88 volatile organic compounds (VOCs) at 37 °C. They used the Abraham solvation equation and obtained eq 2; we shall explain the descriptors in eq 2 later. Although the statistics of eq 2 are very good, the data set was composed of relatively simple compounds and refers, of course, only to fitting data and not to prediction. In eq 2 and elsewhere, N is the number of data points, usually the

number of compounds, R is the correlation coefficient, SD is the standard deviation, and F (see later) is the F-statistic.

$$\log \text{Kolive} = -0.240 - 0.018 \text{ E} + 0.806 \text{ S} + 1.469 \text{ A} + 0.891 \text{ L}$$

$$N = 88, R^2 = 0.997, \text{SD} = 0.082 \quad (2)$$

Abraham and Fuchs⁹ later showed that log Kolive could be correlated with a combination of volume, molar refraction, and dipole moment, as in eq 3, but their aim was not to try to predict further values but to explore the factors that influence log Kolive.

$$\log \text{Kolive} = 0.647 - 0.0384 \text{ V} + 0.2233 \text{ MR} + 0.0869 \mu^2$$

$$N = 52, R^2 = 0.947, \text{SD} = 0.233 \quad (3)$$

The most comprehensive analysis of log Kolive values is that of Klopman et al.¹⁰ who used a group contribution scheme to fit values for 159 compounds with $R^2 = 0.9377$ and SD = 0.295 with 24 fragments. Log Kolive for an independent test set of 36 compounds was predicted with an SD = 0.271, after elimination of three compounds, and a total set of 192 compounds was fitted with 26 fragments to give $R^2 = 0.9678$ and SD = 0.206 log units. The statistics for both fits and predictions appear to be very impressive. Unfortunately, Klopman et al.¹⁰ used previously calculated values of log Kolive in all their analyses. Of the 192 values of log Kolive in the final equation, only 119 were actually experimental values; the other 73 values were calculated in one way or another. Hence the statistics are not based on (calculated value – observed value), and for 73 compounds in the total data set the statistics are based on (calculated value – previously calculated value). The statistics for fits and predictions are therefore not legitimate and cannot be compared to those obtained from calculated and observed values only.

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Table 1. Statistics for Test Sets in the Prediction of Log Kolive, as Calculated from the Results of Katritzky et al.¹¹ and from Eq 8 in This Work

	ref 11	this work
N	33	107
AE	0.170	0.025
AAE	0.375	0.150
SD	0.487	0.224

More recently, Katritzky et al.¹¹ have used descriptors calculated by their CODESSA PRO software to correlate 100 values of log Kolive and to predict 33 additional values in an independent test set. Five descriptors were selected and used in a multiple linear correlation that yielded the statistics $N = 100$, $R^2 = 0.922$, and $SD = 0.232$ log units. They then showed that a plot of log Kolive(pred) against logKolive(obs) had $R^2 = 0.846$ for 33 compounds. Such a plot is not the best way of assessing the predictive capability of an equation, especially when the plot does not go through the origin, as is the case here. We have therefore used the given observed and predicted values for 33 compounds¹¹ to calculate the statistics in Table 1, in terms of average error, AE, average absolute error, AAE, and standard deviation, SD. The AE (obs - pred) of 0.17 shows that there is considerable bias in the predictions, and the AAE and SD values are very high for what is a straightforward physico-chemical process.

It is the aim of the present work to assemble a large data set of values of log Kolive, comprising only experimental values, and to attempt to obtain a predictive model using one of the Abraham solvation equations.

METHODS AND RESULTS

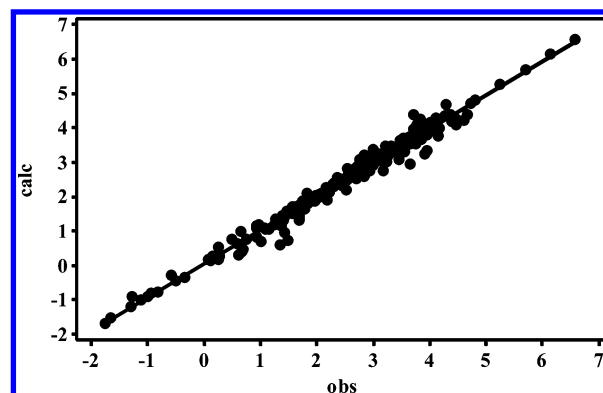
The equation that we use, eq 4, is one of the two linear free energy relationships devised by Abraham et al.¹² for the analysis of transport related properties

$$SP = c + e \mathbf{E} + s \mathbf{S} + a \mathbf{A} + b \mathbf{B} + l \mathbf{L} \quad (4)$$

$$SP = c + e \mathbf{E} + s \mathbf{S} + a \mathbf{A} + b \mathbf{B} + v \mathbf{V} \quad (5)$$

