Solubility of fatty acids and other hydrophobic molecules in liquid trioleoylglycerol

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Abstract The fat solubilities of some long chain fatty acids, alcohols, alkanes, and triacylglycerols, and of some aromatic, chlorinated aromatic, and chlorinated aliphatic hydrocarbons were measured in trioleoylglycerol. Above their melting temperature, all test compounds are theoretically miscible with liquid fat. Below their melting temperature the solubility of all test compounds can be estimated by the equation:

$$\log\text{(mole fraction solubility)} = \frac{-\Delta S_f\,(Tm - T)}{2.303\ RT},$$

where ΔS_f, the entropy of fusion, can be estimated from chemical structure according to Yalkowsky and Valvani (*J. Pharm. Sci.* 1980. **69:** 912–922), and the melting point (Tm) is either known or experimentally determined. For long chain compounds, solubility in trioleoylglycerol dropped precipitously with an increase in melting point. For the aromatic and chlorinated compounds, the drop was more gradual. Since the entropy of fusion of rigid aromatic compounds is approximately 13.5 e.u. at room temperature, their solubility in triacylglycerol is a linear function of melting point.—**Patton, J. S., B. Stone, C. Papa, R. Abramowitz, and S. H. Yalkowsky.** Solubility of fatty acids and other hydrophobic molecules in liquid trioleoylglycerol. *J. Lipid Res.* 1984. **25:** 189–197.

Supplementary key words lipophilicity • octanol-water partition coefficient

Although many drugs, vitamins, xenobiotics, and secondary metabolites are said to be 'fat-soluble', actual measurements of their solubility in long chain triacylglycerol are scarce, and no compilation of data exists. After extensive literature searches, we found only scattered measurements in the pharmacology literature (i.e., 1–3) and some data for cholesterol (4–7). At 37°C cholesterol is soluble in natural oils to the extent of 2–5% (by weight) with solubility decreasing as the degree of unsaturation of the oil increases. Addition of 2% fatty acids to the oil causes an increase (~37%) in cholesterol solubility (6). At 21°C the solubility of cholesterol in trioleoylglycerol drops from 2.8% to 1.9% with the addition of water because of the formation of less-soluble cholesterol monohydrate (7). In a related study the solubility of sodium octanoate in trioctanoin was shown to be dependent on the presence of octanoic acid for the formation of fat-soluble acid-soap aggregates (8). Some additional fat solubility information may be found in studies of the melting and solidification of fats (9, 10) and the solubility of gases in liquids (11). In spite of these studies, however, little is known about the solubility of series or families of molecules in triacylglycerol.

The paucity of solubility data for triacylglycerol appears to be related to the preeminence of the octanol-water partition coefficient, particularly among pharmacologists and environmental chemists, as a measure of lipophilicity of organic molecules (12–14). This useful measurement is often easier to obtain than solubility and is usually expressed as log K_{ow} or log P. Many of the unifying principles in pharmacology and environmental chemistry are expressed in terms of log K_{ow}. Soil sorption (15, 16), animal bioconcentration (17, 18), water solubility (19, 20), and membrane permeability (21) of organic molecules all show correlations with log K_{ow}. In addition, models of lipophilicity and biological activity of organic molecules are based on the log K_{ow} (22, 23). Thus, the use of octanol to represent biological lipid and log K_{ow} to represent lipophilicity of a molecule has been a good general model.

Biological lipid contains a number of distinct hydrophobic domains, i.e., triacylglycerol droplets, membranes, and hydrophobic pockets in proteins, each of which interact with organic molecules with varying degrees of specificity and with varying solvent capacities. Octanol, an amphipathic molecule that can dissolve substantial water (2–3 M) and is also somewhat soluble in water (4.5×10^{-3} M) (24) is thus only a simplified approximation of biological lipid. Some partition measurements have been made in more biologically relevant systems such as phospholipid-water (25), phospholipid-triacylglycerol (26), and triacylglycerol-water (27) systems. We are unaware of any three-phase partitioning measurements such as might occur when a molecule partitions between water-

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Abbreviations: GLC, gas–liquid chromatography; TLC, thin-layer chromatography; FID, flame ionization detector.

phospholipid, and triacylglycerol (i.e., a phospholipid-stabilized fat droplet in water). As useful as unitless partition coefficients are, solubility measurements are more fundamental thermodynamic quantities (28, 29).

