Correlation and Estimation of Gas–Chloroform and Water–Chloroform Partition Coefficients by a Linear Free Energy Relationship Method

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Abstract □ A linear free energy relationship, LFER, has been used to correlate 150 values of gas–chloroform partition coefficients, as log L^{chl} with a standard deviation, sd, of 0.23 log units, a correlation coefficient r^2 of 0.985, and an *F*-statistic of 1919. The equation reveals that bulk chloroform is dipolar/polarizable, of little hydrogen-bond basicity, but as strong a hydrogen-bond acid as bulk methanol or bulk ethanol. However, the main influence on gaseous solubility in chloroform is due to solute–solvent London dispersion interactions. A slightly modified LFER has been used to correlate 302 values of water–chloroform partition coefficients, as log P_{chl}. The correlation equation predicts log P_{chl} for a further 34 compounds not used in the equation with sd = 0.17 log units. When the LFER is applied to all 335 log P_{chl} values, the resulting equation has sd = 0.25, $r^2 = 0.971$, and F = 2218.

Introduction

The partition coefficient of a solute, as log *P*, has widespread applications in such diverse areas as environmental chemistry, biochemistry, pharmaceutical chemistry, toxicology, and chemical engineering.[1] Following the work of Hansch and Leo,[2] the water−octanol partition coefficient, as log P_{oct}, has become a standard parameter in quantitative structure−activity relationships (QSARs), and in the definition of solute lipophilicity.[3] However, other water−solvent systems have been used, especially as models for biochemical proceses;[3,4] indeed the first such system used in this way was water−olive oil.[4]

The water−chloroform system has been used to estimate solute lipophilicity, as log P_{chl},[5] and both the water−cyclohexane and water−chloroform systems have been used to examine the hydrophobicities of nucleic acid bases.[6] The later system has been put forward as one of a "critical quartet" of water−solvent systems that encapsulates most of the information contained in water−solvent systems, in general.[7] Comparisons of water−solvent log *P* values, including log P_{chl}, have been made,[8] but only recently have attempts been made to compute log P_{chl} values. Some of these computations refer to relative partition coefficients,[9,10] but others to absolute values;[11−14] we comment only on these latter calculations.

All the reported computations of log P_{chl} involve the separate calculation of gas−water partition coefficients, L^w, and gas-chloroform partition coefficients, L^{chl}. Various standard states can be used to define *L*, or the related Gibbs free energy change, $\Delta G° = -RT \ln L$. We prefer to work with equilibrium constants[15] and define *L* as a dimensionless quantity via eq 1.

$$L = \text{concn (M) solute in solvent/concn (M) solute in gas phase} \quad (1)$$

Then log P_{chl} is given by eq 2. As we shall see, eq 2 is valuable, not only in the calculation of log P_{chl}, but also as one method of experimental determination of log P_{chl}.

$$\log P_{chl} = \log L^{chl} - \log L^w \quad (2)$$

A GB/SA continuum model together with the OPLS all atom force field was used by Reynolds[11] to compute log L^w, log L^{chl}, and hence log P_{chl} for 30 diverse, but monofunctional, compounds. The standard deviation, sd, between the 30 calculated and observed log P_{chl} values was 0.87 log units with sd defined as $[(Y_{calcd} - Y_{obsd})^2/(n-V-1)]^{1/2}$; n is the number of data points and V the number of variables (zero in the present case). The average deviation, $(Y_{calcd} - Y_{obsd})/n$ was only 0.01 log units, but it was suggested that systematic deviations at low log P_{chl} and high log P_{chl} values occurred. A plot of observed vs calculated log P_{chl} values indeed yielded a smaller standard deviation; see eq 3. In eq 3 and elsewhere *r* is the correlation coefficient and *F* is the Fischer *F*-statistic.

$$\log P_{chl}(obsd) = 0.055 + 0.732 \log P_{chl}(calcd) \quad (3)$$

$$n = 30,\ sd = 0.51,\ r^2 = 0.919,\ F = 318$$

Various other computations of log L^{chl} have been made[12−14] on data sets that vary from only 16 compounds to 88 compounds; see Table 1. In general, the computations summarized in Table 1 lead to log L^{chl} values with an sd of 0.3 to 0.7 log units and to log P_{chl} values with a much larger sd of 0.5−1.0 log units, even when trained on experimental values. The larger error in log P_{chl} is expected, because this will include errors in both log L^{chl} and in log L^w. Additionally, any experimental errors in log P_{chl} will also contribute to the overall sd value, and it is not easy to assess this contribution, especially for small data sets. In general, the more compounds in a data set, the larger will be the sd value, because of the more varied and more complicated structures in the data set.

The method of multiple linear regression analysis (MLRA) has been applied to the correlation of log P_{chl} values, using various physicochemical parameters as descriptors.[1,6,18−20] A summary of results is in Table 1. Only one, preliminary MLRA of log L^{chl} has been reported,[19] as shown in Table 1 also. The disadvantage of the MLRA method, as compared

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Table 1—Computations and Calculations of log P_{chl} and log L^{chl}

reference	untrained set		trained set			
	n	sd	*n*	sd	r^2	*F*
		A. log P_{chl}				
Reynolds[11]	30	0.87	30	0.51	0.919	318
Cramer (SM5.4A)[13]			26	0.93		
Cramer (SM5.4P)[13]			26	0.96		
Jorgensen[14]			16	0.67		
Marcus (MLRA)[18]			66	0.16	0.994	2973
Taylor (MLRA)[7a]			33	0.11	0.993	610
Maurer (MLRA)[1d]			50	0.12		
Testa (MLRA)[19b]			60	0.29	0.950	369
Abraham (MLRA)[19a]			112	0.11	0.994	3785
this work (MLRA)			335	0.25	0.971	2218
		B. log L^{chl}				
Luque (6-31G)[12]	27	0.28				
Luque (AM1)[12]	27	0.30				
Luque (MNDO)[12]	27	0.28				
Luque (PM£)[12]	27	0.30				
Cramer (OSM5.4A)[13]	88					
Cramer (OSM5.4P)[13]	88					
Cramer (SM5.4A)[13]			88	0.53		
Cramer (SM5.4P)[13]			88	0.67		
Jorgensen[14]	16	0.69	16	0.52	*a*	272
Abraham (MLRA)[19a]			35	0.15	0.994	754
this work			150	0.23	0.985	1919

[a] See note 17.

with computational methods, is that it requires experimental values to use as a training set. However, the untrained computations reported in Table 1 lead to very considerable errors, and if computations have to be trained on experimental data in order to reduce errors to reasonable values, much of the computational advantage disappears. In the event, the trained MLRA method seems capable of leading to rather smaller sd values than do the trained computational methods reported to date. Hence the aim of this work is to determine further log P_{chl} values in order to extend the experimental database and then to apply MLRA methods to a very much enlarged database. Not only will this provide very general correlations, but it will overcome difficulties inherent in the use of small data sets.

There are several problems with the use of small data sets. First, the data set might not be representative. Indeed, a very small data set cannot be representative, in that it will not contain examples of many types of compound that could be included in a full data set. For example, neither the 30 compound data set[11] nor the 16 compound data set[14] contain any compound with a sulfur or with an iodine atom. Second, it is very difficult to assess the effect of possible experimental error when using a small data set. It was suggested that large values of (calculated − observed) log P_{chl} for trimethylamine (1.68) and dimethylamine (1.29) in the 16 compound data set and for diethylamine (1.24) in the 30 compound set were possibly due to experimental errors arising from protonation of the amine in the aqueous layer, but the large differences could also be due to a systematic computational error for aliphatic amines. Third, we know from our own experience in the measurement of log P_{chl} values, that experimental errors, especially with large values of log P_{chl}, can be much greater than expected from measurement of log P_{oct}, for example. A very erroneous experimental value in a small training set might bias a correlation so that the error becomes undetected (and the correlation becomes incorrect), whereas this is much less likely to occur with a large training set.