In eqs 4 and 5, the dependent variable, SP, is a set of solute properties in a given system. Equation 4 is used for gas to solvent partitions, and SP is then, for example, log Kolive. Equation 5 is used for processes in condensed phases. The independent variables in eqs 4 and 5 are solute descriptors as follows.¹² \mathbf{E} is the solute excess molar refractivity in units of $(\text{dm}^3 \text{ mol}^{-1})/10$, \mathbf{S} is the solute dipolarity/polarizability, \mathbf{A} and \mathbf{B} are the overall or summation hydrogen bond acidity and basicity, \mathbf{V} is the McGowan characteristic volume in units of $(\text{dm}^3 \text{ mol}^{-1})/100$, and \mathbf{L} is the logarithm of the gas to hexadecane partition coefficient at 25 °C.

We use eq 4, set up for gas to solvent partitions, and in Table 2 give values of log Kolive for 218 compounds,^{6,8,9,10,13-19} together with their descriptors in eq 4. This is by far the largest data set of observed values yet reported. Application of eq 4 yielded eq 6. The bB term was statistically not significant and was removed to give eq 7. There were three large outliers that have been omitted, viz: 2-methyl-1,3-butadiene (obs 0.95, calc 1.80), *N*-methylimidazole (obs 4.84, calc 3.83), and 1,1,2,4,4-pentafluorobutane (obs 0.12, calc 1.45). We have no explanation for 2-methyl-

**Figure 1.** Calculated values of log Kolive in eq 7 versus observed values.

1,3-butadiene, although we note that the calculated value of Katritzky et al.¹¹ was 1.96, but for *N*-methylimidazole the experimental is very difficult, and for 1,1,2,4,4-pentafluorobutane the observed value seems quite incompatible with the observed values for other polyfluoroalkanes. The number of compounds used in eq 6 and eq 7 is thus 215. A plot of calculated values on eq 7 against observed values of log Kolive is shown in Figure 1.

$$\log \text{Kolive} = -0.159 - 0.277 \mathbf{E} + 0.904 \mathbf{S} + 1.695 \mathbf{A} - 0.090 \mathbf{B} + 0.876 \mathbf{L}$$

$$N = 215, R^2 = 0.981, SD = 0.196, F = 2121.1 \quad (6)$$

$$\log \text{Kolive} = -0.156 - 0.254 \mathbf{E} + 0.859 \mathbf{S} + 1.656 \mathbf{A} + 0.873 \mathbf{L}$$

$$N = 215, R^2 = 0.981, SD = 0.196, F = 2644.6 \quad (7)$$

To assess the predictive capability of eq 7, compounds were arranged in order of increasing values of log Kolive, and every other compound was selected as the training set. Application of eq 4 to the training set yielded eq 8.

$$\log \text{Kolive} = -0.135 - 0.244 \mathbf{E} + 0.778 \mathbf{S} + 1.371 \mathbf{A} + 0.879 \mathbf{L}$$

$$N = 108, R^2 = 0.985, SD = 0.178, F = 1670.8 \quad (8)$$

Eq 8 was used to predict the remaining 107 compounds in the (unused) test set with an AE = 0.025, AAE = 0.150, and SD = 0.224 log unit, considerably better than those reported before, see Table 1. The training equation, eq 8, is reasonably close to the full equation, eq 7, and the statistics of the test set show that there is almost no bias in the predictions (AE = 0.025). The SD values of the full equation and of the predicted test set show that eq 7 is capable of predicting further values of log Kolive to about 0.2 log units. There is little cross-correlation between the descriptors in eq 7, the maximum values of R^2 being 0.35 between \mathbf{E} and \mathbf{S} and 0.28 between \mathbf{E} and \mathbf{L} , so that eq 7 can be regarded as soundly based.