The present study grew out of the observations that colored and fluorescent molecules that were dissolved in fat could, under certain conditions, flow quantitatively into the liquid crystalline product phases produced by pancreatic lipase during fat digestion (30, 31). This transport of dissolved solutes by lipase into the bile salt-dispersable product phases of fatty acid and monoglyceride may explain the historical observation that fat can greatly enhance the intestinal absorption of poorly soluble molecules (31, 32). Before triacylglycerol can be widely exploited as a versatile drug delivery vehicle, its solvent properties for a wide range of compounds must be known. The following study presents measurements of triacylglycerol solubility for some long chain and aromatic compounds and shows a correlation between fat solubility and the solutes ideal solubility.

THEORETICAL

It is known that the solubility (in any solvent) of a crystalline solute is at least partially dependent on certain properties of the crystal. The reduction in solubility that is attributable to solute crystallinity is given by the Hildebrand equation:

$$\log \frac{X^{c}}{X^{SCL}} = \frac{-\Delta S_f\,(Tm - T)}{2.303\ RT} + \frac{\Delta C_p\,(Tm - T)}{2.303\ RT} - \frac{\Delta C_p}{2.303\ R}\left(\ln \frac{Tm}{T}\right) \qquad \textit{Eq. 1)}$$

where X^C and X^{SCL} are the mole fractional, solubilities[1] of the crystalline solute and of the supercooled liquid, respectively; Tm and T are the melting point and temperature of interest, respectively (both in °K); ΔS_f is the entropy of fusion of the crystal; R is the gas constant ($1.9872\ \text{cal} \cdot \text{degK}^{-1} \cdot \text{mol}^{-1}$) and ΔC_p is the difference in heat capacity between the crystal and the supercooled liquid. The supercooled liquid, SCL, is equivalent to a hypothetical oil form of the melted crystal. Yalkowsky (33) has used a simplification of Eq. 1 to calculate solubilities of polycyclic aromatic hydrocarbons (pah) in benzene which show good agreement with experimental values. According to this simplification $\Delta C_p = 0$ thus:

$$\log \frac{X^{c}}{X^{SCL}} = \frac{-\Delta S_f\,(Tm - T)}{2.303\ RT}\,. \qquad \textit{Eq. 2)}$$

If the supercooled liquid is completely miscible with trioleoylglycerol, X^{SCL} = unity and

$$\log \text{Xcalc} = \frac{-\Delta S_f\,(Tm - T)}{2.303\ RT}\,. \qquad \textit{Eq. 3)}$$

If the supercooled liquid is not completely miscible with trioleoylglycerol, the solubility of the crystalline material will be less than the value calculated by equation 3.

By the method of Fedors (34) trioleoylglycerol has a calculated solubility parameter of approximately 9.2. According to Yalkowsky,[2] any two liquids will be completely miscible at room temperature if their solubility parameters do not differ by more than three units. Therefore, any liquid having a solubility parameter between 6 and 12 will be miscible with trioleoylglycerol. Based upon the estimation techniques of Rheineck and Lin (35) and of Fedors (34), all of the materials used in this study fall within this range. It is therefore expected that equation 3 will provide a reasonable estimate of the solubilities of all of these compounds in trioleoylglycerol.

If there were any systematic deviation in the value of X^{SCL} with chemical structure, it would be expected to be related to the polarity of the solutes. The octanol-water partition coefficient (as calculated by the method of Nys and Rekker) (36) will be taken as a measure of the polarity of the solutes. If either the trioleoylglycerol solubility or the water solubility is independent of polarity, then the relationship between the observed solubility and the solubility calculated by equation 3 would be independent of the partition coefficient. If, on the other hand, the polarity of the solute is a significant factor in controlling its solubility in trioleoylglycerol or in water, there will be a definite relationship between the non-ideal component of solubility and the partition coefficient.

MATERIALS AND METHODS

All of the long chain lipids including trioleoylglycerol were purchased from Sigma Chemical Co. (St. Louis, MO) and, with the exception of docosanol (98% pure), were alleged to be 99% pure or better according to the supplier. The aromatics were purchased from Aldrich Chemical Co. with the following alleged purities: naphthalene, 99+%; p-dichlorobenzene, 97+%; acenaphthene, 99%; biphenyl, 99%; 2,6-dimethyl naphthalene, 100%; 2,3-dimethyl naphthalene, 98%; fluorene, 98%; phenanthrene, 98%; fluoranthene, 98%; 4,4-dichlorobiphenyl, 98%; perylene, 99+%; benzo(a)pyrene, 98%; hexachlorobenzene, 97%; and *p,p'*-DDT, 99+%. Heptachlor, dieldrin, and endrin were purchased from Chem Service (West Chester, PA) and alleged to be 98% pure or better.