Methodology

A number of sources of data were used to compile the log P_{chl} and log L^{chl} values. Most of the log P_{chl} values were taken from the MedChem database,[21] and others were measured by the usual shake-flask method. For compounds that are gaseous at room temperature, log P_{chl} could often be obtained from experimental values of log L^{chl} and log L^{w} through eq 2. Directly determined log L^{chl} values were available[22] for the rare gases, hydrogen, oxygen, nitrogen, nitrous oxide, carbon monoxide, and a few organic solutes. Other log L^{chl} values could be obtained from known infinite dilution activity coefficients of solutes in chloroform together with known vapor pressures,[23] through $K^{H} = \gamma^{\infty}p^{o}$ where K^{H} is Henry's constant; L is the inverse of K^{H} with due regard to units. A large number of log L^{chl} values were deduced from log P_{chl} and known[24,25] values of log L^{w} through eq 2. We finally assembled 335 values of log P_{chl} and 150 values of log L^{chl} to use in our correlative equations, as set out in Table 2.

The MLR equation we use to correlate log L^{chl} is the linear free energy relationship (LFER)[26] shown as eq 4.

$$\log SP = c + rR_2 + s\pi_2^{H} + a\Sigma\alpha_2^{H} + b\Sigma\beta_2^{H} + l \log L^{16} \quad (4)$$

Here, SP is a set of solute properties in a given system, for example L^{chl} values, and the independent variables are solute descriptors as follows.[26] R_2 is an excess molar refraction, π_2^{H} is the dipolarity/polarizability, $\Sigma\alpha_2^{H}$ is the overall hydrogen-bond acidity, $\Sigma\beta_2^{H}$ is the overall hydrogen-bond basicity, and L^{16} is the gas−liquid partition coefficient on hexadecane at 298 K.[28]

The coefficients in eq 4 are found by MLRA. They are not just fitting constants, but contain information on the properties of the system under investigation; in particular they refer to chemical properties of the solvent phase. The *r*-coefficient reflects the interaction of the phase with solute π- and σ-lone pairs, the *s*-coefficient is a measure of the phase dipolarity/polarizability, the *a*-coefficient is a measure of the phase hydrogen-bond basicity, the *b*-coefficient is a measure of the phase hydrogen-bond acidity, and the *l*-coefficient is a measure of the phase hydrophobicity. Equation 4 has been applied to numerous sets of gas−liquid chromatographic data,[26,27] to gas−solid adsorption,[28] to the solubility of gases and vapors in water,[24] organic solvents,[20] biological systems,[29] polymers,[30] and petroleum oils,[31] to the characterization of phases for chemical sensors,[32] to the characterization of fullerene,[33] and in the analysis of the effect of gases and vapors in nasal pungency[34] and eye irritation.[35]

A very similar equation to eq 4 is used[26] to correlate processes within condensed phase; it differs only in that the final descriptor is the McGowan[36] characteristic volume, V_X, in (mL mol^{-1})/100. The interpretation of eq 5 follows closely that of eq 4, but now the coefficients refer to the difference of properties of the (two) condensed phases. Equation 5 is also a well-tested equation and has been applied to the solubility of gases and vapors in water,[24] to numerous water−solvent partition systems,[19] to HPLC systems,[37] to thin-layer chromatography,[38] to microemulsion electrokinetic chromatography,[39] to water−micelle partitions,[40] to micellar electrokinetic chromatography,[41] to aqueous anesthesia,[42] to blood−brain distribution,[43] to brain perfusion,[44] and to skin permeation.[45]

$$\log SP = c + rR_2 + s\pi_2^{H} + a\Sigma\alpha_2^{H} + b\Sigma\beta_2^{H} + vV_X \quad (5)$$

Results

The values of log L^{chl} and log P_{chl} that were used in the regression equations are in Table 2. There are far fewer