DISCUSSION

The full equation, eq 7, can fit 215 observed values of log Kolive with a standard deviation of 0.196 log units, better than any previously reported fit, other than that of Abraham and Weathersby⁸ which was obtained for a much simpler

Table 2. Gas to Olive Oil Partition Coefficients, as Log K_{olive}, at 37 °C, and Descriptors for 218 Compounds^a

solute	log K _{olive}	reference	E	S	A	B	L
1,1,1,2-tetrachloroethane	3.56	6–8, 10, 13, 17	0.542	0.63	0.10	0.08	3.641
1,1,1-trichloroethane	2.49	6–10, 13, 17, 18	0.369	0.41	0.00	0.09	2.733
1,1,2,2-tetrachloroethane	4.03	6, 8–10, 17, 18	0.595	0.76	0.16	0.12	3.803
1,1,2-trichloroethane	3.31	6–8, 10, 13, 17, 18	0.499	0.68	0.13	0.13	3.290
1,1-dichloro-1-fluoroethane	1.74	15	0.084	0.43	0.01	0.05	1.920
1,1-dichloroethane	2.27	6–10, 13, 17, 18	0.322	0.49	0.10	0.10	2.316
1,1-dichloroethylene	1.81	6, 17	0.362	0.34	0.00	0.05	2.110
1,2,3-trimethylbenzene	4.01	6, 7	0.728	0.61	0.00	0.19	4.565
1,2,4-trifluorobenzene	2.79	6	0.410	0.65	0.00	0.02	2.850
1,2,4-trimethylbenzene	3.96	6, 7	0.677	0.56	0.00	0.19	4.441
1,2-dibromoethane	3.38	6, 9, 10, 13, 17	0.747	0.76	0.10	0.17	3.382
1,2-dichlorobenzene	4.60	6, 8, 10, 13	0.872	0.78	0.00	0.04	4.518
1,2-dichloroethane	2.62	6–10, 13, 17, 18	0.416	0.64	0.10	0.11	2.573
1,2-dichloropropane	2.80	6, 8, 10, 13, 17	0.371	0.68	0.00	0.15	2.866
1,2-difluorobenzene	2.93	6	0.390	0.63	0.00	0.06	2.843
1,2-dimethoxyethane	2.55	10, 13	0.116	0.67	0.00	0.68	2.654
1,3,5-trifluorobenzene	2.53	6	0.390	0.49	0.00	0.00	2.660
1,3,5-trimethylbenzene	3.91	6, 7	0.649	0.52	0.00	0.19	4.344
1,3-dichlorobenzene	4.47	6, 8, 10, 13	0.847	0.73	0.00	0.02	4.410
1,4-difluorobenzene	2.82	6	0.384	0.60	0.00	0.06	2.766
1,4-dioxane	2.83	9, 10, 13	0.329	0.75	0.00	0.64	2.892
1-bromo-2-chloroethane	2.76	6, 17	0.572	0.70	0.10	0.09	2.982
1-butanol	2.99	6, 10, 13	0.224	0.42	0.37	0.48	2.601
1-chlorobutane	2.48	6, 8–10, 13	0.210	0.40	0.00	0.10	2.722
1-chloropentane	2.99	6, 8–10, 13	0.208	0.38	0.00	0.09	3.223
1-chloropropane	2.06	6, 8–10, 13, 17	0.216	0.40	0.00	0.10	2.202
1-fluoropropane	0.92	8, 10, 13	0.034	0.35	0.00	0.13	1.103
1-heptanol	4.26	10, 13	0.211	0.42	0.37	0.48	4.115
1-hexanol	3.90	6, 10, 13	0.210	0.42	0.37	0.48	3.610
1-methoxy-2-propanol	2.84	6	0.218	0.61	0.35	0.62	2.655
1-nitropropane	3.03	6, 17	0.240	0.95	0.00	0.31	2.894
1-pentanol	3.30	6, 10, 13	0.219	0.42	0.37	0.48	3.106
