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Densitometric Determination of the Solubility Parameter and Molal Volume of Compounds of Medicinal Relevance

ZVI LIRON and SASSON COHEN [x]

Abstract □ A procedure is described for the simultaneous determination of molal volumes (v_2^0) and solubility parameters (δ) of compounds of medicinal interest. These include alkanoic acids of various chain length and branching (some solid at room temperature), cholesterol, and cholesteryl esters. The procedure is based on the determination of partial molal volumes ($\bar{v}_2$) from high-precision density measurements of dilute solutions of these compounds in reference solvents, which range in polarity from carbon tetrachloride ($\delta = 8.6$) to nitrobenzene ($\delta = 10.0$). In some cases, the present results do not agree with values of δ published in the literature. Values calculated from group contributions proposed by other authors are prone to error particularly in the case of branched acids and cholesteryl esters.

Keyphrases □ Densitometric determination—solubility parameter and molal volume of compounds of medicinal relevance □ Solubility—densitometric determination of parameters, molal volume of compounds of medicinal relevance □ Molal volume—densitometric determination of solubility parameter of compounds of medicinal relevance

In a series of studies with structurally nonspecific ethers, it was found that the pharmacological profile of a given member could be a consequence of its solubility parameter (1–3). This finding led to the proposition that such molecules associate with a particular membrane subregion, such as an ionic channel or boundary lipid, in accordance with regular solution theory (4). That is, a given substrate will partition between two phases that differ in solubility parameter at a ratio that can be predicted from the solubility parameters of the interacting species and their partial molal volumes (5). Further exploration of this concept in pharmacology and its possible application in medicinal chemistry required knowledge of reliable data pertaining to these parameters or a suitable experimental procedure for their determination. The main sources on this subject are the works of Hildebrand *et al.* (6) and reviews by

Barton (7) and Burrell and Immergut (8). Although helpful, they did not meet the need because they made no reference to compounds of medicinal relevance and lack data on molal volumes, especially for solids. Therefore, this study explores the simultaneous determination of partial molal volumes and solubility parameters from high-precision density measurements of dilute regular solutions. Alkanoic acids, cholesterol, and cholesteryl esters were the compounds of choice for this exploratory study.

BACKGROUND

Definitions—The solubility parameter (δ) of a pure liquid is the square root of the cohesive energy density, and is usually given by:

$$\delta = \left(\frac{-E}{v}\right)^{1/2} = \left(\frac{\Delta H^v - RT}{v}\right)^{1/2} \text{cal}^{1/2}\,\text{cm}^{-3/2} \qquad \text{(Eq. 1)}$$

where, E is the energy of the liquid expressing the molal heat of vaporization to the gas state at zero pressure, v is the molal volume of the liquid, and ΔH^v is the heat of vaporization at low vapor pressure. Under conditions of high vapor pressure, the gas law correction should be applied and ZRT should replace RT (1), Z being the compressibility factor.

If no calorimetric data are available, the Clausius–Clapeyron equation may be applied to derive the apparent heat of vaporization from pressure–temperature data:

$$\frac{d\ln P}{dT} = \frac{\Delta H^v}{RT\Delta v^v} = \frac{\Delta H^v_{app}}{RT^2} \qquad \text{(Eq. 2)}$$

where Δv^v is the change in volume on vaporization, $v^g - v^l$. The apparent heat of vaporization is equal to the true one only if the vapor is ideal. Otherwise, the compressibility factor must be used, and Eq. 1 then assumes the form:

$$\delta = \left\{\frac{(\Delta H^v_{app} - RT)Z}{v}\right\}^{1/2} \qquad \text{(Eq. 3)}$$

