Solubility Properties in Polymers and Biological Media. 2. The Correlation and Prediction of the Solubilities of Nonelectrolytes in Biological Tissues and Fluids

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Solubilities of a range of nonelectrolyte solutes in biological systems, such as blood, plasma, brain, lung, liver, kidney, muscle tissue, and human fat, are correlated and predicted through an equation that takes the form $\log L^{tissue} = c + w \log L^{water} + o \log L^{oil}$, where L is the Ostwald solubility coefficient (or gas/liquid partition coefficient). The ratio of the constants o and w gives a measure of the "oiliness" of a given biological tissue or fluid. The strong possibility exists that, for many types of nonelectrolyte solutes, simple measurements of solubilities in water and oil (gas/liquid partition coefficients) will allow accurate predictions of solubilities in the above biological solvents, as well as tissue/blood partition coefficients. The solubility of rare gases and the inorganic gases H_2, N_2, CO, and O_2 may be correlated through the simpler equation $\log L^{tissue} = l'R_G + d'$, where l' and d' are constants that characterize the phase, and R_G is a known parameter, obtained by normalizing and averaging solubilities over a range of solvent systems, that characterizes the solute. Both of the above equations allow prediction of L in biological solvents to within about 20%, which compares well with the precision of the experimental measurements.

The solubility of permanent gases and vapors in biological fluids and tissues is a topic of fundamental importance in anesthesiology, toxicology, pulmonary, and hyperbaric physiology. In the present series of investigations,[1] it also serves as an introduction to the study of solubility of pharmacologically active higher boiling liquid and solid nonelectrolytes in such systems. A knowledge of solubility is required, not only to estimate quantities of solutes contained in tissue but also to predict transients (most theories predict that the rate of approach to equilibrium is directly proportional to the ratio of blood and tissue solubilities).

Because of the great importance of the solubility of solutes in biological systems, there have been several attempts to correlate and to predict such solubilities, especially for gaseous solutes in blood.[2,3] Following a suggestion by Featherstone et al.,[4] Feingold[5] and later Sako and Nakajima[6,7] attempted to correlate Ostwald solubility coefficients for solutes in blood, either as L^{blood} or $\log L^{blood}$, with combinations of Ostwald solubility coefficients for solutes in water and in oil. However, no general conclusions have hitherto been drawn, mainly because the reported correlations have been restricted to particular classes of solute, for example 13 anesthetics,[5] 20 chlorinated compounds,[6] and 10 aromatic hydrocarbons.[7] The problem is, of course, greater than with pure solvents, since biological systems can be extremely heterogeneous, and cases of specific chemical binding of solute molecules are known. Examples include not only the oxygen/hemoglobin system but also oxygen and myoglobin, carbon monoxide and hemoglobin, and xenon with some components of rat brain.[8] In systems having a very strong chemical binding effect, Henry's law is not obeyed, and these systems are therefore excluded from general correlations based ultimately on Henry's law. Other interactions have been reported in which Henry's law (or its equivalent) is nevertheless followed, and these cases will therefore be included in general correlations, although the extent of specific interactions may determine the extent of deviations from correlation. Such specific interacting systems include xenon and hydrocarbon gases with a number of proteins.[9-11]

The solubility of a number of gases in a variety of biological media, as well as water, has been comprehensively reviewed[2,3] and the major aim of the present work is to set out correlations of these data that will enable predictions of solubility to be made not only for the types of gases and vapors considered here but ultimately also for all sorts of pharmacologically active nonelectrolytes, be they gases, liquids, or solids. We will describe equations whereby, from simple measurements of gas/water and gas/oil partition coefficients, it may be possible to predict solubilities in blood, plasma, brain, muscle, lung, liver, kidney, and fat, as well as distributions between pairs of these media.

It should be noted that solubility predictions by the methods suggested here cannot be expected to be better than the average errors in the solubilities used to set up the correlations. For typical cases in which several independent determinations of solubility have been made, the standard deviation amounts to about 20%; thus, for nitrogen in blood, six independent determinations lead to a 16% standard deviation, whereas for cyclopropane in oil, four independent determinations result in a standard deviation of 23% of the mean solubility.

There are a variety of units used to specify the solubility of a gas in a solvent medium; the most widely quoted unit is that of Henry's constant, K^H, in terms of the partial pressure of gas in atmospheres and the mole fraction of dissolved gas in the solvent. For systems, such as biological fluids, that do not possess a well-defined molecular weight, it is not possible to calculate the mole fraction of gas in solution, and hence solubilities are generally tabulated[2,3] in terms of the Ostwald coefficient, L, defined as the volume of gas, at 1 atm of pressure and temperature T,