1-propanol	2.49	6, 8, 10, 13	0.236	0.42	0.37	0.48	2.031
2,2,4-trimethylpentane	2.58	6, 17, 18	0.000	0.00	0.00	0.00	3.106
2,2-dichloro-1,1,1-trifluoroethane	1.81	14	–0.160	0.40	0.22	0.00	1.746
2,2-dimethylbutane	1.85	6, 8	0.000	0.00	0.00	0.00	2.352
2,3,4-trimethylpentane	2.82	6, 17	0.000	0.00	0.00	0.00	3.481
2-butoxyethanol	3.74	6	0.201	0.50	0.30	0.83	3.806
2-chloropropane	1.84	6, 17	0.177	0.35	0.00	0.12	1.970
2-ethoxyethanol	2.98	6	0.237	0.52	0.31	0.81	2.792
2-fluoropropane	1.09	8, 10, 13	0.004	0.32	0.00	0.10	1.070
2-heptanone	3.85	6, 10, 13	0.123	0.68	0.00	0.51	3.760
2-hexanone	3.08	6–10, 13	0.136	0.68	0.00	0.51	3.286
2-isopropoxyethanol	3.21	6	0.196	0.47	0.30	0.91	3.170
2-methoxyethanol	2.72	6	0.269	0.50	0.30	0.84	2.490
2-methyl-1,3-butadiene	(0.95) ^b	6, 17	0.313	0.23	0.00	0.10	2.101
2-methyl-1-propanol	2.71	6, 8	0.217	0.39	0.37	0.48	2.413
2-methyl-2-propanol	2.25	6, 10, 13	0.180	0.30	0.31	0.60	1.963
2-methylpentane	2.01	6, 8	0.000	0.00	0.00	0.00	2.503
2-methylpyridine	3.54	10, 13	0.598	0.75	0.00	0.58	3.422
2-nitropropane	2.81	6, 17	0.216	0.92	0.00	0.33	2.550
2-pentanone	2.65	6–10	0.143	0.68	0.00	0.51	2.755
2-propanol	2.17	6, 8, 10, 13	0.212	0.36	0.33	0.56	1.764
3-carene	3.70	16	0.511	0.22	0.00	0.10	4.649
3-methyl-1-butanol	3.00	6	0.192	0.39	0.37	0.48	3.011
3-methylhexane	2.49	6, 8	0.000	0.00	0.00	0.00	3.044
3-methylpentane	2.07	6, 8	0.000	0.00	0.00	0.00	2.581
3-methylpyridine	3.74	10, 13	0.631	0.81	0.00	0.54	3.631
3-pentanone	2.68	6–10, 13	0.154	0.66	0.00	0.51	2.811
4-methyl-2-pentanone	3.03	6, 8	0.111	0.65	0.00	0.51	3.089
4-methylpyridine	3.75	10, 13	0.630	0.82	0.00	0.54	3.640
acetic acid	3.64	13	0.265	0.64	0.62	0.44	1.816
acetone	1.85	6–10, 13	0.179	0.70	0.04	0.49	1.696
acetylene	0.24	8, 10, 13	0.190	0.60	0.06	0.04	0.140
allyl chloride	2.04	6, 17	0.327	0.56	0.00	0.05	2.109
allylbenzene	3.85	6–8, 10, 13	0.717	0.60	0.00	0.22	4.136
argon	–0.82	8, 13	0.000	0.00	0.00	0.00	–0.688
benzene	2.65	6–10, 13, 17, 18	0.610	0.52	0.00	0.14	2.786
benzyl alcohol	4.73	10, 13	0.803	0.87	0.39	0.56	4.221
bromobenzene	4.14	9, 10, 13	0.882	0.73	0.00	0.09	4.041
bromochloromethane	2.56	6, 17	0.541	0.80	0.01	0.06	2.445
butan-2-one	2.30	6–10, 13	0.166	0.70	0.00	0.51	2.287
butane	1.27	6, 9, 10, 13	0.000	0.00	0.00	0.00	1.615
butyl acetate	3.20	6, 9, 10, 13	0.071	0.60	0.00	0.45	3.353
butyl formate	2.87	10, 13	0.121	0.63	0.00	0.38	2.958