In the case of solid substances, application of the above relationships is not straightforward. First, many of these are nonvolatile or poorly
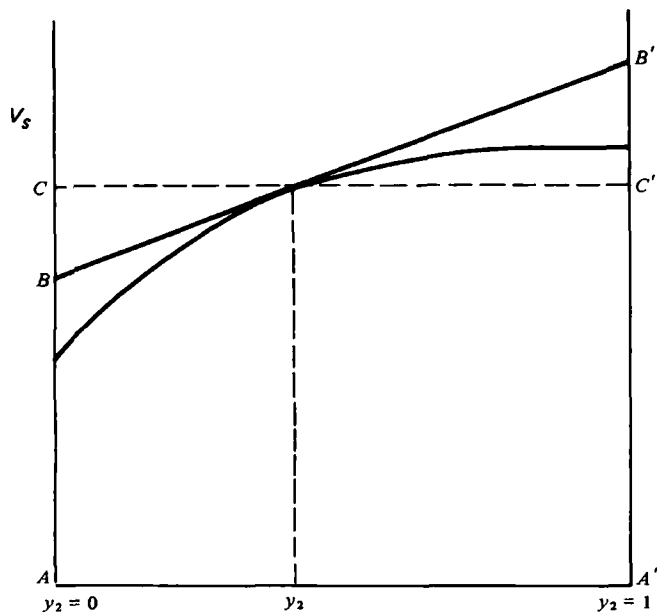
Figure 1—*The relation between the specific volume* V_s *and the mass fraction* y_2 *in a mixture of two components.* $AB = \overline{V}_{s1}$; $A'B' = \overline{V}_{s2}$ *at mass fraction = 0 of the second component.*

volatile. Second, there is an uncertainty in the value of v which must be approximated by extrapolating from the fused substance to the supercooled liquid. In this case, δ is calculated from experimental solubility data, as in the following relationship offered previously (9):

$$RT \ln\left(\frac{a_2^s}{X_2}\right) = v_2\phi_1^2(\delta_2 - \delta_1)^2 \tag{Eq. 4}$$

where the subscripts 1 and 2 refer to solvent and solute, respectively, X_2 is the solubility at saturation in mole fraction, v_2 is the molal volume of solute as supercooled liquid, ϕ_1 is the solvent volume fraction, and a_2^s is the activity of the solute as a solid. Calculation of the latter term is an intricate operation which requires knowledge of the heat of fusion at the temperature of fusion and also of the difference between the heat capacity of the liquid and solid states. In a more empirical approach (10), the solubility at saturation of a substance was determined in each of a series of solvents or solvent mixtures of known solubility parameter. The solubility parameter of the solute was then approximated with that of the best solvent. This method has many limitations, especially the need to use high solute concentrations which must inevitably alter the solubility parameter of the reference solvents, since:

$$\delta_{\text{app}} = \sum \delta_i \phi_i \tag{Eq. 5}$$

where ϕ is the volume fraction. It is particularly doubtful when water is one of the solvent components, because its solubility parameter is still uncertain (11). A previous review gives other empirical procedures (12).

Table I—Determination of the Densities of Various Solutions of Cholesterol in Toluene at 25° [a]

Sample	Mass fraction, $y_2 \, 10^3$	Densitometer T value	d Calc, gcm^{-3}	V_{s2}, $\text{cm}^3 \text{g}^{-1}$
Toluene	0	1781331	0.86216	1.15987
1	1.129	1781391	0.86229	1.15970
2	2.685	1781473	0.86247	1.15946
3	3.901	1781536	0.86260	1.15928
4	5.233	1781607	0.86276	1.15908
5	6.313	1781662	0.86287	1.15892
6	7.947	1781746	0.86306	1.15868
7	9.910	1781848	0.86327	1.15838
8	11.598	1781935	0.86346	1.15813