Table 2—Values of log L^{chl} and log P_{chl} Used in the Regressions

compound name	log L^{Wa}	log L^{chlb} obsd	log L^{chlb} calcd	log P_{chl}^{c} obsd	log P_{chl}^{c} calcd	compound name	log L^{Wa}	log L^{chlb} obsd	log L^{chlb} calcd	log P_{chl}^{c} obsd	log P_{chl}^{c} calcd
krypton	–1.21	0.01[d]	–0.039	1.22[e]	1.358	propan-2-ol	3.48	3.13	3.084	–0.35	–0.286
xenon	–0.97	0.53[d]	0.539	1.50[e]	1.706	butan-1-ol	3.46	3.88	3.876	0.42	0.431
radon	–0.65	1.12[d]	1.029	1.72[e]	1.936	2-methylpropan-1-ol	3.30	3.64	3.658	0.34	0.441
hydrogen	–1.72	–1.18[d]	–1.01	0.54[e]	0.782	butan-2-ol	3.39	3.69	3.645	0.30	0.306
nitrogen	–1.80	–0.87[d]	–0.792	0.93[e]	1.258	2-methylpropan-2-ol	3.28	3.26	3.273	–0.02	0.25
nitrous oxide	–0.23	0.71[d]	0.865	0.94[e]	1.035	pentan-1-ol	3.35	4.40	4.374	1.05	1.02
carbon monoxide	–1.63	–0.71[d]	–0.598	0.92[e]	1.12	hexan-1-ol	3.23	4.92	4.874	1.69	1.61
hexane	–1.82	2.87[f]	2.786	4.69[e]	4.325	heptan-1-ol	3.09	5.50	5.369	2.41	2.2
octane	–2.11	3.90[g]	3.777	6.01[e]	5.506	cyclohexanol	4.01	5.13	5.131	1.12	0.997
cyclohexane	–0.90	3.26	3.021	4.16	3.879	prop-2-en-1-ol	3.69	3.18	3.22	–0.51	–0.369
chloromethane	0.40	1.82[h]	1.811	1.42[e]	1.481	2-chloroethanol				–0.40	–0.902
dichloromethane	0.96	2.69[i]	2.731	2.00[e]	1.745	3-chloropropan-1-ol				–0.03	0.035
trichloromethane	0.79	3.07[j]	3.034	2.28[e]	2.239	propan-1,3-diol				–2.90	–2.626
tetrachloromethane	–0.06	3.25[l]	3.143	3.31[e]	3.348	diethyl sulfide	1.07	4.71	3.908	3.64	2.64
1,1-dichloroethane	0.62	3.01[l]	3.029	2.39[e]	2.185	dimethyl sulfoxide	7.41	6.56[n]	6.642	–0.85[e]	–0.729
1,2-dichloroethane	1.31	3.44[l]	3.428	2.13[e]	2.107	thiourea				–3.14	–2.922
1,1,1-trichloroethane	0.14	3.24[l]	3.269	3.10[e]	3.09	tributylphosphine oxide				3.08	2.856
1,1,2-trichloroethane	1.46	3.87[l]	4.168	2.41[e]	2.453	trimethyl phosphate	6.52[m]	7.28		0.76	0.546
1-chloropropane	0.24	2.66[h]	2.84	2.46[e]	2.6	triethyl phosphate	5.53	7.81	7.537	2.28	2.133
bromoethane	0.54	2.78[f]	2.697	2.24[e]	2.185	tripropyl phosphate				3.67	3.587
iodomethane	0.65	2.78[k]	2.55	2.13[e]	1.946	benzene	0.63	3.39	3.384	2.76	2.741
1,1,2-trifluorotrichloroethane	–1.30	2.54[i]	2.494	3.84[e]	3.675	toluene	0.65	4.06	3.918	3.41[l]	3.33
diethyl ether	1.17	3.05	3.051	1.88	1.752	ethylbenzene	0.58	4.28	4.357	3.70	3.892
diisopropyl ether	0.39	2.77	3.404	2.38[l]	3.088	*o*-xylene	0.66	4.57	4.561	3.91	3.846
tetrahydrofuran	2.55	3.86[f]	3.893	1.31[e]	1.127	*m*-xylene	0.61	4.29	4.437	3.68	3.855
tetrahydropyran	2.29	4.28	4.348	1.99	1.77	biphenyl	1.95	6.62	6.86	4.67	4.81
1,4-dioxane	3.71	4.44[g]	4.629	0.73[e]	0.74	naphthalene	1.73	5.78	5.865	4.05	4.039
propanone	2.79	3.29	3.287	0.50	0.562	phenanthrene	2.80	7.86	8.452	5.06	5.244
butanone	2.72	3.87	3.891	1.15	1.209	fluorobenzene	0.59	3.13	3.473	2.54	2.912
diethyl carbonate				3.22	2.216	chlorobenzene	0.82	4.22	4.242	3.40	3.46
propylene carbonate				0.60	0.589	1,3-dichlorobenzene	0.72	4.59	4.936	3.87	4.134
δ-pentanolactone				0.95	0.928	1,4-dichlorobenzene	0.74	4.63	4.999	3.89	4.123
methyl acetate	2.30	3.46	3.379	1.16	1.091	2-chloronaphthalene				4.56	4.754
ethyl acetate	2.16	3.98	3.771	1.82	1.683	bromobenzene	1.07	4.70	4.649	3.63	3.606
propyl acetate	2.05	4.61	4.25	2.56	2.28	iodobenzene	1.28	4.85	5.073	3.57	3.865
butyl acetate	1.94	4.99	4.786	3.05	2.867	methyl phenyl ether	1.80	4.92	4.903	3.12	2.987
pentyl acetate	1.84	5.44	5.27	3.60	3.457	ethyl phenyl ether	1.63	5.25	5.243	3.62	3.49
methyl propanoate	2.15	4.02	3.847	1.87	1.695	benzaldehyde	2.95	5.20	5.403	2.25	2.383
methyl pentanoate	1.88	4.89	4.802	3.01	2.873	2-methoxybenzaldehyde				2.53	2.807
methyl hexanoate	1.83	5.31	5.292	3.48	3.459	phenylacetaldehyde				2.07	2.222
ethyl acetoacetate				1.49	1.566	acetophenone	3.36	6.15	6.024	2.79	2.66
ethyl trifluoroacetate				2.00	1.942	benzyl methyl ketone				3.53[l]	2.664
ethyl trichloroacetate				3.47	3.537	9-fluorenone				3.95	3.772
acetonitrile	2.85	3.25	3.321	0.40	0.383	methyl benzoate	2.88	5.68	6.046	2.80	3.024
ammonia	3.15	1.77	1.699	–1.38	–1.366	phenyl acetate				2.33	2.628
methylamine	3.34	2.32	2.574	–1.02	–0.811	dimethyl phthalate				3.09	3.003
ethylamine	3.30	2.95	2.993	–0.35	–0.326	diethyl phthalate				3.69	4.107
propylamine	3.22	3.47	3.455	0.25	0.263	benzonitrile	3.09	5.75	5.536	2.66	2.526
butylamine	3.11	3.86	3.924	0.75	0.854	phenylacetonitrile				2.25	2.69
dimethylamine	3.15	2.71	2.929	–0.44	–0.23	1,2-dicyanobenzene				2.60[l]	2.421
diethylamine	2.99	3.78	3.771	0.79	0.843	1,3-dicyanobenzene				2.12	2.147
diisopropylamine	2.36	3.97	4.299	1.61	1.894	1,4-dicyanobenzene				2.60	2.304
trimethylamine	2.35	2.86	2.843	0.51	0.613	aniline	4.30[o]	5.65	5.3	1.35	1.283
triethylamine	2.36	4.22	4.362	1.86	1.986	*o*-toluidine	4.06	6.02	5.788	1.96	1.85
nitromethane	2.95	3.39[g]	3.473	0.44[e]	0.523	*p*-toluidine	4.09	6.04	5.861	1.95	1.831
acetamide	7.12	5.15		–1.97	–2.049	4-ethylaniline				2.28	2.44
proprionamide	6.88	5.48		–1.40	–1.494	4-propylaniline				2.99	2.928
N,*N*-dimethylacetamide				–0.13	0.484	4-isopropylaniline				2.51	2.768
2,2,2-trichloroacetamide				0.31	0.427	4-butylaniline				3.37	3.521
ethyl carbamate				0.12	–0.32	4-chloroaniline	4.33	6.42	6.263	2.09	1.964
formic acid				–2.12	–2.044	2-nitroaniline	5.41	7.24	7.285	1.83	1.933
acetic acid	4.91	3.45	3.317	–1.46	–1.397	3-nitroaniline	6.49	8.09	7.963	1.60	1.518
propanoic acid	4.74	3.88	3.877	–0.86	–0.814	4-nitroaniline	7.54	8.80	8.703	1.26	1.276
butanoic acid	4.66	4.39	4.383	–0.27	–0.215	3-aminoacetophenone				1.73	1.67
2-methylpropanoic acid				–0.26	–0.334	4-aminopropriophenone				2.13	1.972
pentanoic acid	4.52	4.84	4.901	0.32	0.383	2,4-dimethylaniline				2.27	2.384
3-methylbutanoic acid	4.47	4.66	4.699	0.19	0.253	*N*-methylaniline	3.44	5.84	5.765	2.40	2.115
hexanoic acid	4.56	5.58	5.449	1.02	0.968	*N*,*N*-dimethylaniline	2.53	6.01	5.791	3.48	3.353
2-methylpentanoic acid				0.90	0.843	*N*,*N*-diethylaniline				4.26	4.538
octanoic acid	4.44[m]	6.61	6.524	2.17	2.146	1-naphthylamine	5.34	7.94	7.962	2.60	2.466
2-methylpropenoic acid				0.00	–0.291	2-naphthylamine	5.48	8.18	8.014	2.70	2.463
chloroacetic acid				–1.65	–1.176	4-aminobiphenyl				3.14	3.483
trichloroacetic acid				–1.11	–0.608	benzylamine				1.18	1.33
succinic acid				–1.92	–1.824	1-amino-2-phenylethane				1.37	1.222
water	4.64	1.54	1.697	–3.10	–2.968	nitrobenzene	3.02	5.71	5.899	2.69	2.8
methanol	3.74	2.41	2.271	–1.33	–1.497	2-nitrotoluene	2.63	6.02	6.217	3.39[l]	3.389
ethanol	3.67	2.80	2.767	–0.87	–0.747	3-nitrotoluene	2.53	5.98	6.374	3.45	3.498
propan-1-ol	3.56	3.26	3.309	–0.30	–0.158	4-nitrotoluene				3.31	3.39

Table 2—(Continued)