Table 2. (Continued)

solute	log K _{olive}	reference	E	S	A	B	L
butyl propanoate	3.67	10, 13	0.058	0.56	0.00	0.47	3.833
butylbenzene	4.46	10, 13	0.600	0.51	0.00	0.15	4.730
carbon dioxide	0.13	8, 13	0.000	0.28	0.05	0.10	0.058
carbon disulfide	2.18	8, 13	0.876	0.26	0.00	0.03	2.370
carbon monoxide	-1.01	8, 13	0.000	0.00	0.00	0.04	-0.836
carbon tetrachloride	2.56	6, 8-10, 13, 17-18	0.458	0.38	0.00	0.00	2.823
1,1-difluoro-2-chloroethene	1.15	8, 10, 13	-0.340	0.29	0.15	0.00	0.723
1,2-dichlorotetrafluoroethane	1.25	8	-0.190	0.05	0.00	0.00	1.427
1,1,2,2,3,3,4,4-octafluorobutane	1.48	6	-0.710	0.04	0.09	0.00	0.590
1,1,2,2,3,3-hexafluoropropane	1.01	6	-0.450	0.17	0.00	0.03	0.680
1,1,2,2-tetrafluoroethane	0.67	6	-0.280	-0.30	0.30	0.00	0.289
1,1,2,4,4-pentafluorobutane	(0.12) ^b	6	-0.500	0.55	0.07	0.20	1.000
1,1-difluoroethane	0.93	6	-0.250	0.49	0.04	0.05	0.517
halothane	2.30	6, 8, 10, 13, 14, 17	0.102	0.38	0.15	0.05	2.177
teflurane	1.46	6, 8, 10, 13	-0.070	0.21	0.20	0.02	1.370
1,1,1,2,2,3,3,4,4-nonafluorobutane	0.61	6	-0.780	-0.30	0.10	0.10	0.420
1,1,1,2-tetrafluoroethane	0.48	6	-0.640	0.20	0.24	0.00	0.226
1,1,1,2,3,4,4,4-octafluorobutane	1.34	6	-0.710	-0.09	0.09	0.04	0.590
1-chloro-2,2,2-trifluoroethane	1.38	6, 8, 10, 13, 17	0.010	0.40	0.15	0.00	1.168
fluroxene	1.68	6, 8, 10, 13	0.183	0.30	0.00	0.27	1.600
bis-(2,2,2-trifluoroethyl)ether	1.67	8	-0.510	0.03	0.08	0.36	1.419
carbon tetrafluoride	-1.28	6	-0.550	-0.20	0.00	0.00	-0.819
1,3-difluoropropane	1.67	6	-0.190	0.27	0.05	0.05	1.280
halopropane	2.51	8, 10, 13	-0.070	0.28	0.20	0.00	2.030
enflurane	2.01	6, 8, 10	-0.230	0.40	0.12	0.13	1.750
isoflurane	1.96	6, 8, 10, 13, 17	-0.240	0.50	0.10	0.10	1.576
desflurane	1.27	8	-0.300	0.11	0.07	0.00	1.404
sevoflurane	1.70	6, 8	-0.465	0.23	0.08	0.14	1.688
CF ₃ CHFOCHFCI	1.98	19	-0.240	0.50	0.00	0.11	1.865
CF ₃ CH ₂ OCF ₂ CI	1.41	19	-0.24	0.14	0.00	0.06	1.579
chlorobenzene	3.44	6, 8-10, 13, 17	0.718	0.65	0.00	0.07	3.657
chlorodibromomethane	3.43	6, 17	0.775	0.71	0.07	0.08	3.304
chloroethane	1.57	6, 8, 9, 13, 17	0.227	0.40	0.00	0.10	1.678
chloroform	2.60	6, 8, 9, 13, 17, 18	0.425	0.49	0.15	0.02	2.480
cis-1,2-dichloroethene	2.36	6-8, 13, 17	0.436	0.61	0.11	0.05	2.439
cycloheptane	3.44	6	0.350	0.10	0.00	0.00	3.704
cyclohexane	2.47	6, 8-10, 13, 17, 18	0.305	0.10	0.00	0.00	2.964
cyclohexene	2.66	18	0.395	0.28	0.00	0.09	2.952
cyclopentane	2.05	6, 9, 10	0.263	0.10	0.00	0.00	2.477
cyclopentanone	3.21	10, 13	0.373	0.86	0.00	0.52	3.221
cyclopropane	1.07	6, 8, 10	0.408	0.23	0.00	0.00	1.314
decane	3.98	6, 9, 10, 13	0.000	0.00	0.00	0.00	4.686
dibromomethane	2.98	6	0.714	0.69	0.11	0.07	2.886
dichloromethane	2.15	6, 8-10, 13, 17, 18	0.387	0.57	0.10	0.05	2.019
diethyl ether	1.80	6, 8-10, 13, 17	0.041	0.25	0.00	0.45	2.015
difluorochloromethane	0.64	8, 10, 13	0.000	0.25	0.20	0.00	0.690
difluoromethane	0.68	6, 17	-0.320	0.49	0.06	0.05	0.040
diisopropyl ether	2.15	10, 13	-0.060	0.16	0.00	0.58	2.530
dimethoxymethane	1.96	10, 13	0.099	0.46	0.00	0.52	1.894
dimethyl ether	0.97	8	0.000	0.27	0.00	0.41	1.285
dimethylacetamide	3.90	9, 13	0.363	1.35	0.00	0.77	3.638
dimethylformamide	3.46	9, 13	0.367	1.31	0.00	0.74	3.173
dimethyl sulfoxide	4.38	13	0.522	1.72	0.00	0.97	3.459
di- <i>n</i> -butyl ether	3.42	9, 10, 13	0.000	0.25	0.00	0.45	3.924
divinyl ether	1.78	6, 8, 13	0.259	0.39	0.00	0.13	1.760
dodecane	4.80	9, 10	0.000	0.00	0.00	0.00	5.696
ethane	0.26	6, 8, 10	0.000	0.00	0.00	0.00	0.492
ethanol	1.98	6, 8, 10, 13	0.246	0.42	0.37	0.48	1.485
ethene	0.10	6, 8, 10, 13	0.107	0.10	0.00	0.07	0.289
ethyl acetate	2.33	6, 9, 10, 13	0.106	0.62	0.00	0.45	2.314
ethyl formate	1.96	8, 10, 13	0.146	0.66	0.00	0.38	1.845
ethyl propanoate	2.71	10, 13	0.087	0.58	0.00	0.45	2.807
ethyl <i>tert</i> -butyl ether	2.28	6	-0.020	0.16	0.00	0.60	2.720
ethyl <i>tert</i> -pentyl ether	2.53	6	0.030	0.23	0.00	0.37	3.200
ethylbenzene	3.54	6-10, 13	0.613	0.51	0.00	0.15	3.778
iodoethane	2.16	13	0.640	0.40	0.00	0.14	2.573
fluorobenzene	2.82	6	0.477	0.57	0.00	0.10	2.788