[a] From $d_{\text{sample}} = d_{\text{air}} + 6.03449 \times 10^{-13} \, (T_{\text{sample}}^2 - T_{\text{air}}^2)$; T value for air, 1321506; density of air, 0.001185 gcm^{-3}; T value for water, 1843002; density of water, 0.997043. In this particular example, the relationship between V_{s2} and y_2 is given by: $V_{s2} = 1.15987 - 0.14987y$ ($r^2 = 0.99995$). At $y_2 = 1$, $\overline{V}_{s2} = 1.01000$ which is the partial specific volume of cholesterol in toluene. Multiplication by 386.66 gives $\overline{v}_2 = 390.53$ which is the partial molal volume of cholesterol in toluene at a concentration approaching zero.
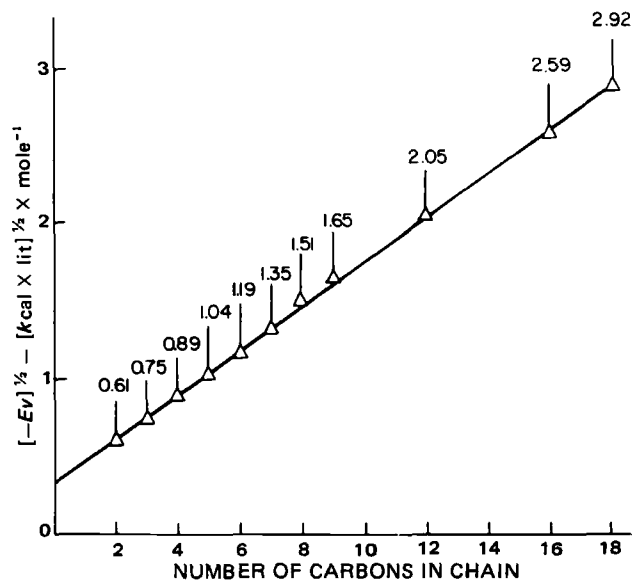
Figure 2—*Alkanoic acids: square root of volume cohesive energy product as a function of acid carbon number* (n).

In a more recent extension of Eq. 4 (13), the geometric mean $\delta_1\delta_2$ of the Hildebrand approach has been replaced by $K\delta_1\delta_2$, which is the solute–solvent interaction energy.

An experimental method of general applicability is now described for the determination of the solubility parameter from partial molal volumes. The method dwells on the same theoretical principles as the dilatometric method described previously (14) and applied earlier (1), but is based on a measurement of density rather than volume change, and does not require prior knowledge of the molal volume of the pure solute.

THEORETICAL

The partial molal volume of a solute, $\overline{v}_2$, is the rate of change of volume of its solution, V, referred to the rate of change of the mole number of solute, n_2:

$$\overline{v}_2 = \frac{\partial v}{\partial n_2} \tag{Eq. 6}$$

Now, consider a solution of two components, 1 and 2. A plot of the specific volume, V_s, which is the reciprocal of density, d, against the mass fraction of component 2, y_2, yields a curve as shown in Fig. 1. A tangent to this curve at any point must intercept the ordinate at $y_2 = 0$ at a point B, so that $AB = \overline{V}_{s1}$, the partial specific volume of component 1, and at $y_2 = 1$ at a point B', so that $A'B' = \overline{V}_{s2}$, the partial specific volume of component 2. It can be shown (15) that:

$$\overline{V}_{s1} = V_s - y_2 \frac{dV_s}{dy_2} \tag{Eq. 7}$$

$$\overline{V}_{s2} = V_s + y_1 \frac{dV_s}{dy_2} \tag{Eq. 8}$$

The partial molal volume, $\overline{v}_2$, is given by:

$$\overline{v}_2 = M_2 \overline{V}_{s2} \tag{Eq. 9}$$

where M_2 is the molecular weight of component 2.

An experimental curve as shown in Fig. 1 can be constructed from density measurements of solutions having a predetermined mass fraction of component 2 in the mixture. However, we are interested in the partial molal volume of the solute at a vanishingly small mass fraction, corresponding to a point on the curve at $y_2 = 0$. Hence, a tangent to the curve must be drawn at $y_2 = 0$. In practice, this tangent has the function of a straight line drawn through a series of points having y_2 values $<10^{-2}$. The desired value:

$$y_2 \xrightarrow{\overline{v}_2} 0$$

is calculated by multiplying the intercept of this tangent at the ordinate $y_2 = 1$ by the molecular weight (see Table I).