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[1] Mole fraction solubility = $\dfrac{\text{moles of solute}}{\text{moles of solute + moles of solvent}}$.

[2] Yalkowsky, S. H. Unpublished results.

No attempts were made to verify experimentally the stated purities of the chemicals. Vacuum desiccation over anhydrous calcium sulfate at room temperature for 3 days was used to remove any traces of water. Gravimetric analyses of the trioleoylglycerol and fatty acids before and after desiccation suggested that the stock chemicals contained less than 0.1% water. No attempts were made following desiccation to quantify any last traces of water that remained in the chemicals. All solvents were Baker Resi-Analyzed.

Solubility measurements

All mixtures were made in Teflon-lined screw-cap glass test tubes (13 × 98 mm). To approximately 600 mg of pure trioleoylglycerol was added 50–100 mg of test solid. The tubes were then flushed with nitrogen, covered with aluminum foil, and placed on a shaker for 2 weeks either in the cold room (14 ± 1°C), at room temperature, or in the warm room (37 ± 1°C). If a solute was completely dissolved during the initial period then more would be added and a new 2-week shaking period was started. After the shaking period, an additional 2-day settling period was given. Aliquots of the clear oil were then taken with a glass pipette fitted with a plug of solvent-washed glass wool. Microcrystals of solute in the unfiltered clear oil could not be seen by polarizing light microscopy. Once trioleoylglycerol was saturated with a long chain lipid, a slight 1 or 2 degree drop in temperature usually caused the entire clear oil phase to become opaque. Centrifugation at 3,000 *g* had no effect on this opaque phase and microscopic examination revealed a network of wide flat plates in oil. By contrast, if a temperature drop occurred with a saturated oil sample containing aromatic compounds, then new crystals grew on pieces of undissolved solute at the bottom of the test tube.

The solubility of the saturated triacylglycerols was measured by GLC. An aliquot, 1–2 mg, of the clear oil was saponified and methylated as previously described (37) and the resulting methyl esters were analyzed on a 10 M methyl silicone fused silica capillary column on a Hewlett Packard 5840A gas chromatograph. Individual response curves were made for each fatty acid methyl ester and triplicate analyses of each unknown were made.

The solubility of the normal fatty acids, alcohols, and alkanes was determined by thin-layer chromatography and flame ionization detection (TLC–FID) on chromorods. An aliquot of the clear oil was dissolved in chloroform–methanol to give a concentration of about 30 mg/ml. The ratio of chloroform to methanol varied. For example, fatty acids could be dissolved with a 2:1 mixture while the hydrocarbons required 3:1. One μl of the sample solutions was then spotted on chromarods and chromatographed in the following solvent systems: for fatty acids, ethyl ether–ammonium hydroxide 100:1 (v/v); for fatty alcohols, ethyl ether–petroleum ether 50:50 (v/v); for hydrocarbons, ethyl ether–petroleum ether 3:97 (v/v). Quantification of the solvent (trioleoylglycerol) and the solute were then made by FID with an Iatroscan TH-10 Analyzer fitted with a Hewlett Packard 3310 Integrator. The data from the Analyzer are in the form of area under peaks. Because each compound gave a different mass response to the FID detector, a correction factor was necessary to account for the response differences of the different compounds. Known weights of solute and solvent were placed in a tube, then heated until complete dissolution took place. A sample was then taken from this tube and dissolved in chloroform–methanol to give a concentration similar to that of the unknowns. This was then spotted on the rods and run under the same conditions as the unknowns. The correction factor (Cf) was found by the equation % by weight = (Cf) (% by area). The known and unknowns were then run at the same time, five rods being spotted with known samples and five with unknowns. The average of the five figures for the unknowns was used to get Cf. Then the % by area for each run of the unknown was multiplied by Cf to get five actual solubilities. These were then averaged to get the final solubility of the unknown.