compound name	log L^{Wa}	log L^{chlb} obsd	log L^{chlb} calcd	log $P_{chl}{}^{c}$ obsd	log $P_{chl}{}^{c}$ calcd	compound name	log L^{Wa}	log L^{chlb} obsd	log L^{chlb} calcd	log $P_{chl}{}^{c}$ obsd	log $P_{chl}{}^{c}$ calcd
4-nitroanisole				3.18	3.169	methyl phenyl sulfoxide				1.41	1.193
1,2-dinitrobenzene				2.64	3.002	diphenyl sulfoxide				3.36	3.111
1,3-dinitrobenzene				2.63	2.729	methyl phenyl sulfone				1.93	1.931
1,4-dinitrobenzene				2.62	2.748	phenylthiourea				0.56	0.541
benzamide	8.07	8.19	8.177	0.12	0.106	benzenesulfonamide				–0.24	–0.009
N-methylbenzamide				0.95	0.844	*N*-methylbenzenesulfonamide				1.31	1.326
N-ethylbenzamide				1.54	1.432	*N*,*N*-dimethylbenzenesulfonamide				2.69	2.736
N,*N*-dimethylbenzamide				1.75	1.819	3-methylbenzenesulfonamide				0.32	0.405
acetanilide	7.01[o]	7.81		0.80	0.76	4-methylbenzenesulfonamide				0.33	0.337
phthalimide				1.46	1.253	pyridine	3.44	4.73	4.525	1.29	1.14
benzoic acid				0.60	0.737	2-methylpyridine	3.40	5.12	4.907	1.72	1.555
2-methylbenzoic acid				1.76	1.502	3-methylpyridine	3.50	5.39	5.113	1.89	1.674
4-methylbenzoic acid				1.36	1.295	4-methylpyridine	3.62	5.50	5.135	1.88	1.67
4-ethylbenzoic acid				1.85	1.856	2-ethylpyridine	3.18	5.44	5.275	2.26	2.129
4-butylbenzoic acid				2.86	3.067	2-chloropyridine	3.22	5.22	5.345	2.00	2.077
2-chlorobenzoic acid				0.90	0.945	2-bromopyridine				2.22	2.383
4-chlorobenzoic acid				1.72	1.585	3-bromopyridine				1.65	2.375
2-bromobenzoic acid				0.91	0.95	2-methoxypyridine	2.96[m]	5.17	4.96	2.21	2.182
3-bromobenzoic acid				2.04	1.713	2-acetylpyridine				1.93	1.856
2-iodobenzoic acid				1.09	1.067	2-cyanopyridine				1.42	1.605
2-methoxybenzoic acid				1.65	2.32	3-cyanopyridine	4.95	6.29	6.239	1.34	1.3
4-methoxybenzoic acid				1.19	1.369	4-cyanopyridine	4.42	5.71	6.007	1.29	1.422
2-nitrobenzoic acid				–0.08	0.312	4-aminopyridine				–0.71	–0.656
3-nitrobenzoic acid				0.48	0.482	2-(*N*,*N*-dimethylamino)pyridine				2.45	2.389
4-nitrobenzoic acid				0.67	0.864	nicotine				1.89	2.552
4-aminobenzoic acid				–0.92	–0.901	piperidine	3.75	4.67	4.705	0.92	0.832
phenylacetic acid				0.49	0.546	*N*-methylpiperidine	2.77	4.21	4.66	1.44	1.731
3-phenylpropanoic acid				1.20	1.15	atropine				2.44	2.534
4-phenylbutanoic acid				1.78	1.9	*N*-methyl-2-pyridone				0.26	0.762
phenol	4.85	5.17	5.081	0.32	0.408	quinoline	4.20	7.34	6.726	3.14	2.668
2-methylphenol	4.31	5.54	5.444	1.23	1.271	isoquinoline				2.98	2.647
3-methylphenol	4.60[o]	5.49		0.89	0.963	pyrrole				0.91	0.252
4-methylphenol	4.50	5.56	5.588	1.06	1.07	indole				2.95	1.882
2,4-dimethylphenol	4.41	5.91	6.035	1.50	1.544	3-methylindole				2.24	2.496
2,5-dimethylphenol	4.34	5.93	6.003	1.59	1.585	carbazole				3.75	3.592
3,5-dimethylphenol	4.60	6.20	6.153	1.60	1.5	imidazole				–0.83	–1.667
2-ethylphenol				1.73	1.627	*N*-methylimidazole				0.29	0.137
3-ethylphenol	4.59	6.00	6.142	1.41	1.501	benzimidazole				–0.02	–0.096
4-ethylphenol	4.50	5.97	6.118	1.47	1.538	2-cyanopyrazine				1.03	1.012
2-isopropyl-5-methylphenol				2.80	2.586	pyrazine	4.18[o]	4.77	4.688	0.59	0.616
2-fluorophenol	3.88	4.45	4.557	0.57	0.643	2-methylpyrazine	4.04	5.08	5.007	1.04	1.088
2-chlorophenol	3.34	4.70	5.38	1.36	1.792	2,3-dimethylpyrazine				1.46	1.435
3-chlorophenol	4.85	5.87	6.041	1.02	1.099	2,6-dimethylpyrazine				1.54	1.465
4-chlorophenol	5.16	6.23	6.127	1.07	0.984	trimethylpyrazine				1.93	1.82
2-bromophenol				1.64	1.937	tetramethylpyrazine				2.32	2.145
4-bromophenol	5.23	6.30	6.495	1.07	1.195	2-ethylpyrazine	4.00	5.66		1.66	1.642
2-iodophenol	4.55	6.52	6.077	1.97	2.001	2,3-diethylpyrazine				2.47	2.413
4-iodophenol				1.56	1.54	2-methyl-3-isobutylpyrazine				2.85	2.935
2,4-dichlorophenol				2.09	2.079	2-fluoropyrazine				1.07	1.087
2-methoxyphenol	4.09	5.79	5.953	1.70[l]	1.698	2-chloropyrazine				1.59	1.698
3-methoxyphenol	5.62	6.39	6.527	0.77	0.869	2-methoxypyrazine				1.71	1.701
4-methoxyphenol				0.46	0.627	2-ethoxypyrazine				2.25	2.23
2-hydroxybenzaldehyde				2.21	2.516	2-propoxypyrazine				2.89	2.761
4-hydroxybenzaldehyde	7.68	7.54	7.356	–0.14	–0.196	methyl 2-pyrazinecarboxylate				1.36[l]	1.289
4-hydroxyacetophenone				0.08	0.109	ethyl 2-pyrazinecarboxylate				1.88	1.789
2-nitrophenol	3.36	5.89	6.075	2.53	2.623	2-acetylpyrazine				1.42	1.342
3-nitrophenol	7.06	7.56	7.637	0.50	0.545	2-(dimethylamino)pyrimidine				1.99	1.905
4-nitrophenol	7.81	8.01	8.043	0.20	0.29	5-(dimethylamino)pyrimidine				1.33	1.272
2,4-dinitrophenol				2.25	2.428	2-cyanopyrimidine				0.84	0.801
2-hydroxybenzoic acid				0.58	0.637	2-thiomethoxypyrimidine				1.93	1.836
resorcinol				–1.34	–1.919	pyrimidine				0.32	0.455
methyl 4-hydroxybenzoate				1.23	0.925	2-methylpyrimidine				0.67	0.873
ethyl 4-hydroxybenzoate				1.78	1.517	5-methylpyrimidine				0.95	0.941
methyl 2-hydroxybenzoate				3.15	3.165	2-fluoropyrimidine				0.85	0.865
ethyl 2-hydroxybenzoate				3.91	3.812	5-fluoropyrimidine				0.89	0.891
2-hydroxybenzamide				0.62	0.538	2-chloropyrimidine				1.16	1.197
4-hydroxy-3-methoxybenzaldehyde				1.42	1.501	5-chloropyrimidine				1.43	1.398
4-hydroxypropriophenone				0.71	0.692	2-bromopyrimidine				1.35	1.328
4-hydroxyacetanilide				–1.60	–1.552	5-bromopyrimidine				1.65[l]	1.586
1-naphthol	5.63	7.13	7.272	1.50	1.764	2-methoxypyrimidine				1.28	1.173
2-naphthol	5.95	7.69	7.423	1.74	1.617	2-ethoxypyrimidine				1.77	1.68
benzyl alcohol	4.86	5.82	5.801	0.96	0.783	5-ethoxypyrimidine				1.59	1.513
4-methylbenzyl alcohol				1.83	1.233	methyl 2-pyrimidinecarboxylate				0.73	0.638
2-hydroxybenzyl alcohol				–0.51	–0.378	methyl 5-pyrimidinecarboxylate				1.55	1.419
2-phenylethanol	4.98	6.29	6.33	1.31	1.371	ethyl 2-pyrimidinecarboxylate				1.13	1.038
ephidrine				1.10	1.346	antipyrine				1.45[l]	1.358
thiophenol	1.87	5.58	4.855	3.71	3.022	*N*,*N*-dimethylpiperazine				–0.20[l]	0.525
phenyl methyl sulfide	2.00	4.38		2.38	3.38	1,2,4-triazole				–2.42[l]	–2.295

Table 2—(Continued)

compound name	log L^{Wa}	log L^{chlb} obsd	log L^{chlb} calcd	log $P_{chl}{}^{c}$ obsd	log $P_{chl}{}^{c}$ calcd	compound name	log L^{Wa}	log L^{chlb} obsd	log L^{chlb} calcd	log $P_{chl}{}^{c}$ obsd	log $P_{chl}{}^{c}$ calcd
purine				–1.95	–1.858	thiophene	1.04	4.22	3.447	3.18	2.383
adenine				–2.48	–2.363	thiazole				1.03	1.116
morpholine	5.26	4.93	5.393	–0.33	–0.207	digitoxin				2.40	2.481
N-methylmorpholine	4.64	5.10	5.341	0.46	0.614	phenylurea				–0.68	–0.655
scopolamine				1.64	1.734	1-phenyl-3,3-dimethylurea				1.29[l]	1.138
uracil				–1.70	–1.628	barbituric acid				–2.10	–2.026
1,3-dimethyluracil				0.52[l]	0.442	5-methyl-5-ethylbarbituric acid				–0.72	–0.325
theophylline				–0.48[l]	–1.269	5,5-diethylbarbituric acid				–0.15[l]	0.246
theobromine				–0.43[l]	–1.279	5-ethyl-5-propylbarbituric acid				0.30	0.836
caffeine				1.23	1.079	5-ethyl-5-(2-pentyl)barbital				1.59	1.857
guanine				–3.25	–3.122	5-allyl-5-ethylbarbital				0.64	0.302
codeine				2.20	1.918	5-ethyl-5-phenylbarbital				0.65	0.721