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Table I. Values of log L Used in the Correlations[a]

no.	solute	R_G	water (25 °C)	water	blood	plasma	brain	muscle	lung	liver	kidney	oil
1	He	1.32	−2.0230	−2.0101	−2.0044	−2.0655		−1.9318	−1.9788			−1.7565
2	Ne	1.39	−1.9571	−1.9626	−2.0088		−1.8097					−1.6626
3	Ar	1.75	−1.4667	−1.5272	−1.5157	−1.5824	−1.4855	−1.6383				−0.8244
4	Kr	1.95	−1.2138	−1.2976	−1.2219	−1.2924	−1.3767	−1.3768		−1.1367	−1.3665	−0.3462
5	Xe	2.19	−0.9712	−1.0788	−0.8477	−1.0410	−0.8153	−1.0862		−0.9208	−0.9066	0.2372
6	H_2	1.54	−1.7182	−1.7235	−1.7696	−1.7595		−1.7570				−1.3054
7	N_2	1.64	−1.7991	−1.8447	−1.8327	−1.8729	−1.7986					−1.1308
8	CO	1.71	−1.6319	−1.6840[b]	−1.6676[c]				−1.6925			−1.0114
9	O_2	1.74	−1.5071	−1.5654	−1.5834[c]	−1.6144[d]			−1.6162		−1.5229[e]	−0.8761
10	N_2O	2.22[f]	−0.2264	−0.3487	−0.3439	−0.3429	−0.3188	−0.4559	−0.3354	−0.3768	−0.3872	0.2454[g]
11	CH_4	1.90	−1.4616	−1.5258[h]	−1.4225	−1.5901	−1.3872	−1.4089				−0.5100
12	C_2H_2	2.21[i]	−0.0056	−0.0711	−0.0605	−0.1079		0.0294	−0.0605			0.2430
13	C_2H_4	2.17[j]	−0.9348	−1.0155	−0.7447							0.1004
14	C_2H_6	2.26	−1.3367	−1.4425[h]	−0.9706	−1.3372			−1.2840			0.3370[g]
15	SF_6	1.98	−2.2254	−2.3233	−2.1427	−2.2757	−1.7825[k]	−1.8478[l]	−2.1427			−0.5834
16	CO_2		−0.0820	−0.1925			−0.2518					0.1303
17	c-C_3H_6		−0.5514	−0.6440	−0.2147	−0.6162	0.0000	−0.3372	−0.5086	−0.1805	−0.2840	1.0682
18	MeOMe		1.3927	1.1847	1.1553	1.1173[m]						
19	EtOEt		1.2828	1.1553	1.0828	1.0755	1.0792	1.0414	1.1399	1.0607	1.0212	1.8129
20	MeCOMe		2.7927	2.5246[n]	2.4843	2.5378			2.4624			1.9542[o]
21	$CHClF_2$		−0.0806	−0.2218				0.0334				0.6435
22	$CHCl_3$		0.7477	0.5911	0.9395		1.3010	1.1139		1.2304	1.0414	2.5855[p]
23	$CHCl{=}CCl_2$		0.3225	0.1903	0.9395		1.3222	1.0414		1.3711	1.0792	
24	divinyl ether			0.1614	0.4150		0.5315	0.3424		0.4914	0.3617	
25	CS_2			−0.0969	0.3010	−0.0969	0.9030			0.7782	0.8976	
26	$CF_3CH_2OCH{:}CH_2$			−0.0506	0.1523		0.2788	0.4472		0.3802	0.1461	1.6812
27	$MeOCF_2CHCl_2$			0.6232	1.0792		1.3979	1.2304		1.3802	1.3802	2.9750[q]
28	CF_3CHFBr			−0.4949	−0.2218		0.0453	0.3424		0.0000		1.4624
29	$CHF_2OCHClCF_3$			−0.2147	0.1523		0.5682	0.7482		0.5441		1.9912
30	$CF_3CHClBr$			−0.0757	0.4314	0.3979	0.7782	0.7160	0.3010	0.8195	0.6532	2.3522
31	CHF_2OCF_2CHFCl				0.2833		0.4150	0.4771		0.5682		1.9912
32	$CHF_2CF_2CH_2Br$				0.7482							2.5092
33	CH_3F		0.0719	0.0719	0.0294	0.0128						0.0569
34	C_2H_5F		0.0899	0.0899	0.0864	0.0719						0.5775
35	n-C_3H_7F		−0.0506	−0.0506	0.0212	−0.0132						0.9243
36	i-C_3H_7F		−0.0273	−0.0273	0.0607	0.0000						1.0900
37	C_2H_5I		0.5368	0.4314	0.8282	0.6902						2.1590[r]
38	MeCOEt		2.7212	2.4048	2.3054							2.4200
39	MeCOPr[n]		2.5820	2.2201	2.1761							2.7966
40	EtCOEt		2.5012	2.2577	2.2253							2.9074
41	MeCOBu[n]		2.4133	2.0453	2.1038							3.2135
42	MeCOBu[i]		2.2442	1.8976	1.9542							2.9666
43	MeCOPe[n]		2.2300	1.9823	2.2989							3.8319
44	benzene		0.6467	0.4440	0.8920							2.6920
45	toluene		0.5808	0.3483	1.1931							3.1676
46	ethylbenzene		0.4855	0.2279	1.4533							3.5788
47	o-xylene		0.6605	0.4200	1.4928							3.6395
48	m-xylene		0.6131	0.2201	1.4216							3.5846
49	p-xylene		0.5904	0.1959	1.5752							3.5675
50	n-propylbenzene		0.3828	0.1139	1.6721							3.9901
51	cumene		0.2207	0.1584	1.5682							3.7934
52	styrene			0.6702	1.7152							3.7376
53	alkylbenzene			0.5502	1.7067							3.9057
54	chlorobenzene[s]		0.8349	0.6128	1.4886							3.5755
55	o-dichlorobenzene[s]		1.1034	0.9542	2.6263							4.6012
56	m-dichlorobenzene[s]		0.8308	0.7404	2.3041							4.4326
57	CH_2Cl_2[s]		0.9726	0.8573	0.9868							2.1818
58	CCl_4[s]		0.0598	−0.6021	0.3802							2.5575
59	$CHCl_2CH_3$[s]		0.6271	0.4314	0.6721							2.2718
60	CH_2ClCH_2Cl[s]		1.3608	1.0531	1.2900							2.6503
61	CCl_3CH_3[s]		0.0915	−0.0315	0.5185							2.5515
62	$CHCl_2CH_2Cl$[s]		1.3079	1.2330	1.5866							3.3566
63	CCl_3CH_2Cl[s]		0.9424	0.7404	1.4829							3.6340
64	$CHCl_2CHCl_2$[s]		1.7085	1.5527	2.0842							4.1209
65	*cis*-$CHCl{=}CHCl$[s]		0.5128	0.4624	0.9638							2.4314
66	*trans*-$CHCl{=}CHCl$[s]		0.5688	0.3222	0.7634							2.2765
67	$CCl_2{=}CCl_2$[s]		−0.0741	−0.3665	1.1173							3.2826
68	n-C_3H_7Cl[s]		0.2436	0.0414	0.4624							2.0755
69	$CH_3CHClCH_2Cl$[s]		0.8319	0.7324	1.0294							2.8733
70	n-C_4H_9Cl[s]		0.1190	−0.0655	0.6335							2.5440
71	n-$C_5H_{11}Cl$[s]		0.0457	−0.1549	0.8692							2.9899