The solubilities of the aromatic and chlorinated compounds were measured by absorbance spectrophotometry on a Carey Model 219 Spectrophotometer. Known amounts of the test compounds were weighed and dissolved in 5–500 ml of cyclohexane. An ultraviolet absorbance spectrum was obtained for each compound and an extinction coefficient was calculated at the wavelength of maximum absorbance. Unknowns, 5–15 mg of trioleoylglycerol plus solute, were then dissolved in cyclohexane and the absorbance was read at the chosen wavelength against a blank of trioleoylglycerol. The mass of solute in the sample was then calculated according to Beer's law and the solvent mass was obtained by subtraction of the solute mass. Triplicate analyses were made for each unknown.

Calculation of log K_{ow}

The partition coefficients of the various long chain compounds were calculated by using a group contribution approach formulated by Nys and Rekker (36). The overall equation for this system of predicting partition coefficients can be expressed as:

$$\log K_{ow}\ \text{molecule} = \sum_{\text{all G}} \int G \qquad \textit{Eq. 4)}$$

where G represents the groups on the molecule.

Calculation of ΔS_f

To calculate the mole fraction solubility of the long chain compounds in trioleoylglycerol, ΔS_f, the entropy

TABLE 1. Solubility of aliphatic solutes in trioleoylglycerol

Compound	Mol Wt	Melting point[a] °C	Log K_{ow}		ΔS_f		Temp. °C	Trioleoylglycerol solubility			
			(Est)	(Lit)[b]	(Est)	(Lit)[c]		g solute/100 g fat	Log Xo (obs)	Log Xo (ideal)	Difference
Fatty acids											
Decanoic acid (capric)	172.26	32.0	3.92	4.09	26	22	14	15.13 ± 0.98	−0.36	−0.36	0
							27	123.44 ± 5.43	−0.06	−0.09	−0.03
							37	miscible	1.0	1.0	0
Dodecanoic acid (lauric)	200.31	43.1	4.97	4.2	31	27.6	14	4.36 ± 0.27	−0.79	−0.68	+0.11
							27	16.14 ± 1.06	−0.38	−0.36	+0.02
							37	62.86 ± 3.46	−0.13	−0.13	0
Tetradecanoic acid (myristic)	214.38	54.0	6.02		36	32.9	14	2.37 ± 0.24	−1.08	−1.1	−0.02
							27	4.91 ± 0.35	−0.8	−0.71	+0.09
							37	13.42 ± 0.63	−0.47	−0.43	+0.04
Hexadecanoic acid (palmitic)	256.42	61.8	7.08		41	38.7	14	0.76 ± 0.21	−1.59	−1.49	+0.09
							27	1.71 ± 0.23	−1.25	−1.04	+0.21
							37	4.72 ± 0.31	−0.85	−0.72	+0.14
Octadecanoic acid (stearic)	284.47	68.8	8.13		46	39.5	14	0.42 ± 0.83	−1.89	−1.92	−0.03
							27	1.10 ± 0.11	−1.49	−1.40	+0.08
							37	2.19 ± 0.15	−1.19	−1.03	+0.16
Eicosanoic acid (arachidic)	312.52	75.3	9.19		51	48.8	27	0.86 ± 0.30	−1.62	−1.79	−0.17
							37	1.06 ± 0.30	−1.54	−1.38	+0.16
Docosanoic acid (behenic)	340.57	80.0	10.24		56	53.2	27	0.70 ± 0.24	−1.74	−2.16	−0.42
							37	1.06 ± 0.25	−1.57	−1.70	−0.13
Alcohols											
Dodecanol (lauryl)	186.33	24.0	5.06	5.13	31		14	9.36 ± 0.44	−0.51	−0.24	+0.27
Tetradecanol (myristyl)	214.38	38.0	6.11		36		14	3.60 ± 0.69	−0.89	−0.66	+0.23
							27	19.33 ± 0.77	−0.35	−0.29	+0.06
							37	188.32 ± 1.51	−0.05	−0.03	+0.03
Hexadecanol (cetyl)	242.43	49.9	7.17		41	37	14	2.45 ± 0.43	−1.08	−1.12	−0.04
							27	4.80 ± 0.41	−0.82	−0.68	+0.14
Octadecanol (stearyl)	270.48	58.4	8.22		46		14	0.79 ± 0.25	−1.6	−1.55	+0.05
							27	2.42 ± 0.26	−1.13	−1.05	+0.08
							37	6.27 ± 0.29	−0.77	−0.69	+0.08
Eicosanol (arachidyl)	298.56	65.4	9.28		51		14	0.49 ± 0.32	−1.85	−1.99	−0.14
							27	2.18 ± 0.32	−1.23	−1.43	−0.20
							37	3.50 ± 0.32	−1.03	−1.02	+0.01
Docosanol (behenyl)	326.61	70.9	10.33		56		14	0.41 ± 0.23	−1.96	−2.42	−4.7
							27	1.24 ± 0.23	−1.48	−1.79	−0.31
							37	1.70 ± 0.25	−1.36	−1.34	+0.02