Table II—Specific Volumes (V_{s2}^0) and Partial Specific Volumes ($\overline{V}_{s2}$) of Straight-Chain Alkanoic Acids in Two Reference Solvents, at 25°

Number of Carbons in Molecule	V_{s2}^0, cm^3 g^{-1}	$\overline{V}_{s2}$ in Carbon Tetrachloride		SE^b	$\overline{V}_{s2}$ in Toluene		SE^b
		cm^3 g^{-1}	$r^{2\,a}$		cm^3 g^{-1}	$r^{2\,a}$	
2	0.95768	1.00075	0.99898	1	0.99706	0.99985	1
3	1.01200	1.03706	0.99968	1	1.02327	0.99968	1
4	1.04960	1.06063	0.99947	1	1.05565	0.99972	1
5	1.07008	1.08048	0.99932	1	1.07396	0.99985	0
6	1.08294	1.09267	0.99994	1	1.08529	0.99704	2
7	1.09436	1.10612	0.99980	1	1.09822	0.99987	1
8	1.10313	1.11254	0.99946	1	1.10758	0.99961	1
9	1.11005	1.11768	0.99885	1	1.11423	0.99903	1
12	S^c	1.13334	0.99997	0	1.13063	0.99995	0
16	S	1.14462	0.99992	1	1.14391	0.99954	0
18	S	1.15010	0.99972	1	1.14877	0.99969	1

^{a} r^2 = Coefficient of determination. ^{b} SE = standard error × 10^5 for a sample of 8. ^{c} Solid at room temperature.

According to Hildebrand (14) the partial molal volume of a solute is related to its solubility parameter, as follows:

$$\frac{\overline{v}_2 - v_2^0}{v_2^0} = \frac{(\delta_1 - \delta_2)^2}{(\partial E/\partial v)_T} \quad \text{(Eq. 10)}$$

Now, if $(\overline{v}_2 - v_2^0)$ and v_2^0 are divided by M_2, the molecular weight of the solute, a form is obtained in which δ could be related directly to specific volume:

$$\frac{\overline{V}_{s2} - V_{s2}^0}{V_{s2}^0} = \frac{(\delta_1 - \delta_2)^2}{(\partial E/\partial v)_T} \quad \text{(Eq. 11)}$$

For liquids, V_s^0 can be determined by direct measurement of density; hence, δ_2 can be calculated by measurement of $\overline{V}_{s2}$ in a reference solvent for which δ_1 and $(\partial E/\partial v)_T$ must be known. For solids, V_{s2}^0 is not usually readily accessible; in this case, measurements of $\overline{V}_{s2}$ in two reference solvents yield a set of two simultaneous equations from which the two unknowns, V_{s2}^0 and δ_2, may be calculated (*Appendix*).

EXPERIMENTAL

Apparatus—The high-precision, density-measuring assembly used consisted of a measuring cell unit and density meter with digital display[1]. The assembly was placed in a room in which the temperature was thermostatically controlled at 23 ± 1°. The measuring cell unit contained a U-shaped sample tube which was rigidly supported at its open ends. The sample tube was electromagnetically excited to vibrate at its natural frequency. The period of oscillation, T, of the sample tube was related to the density, d, of the sample contained within by the following relationship:

$$d = A(T^2 - B) \quad \text{(Eq. 12)}$$

where A and B were apparatus constants that had been predetermined by calibration with two fluids of known densities. The sample, ~0.7 ml, was injected into the sample tube with a hypodermic syringe. Excess fluid was allowed to overflow past the vibrating segment. After 2–3 min, thermal equilibration was reached and the period of oscillation was directly read on the digital display. The sample was removed and the tube flushed with solvent and dried with a stream of air until it reached the oscillation period of the empty tube; then a new sample was introduced. The thermostatic system consisted of a main thermostat—a circulator with suction and pressure pumps. The instrument had a digital temperature setting, an antidrift control, a heater capacity of 1000 W, and a cooling coil through which cold water could be run when necessary. The circulator was immersed in a glass cylindrical bath which contained 50 liters of water. The temperature in the bath was measured with a calibrated and tested glass thermometer[2] with a scale division of 0.1°. The temperature deviations in the bath and in the effluent line of the density-measuring cell were measured with thermometers[3] with a 0.01° scale division. Measurements at 25° required the use of a cooler system, which was coupled to the circulator of the main thermostat and which consisted of a control unit and a circulator. The cooler was immersed in 50 liters of water at 20 ± 0.5°. Altogether, the accuracy achieved inside the density-measuring cell that contained the sample was ±0.005°.