[a] Values of Ostwald coefficients at 37 °C[2,3,7,17] and at 25 °C[14,15,18,19] given to four decimal places in log L to avoid rounding-off errors. [b] Reference 19. [c] Hemoglobin binding site for CO and O_2 poisoned by nitrite or ferrocyanide ion; see: Power, G. *J. Appl. Physiol.: Resp. Environ. Exercise Physiol.* **1968**, *24*, 468. [d] Given[2] as L = 0243, a misprint for L = 0.0243, the value used here. [e] Sendroy, J.; Dillon, R. T.; Van Slyke, D. D. *J. Biol. Chem.* **1934**, *105*, 597. [f] Average of six values in nonaqueous solvents. [g] Estimated values using a log L_{37}^{oil} vs. R_G

Footnotes to Table I Continued

correlation. [h] Reference 20. [i] Average of three values in hydrocarbon solvents; R_G increases markedly with increase in solvent dipolarity. [j] Average of values in hexane and CCl_4; R_G increases slightly with increase in solvent dipolarity. [k] Ohta, Y.; Ar, A.; Fahri, L. E. *J. Appl. Physiol.: Resp. Environ. Exercise Physiol.* **1979**, *46*, 1169. [l] Meyer, M.; Tebbe, U.; Piiper, J. *Pfluegers Arch.* **1980**, *384*, 131. [m] Jibelinn, G.; Mitchell, R.; Overland, E. S. *J. Appl. Physiol.: Resp. Environ. Exercise Physiol.* 1981, *51*, 1357. [n] Average of values in ref 2 and 17. [o] Reference 17. [p] Reference 22. [q] From ref 22 and Cooper, J. B.; Joseph, D. M. *Anesthesiology* 1981, *55*, 720, and Resan, M. J.; Eger, E. I. *Anesthesiology* **1967**, *28*, 689. [r] Estimated value using a log L_{37}^{oil} vs. R_G correlation, with the latter determined as 3.052 from values in hexane, cyclohexane, and diethyl ether. [s] Sato and Nakajima (ref 6) give values of L_{37}^{water}, L_{37}^{blood}, and L_{37}^{oil}. Values of L_{25}^{water} are from ref 15 and Mackay, D.; Shiu W. Y. *J. Phys. Chem. Ref. Data* 1981, *10*, 1175.

which dissolves in unit volume of fluid at the given temperature. For water, K^H and L are related through eq 1 and 2.

$$K^H = 1354/L \text{ at } 25.0\ ^\circ\text{C} \quad (1)$$

$$K^H = 1402/L \text{ at } 36.9\ ^\circ\text{C} \quad (2)$$

A problem related to that of the solubility of gases is the partition of gases between two solvent systems. There is a paucity of results that refer to biological systems, but a few partition coefficients, P, of gases between blood and a number of biological tissues have been listed.[2] The tissue/blood partition coefficient may be defined as the volume of gas at temperature T dissolved in the tissue per volume of gas, at the same temperature, dissolved in blood. The partition coefficient is related to the two Ostwald coefficients through eq 3, so that if L^{blood} and L^{tissue} can be predicted in some way, the corresponding partition coefficient can also be predicted. In principle, there have