Hydrocarbons									
Octadecane	254.48	28.2	9.84	46		14	9.26 ± 0.86	−0.61	−0.50	+0.12
						27	82.69 ± 1.29	−0.13	−0.04	+0.09
Eicosane	282.54	36.8	10.89	51	53.9	14	4.02 ± 0.26	−0.95	−0.88	+0.07
						27	9.55 ± 0.31	−0.64	−0.36	+0.27
Docosane	310.61	44.4	11.94	56	36.9	14	0.60 ± 0.37	−1.77	−1.3	+0.47
						27	2.12 ± 0.40	−1.24	−0.71	+0.53
						37	12.69 ± 0.52	−0.58	−0.29	+0.28
Triacylglycerols										
Tripalmitoylglycerol	807.29	65.8	21.9	103.5	94.9	23	1.04 ± 0.23	−1.96	−3.27	−1.31
						32	1.95 ± 0.36	−1.68	−2.51	−0.83
						42	4.97± 0.43	−1.29	−1.71	−0.42
Tristearoylglycerol	891.45	71.2	25.11	118.5	105.9	23	0.02 ± 0.02	−3.70	−4.21	−0.52
						32	0.21 ± 0.10	−2.68	−3.3	−0.65
						42	0.49 ± 0.23	−2.32	−2.4	−0.08

[a] 0°C = 273°K.

[b] From reference 40.

[c] From reference 41.

of fusion, was estimated using the equation of Yalkowsky and Valvani (38) for molecules having greater than five nonhydrogen atoms in a flexible chain where

$$\Delta S_f = \Delta S_{exp} + \Delta S_{pos} + \Delta S_{rot} + \Delta S_{int}$$

$$= 13.5 + 2.5\,(n\text{-}5)\ \text{e.u.}, \qquad \textit{Eq. 5)}$$

where ΔS_{exp} equals the entropy of expansion, ΔS_{pos} equals the positional entropy, ΔS_{rot} equals the rotational entropy, and ΔS_{int} equals the internal entropy of fusion. The internal or conformational entropy of fusion results from the fact that molecular configuration is fixed in the crystal but not in the liquid. For rigid molecules such as the aromatic compounds, ΔS_{int} is assumed to be 0 and the ΔS_f for aromatics is roughly a constant of 13.5 e.u.[3] For spherical molecules such as dieldrin and endrin, the ΔS_f usually falls between 2 and 4 e.u. The observed ΔS_f for these spherical molecules can be thought as composed of ΔS_{pos} plus ΔS_{exp}.

DISCUSSION

Log K_{ow} and ΔS_f

In all cases the literature values of both log K_{ow} and ΔS_f are in good agreement with the estimated values. We have elected to use calculated values of these parameters in all cases. This assures a consistent manner of treatment of all data. Furthermore it reduces the chance of utilizing an erroneous literature value in the calculations.

Solubility of long chain compounds in trioleoylglycerol (Table 1)

All of the long chain compounds have polarities similar to that of trioleoylglycerol. Therefore their solubilities in that solvent are very nearly equal to their respective ideal solubilities. The values calculated by equation 3 are generally in excellent agreement with the observed values. The primary source of error is in the estimation of ΔS_f. Inasmuch as this was done by a group contribution approach, the errors can be expected to be largest for the largest molecules. The difference between the observed and calculated values is clearly greatest for the two triglycerides. It is ironic that there is a significant error for these compounds. They more than any others in Table 1 are likely to form ideal solutions in trioleoylglycerol which is a very similar triglyceride.

Solubility of aromatic compounds in trioleoylglycerol (Table 2)

Like the long chain aliphatic solutes the aromatic solutes have solubilities in trioleoylglycerol which do not differ

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[3] e.u. = entropy unit in cal·mol^{-1} degK^{-1}.