[a] Observed values from refs 24 and 25 unless otherwise shown. Calculated values on eq 6. [b] Observed values obtained from log L^{W} and log P_{chl} unless otherwise shown. Calculated values on eq 9. [c] Directly determined values from ref 21 unless otherwise shown. [d] Solubility Data Project Series. [e] From log L^{chl} and log L^{W}. [f] Thomas, E. R., Newman, B. A., Nicolaider, G. L., Eckert, C. A. *J. Chem. Eng. Data* **1982**, *27*, 233. [g] Park, J. H., Hussam, A., Cousanon, P., Fritz, D., Carr, P. W. *Anal. Chem.* **1987**, *59*, 1970. [h] Gerrard, W. *J. Appl. Chem. Biotechnol.* **1972**, *22*, 623. [i] Dohnal, V., Vrbka, P. *Fluid Phase Equilib.* **1990**, *54*, 121. [j] Taking $\gamma^{inf} = 1$. [k] *Trans. Faraday Soc.* **1957**, *53*, 607. [l] This work. [m] See footnote c. [n] Phillippe, R., Jose, J., Clechet, P. *Bull. Soc. Chim. Fr.* **1971**, 2866. [o] Abraham, M. H. Unpublished results.

Table 3—Descriptors for Some Solutes

solute	*R*	π	α	β	V_x
9-fluorenone	1.37	0.91	0.00	0.63	1.3722
acetanilide	0.87	1.36	0.46	0.69	1.1137
phthalimide	1.18	2.09	0.40	0.42	1.0208
ephidrine	0.92	0.65	0.20	1.24	1.4385
atropine	1.19	1.94	0.36	1.64	2.2820
1,2,4-triazole	0.72	0.98	0.60	0.77	0.4952
scopoloamine	1.07	1.45	0.28	0.71	2.2321
caffeine	1.50	1.60	0.00	1.33	1.3632
codeine	1.78	1.95	0.33	1.78	2.2057
digitoxin	4.50	5.60	1.47	4.52	5.6938

log L^{chl} values, because the values of log L^{w} required in order to obtain log L^{chl} from log P_{chl} via eq 2 were unavailable. Descriptors for most of the compounds have been published before,[19,20,24,26–45] but some new values are in Table 3.

Analysis of log L^{chl}—The 150 values of log L^{chl} in Table 2 cover quite a good range of compound type, from inorganic gases such as hydrogen to organic molecules such as triethyl phosphate and benzamide, with a total range of 9.4 log units in log L^{chl}. When regressed according to eq 4, the 150 log L^{chl} values yielded the statistically very good eq 6, considering that the experimental uncertainty in log L^{chl} must be not less than 0.1 log units. The calculated log L^{chl} values from eq 6 are given in Table 2.

$$\log L^{chl} = \underset{3.19}{0.168} - \underset{-6.46}{0.595} R_2 + \underset{14.13}{1.256}\pi_2^{H} + \underset{3.45}{0.280}\Sigma\alpha_2^{H} + \underset{14.39}{1.370}\Sigma\beta_2^{H} + \underset{41.82}{0.981}\log L^{16} \quad (6)$$

$$n = 150,\ \mathrm{sd} = 0.23,\ r^2 = 0.985,\ r^2_{cv} = 0.984,\ F = 1919$$

In eq 6, r^2_{cv} is the cross-validated squared correlation coefficient; the *t*-ratio for each coefficient is given below the coefficient. The correlation matrix in r^2 is given below,

	R_2	π_2^{H}	$\Sigma\alpha_2^{H}$	$\Sigma\beta_2^{H}$
π_2^{H}	0.591			
$\Sigma\alpha_2^{H}$	0.051	0.108		
$\Sigma\beta_2^{H}$	0.005	0.042	0.006	
log L^{16}	0.677	0.599	0.077	0.019

There are three pairs of coefficients that have rather high cross-correlations, but it must be stressed that we have not designed the data set; we have had to use the available data. The sd value of only 0.23 log units suggests that eq 6 could be useful for the estimation of further values of log L^{chl}. However, the importance of eq 6 lies also in the information that can be extracted from the coefficients in the equation. As outlined above, these coefficients are related to definite chemical properties of the condensed solvent phase. To put these coefficients in context, especially the *b*-coefficient, we summarize in Table 4 the corresponding coefficients for some other solvent phases.[24,43–45] The *r*-coefficient in eq 6 is not exceptional and seems to be related, at least in part, to lone pair–lone pair repulsion. The *s*-coefficient is a measure of the solvent dipolarity/polarizability; the rather large coefficient for chloroform is clearly due to polarizability effects, just as for 1,2-dichloroethane. The *a*-coefficient, a measure of solvent hydrogen-bond basicity, is very low, as expected, but the *b*-coefficient indicates that bulk chloroform can act as a hydrogen-bond acid. However, the magnitude of the *b*-coefficient (1.37) is of the same order as that for methanol (1.43)[46] and ethanol (1.31)[47] solvents, so that to external solutes chloroform is as strong a hydrogen-bond acid as are the alcohols. We give in Table 5 some previous measures of the hydrogen-bond acidity of bulk chloroform; the acceptor number (AN),[49] the solvatochromic α-value,[50,51] and the enthalpic $\Delta_{acid}H$ scale.[51] None of these scales ranks

Table 4—Coefficients in Eq 4 for the Solubility of Gases and Vapors in Solvents, as log *L* Values at 298 K

solvent	*c*	*r*	*s*	*a*	*b*	*l*
chloroform	0.17	–0.60	1.26	0.28	1.37	0.981
water[24]	–1.27	0.82	3.74	3.90	4.80	–2.13
methanol[46]	0.00	–0.22	1.17	3.70	1.43	0.769
ethanol[47]	0.01	–0.21	0.79	3.63	1.31	0.853
1,2-dichloroethane[48]	0.01	–0.15	1.44	0.65	0.74	0.936
benzene[48]	0.11	–0.31	1.05	0.47	0.17	1.020
hexadecane	0.00	0.00	0.00	0.00	0.00	1.000

Table 5—Some Measures of the Hydrogen-Bond Acidity of Solvents

solvent	AN[49]	α^{49}	α^{50}	α^{51}	$\Delta_{acid}H^{51}$	*b*[a]
water	54.8	1.17	1.17	1.16	–10.60	4.81
methanol	41.3			1.09	–11.15	1.43
ethanol	37.1	0.86	0.83	0.88	–9.14	1.31
chloroform	23.1	0.20	0.44		–5.60	1.37
cyclohexane	0.0	0.00	0.00	0.00	2.10	0.00

[a] The *b*-coefficient in eq 4.