Materials—Straight-chain (>99% pure) and branched-chain (>98%) alkanoic acids, cyclopropane carboxylic acid (97%), cholesterol (>98%),

and cholesteryl esters (97–98%) were purchased from commercial sources. The solvents were carbon tetrachloride, chlorobenzene, and toluene (>99.5%); chloroform (99.8%); and nitrobenzene (>99%). Chloroform was pretreated with molecular sieves and redistilled before use.

Procedure—For each solute tested, at least eight different samples were weighed, each in a calibrated volumetric flask. The desired weight of solvent was then added. The solute mass fraction (y_2), which was usually in the range of 10^{-4} to 10^{-3}, was determined for each solution to the nearest hundred thousandth. The density meter was calibrated by measuring the oscillatory periods for air and distilled water. The solutions were introduced into the sample tube in order of increasing mass fraction, the oscillatory periods were determined, and the densities calculated. The actual data from these measurements is too voluminous for inclusion in this report; one example is reproduced to illustrate the operation involved (Table I). Thus, for each solution a set of data points was obtained giving the specific volume as a function of mass fraction. Curve fitting was made by a linear least-squares regression analysis program using a desk calculator. The coefficient of determination r^2, the value of $\overline{V}_{s2}$ at $y_2 = 1$, and the standard error, SE, in the estimate of $\overline{V}_{s2}$ on y_2 were derived through the same operation.

RESULTS AND DISCUSSION

Straight-Chain Alkanoic Acids—The partial specific volumes of straight-chain alkanoic acids, in each of two solvents, are given in Table II. The accuracy of measurement can be ascertained from the value of r^2, the coefficient of determination. The precision of data can be checked in each case from the intercept of the regression line with the ordinate at a mass fraction of solute $y_2 = 0$ (Fig. 1). Whenever the assumption of the working hypothesis was satisfied (*i.e.*, there should occur no detectable change in the specific volume of the solvent under working conditions), then the value of this intercept agreed with the specific volume of the solvent which could be determined independently. If this was not the case, then it could be inferred that there occurred an appreciable change in the slope of $\overline{V}_{s2}$ versus mass fraction y_2 over the range of concentrations tested. Usually, deviation from linearity became detectable in the mass fraction range $>10^{-2}$.

From the data of Table II the partial molal volumes were derived by application of Eq. 9 and solubility parameters by application of Eq. 11 for liquids (C_2–C_9) and solids (C_{12}–C_{18}) alike, the latter as supercooled liquids at room temperature (Table III). One sees a gradual decrease in δ as the contribution of the polar head becomes less important with the increasing length of the hydrocarbon chain. For a comparison of results with values of δ reported in the literature, some authors have made a distinction between a single solubility parameter, which is usually calculated from the heat of vaporization, and the total solubility parameter, which is the calculated sum total of dispersion, polar, and hydrogen-bond forces (16). The reported single solubility parameters for the acids, propionic (9.9) and valeric (9.8), are in fair agreement with the values presently reported; but that of butyric acid (10.5) is higher than the value found in this study (9.7). The opposite is true for acetic acid for which the total solubility parameter (10.5) (16) is closer to the present value (10.6) than its single parameter (10.1). The calculated value of the total solubility parameter of stearic acid (8.6) is significantly lower than found here (8.9). With the exception of this last example, no records of the solubility parameters of alkanoic acids that exist in solid form at room temperature were found.

The group contributions to v_2^0 and δ, derived from the present data, do not agree in all cases with values published previously (17). The mean

Table III—Molal Volumes (v_2^0), Partial Molal Volumes ($\bar{v}_2$), and Solubility Parameters (δ) of Straight-Chain Alkanoic Acids at 25° [a]