TABLE 2. Solubility of some aromatic, chlorinated aromatic, and chlorinated aliphatic solutes in trioleoylglycerol

						Trioleoylglycerol Solubility at 23 ± 1°C			
Compound	Mol Wt	MP (°C)	$LogK_{ow}$	ΔS_f (Est)	ΔS_f (Lit)	g/100 g	Log Xo (Obs)	Log Xo (Ideal)	Difference
Benzene	78.12	5.5	2.13	13.5	8.5[a]	miscible	1.0	1.0	0
Naphthalene	128.19	80.2	3.30	13.5	12.9[a]	18.41 ± 3.31	−0.25	−0.57	−0.32
p-Dichlorobenzene	147.01	53.1	3.38	13.5	13.3[a]	56.70 ± 7.92	−0.11	−0.30	−0.19
Acenaphthene	154.21	96.2	4.03	13.5	13.6[a]	10.30 ± 1.81	−0.43	−0.73	−0.30
Biphenyl	154.21	71.0	4.09	13.5	13[b]	19.93 ± 6.47	−0.27	−0.48	−0.20
2,6-Dimethyl naphthalene	156.23	108	4.31	13.5	15.1[a]	5.47 ± 1.64	−0.63	−0.85	−0.22
2,3-Dimethyl naphthalene	156.23	105	4.40	13.5	12.5[a]	7.91 ± 2.31	−0.51	−0.82	−0.31
Fluorene	166.23	116	4.18	13.5	11.6[c]	9.56 ± 1.01	−0.47	−0.93	−0.45
Phenanthrene	178.24	101	4.46	13.5	12[a]	10.22 ± 2.37	−0.47	−0.78	−0.30
Fluoranthrene	202.26	111	5.22	13.5	11.8[c]	7.82 ± 1.75	−0.59	−0.88	−0.28
4,4-Dichlorobiphenyl	223.11	149	5.58	13.5		11.50 ± 0.65	−0.50	−1.26	−0.75
Perlyene	252.32	277	6.50	13.5	13.7[c]	0.183 ± 0.02	−2.19	−2.53	−0.34
Benzo(a)pyrene	252.32	176.5	6.53	13.5	8.72	1.98 ± 0.39	−1.19	−1.53	−0.34
Hexachlorobenzene	284.61	230	6.53	13.5	11.3[d]	0.75 ± 0.28	−1.64	−2.06	−0.42
p,p′-DDT	354.49	109	6.19	13.5	15.9[d]	8.00 ± 3.10	−0.78	−0.86	−0.08
Heptachlor	373.11	96	5.37	3	1.2[d,e]	23.79 ± 4.42	−0.44	−0.16	+0.28
Dieldrin	380.27	decomposes	5.48	3	1.4[d,e]	13.12 ± 2.15	−0.63	−0.34	+0.29
Endrin	380.27	decomposes	5.34	3		15.16 ± 3.71	−0.58	−0.49	+0.09

[a] Reference 42.
[b] Reference 43.
[c] Reference 45.
[d] Reference 44.
[e] Nonideal.

greatly from their ideal values. Because all of the rigid aromatic molecules have the same entropies of fusion, their solubilities in trioleoylglycerol are a linear function of their melting points (MP in °C). At 23°C this is:

$$\log \text{Xcalc} = -0.01\ (\text{MP-23}). \qquad \textit{Eq. 6)}$$

Solubility of all compounds in trioleoylglycerol

The differences between the observed and predicted solubilities for all of the compounds in both Tables 1 and 2 are plotted against log K_{ow} in **Fig. 1.** The figure shows no clear relationship between the difference and the polarity of the solute. Regression analysis gives

$$\log S\ (\text{ideal}) - \log S\ (\text{obs}) = 0.015 \log K_{ow}$$

with a correlation coefficient of only 0.173. Whatever the reason for the difference between the observed and the ideal solubilities, it appears not to be due solely to the polarity of the solute. One potential source of error in all of the calculations is the incorporation of trioleoylglycerol into the crystal structure of each of the solutes. This would reduce the purity of the solute and possibly alter the melting point. This effect could very well be most dramatic for the triglycerides that have a very similar structure to the solvent. **Fig. 2** shows the relationship between fat solubility and melting point. For long chain compounds, fat solubility dropped precipitously with an increase in melting point. For aromatic and chlorinated aromatic compounds, the drop was more gradual.