Table 6—Factors That Influence the Solubility of Gases and Vapors in Chloroform and in Water at 298 K

solute	rR_2	$s\pi_2^H$	$a\Sigma\alpha_2^H$	$b\Sigma\beta_2^H$	l log L^{16} cav	disp	total[a]
			Solvent Chloroform				
methane	0.00	0.00	0.00	0.00	–2.38	2.06	–0.15
ethanol	–0.15	0.53	0.10	0.66	–3.31	4.77	2.77
butanone	–0.10	0.88	0.00	0.70	–4.19	6.43	3.89
hexane	0.00	0.00	0.00	0.00	–4.85	7.47	2.79
			Solvent Water				
methane	0.00	0.00	0.00	0.00	–4.04	4.11	–1.34
ethanol	0.20	1.15	1.44	2.31	–5.81	5.49	3.51
butanone	0.14	1.92	0.00	2.46	–7.50	7.01	2.76
hexane	0.00	0.00	0.00	0.00	–8.78	8.21	–1.84

[a] This includes the constant 0.168 in eq 6 and –1.271 in eq 7. Observed values are in chloroform 2.80 (ethanol), 3.87 (butanone) and 2.87 (hexane) and in water –1.46 (methane), 3.67 (ethanol), 2.72 (butanone), and –1.82 (hexane).

chloroform as acidic as alcohols, although it must be noted that only the $\Delta_{acid}H$ scale is based on a thermodynamic property, the enthalpy, in contrast to the *b*-coefficient that is related to Gibbs energy. The *l*-coefficient in eq 4 can be regarded as a measure of the solvent hydrophobicity; chloroform is not exceptional, with an *l*-coefficient close to those for benzene or hexadecane.

From the coefficients of eq 6 and solute descriptors, it is possible to dissect the observed log L^{chl} value for any given solute into contributions from the various terms in eq 6. However, the l log L^{16} term includes two opposing effects: (i) an endoergic cavity term that arises through disruption of solvent−solvent interactions, and which will make a negative contribution to l log L,[16] and (ii) an exoergic term due to London dispersion solute−solvent interactions, and which will make a positive contribution to l log L.[16] Indeed, as we have pointed out,[24,32,52] the London interaction term is nearly always larger than any specific solute−solvent interaction involving nonionic solutes.

We can make some headway by calculating the cavity term using scaled particle theory (SPT),[53] and then obtaining the London dispersion term by difference. Even an approximate estimation will suffice to show general trends, and as noted before,[13] there may be a number of possible divisions of experimental log L values into various contributions. To apply SPT we need to know the solvent hard-sphere diameter, σ_1, and Lennard−Jones potential, ϵ_1/k. We calculated these from log L^{chl} for nonpolar solutes, as indicated before,[54] and obtained values of 4.80 Å and 320 K, respectively. Then taking σ_2 as 3.82 (methane), 6.03 (hexane), 4.75 (ethanol), and 5.51 (butanone) for representative solutes, we can calculate the cavity term (Cav) and deduce the dispersion term (Disp) as [Disp = l log L^{16} − Cav]. For comparison, we have done the same for solvent water using eq 7,[24] with σ_1 taken as 2.77 Å.[53] Results are in Table 6. Note that our calculation refers to the separation of cavity and dispersion effects in the l log L^{16} term only. The constant term, which is appreciably more negative for solvent water than for any nonaqueous solvent, may also contain some cavity/dispersion contribution.

$$\log L^w = -1.271 + 0.822R_2 + 2.743\pi_2^H + 3.904\Sigma\alpha_2^H + 4.814\Sigma\beta_2^H - 0.213 \log L^{16} \quad (7)$$

In chloroform, the solute−solvent dispersion term, that increases with increase in solute size, outweighs the various specific interaction terms. This is not unique to chloroform solvent, but is the case for all the nonaqueous solvents we have investigated. The specific interaction terms merely discriminate between solutes of about the same size and hence of about the same cavity/dispersion effect. Thus butanone is more soluble than hexane, even though it is somewhat smaller. In any homologous series, with a constant functionality, log L^{chl} increases with carbon number because the positive dispersion effect increases faster than the negative cavity effect. However log L^w decreases along any homologous series because the positive dispersion effect now increases slower than the cavity effect.

In summary, application of the MLR eq 4 to the 150 log L^{chl} values yields eq 6 that can be used for the prediction of further values and can be used to quantify the various solute and solvent factors that influence the magnitude of log L^{chl}.

Analysis of log P_{chl}—Table 2 contains 335 values of log P_{chl}, enough to divide into a training set and a test set for the purpose of assessing the predictive capability of any MLR equation. We arbitrarily removed 10% of all the log P_{chl} values to leave 302 as a training set. Application of eq 5 to this set yielded eq 8, where again the *t*-scores are given below the coefficients.

$$\log P_{chl} = \underset{5.87}{0.321} + \underset{2.59}{0.168}R_2 - \underset{-5.94}{0.379}\pi_2^H - \underset{-52.04}{3.170}\Sigma\alpha_2^H - \underset{-52.00}{3.409}\Sigma\beta_2^H + \underset{59.10}{4.149}V_X \quad (8)$$

$$n = 301,\ \text{sd} = 0.28,\ r^2 = 0.965,\ r^2_{cv} = 0.963,\ F = 1635$$

The correlation matrix for eq 8 is,

	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$
π_2^H	0.539			
$\Sigma\alpha_2^H$	0.077	0.067		
$\Sigma\beta_2^H$	0.075	0.234	0.004	
V_X	0.312	0.278	0.010	0.251

The statistics of eq 8 are not as good as those for many other water−solvent partitions,[19] but we have already referred to the difficulty of the experimental measurement of log P_{chl} values. The predictive capability of eq 8 can be assessed by the calculation of log P_{chl} for the 34 compounds left out as a test set. These are in Table 7 together with the predicted and observed values of log P_{chl}. Over a range of 6 log units in log P_{chl} the sd between predicted and observed values is only 0.17 log unit; the average unsigned error is 0.13 log unit, and the average signed error is −0.03 log unit. As shown in Figure 1, there are no systematic deviations. None of the other computational or calculational methods summarized in Table 1 employed a test set of compounds to estimate predictive power, so that comparisons are not possible.

Once the predictive power of eq 8 is established, we can use all the available data to construct eq 9. The differences between eq 8 and eq 9 are marginal, but the latter equation is preferred since it covers more compounds, with log P_{chl} covering a range of over nine log units, from −3.25 (guanine) to 6.01 (octane). The calculated values of log P_{chl} on eq 9 are given in Table 2.

$$\log P_{chl} = \underset{8.57}{0.327} + \underset{2.86}{0.157}R_2 - \underset{-7.17}{0.391}\pi_2^H - \underset{-61.93}{3.191}\Sigma\alpha_2^H - \underset{-61.23}{3.437}\Sigma\beta_2^H + \underset{72.40}{4.191}V_X \quad (9)$$

$$n = 335,\ \text{sd} = 0.25,\ r^2 = 0.971,\ r^2_{cv} = 0.970,\ F = 2223$$

The correlation matrix of eq 9 is very similar to that of eq 8. The interpretation of eq 9 follows closely that of eq 6,

Table 7—Predicted Values from Eq 8 and Observed Values of log P_{chl} for the 33 Compound Test Set

compound	predicted	observed
cyclohexane	3.87	4.16
bromoethane	2.18	2.24
propyl acetate	2.28	2.56
ethyl trifluoroacetate	1.94	2.00
diethylamine	0.85	0.79
formic acid	–2.03	–2.12
hexanoic acid	0.98	1.02
2-methylpropan-2-ol	0.26	–0.02
propane-1,3-diol	–2.60	–2.90
triethyl phosphate	2.14	2.28
fluorobenzene	2.90	2.54
benzaldehyde	2.38	2.25
dimethyl phthalate	2.86	3.09
aniline	1.28	1.35
1-naphthylamine	2.46	2.60
4-nitroanisole	3.16	3.18
phthalimide	1.25	1.46
2-bromobenzoic acid	0.96	0.91
4-aminobenzoic acid	–0.88	–0.92
3-phenylpropanoic acid	1.16	1.20
2-ethylphenol	1.63	1.73
2-iodophenol	2.00	1.97
2-nitrophenol	2.62	2.53
methyl 2-hydroxybenzoate	3.16	3.15
benzyl alcohol	0.79	0.96
methyl phenyl sulfone	1.93	1.93
3-methylbenzenesulfonamide	0.42	0.32
2-bromopyridine	2.37	2.22
quinoline	2.66	3.14
pyrazine	0.62	0.59
2-(dimethylamino)pyrimidine	1.91	1.99
5-chloropyrimidine	1.39	1.43
antipyrine	1.37	1.45
digitoxin	2.56	2.40