Table 2. (Continued)

solute	log K _{olive}	reference	E	S	A	B	L
fluoroethane	0.58	8, 10, 13	0.052	0.35	0.00	0.10	0.576
fluoromethane	0.06	8, 10, 13	0.066	0.35	0.00	0.09	0.057
fluorotrichloromethane	1.60	8	0.207	0.24	0.00	0.07	1.950
fluorochloromethane	1.35	6, 17	-0.080	0.27	0.09	0.03	1.030
formic acid	3.23	13	0.343	0.75	0.76	0.33	1.545
helium	-1.76	8, 13	0.000	0.00	0.00	0.00	-1.741
heptane	2.61	6, 8-10, 13, 17, 18	0.000	0.00	0.00	0.00	3.173
hexachloroethane	3.70	6, 17	0.680	0.68	0.00	0.00	4.718
hexadecane	6.57	9, 10	0.000	0.00	0.00	0.00	7.714
hexafluorobenzene	2.40	6	0.088	0.56	0.00	0.01	2.345
hexane	2.16	6, 8-10, 13, 17, 18	0.000	0.00	0.00	0.00	2.668
hydrogen	-1.31	8, 13	0.000	0.00	0.00	0.00	-1.200
isobutyl acetate	3.11	6	0.052	0.57	0.00	0.47	3.161
isopentyl acetate	3.47	6	0.051	0.57	0.00	0.47	3.740
isopropyl acetate	2.69	6, 10, 13	0.055	0.57	0.00	0.47	2.546
isopropyl bromide	2.21	6, 17	0.332	0.35	0.00	0.14	2.390
isopropylbenzene	3.75	6-8, 10, 13	0.602	0.49	0.00	0.16	4.084
tricyclo[5.2.1.0 ^{2,6}]decane (JP10)	4.11	17	0.590	0.45	0.00	0.06	4.840
krypton	-0.35	8, 13	0.000	0.00	0.00	0.00	-0.211
limonene	3.76	16	0.488	0.28	0.00	0.21	4.725
methoxyflurane	2.94	6, 8, 10, 13	0.109	0.67	0.07	0.14	2.864
methanal	1.41	10, 13	0.220	0.62	0.00	0.33	0.730
methane	-0.51	8, 13	0.000	0.00	0.00	0.00	-0.323
methanol	1.56	6, 8, 10, 13	0.278	0.44	0.43	0.47	0.970
methyl acetate	2.00	6, 9, 10, 13	0.142	0.64	0.00	0.45	1.911
methyl formate	1.56	9, 10, 13	0.192	0.68	0.00	0.38	1.285
methyl <i>tert</i> -butyl ether	2.08	6	0.024	0.21	0.00	0.59	2.380
methyl chloride	0.93	6, 17	0.249	0.43	0.00	0.08	1.163
methylcyclopentane	2.31	6, 8	0.225	0.10	0.00	0.00	2.907
methylcyclohexane	2.82	18	0.244	0.06	0.00	0.00	3.319
methylpentafluorobenzene	3.17	6	0.240	0.45	0.04	0.00	2.900
<i>m</i> -methylstyrene	4.17	6, 17	0.866	0.65	0.00	0.18	4.375
<i>m</i> -xylene	3.56	6-8, 10, 13, 17, 18	0.623	0.52	0.00	0.16	3.839
neon	-1.66	8, 13	0.000	0.00	0.00	0.00	-1.575
nitroethane	2.75	9, 10, 13	0.270	0.95	0.02	0.33	2.414
nitrogen	-1.13	8	0.000	0.00	0.00	0.00	-0.978
nitromethane	2.44	8-10, 13	0.313	0.95	0.06	0.31	1.892
nitrous oxide	0.15	8, 9	0.068	0.35	0.00	0.10	0.164
<i>N</i> -methylimidazole	(4.84) ^b	13	0.589	0.95	0.00	0.80	3.805