$$P^{tissue/blood} = L^{tissue}/L^{blood} \quad (3)$$

been two main approaches to the correlation of gas and vapor solubilities in liquid solvents. First, correlations may be set up for a given solute in a variety of solvents on the basis, for example, of Hildebrand's solubility parameter, δ_H, and (for dipolar solutes) the solvatochromic parameter, π^*, of the solvent. Apart from the difficulty in determining δ_H and π^* for many biological solvent systems (which, however, is a long-range aim of the present series of investigations), this method is not easy to apply to some solutes in aqueous solvent systems, although it has been successfully used by the present authors with a number of inert[12] and dipolar[13] solutes in aliphatic aprotic solvents. Secondly, correlations may be evaluated for a series of gases in a given solvent, such as suggested by Abraham,[14,15] who is this way successfully reproduced the solubility of 489 solute/solvent systems to within 0.06 log unit. The solutes were all nondipolar organic or inorganic molecules, and the solvents included all nonaqueous solvents for which sufficient results were available.

The equations used by Abraham were in the form of eq 4;[16] the log L values refer to solution in a given solvent,

$$\log L = l'R_G + d' \quad (4)$$

l' and d' then characterize the solvent, and R_G is a solute parameter obtained by normalizing and averaging solubility values over the entire set of solvent systems. Values of R_G were given by Abraham for 28 inert solutes.[15] Although eq 4 could be applied to the solution of rare gases and inorganic gases such as H_2, N_2, CO, and O_2 in water, hydrophobic solutes, such as the alkanes, did not conform to the equation. Our strategy in the present investigation has been (a) to ascertain to what extent solubility equations, such as eq 4, derived to describe behaviour of inert solutes in pure monomolecular solvents, apply to solubilities in biological solvent systems, and (b) to determine empirical relationships that describe and predict solubilities of hydrophobic and dipolar solutes in such partially aqueous media. In Table I are listed data on log L values, mostly from the extensive reviews of Weathersby and Homer[2] and of Fiserova-Bergerova,[3] supplemented with results from Sato and Nakajima,[6,7] and from Gatley et al.[17] at 37 °C, and from Abraham,[14,15] Hine and Mukherjee,[18] and Battino et al.[19,20] at 25 °C.

Table II. Correlations of log L against R_G for Nonhydrophobic Solutes 1–9

regression equation	r	s	n
$\log L_{25}^{water} = (-3.699 \pm 0.161) + (1.246 \pm 0.094)R_G$	0.9806	0.0715	9
$\log L_{37}^{water} = (-3.500 \pm 0.172) + (1.104 \pm 0.100)R_G$	0.9723	0.0761	9
$\log L_{37}^{blood} = (-3.922 \pm 0.199) + (1.369 \pm 0.117)R_G$	0.9755	0.0884	9
$\log L_{37}^{plasma} = (-3.696 \pm 0.213) + (1.208 \pm 0.121)R_G$	0.9756	0.0835	7
$\log L_{37}^{brain} = (-3.692 \pm 0.485) + (1.253 \pm 0.269)R_G$	0.9374	0.1633	5
$\log L_{38}^{muscle} = (-3.247 \pm 0.155) + (0.965 \pm 0.087)R_G$	0.9880	0.0590	5
$\log L_{37}^{oil} = (-4.888 \pm 0.115) + (2.318 \pm 0.067)R_G$	0.9971	0.0510	9

Correlations with the R_G Solute Parameter. The success of eq 4 in correlating log L values for rare gases and some inorganic gases (solutes 1–9 in Table I) in water as well as in nonaqueous solvents suggests that for these particular solutes eq 4 could be applied to solubilities in (aqueous) biological media. In Table II are the regression equations thus obtained, using all the available results for solutes 1–9 in Table I. The correlations via eq 4 are reasonably good; for the seven correlation equations the standard deviation, s,[21] is 0.08 log unit, corresponding to an error in L of about 20%, which is of the same order as the probable experimental error in the observed L values. It is known[14,15] that eq 4 does not apply to hydrophobic solutes in aqueous solution, and we confirmed that, as expected, eq 4 breaks down when applied to solutes other than the set 1–9. We therefore turned to a more general equation in order to accommodate all solutes listed in Table I.

Correlations Using the Double Linear Regression Equation. For the entire set of solutes in Table I, we first set up correlation equations of the form of eq 5 and 6. For