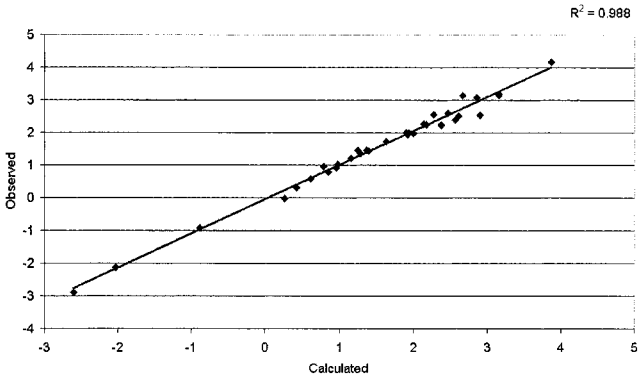

Figure 1—A plot of observed log P_{chl} vs predicted log P_{chl} values on eq 8.

except that now the coefficients refer to differences in properties of chloroform and water. A comparison with coefficients for other water–solvent partitions[19,20] is in Table 8. The *c*- and *r*-coefficients are not exceptional. The *s*-coefficient refers to the difference in dipolarity/polarizability of chloroform and water; a value of −0.39 places chloroform between CCl_4 (−1.15) and 1,2-dichloroethane (0.00) or dichloromethane (0.02). The hydrogen-bond basicity of bulk chloroform, as indicated by eq 6, is very small; hence, the *a*-coefficient in eq 9 is very negative (−3.19) and approaches that for the systems with nonbasic solvents such as hexadecane, cyclohexane, and CCl_4. In view of our discussion, above, on the hydrogen-bond acidity of chloroform, the *b*-coefficient in eq 9 is of some interest. A value of −3.43 places chloroform as acidic as wet octanol (−3.46), exactly in line with the *b*-coefficients in Table 4, and much more acidic than dichloromethane ($b = -4.14$) or 1,2-dichloroethane ($b = -4.29$). The *v*-coefficient in eq 5, just as the *l*-coefficient in eq 4, can be regarded as a measure of the solvent hydrophobicity. Chloroform is no different to most non-hydroxylic solvents which have *v*-coefficients between 4.2 and 4.6 units.

Table 8—Coefficients in Eq 5 for Water–Solvent Partitions

solvent	*c*	*r*	*s*	*a*	*b*	*v*
hexadecane[a]	0.09	0.67	–1.62	–3.59	–4.87	4.43
cyclohexane[a]	0.13	0.82	–1.73	–3.78	–4.90	4.65
benzene[b]	0.02	0.49	–0.60	–3.01	–4.63	4.59
nitrobenzene[b]	–0.18	0.58	0.00	–2.36	–4.42	4.26
decanol, wet[c]	0.01	0.48	–0.97	0.02	–3.80	3.95
octanol, wet[a]	0.09	0.56	–1.05	0.03	–3.46	3.81
isobutanol, wet[c]	0.23	0.51	–0.69	0.02	–2.26	2.78
olive oil[d]	0.01	0.58	–0.80	–1.47	–4.92	4.17
dibutyl ether[d]	0.18	0.82	–1.50	–0.83	–5.09	4.69
CCl_4[b]	0.22	0.56	–1.15	–3.51	–4.54	4.50
1,2-dichloroethane[b]	0.16	0.12	0.00	–3.05	–4.29	4.30
dichloromethane	0.31	0.00	0.02	–3.24	–4.14	4.26
chloroform	0.32	0.16	–0.39	–3.19	–3.43	4.19

[a] Reference 43. [b] Reference 19a. [c] Reference 48. [d] Reference 20.

Table 9—Calculated and Observed log P_{chl} Values for Some Solutes Previously Studied

solute	calcd[11a]	calcd[11b]	calcd[14]	calcd[13c]	calcd[d]	obsd[e]
$MeNH_2$	–0.56	–0.35	–0.33	–1.2	–0.88	–1.02
Me_2NH			0.85		–0.27	–0.44
Me_3N			2.25		0.61	0.51
Et_2NH	2.79	2.09		1.4	0.86	0.79
benzene	4.30	3.20	2.71	2.8	2.78	2.76
MeOAc			0.33		1.08	1.16
4-hexylpyridine	5.38	3.99		4.7	4.47[f]	5.00[g]

[a] Untrained computations. [b] Trained computations. [c] SM5.4P; the SM5.4A results are very similar. [d] On eq 9, this work. [e] Table 2. [f] Not part of the 335 data set. [g] Not corrected for salting-out; see text.

Table 10—Calculated and Observed log P_{chl} Values for Solutes Not Included in Eq 9

solute	calcd[a]	calcd[b]	obsd
hydroquinone	–2.18	–1.54	0.23
cocaine	4.26	6.67	1.21
hydrocortisone	2.21	3.67	0.81

[a] This work. [b] As in ref 13 (see text).

It is possible to analyze eq 9 term-by-term in order to quantify the particular interactions leading to log P_{chl} values for a given solute, just as we have done for log L^{chl} in Table 6, but the arithmetic is trivial. We conclude by examining a number of solutes for which log P_{chl} has not been well calculated by previous methods or by eq 9. The experimental values of log P_{chl} for aliphatic amines have been questioned[11,14] on the grounds that protonation in the aqueous phase could lead to erroneously low values. In Table 9 we collect observed and calculated log P_{chl} values for the aliphatic amines noted before. Values calculated through eq 9 are in good agreement with the observed values, and in our view the experimental log P_{chl} values must be substantially correct. Other workers[13] also calculate values reasonably close to those observed. Values of log P_{chl} for benzene[11] and methyl acetate[14] are also poorly computed, Table 9, but again our procedure suggests that the observed values are correct. We did find that there were three log P_{chl} values that were considerable outliers to eq 9, and which we omitted in the regression analysis; these outliers are shown in Table 10.

We can check our descriptors for hydroquinone, because values of log *P* are available[21] for many water–solvent partition systems for which we have[19] the coefficients in

Table 11—Water-Solvent Partitions (*P*) and HPLC Capacity Factors (*k′*) for Hydroquinone

solvent	log *P* or log *k′* obsd	calcd[a]	calcd[b]
octanol (*P*)	0.59	0.77	0.58
isobutanol (*P*)	0.82	0.99	0.88
hexanol (*P*)	0.74	1.00	0.81
cyclohexane (*P*)	–3.97[c]	–4.19	–4.11
toluene (*P*)	–2.15	–2.61	–2.37
heptane (*P*)	–4.26[d]	–4.07	–4.00
diethyl ether (*P*)	0.39[e]	0.34	0.18
dibutyl ether (*P*)	–0.77	–0.55	–0.73
diisopropyl ether (*P*)	0.02[f]	0.15	–0.03
ethyl acetate (*P*)	0.79	0.88	0.61
butyl acetate (*P*)	0.66[g]	0.88	0.85
1,2-dichloroethane (*P*)	–1.61[h]	–2.00	–1.64
tetrachloromethane (*P*)	–3.30[i]	–3.38	–3.21
ref 67, 50% methanol (*k′*)	–0.84	–0.43	–0.55
ref 67, 75% methanol (*k′*)	–1.42	–1.03	–1.09
ref 68, 60% methanol (*k′*)	–1.11	–0.94	–0.99
ref 68, 75% methanol (*k′*)	–1.46	–1.28	–1.31
ref 68, 90% methanol (*k′*)	–1.81	–1.42	–1.52
ref 69, Column B (*k′*)	–1.10	–1.15	–1.09
ref 70, Column A (*k′*)	–0.60	–0.56	–0.55
ref 70, Column B (*k′*)	–0.62	–0.60	–0.58
ref 70, Column C (*k′*)	–0.77	–0.72	–0.71
ref 46a, 40% methanol (*k′*)	–0.51	–0.38	–0.47
ref 46a, 50% methanol (*k′*)	–0.57	–0.54	–0.60
ref 46a, 60% methanol (*k′*)	–0.70	–0.66	–0.73
ref 46a, 60% methanol (*k′*)	–0.75	–0.79	–0.85
ref 46a, 80% methanol (*k′*)	–0.75	–0.87	–0.92
ref 46a, 30% acetonitrile (*k′*)	–0.46	–0.45	–0.47
ref 46a, 40% acetonitrile (*k′*)	–0.37	–0.50	–0.52
ref 46a, 50% acetonitrile (*k′*)	–0.46	–0.62	–0.63
ref 46a, 60% acetonitrile (*k′*)	–0.60	–0.69	–0.71
ref 46a, 70% acetonitrile (*k′*)	–0.69	–0.79	–0.80
ref 46a, 80% acetonitrile (*k′*)	–0.85	–0.85	–0.87
sd ($n = 33$):		0.20	0.15
benzene (*P*)	0.15		
benzene (*P*)	–1.85	–2.58	–2.29
benzene (*P*)	–2.16		
chloroform	0.23	–2.18	–1.84