Number of Carbons in Molecule	v_2^0, cm³ mole⁻¹	$\bar{v}_2$, cm³ mole⁻¹ Carbon Tetrachloride	$\bar{v}_2$, cm³ mole⁻¹ Toluene	Increment per CH₂ Pure	Increment per CH₂ Carbon Tetrachloride	Increment per CH₂ Toluene	δ, cal^{1/2} cm^{-3/2} Carbon Tetrachloride	δ, cal^{1/2} cm^{-3/2} Toluene
2	57.51	60.09	59.87				10.5	10.7
				17.46	16.74	16.00		
3	74.96	76.83	75.80				10.0	9.9
				17.51	16.89	17.14		
4	92.47	93.72	93.01				9.7	9.6
				16.92	16.64	16.68		
5	109.29	110.36	109.69				9.5	9.5
				16.50	16.56	16.45		
6	125.80	126.92	126.14				9.5	9.4
				16.67	17.09	16.65		
7	142.47	144.01	142.79				9.5	9.3
				16.62	16.44	17.08		
8	159.09	160.45	159.87				9.4	9.5
				16.56	16.41	16.45		
9	175.65	176.86	176.32				9.3	9.5
				16.92	16.72	16.72		
12	226.41[b]	227.03	226.49				9.1	
				16.72	16.62	16.71		
16	293.28[b]	293.52	293.33				8.8	
				16.76	16.84	16.69		
18	326.81[b]	327.19	326.72				8.9	

[a] Derived from the data in Table II, by application of Eqs. 9 and 11; δ and $(\partial E/\partial V)_T$ for carbon tetrachloride, 8.6 and 81.0; for toluene, 8.9 and 83.0. [b] As supercooled liquid.

Table IV—Specific Volumes (V_{s2}^0), Partial Specific Volumes ($\bar{V}_{s2}$), Molal Volumes (v_2^0), and Solubility Parameters (δ) of Branched and Other Congeners of Butyric Acid [a]

Acid	V_{s2}^0, cm³ g⁻¹	$\bar{V}_{s2}$ in Carbon Tetrachloride, n = 8 cm³ g⁻¹	r^2	$SE \times 10^5$	v_2^0, cm³ mole⁻¹	δ, cal^{1/2} cm^{-3/2}
2-Methylbutyric	1.07352	1.08074	0.99996	0	109.65	9.3
3-Methylbutyric	1.08512	1.09830	0.99936	1	110.83	9.6
2-Ethylbutyric	1.08836	1.09961	0.99988	1	126.42	9.5
3,3-Dimethylbutyric	1.10194	1.10909	0.99992	1	128.00	9.3
Pivalic	S[b]	1.11104	0.99987	1	109.71	10.3
2-Phenylbutyric	S[b]	0.93129	0.99982	1	150.83	7.8
Cyclopropane carboxylic	0.92362	0.93187	0.99982	1	79.51	9.5

[a] At 25°; solvent data as in Table III. [b] Solids at room temperature; v_2^0 and δ were calculated by use of Eq. 11 and the following additional parameters: $\bar{V}_{s2\text{(toluene)}}$ for pivalic acid, 1.09819 (r^2 = 0.99918), for phenylbutyric acid, 0.93004 (r^2 = 0.99972).

incremental molal volume per CH₂ group for all compounds tested is 16.86 ± 0.60 (pure), 16.72 ± 0.45 (carbon tetrachloride), and 16.66 ± 0.57 (toluene) cm³ mole⁻¹. However, the inclusion of the lower alkanoic acids in the sample is questionable, in view of the observation that the incremental volume of propionic acid over acetic acid is larger in the pure state (17.46) than in solution in either carbon tetrachloride (16.74) or toluene (16.00), implying considerable contraction in these solvents. The significance of this observation is that a CH₂ group adjacent to a COOH group occupies relatively more space in the pure state than in solution in either solvent; i.e., its contribution to the partial molal volume in these states is reduced, even though $\bar{v}_2 > v_2^0$ for the molecule as a whole in almost all cases. In fact, the mean incremental molal volume for the series exclusive of propionic acid, 16.71 ± 0.15 (pure) or 16.68 ± 0.19 (toluene), is significantly different from the corresponding value in propionic acid ($p < 0.001$). The group contribution of a CH₂ group is listed (17) as 16.1 cm³ mole⁻¹ which, obviously, does not apply in the case of a CH₂ adjacent to COOH.