<i>N,N</i> -dimethylaniline	4.66	10, 13	0.957	0.81	0.00	0.41	4.701
nonane	3.48	9, 10, 13	0.000	0.00	0.00	0.00	4.182
octane	3.07	6, 8-10, 13, 18	0.000	0.00	0.00	0.00	3.677
oxygen	-0.94	8, 13	0.000	0.00	0.00	0.00	-0.723
<i>o</i> -xylene	3.64	6-8, 10, 13, 17, 18	0.663	0.56	0.00	0.16	3.939
<i>p</i> -xylene	3.55	6-10, 13, 17, 18	0.613	0.52	0.00	0.16	3.839
pentachloroethane	3.83	6, 17	0.648	0.66	0.17	0.06	4.267
pentadecane	6.13	10	0.000	0.00	0.00	0.00	7.209
pentafluorobenzene	2.59	6	0.154	0.68	0.00	0.02	2.578
pentane	1.71	6, 8-10, 13, 18	0.000	0.00	0.00	0.00	2.162
pentyl acetate	3.52	6, 10, 13	0.067	0.60	0.00	0.45	3.844
phenol	4.29	10, 13	0.805	0.89	0.60	0.30	3.766
piperidine	3.91	13	0.422	0.46	0.13	0.68	3.304
<i>p</i> -methylstyrene	4.14	6, 17	0.871	0.65	0.00	0.18	4.399
propane	0.74	9	0.000	0.00	0.00	0.00	1.050
propanoic acid	3.94	13	0.233	0.65	0.61	0.44	2.276
propyl acetate	2.75	6, 10, 13	0.092	0.60	0.00	0.45	2.819
propyl bromide	2.43	6, 17	0.366	0.40	0.00	0.12	2.620
propyl formate	2.42	10	0.132	0.63	0.00	0.38	2.433
propylbenzene	3.95	6-8, 10, 13	0.604	0.50	0.00	0.15	4.230
pyridine	3.20	9, 10, 13	0.631	0.84	0.00	0.52	3.022
styrene	3.65	6-8, 10, 13, 17, 18	0.849	0.65	0.00	0.16	3.856
sulfur hexafluoride	-0.58	8, 13	-0.600	-0.20	0.00	0.00	-0.120
tetrachloroethene	3.25	6-9, 13, 17, 18	0.639	0.44	0.00	0.00	3.584
tetradecane	5.69	10	0.000	0.00	0.00	0.00	6.705
tetrahydrofuran	2.39	9, 10, 13	0.289	0.52	0.00	0.48	2.636
toluene	3.10	6-10, 13, 17, 18	0.601	0.52	0.00	0.14	3.325
<i>trans</i> -1,2-dichloroethene	2.22	6-8, 10, 13, 17	0.425	0.41	0.09	0.05	2.278

Table 2. (Continued)

solute	log K _{olive}	reference	E	S	A	B	L
trichloroethene	2.79	6–8, 13, 17, 18	0.524	0.37	0.08	0.03	2.997
tridecane	5.24	10	0.000	0.00	0.00	0.00	6.200
triethylamine	2.83	9, 10, 13	0.101	0.15	0.00	0.79	3.040
undecane	4.36	9, 10	0.000	0.00	0.00	0.00	5.191
vinyl bromide	1.75	6, 17	0.564	0.50	0.00	0.07	1.846
vinyl chloride	1.39	6, 17	0.258	0.38	0.00	0.05	1.404
xenon	0.24	8, 10	0.000	0.00	0.00	0.00	0.378
α -pinene	3.46	16	0.446	0.14	0.00	0.12	4.308
β -pinene	3.63	16	0.530	0.24	0.00	0.19	4.394

^a The descriptors are those in eq 4 and are defined in the text (Methods and Results). ^b Not used.