Solubility of aromatic compounds in water (Table 3)

The difference between the observed and the ideal solubility of the aromatic compounds is plotted against the logarithm of the octanol-water partition coefficient in **Fig. 3.** In this figure, unlike the previous one, there

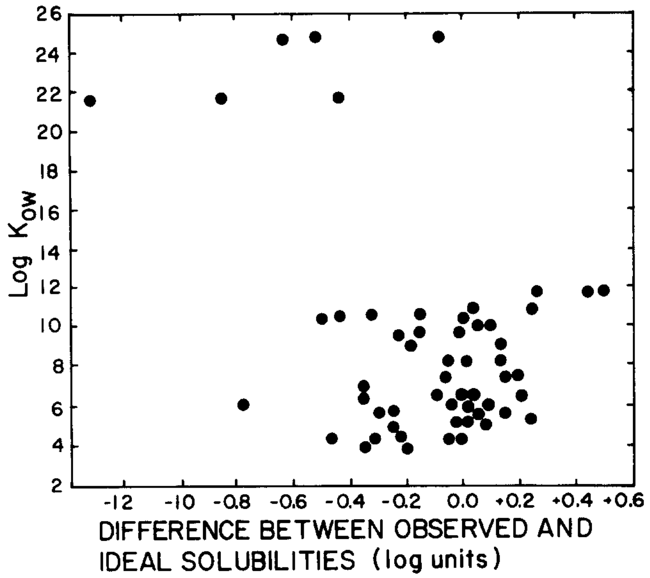

Fig. 1. The difference between the observed fat solubility for all compounds from Tables 1 and 2 and their ideal solubilities calculated by equation 3 plotted against their calculated log K_{ow} values.

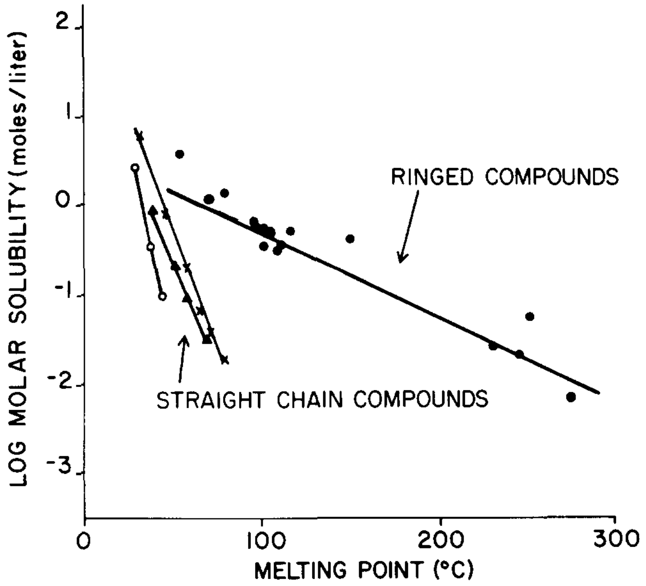

Fig. 2. The effect of melting point (°C) on the trioleoylglycerol solubility of crystalline nonelectrolyte compounds at 23°C. (○) alkanes, (▲) fatty alcohols, (×) fatty acids, (●) aromatic, chlorinated aromatic, and chlorinated aliphatic compounds. (See Tables 1 and 2).

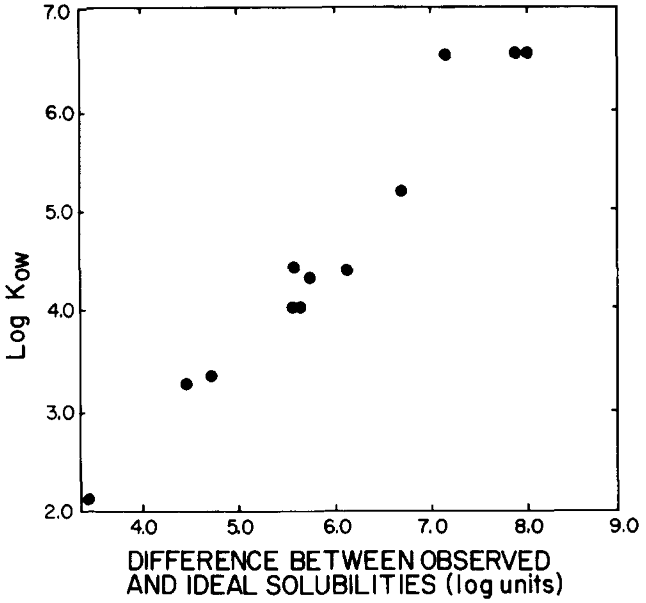

Fig. 3. The difference between the observed water solubilities of the aromatic compounds from Table 3 and their ideal solubilities calculated by equation 3 plotted against their calculated log K_{ow} values.