$$\log L_{37} = c + w \log L_{37}^{water} \quad (5)$$

(12) Kamlet, M. J.; Carr, P. W.; Taft, R. W.; Abraham, M. H. *J. Am. Chem. Soc.* 1981, *103*, 6062.
(13) Abraham, M. H.; Kamlet, M. J.; Taft, R. W. *J. Chem. Soc., Perkin Trans. 2* 1982, 923.
(14) Abraham, M. H. *J. Am. Chem. Soc.* **1979**, *101*, 5477.
(15) Abraham, M. H. *J. Am. Chem. Soc.* 1982, *104*, 2085.
(16) The equation given is ΔG°_s or $2.303\,RT \log K^H = lR_G + d$, but since (at 25 °C) $\log K^H = 3.1316 - \log L$, through eq 1, the above equation is equivalent to eq 4.
(17) Gatley, S. J.; Hichwa, R. D.; Shaughnessy, W. J.; Nickles, R. J. *Int. J. Appl. Radiat. Isotopes* 1981, *32*, 211.
(18) Hine, J.; Mukherjee, P. K. *J. Org. Chem.* **1975**, *40*, 292.
(19) Wilhelm, E.; Battino, R.; Wilcox, R. J. *Chem. Rev.* **1977**, *77*, 219.
(20) Rettich, T. R.; Handa, Y. P.; Battino, R.; Wilhelm, E. *J. Phys. Chem.* 1981, *85*, 3230.
(21) The standard deviation for a simple regression is defined as $\{[\log L_{obsd} - \log L_{calcd}]^2/(n-2)\}^{1/2}$, where n is the number of data points. For a double regression the factor $(n-3)$ is used instead of $(n-2)$.

$$\log L_{37} = c + o \log L_{37}^{oil} \quad (6)$$

rather aqueous biological systems, such as plasma, quite a good correlation of log L_{37} with log L_{37}^{water} is found; see Table III ($r = 0.9947$, $s = 0.128$, $n = 21$). For other biological systems, such as brain tissue, the better correlation is with log L_{37}^{oil}, rather than with log L_{37}^{water}. We therefore felt that since some systems more resemble water, while others more resemble oil, a double regression via eq 7 might accommodate all the solutes and all the biological systems for which we have log L values. The covariance between

$$\log L_{37} = c + w \log L_{37}^{water} + o \log L_{37}^{oil} \quad (7)$$

log L_{37}^{water} and log L_{37}^{oil} depends, of course, on the data set used. For all solutes in Table I, $n = 65$, $r = 0.752$; so that, as a general rule, these two parameters may be taken as independent explanatory variables.

In Table III are given details of the double regression, using all the available results in Table I (that is all the solutes for which corresponding log L_{37}^{water} and log L_{37}^{oil} values are listed). [In cases where log L_{25}^{water} is known, and log L_{37}^{water} is not known, the following regression equation may be useful: log L_{37}^{water} = (−0.1476 ± 0.0103) + (0.9437 ± 0.0078) log L_{25}^{water}, with $r = 0.9982$, $s = 0.075$, and $n = 56$. The point for CCl_4 has been excluded because it is in error by more than 5 times the standard deviation.] Together with the double regressions, we give also the two single regressions, eq 5 and 6, for the same data set. For the seven biological systems studied, the double regression is always significantly better than either single regression, and both variables in the double regression are always statistically significant (as judged by the standard deviation of the coefficient). The standard deviations in the log L values, s,[21] of the double regressions are quite small, considering the range of solutes studied. For log L_{37}^{blood}, $s = 0.178$ over 63 solutes of varied chemical type, while for log L_{37}^{lung}, $s = 0.060$ but only over 11 solutes. The success of the double regressions, especially for the extensive log L_{37}^{blood} data, shows that, for the first time, it is possible to construct a quite general equation that can be used for the correlation and prediction of the solubilities of gases and vapors in biological systems. Of course, the log L_{37}^{blood} regression can be improved by restricting the solutes to particular solute classes and might well be used in this way for actual practical predictions. We do not pursue this approach (with one exception, see below) because we wished to emphasize the generality of our new double regression equation.

We can extend the range of the biological systems by using values of $L_{37}^{human\ fat}$ and L_{37}^{oil} reported by Stern and Shiah[22] for eight solutes (17, 19, 22, 23, 24, 26, 27, and 30 of Table I). Values of log $L_{37}^{human\ fat}$ are quite well correlated with log L_{37}^{oil}, eq 8, so that the "oiliness" of human fat must be quite large. The double regression eq 9 is marginally better than eq 8, with a reduction in the standard deviation. However, the interest in this particular system (with only eight points) is not in the actual comparison of eq 8 and 9 but to emphasize the generality of the double regression procedure eq 7.

$$\log L_{37}^{human\ fat} = (0.174 \pm 0.058) + (0.910 \pm 0.026) \log L_{37}^{oil} \quad (8)$$

$$r = 0.9976,\ s = 0.047,\ n = 8$$

$$\log L_{37}^{human\ fat} = (0.209 \pm 0.048) + (0.0628 \pm 0.0284) \log L_{37}^{water} + (0.8868 \pm 0.0228) \log L_{37}^{oil} \quad (9)$$

$$r = 0.9988,\ s = 0.036,\ n = 8$$

(22) Stern, S. A.; Shiah, S.-P. *Mol. Pharmacol.* 1981, *19*, 56.