[a] With original descriptors: $R_2 = 1.063$, $V_x = 0.8338$, $\pi_2^H = 1.00$, $\Sigma\alpha_2^H = 1.16$, and $\Sigma\beta_2^H = 0.60$. [b] With "best value" descriptors: $R_2 = 1.063$, $V_x = 0.8338$, $\pi_2^H = 1.25$, $\Sigma\alpha_2^H = 1.05$, and $\Sigma\beta_2^H = 0.58$. [c] Average of –3.89 and –4.04. [d] Average of –4.24 and –4.28; another value is 0.05. [e] Average of 0.36, 0.37, 0.38, and 0.46. [f] Average of –0.13, 0.01, 0.01, and 0.20. [h] Another value is 0.32. [i] Another value is 0.04.

eq 5 (log SP = log *P*). In addition, values of the HPLC capacity factor, *k′*, are known for hydroquinone in systems for which we have again the coefficients in eq 5 (logSP = log *k′*), see Table 11.[37a,57–59] Our original descriptors for hydroquinone reproduce the log *P* and log *k′* values for 33 systems with an sd of 0.20 units. We can calculate the set of descriptors that best reproduces the 33 log *P* and log *k′* values, with an sd value of only 0.15 units, but there is not much difference between the two sets of descriptors, Table 11. In either case, the calculated log P_{chl} value (−2.18 and −1.84) is over two log units smaller than the observed value (0.23). We have to conclude that the experimental value is in error. Such discrepancies are not uncommon, thus log *P* for hydroquinone in water−benzene is given[21] as −2.16, −1.85, and 0.15, and log *P* in water−heptane is given as −4.28, −4.24, and 0.05!

In the case of cocaine, only six log *P* values are available[21] as a check. Our present descriptors reproduce these with an sd value of 0.45 units, and the best fit we can obtain still results in an sd value of 0.38 units, see Table 12. However, either set of descriptors leads to a calculated log

Table 12—Water–Solvent Partitions for Cocaine

solvent	log *P* obsd	calcd[a]	calcd[b]
octanol	2.30	2.40	2.43
diethyl ether	1.52[c]	1.54	1.80
diisopropyl ether	1.19	1.50	1.68
olive oil	2.33	1.44	1.85
ethyl acetate	2.00	2.07	1.97
hexane	0.91	0.60	0.54
sd		0.45	0.38
chloroform	1.21[d]	4.26	4.63

[a] With original descriptors: $R_2 = 1.355$, $V_x = 2.2977$, $\pi_2^H = 1.92$, $\Sigma\alpha_2^H = 0.00$, and $\Sigma\beta_2^H = 1.50$. [b] With "best value" descriptors: $R_2 = 1.355$, $V_x = 2.2977$, $\pi_2^H = 2.44$, $\Sigma\alpha_2^H = 0.00$, and $\Sigma\beta_2^H = 1.33$. [c] Average of values 1.15, 1.28, and 2.14. [d] Average of values 1.04 and 1.38.

Table 13—Water–Solvent Partitions (*P*) and HPLC Capacity Factors (*k′*) for Hydrocortisone

solvent	log *P* or log *k′* obs	calc[a]	calc[b]
octanol (*P*)	1.68[c]	1.67	1.60
isobutanol (*P*)	1.74	2.33	2.24
diethyl ether (*P*)	0.16[d]	0.35	–0.06
ethyl acetate (*P*)	1.09	0.98	1.06
benzene (*P*)	–0.49	0.61	–0.46
ref 67 50% methanol (*k′*)	0.69	0.57	0.60
ref 67 75% methanol (*k′*)	–0.31	–0.49	–0.48
ref 71 IAM column (*k′*)	0.94	1.05	0.99
sd		0.49	0.22
hexadecane (*P*)	–2.04	–3.60	–4.09
chloroform (*P*)	0.81	2.21	1.27

[a] With original descriptors: $R_2 = 2.03$, $V_x = 2.7976$, $\pi_2^H = 3.49$, $\Sigma\alpha_2^H = 0.71$, and $\Sigma\beta_2^H = 1.90$. [b] With "best value" descriptors: $R_2 = 2.03$, $V_x = 2.7976$, $\pi_2^H = 2.77$, $\Sigma\alpha_2^H = 0.85$, and $\Sigma\beta_2^H = 2.13$. [c] Average of 1.53 and 1.81. [d] Average of 0.11, 0.15, 0.18, and 0.21.

P_{chl} value over 3 log units greater than that recorded.[21] We have no explanation other than that the experimental value is in error. It is worth noting that lipophilic strong bases are very difficult to study by the "shake-flask" method.

The number of water−solvent log *P* values for hydrocortisone is surprisingly small, but a few log *k′* values are available in calibrated HPLC systems,[57,60] see Table 13. Our usual descriptors lead to an sd value of 0.49 units, rather large but not unreasonable, and to a discrepancy of 1.4 log units in log P_{chl}. We can define a set of descriptors that leads to an sd value of 0.22 for the same eight systems and to a smaller discrepancy of only 0.45 log units in log P_{chl}. It is thus possible that in the case of hydrocortisone there is some error in the experimental log P_{chl} value combined with errors in our assigned descriptors.

In an attempt to resolve these problems, Dr. Cramer kindly calculated log P_{chl} for the three outliers using his computational method.[13] Results are in Table 10. They seem to confirm our suggestion that the three experimental values are in error.

Finally, we can find no evidence for the suggestion[14] that water-saturated chloroform may behave differently to dry chloroform as a partitioning medium. Other workers[13] also regard water-saturated and dry chloroform to be essentially the same as solvating media.

Care must be taken over experimental values, however. A case in point is 4-hexylpyridine with a calculated value of log P_{chl} as 3.99 with a trained computation,[11] as compared to an observed value of 5.00 log units. This latter value does not refer to water−chloroform partition, but to partition between 1 M sodium chloride and chloroform. Correction for the salting-out effect would lower the value

by 0.15 to 0.55, leading to an "experimental" value of 4.85 to 4.45, more in line with the computational value of 3.99,[11] and in good agreement with another computational value[13] of 4.7 and our calculated value of 4.47 through eq 9.

Our data set of 335 compounds therefore leads to a MLR eq 9 that from a training set of 301 compounds seems capable of predicting further log P_{chl} values with sd = 0.17. Equation 9 can also be used to analyze the solute and solvent interactions that affect log P_{chl}, with results almost identical to those obtained by an analysis of log L^{chl} through eq 6. The importance of these results lies in the recent use of the water−chloroform system as a measure of solute lipophilicity,[5,6,11,12] and of recent calculations of the transfer of nucleic acids from water to chloroform.[9,61] The nucleic acid transfers have been analyzed in terms of functional group contributions,[61] but a breakdown into contributions due to dipolarity/polarizability, hydrogen-bond acidity, etc., through eq 9, leads to more information as to the exact solute influences on the water−chloroform partitions.

Furthermore, if the water−chloroform system is to be generally used as a measure of solute lipophilicity in drug design, it will be of very considerable help to have a predictive procedure available. We have shown, see Table 1, that the MLRA method is capable of correlating log P_{chl} values rather better than computational methods, although the present MLRA method suffers from the possible lack of availability of the required descriptors. Recently, we have remedied this deficiency through a simple method (ABSOLVE) for the calculation of descriptors from structure.[62] Together with eq 6 and eq 9 the ABSOLVE method will enable log L_{chl} and log P^{chl} to be predicted from structure.

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