is a very definite relationship between the non-ideal component of the solubility and log K_{ow}. Regression analysis gives

$$\log S\ (\text{ideal}) - \log S\ (\text{obs}) = 1.3 \log K_{ow}$$

with a correlation efficient of 0.997 and a standard deviation of 0.527. This clearly shows that the deviation of the aqueous solubility of the compounds studied from the ideal solubility can be explained strictly on the basis of the polarity of the solute. These results are in full agreement with previously reported results for the solubility of a large number of organic compounds in water (39).

Terminology

The very low solubility of solid lipids in liquid fat reiterates the importance of including melting point in any discussion of the term "fat-soluble." At temperatures above their melting points, all of the compounds in this study have the *same* solubilities in liquid fat, i.e., they are miscible. Below their melting points, the fat solubility of the individual compounds is determined solely by the strength of their crystal lattice forces (ΔS_f). The octanol-water partition coefficient (log K_{ow}) is widely used as an indicator of the "lipophilicity" of organic compounds. However, as Tables 1 and 2 show for compounds at tem-

TABLE 3. Solubility of aromatic compounds in water at 23°C

Solute	Mole Fraction Water Solubility (obs)	Mole Fraction Ideal Solubility (calc)	log K_{ow}	Difference
Benzene	−3.38	0	2.13	3.38
Naphthalene	−5.04	−0.57	3.30	4.47
p-Dichlorobenzene	−5.01	−0.30	3.38	4.71
Acenaphthene	−6.34	−0.73	4.03	5.61
Biphenyl	−6.09	−0.48	4.09	5.61
2,6-Dimethylnaphthalene	−6.63	−0.85	4.31	5.78
2,3-Dimethylnaphthalene	−6.44	−0.82	4.40	5.62
Fluorene	−6.64	−0.93	4.18	5.71
Phenanthrene	−6.95	−0.78	4.46	6.17
Fluoranthrene	−7.63	−0.88	5.22	6.75
4,4-Dichlorobiphenyl	−8.29	−1.26	5.58	7.03
Perylene	−10.53	−2.53	6.50	8.00
Benzo(a)pyrene	−9.56	−1.53	6.53	8.03
Hexachlorobenzene	−9.27	−2.06	6.53	7.21
p,p'-DDT	−9.80	−0.86	6.19	8.94

peratures below their melting point, as log K_{ow} goes up (i.e., lipophilicity increases) fat solubility goes down. These more "lipophilic" compounds are in fact less lipid-soluble and more "crystal loving" (crystophilic) than their lower molecular weight homologs. Thus for solids the use of log K_{ow} as an indicator of "lipophilicity" is inappropriate.

Biological significance

Although the use of natural biological oils (triacylglycerols and cholesteryl esters) for carrying and delivering medicinal drugs is undoubtedly ancient, modern pharmaceutical use of digestible oil vehicles for drug delivery has not been widespread (46, 47). This situation appears to be changing; however, corticosteroids (48), certain antimalarials (49), morphine (50), and most recently cyclosporin (51), a drug that is revolutionizing the organ transplant field (52), are all crystalline at 37°C and are all delivered more effectively in lipid-based dosage forms than other dosage forms. Glycerides as pro-drugs are also being used to deliver anti-inflammatory drugs such as aspirin (53) and indomethicin (54) without causing gastrointestinal irritation. Chylomicrons, VLDL, and LDL, which all have liquid oil droplet cores, may soon be used as site-specific delivery systems for diagnostic and therapeutic agents (55). Greater than 95% of all drugs are solids (56). This study offers a simple equation (Eq. 3) for calculating lipid solubility of hydrophobic solids from molecular structure and melting point without having to undertake laborious solubility measurements. The compounds used in this study were relatively simple compared to many pharmaceutical agents. The challenge now is to determine if equation 3 can be used to predict the fat solubility of very complex microbial molecules like cyclosporin (51) or ivermectin (57), the potent new antiparasitic agent.

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