Table III. Correlations of log L against log L_{37}^{water} and log L_{37}^{oil}

regression equation	r	s	n
log L_{37}^{blood} = (0.262 ± 0.046) + (0.996 ± 0.036) log L_{37}^{water}	0.9698	0.324	50[a]
log L_{37}^{blood} = (−0.820 ± 0.101) + (0.754 ± 0.047) log L_{37}^{oil}	0.9188	0.525	50[a]
log L_{37}^{blood} = (−0.102 ± 0.035) + (0.675 ± 0.026) log L_{37}^{water} + (0.315 ± 0.020) log L_{37}^{oil}	0.9951	0.133	50[a]
log L_{37}^{plasma} = (0.038 ± 0.032) + (1.019 ± 0.024) log L_{37}^{water}	0.9947	0.128	21
log L_{37}^{plasma} = (−0.848 ± 0.139) + (0.890 ± 0.117) log L_{37}^{oil}	0.8668	0.619	21
log L_{37}^{plasma} = (−0.082 ± 0.028) + (0.894 ± 0.025) log L_{37}^{water} + (0.152 ± 0.025) log L_{37}^{oil}	0.9982	0.076	21
log L_{37}^{brain} = (0.394 ± 0.098) + (1.096 ± 0.084) log L_{37}^{water}	0.9583	0.334	17
log L_{37}^{brain} = (−0.850 ± 0.078) + (0.773 ± 0.051) log L_{37}^{oil}	0.9689	0.290	17
log L_{37}^{brain} = (−0.274 ± 0.079) + (0.537 ± 0.067) log L_{37}^{water} + (0.444 ± 0.047) log L_{37}^{oil}	0.9945	0.127	17
log L_{37}^{muscle} = (0.351 ± 0.099) + (1.108 ± 0.088) log L_{37}^{water}	0.9528	0.351	18
log L_{37}^{muscle} = (−0.852 ± 0.088) + (0.768 ± 0.058) log L_{37}^{oil}	0.9570	0.336	18
log L_{37}^{muscle} = (−0.263 ± 0.109) + (0.575 ± 0.095) log L_{37}^{water} + (0.423 ± 0.066) log L_{37}^{oil}	0.9877	0.187	18
log L_{37}^{lung} = (0.057 ± 0.044) + (0.978 ± 0.029) log L_{37}^{water}	0.9960	0.134	11
log L_{37}^{lung} = (−0.833 ± 0.246) + (0.911 ± 0.186) log L_{37}^{oil}	0.8523	0.789	11
log L_{37}^{lung} = (−0.057 ± 0.027) + (0.870 ± 0.022) log L_{37}^{water} + (0.146 ± 0.024) log L_{37}^{oil}	0.9993	0.060	11
log L_{37}^{liver} = (0.432 ± 0.108) + (1.064 ± 0.149) log L_{37}^{water}	0.9219	0.348	11
log L_{37}^{liver} = (−0.875 ± 0.132) + (0.773 ± 0.075) log L_{37}^{oil}	0.9606	0.250	11
log L_{37}^{liver} = (−0.388 ± 0.063) + (0.502 ± 0.051) log L_{37}^{water} + (0.497 ± 0.036) log L_{37}^{oil}	0.9970	0.073	11
log L_{37}^{kidney} = (0.277 ± 0.107) + (1.111 ± 0.120) log L_{37}^{water}	0.9561	0.323	10
log L_{37}^{kidney} = (−0.920 ± 0.121) + (0.764 ± 0.071) log L_{37}^{oil}	0.9673	0.280	10
log L_{37}^{kidney} = (−0.391 ± 0.091) + (0.550 ± 0.081) log L_{37}^{water} + (0.440 ± 0.055) log L_{37}^{oil}	0.9958	0.108	10

[a] Excluding aromatic solutes 44–56.

Table IV. Comparison of the Oil Coefficient with Tissue Composition

medium	oil coeff[a]	N[b]	fat + protein[c]	fat[d]
water	0.00		(0.00)	(0.00)
plasma	0.14[e]	16	0.07	0.01
lung	0.14	11	0.19	0.01
blood	0.21[e]	24	0.19	0.01
muscle	0.42	18	0.20	0.03
kidney	0.44	10	0.22	0.06
brain	0.45	17	0.19	0.12
liver	0.50	11	0.25	0.09
human fat	0.93	8	0.53[f]	0.84[f]
oil	1.00		(1.00)	(1.00)

[a] Defined as o(oil)/[o(oil) + w(water)]. [b] The number of solutes used in the double regression, Table III. [c] Weight of fat plus protein/weight of fat plus protein plus water. [d] Weight of fat/weight of fat plus weight of water. [e] Using the double regression for solutes 1–30. [f] Adipose tissue.

The coefficients w and o in eq 7 are measures of the resemblance of a given biological solvent system to water

Table V. Calculation of Muscle Tissue/Blood Partition Coefficient for Xenon Using the R_G Regression Equations at 37 °C

log P_{obsd}[a]	log P_{calcd} from log L_{obsd}[b]	log P_{calcd} from log L_{calcd}[c]
−0.114	−0.239	−0.210
−0.161		
−0.161		
−0.201		
−0.208		

[a] Values given by Weathersby and Homer.[2] [b] Using values of log L^{muscle} = −1.0862 and log L^{blood} = −0.8477 in Table I. [c] Using values calculated through the R_G regression equations in Table II of log L^{muscle} = −1.1336 and log L^{blood} = −0.9239.