Table 3. Comparison of Some Experimental Values of Log K_{olive} at 37 °C

VOC	GLC ²⁰	GLC ¹³	VLE ¹³	Table 1
ethanol	1.67	1.96	2.07	1.98
2-methylpropan-2-ol	1.88	2.27	2.27	2.25
acetone	1.72	1.92	1.88	1.85
butanone	2.16	2.36	2.33	2.30
cyclopentanone	2.98			3.21
diethyl ether	1.62			1.80
diisopropyl ether	2.03			2.15

set of compounds. We have discussed the three outliers to eq 7, above. Additionally we did not use the values reported by Cabala et al.,²⁰ as they appeared to be systematically smaller than other corresponding data. Cabala et al. used the same GLC method as did Abraham et al.,¹³ in which retention data are obtained for VOCs on a stationary phase of olive oil. The most common source of error in such experiments is the weight of olive oil in the GLC column; any error in the weight will lead to a systematic error in the obtained partition coefficients. In Table 3 are listed values of log K_{olive} obtained by the GLC method,^{13,20} together with values obtained by a static vapor–liquid equilibrium (VLE) method,¹³ and average values from Table 2. The Cabala et al.²⁰ values are clearly systematically too small.

The coefficients in eq 7 are not just fitting coefficients.^{12,21} Since the descriptors have been devised to take into account the solute properties that influence solvation, so the coefficients must describe the corresponding solvation properties of the solvent. Hence the s-coefficient must be positive as it reflects the ability of the solvent to take part in dipole–dipole and dipole–induced dipole interactions. The a-coefficient refers to the complimentary property to solute hydrogen bond acidity, that is to solvent hydrogen bond basicity, and is quite large as expected for an ester. The b-coefficient is zero, exactly as expected for a solvent that has no hydrogen bond acidic properties. The l-coefficient relates to the solvent hydrophobicity and is of the same order as that of most organic liquids. Unlike the other descriptors for which the gas phase serves as the defining zero line, the E-descriptor is tied to aliphatic alkanes as the baseline, and for most solvents varies above and below zero.

Some comparisons of coefficients in gas to solvent equations are given in Table 4.^{12,21–25} Some coefficients refer to 37 °C and others to 25 °C, but this will not affect any general conclusions. There is nothing outstanding about the coefficients for olive oil. Among solvents that are also oxygen bases, olive oil is not very polar but is reasonably basic, although a weaker hydrogen bond base than ethyl

Table 4. Some Comparisons of Coefficients for Gas to Solvent Partition Equations, at 25 °C and 37 °C

solvent	c	e	s	a	b	l
water 25	−1.271	0.822	2.743	3.904	4.814	−0.213
blood 37	−1.069	0.456	1.083	3.738	2.580	0.376
muscle 37	−1.039	0.207	0.723	3.242	2.469	0.463
brain 37	−0.987	0.263	0.411	3.358	2.025	0.591
olive oil 37	−0.156	−0.254	0.859	1.656	0.000	0.873
ethyl acetate 25	0.203	−0.335	1.251	2.949	0.000	0.917
acetone 25	0.154	−0.277	1.522	3.258	0.000	0.863
ethanol 25	0.012	−0.206	0.789	3.635	1.311	0.853
ethylene glycol 25	−0.898	0.217	1.427	4.474	2.687	0.568

acetate or acetone. The coefficients for partition from the gas phase to biological phases such as blood, muscle, and brain^{22–25} lie between those for water and olive oil, which explains why gas to biological phase partition can be described in an empirical way by a combination of gas to olive oil and gas to saline coefficients.^{6,7}

In conclusion, further values of log K_{olive} can be predicted by eq 7 to around 0.2 log units, provided that the specified compounds are within the chemical space used to construct eq 7 or, more rigorously, within the chemical space of the test set. It should be noted that the chemical space is defined quite differently to chemical space for fragmentation models. For such models, chemical space is determined by the functional groups or functional group interactions, and predictions cannot be made for compounds with functional groups outside those of the data set considered. In models that use a number of descriptors, such as that of Katritzky et al.¹¹ and the present model, chemical space is determined by the spread of descriptors, and predictions can be made for any compound whose descriptors lie within the spread, no matter if the compound has a ‘new’ functional group. Thus in Table 2, there are no iodoalkanes or primary aliphatic amines. However, the descriptors for these compounds lie within the spread of descriptors we have used, and hence it is legitimate to predict log K_{olive} for such compounds. Descriptors are known²⁶ for several thousand compounds, and so a very large number of values of log K_{olive} can be predicted. In addition, it is possible to calculate descriptors just from structure,^{26,27} and so in principle a huge number of predictions can be made.

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