and oil, respectively. We can therefore define a measure of the "oiliness" of a system through an oil coefficient equal to o/(o + w). It should be noted that the exact value of the oil coefficient will depend to some extent on the nature of the solutes used in the correlation eq 7 so that as far as possible a comparison of oil coefficients should be made using the same solvents in the various double regression equations. Inspection of Table I shows that, in the regression equations listed on Table III, the range of solutes is 1–43 and 57–71 for blood, 1–37 for plasma, but only 1–30 for the other biological systems (due to lack of data). We have therefore repeated the double regressions for log L_{37}^{blood} and log L_{37}^{plasma} to cover the same set of solutes, 1–30. We stress that this is solely to provide oil coefficients that can more reasonably be compared. The relevant double regressions are eq 10 and 11.

$$\log L_{37}^{blood} = (-0.074 \pm 0.033) + (0.802 \pm 0.028) \log L_{37}^{water} + (0.218 \pm 0.023) \log L_{37}^{oil} \quad (10)$$

$$r = 0.9978,\ s = 0.085,\ n = 24 \text{ (set 1–30)}$$

$$\log L_{37}^{plasma} = (-0.079 \pm 0.035) + (0.896 \pm 0.031) \log L_{37}^{water} + (0.149 \pm 0.032) \log L_{37}^{oil} \quad (11)$$

$$r = 0.9981,\ s = 0.086,\ n = 16 \text{ (set 1–30)}$$

The calculated oil coefficients with respect to the solute set (1–30) are listed in Table IV, together with coefficients expressing the fat plus protein or the fat content of tissues of "standard Man".[23] Although neither the fat plus protein coefficients nor the fat coefficients are near to our oil coefficients, the general trend is unmistakable and confirms that the oil coefficients (and consequently the double regression equations) do reflect some underlying property of the various biological systems.

Calculation of Tissue/Blood Partition Coefficients. It is very difficult to measure tissue/blood partition coefficients, and only few such coefficients have actually been measured.[2] If values of L_{obsd}^{tissue} and L_{obsd}^{blood} are available for a given solute, then it becomes possible to calculate partition coefficients through eq 3 or the equivalent eq 12.

$$\log P^{tissue/blood} = \log L^{tissue} - \log L^{blood} \quad (12)$$

But if values of L_{obsd}^{tissue} and/or L_{obsd}^{blood} are not available, it is still possible to calculate $P^{tissue/blood}$ by using our regression equations to calculate the unknown L^{tissue} and L^{blood} values from L^{water} and L^{oil}. As an example, we give in Table V the calculation of log $P^{muscle/blood}$ for xenon using firstly the L_{obsd} values for muscle tissue and blood in Table I and secondly the L_{calcd} values for muscle tissue and blood using the R_G regression equations in Table II. There is excellent agreement between log P_{calcd} and log P_{obsd}, particularly noteworthy being the value of log P_{calcd} using only log L_{37}^{water} and log L_{37}^{oil} as input. Because the R_G correlations are restricted to solutes 1–9, a more general predictive method is to use the double regression equations (Table III) to calculate the required L values. An example is given in Table VI for the calculation of the partition coefficient of diethyl ether between brain and blood. Starting only with log L_{37}^{water} and log L_{37}^{oil} values (Table I), it is possible to calculate log L values for brain and blood by use of the double regression equations in Table III and then deduce the log P value of 0.022 (Table VI), in complete agreement with the observed value given by Haggard of −0.036 to +0.117 log unit.[24]

Table VI. Calculation of Brain Tissue/Blood Partition Coefficient for Diethyl Ether Using the Double Regression Equation at 37 °C

log P_{obsd}[a]	log P_{calcd} from log L_{obsd}[b]	log P_{calcd} from log L_{calcd}
−0.036 to +0.117	−0.004	0.022

[a] Five determinations (not given) ranged from −0.036 to +0.117 with an average of 0.053.[24] [b] Using values of log L^{brain} = 1.0792 and log L^{blood} = 1.0828 in Table I. [c] Using values of log L^{brain} = 1.151 and log L^{blood} = 1.129 calculated from the double regression equation in Table III.

Table VII. Nonconformance of Aromatic Solutes with Regression Equation 10

solute	log L_{eq10}^{blood}	log L_{obsd}^{blood}	difference
benzene	0.869	0.892	+0.023
toluene	0.895	1.193	+0.298
ethylbenzene	0.889	1.453	+0.564
o-xylene	1.056	1.493	+0.397
m-xylene	0.884	1.421	+0.537
p-xylene	0.861	1.575	+0.714
n-propylbenzene	0.885	1.672	+0.787
cumene	0.880	1.568	+0.688
styrene	1.278	1.712	+0.434
chlorobenzene	1.197	1.489	+0.292
o-dichlorobenzene	1.694	2.626	+0.932
m-dichlorobenzene	1.486	2.304	+0.818

Anomalous Behavior of the Alkyl- and Chlorobenzenes. It may be noted that the aromatic solvents (44–56) were not included in the correlations leading to the equations for log L_{37}^{blood} in Table III. This is because, for reasons that we do not yet understand, the alkyl- and chloroaromatic solutes are more soluble in blood than calculated by the double regression. This is shown in Table VII, where experimental log L_{37}^{blood} results are compared with values calculated through eq 10.

It is seen that the results are internally consistent; differences between observed and calculated values increase monotonically with the size and number of the alkyl groups (e.g., Δ log L: benzene, +0.02; toluene, +0.30; ethylbenzene, +0.56; *m*-xylene, +0.54; propylbenzene, +0.79) and with the number of chlorine substituents. It may be that the alkyl groups are less hydrophobic in blood than in water or that there is a "surfactant" effect, with solubility being increased at colloidal phase boundaries, or across boundaries, one side of which is more hydrophilic and the other side more hydrophobic.

If the aromatics are included in the double regression correlation, the correlation coefficient remains quite high, but the coefficients of the independent variables change

(23) "Report of the Task Group on Reference Man"; International Commission on Radiological Protection No. 23, Pergamon Press: Oxford, 1975.

(24) Haggard, H. W. *J. Biol. Chem.* **1923**, *55*, 131.

markedly, as shown in comparing eq 13 with eq 10. This

$$\log L_{37}^{\text{blood}} = (-0.295 \pm 0.043) + (0.588 \pm 0.30) \log L_{37}^{\text{water}} + (0.411 \pm 0.020) \log L_{37}^{\text{oil}} \quad (13)$$

$$r = 0.9909,\ s = 0.178,\ n = 63$$

underlines the importance of considering data sets involving similar types of solutes in comparing properties of different biological media. It is highly likely that if solubilities of the aromatics in the other biological media were available and we had included these in the correlations, the absolute values of the oil coefficients would have changed from those in Table IV, but the differences from medium to medium would probably have been quite similar.

Concluding Comments. We underline the potential importance of the correlations described in this paper with the following explicit statement. Given the ability to calculate log L values through the double regression equation, eq 7, it follows that two relatively simple solubility measurements (that is, gas/liquid partition coefficients) of a given solute in water and oil should allow the estimation of solubilities of the solute in the various biological systems listed in Table III and should allow the estimation of the distribution of the solute between any pair of the various biological systems, with a precision of the same order as the average experimental error.

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Tetracyclic Pyridazines as Potential Psychopharmacological Agents

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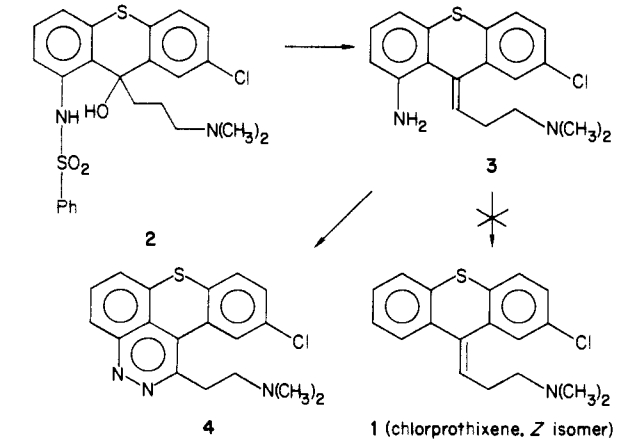
Since the *Z* isomer of chlorprothixene (1) is far more active than its *E* counterpart, it was of interest to develop a stereoselective synthesis for this class of compounds. Insertion of a benzenesulfonamido group at the peri position of a chlorprothixene precursor did affect the stereochemistry of side-chain olefin formation, but after hydrolysis attempted removal of the resulting amine led to a Widman–Stoermer cyclization to afford the corresponding tetracyclic pyridazine-containing compound (4). Since this material displayed encouraging activity in neurotransmitter uptake inhibition studies, compounds in which the sulfur bridge was replaced with an ethano bridge similar to that found in imipramine (8) and with sulfur removed (7) were also prepared. These, together with the corresponding peri amino compounds (3, 5, and 6), were tested as neurotransmitter-uptake inhibitors. The two bridged arylamines 3 and 6 displayed potent and selective inhibition of norepinephrine uptake both when tested in vitro and after in vivo administration. The pyridazine-containing compounds exhibited reasonable activity in vitro, but the activity was lost when they were administered in vivo. None of the compounds displayed significant ability to interfere with spiroperidol binding.

Tricyclic psychopharmacological agents possess a wide variety of central and peripheral nervous system activities. In attempts to select for the desired activity, existing agents have been modified by substitution or have been stereochemically and conformationally defined. The antipsychotic chlorprothixene (1) is an early example of this. The *Z* isomer was originally separated by fractional crystallization and shown[1] to be the active component of the isomeric mixture. The original goal of this project was to develop a general stereoselective synthesis for thioxanthene-type antipsychotics such as chlorprothixene. In particular, a synthetic route (Scheme I) was proposed that utilized a peri-substituted benzenesulfonamido group on the alcohol precursor of chlorprothixene. It was hoped that steric interactions during dehydration of 2 would strongly favor the formation of the isomer analogous to (*Z*)-chlorprothixene and that the sulfonamido group could then be hydrolyzed to the aromatic amine 3 followed by diazotization and reduction to give (*Z*)-chlorprothixene. This strategy eventually led to the desired *E* aromatic amine, but under the diazotization conditions, an initially unex-

Scheme I



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