A more generalized presentation of data, inclusive of that of the lower alkanoic acids, may be made according to a previous study (18) where a linear relationship was found between the number of carbon atoms in a given homologous series and the square root of volume-cohesive energy product, $(-Ev)^{1/2}$, which is numerically equal to δv. A plot of δv of

Table V—Partial Specific Volume ($\bar{V}_{s2}$) of Cholesterol in Five Different Solvents [a]

Solvent	$\bar{V}_{s2}$, cm³ g⁻¹	r^2	SE 10^5
Carbon tetrachloride	1.01094	0.99981	1
Toluene	1.01000	0.99995	0
Chloroform	1.01300	0.99981	1
Chlorobenzene	1.01334	0.99981	0
Nitrobenzene	1.01764	0.99977	1

[a] At 25°, n = 8.

straight-chain alkanoic acids against the number of carbons in the chain is shown in Fig. 2. The fit to a straight line is excellent (r^2 = 1.00). The slope has a value of 0.14 (kcal liter)^{1/2} mole⁻¹ per carbon atom, as compared with 0.13 for hydrocarbons and ethers. A higher slope value is usually taken to mean a greater interaction energy between the CH₂ groups and the polar end groups (18).

Branched-Chain Alkanoic Acids—Table IV shows that branching has little effect on v_2^0 and δ, but with the notable exception of pivalic acid and cyclopropane carboxylic acid. Pivalic acid and 2-methylbutyric acid have practically identical molal volumes, but δ in the former is one unit larger than in its isomer. Also, the incremental molal volume in 3,3-dimethylbutyric acid over pivalic acid is 18.29 cm³ mole⁻¹ in the pure state, and which undergoes apparent contraction to 15.33 cm³ mole⁻¹ in carbon tetrachloride. Again, the relative contribution of α-methylene to molal volume is larger in the pure state (0.142) than in solution (0.119). The reason for the difference in δ between pivalic acid and its isomers is not clear at present. Obviously, it does not arise from a difference in v_2^0 of the respective compounds. Group contributions found previously (17) correctly predict the experimental values of v_2^0 for 2-methylbutyric acid (110.60) and pivalic acid (109.8), but not their δ values (9.6 and 9.9, respectively). The same calculations applied to cyclopropane carboxylic acid yield values that disagree with the experimental ones: v_2^0, 77.70 (calc.) against 79.51 (found); δ, 11.6 (calc.) against 9.5 (found).

The function relating δv to the number of carbon atoms in the straight chain alkanoic acids (Fig. 2) applies also to the branched-chain acids, but again with the exception of pivalic and cyclopropane carboxylic acids. Inclusion of 2-methyl-, 3-methyl-, 3,3-dimethyl-, and 2-ethylbutyric acids in the graph does not alter the correlation coefficient (r^2 = 1.00); but pivalic acid deviates by +0.1000 from the predicted value and cyclopropane carboxylic acid by −0.1350 (kcal liter)^{1/2} mole⁻¹. This may be taken as an indication that there is more interaction with the polar head in the former and less in the latter, relative to the corresponding straight-chain member.

Cholesterol—The partial specific volumes of cholesterol in five dif-

Table VI—Solubility Parameter (δ) and Molal Volume (v_2^0) of Cholesterol [a]

Solvent	Toluene		Carbon Tetrachloride		Chlorobenzene		Chloroform		Nitrobenzene	
	δ	v_2^0	δ	v_2^0	δ	v_2^0	δ	v_2^0	δ	v_2^0
Toluene			8.9	390.89	8.9	390.52	8.8	390.46	9.0	390.43
Carbon tetrachloride	8.9	390.89			8.9	390.17	8.8	390.65	9.0	390.13
Chlorobenzene	8.9	390.52	8.9	390.17			9.3	391.68	9.2	391.52
Chloroform	8.8	390.46	8.8	390.65	9.3	391.68			9.3	391.68
Nitrobenzene	9.0	390.43	9.0	390.13	9.2	391.52	9.3	391.68		
Mean	8.9	390.58	8.9	390.46	9.1	390.97	9.1	391.12	9.1	390.94
SD	0.1	0.21	0.1	0.37	0.2	0.74	0.3	0.65	0.2	0.77

[a] Derived from the data in Table V by application of Eq. 11 for solvent pairs; δ and $(\partial E/\partial V)_T$ of reference solvents: chlorobenzene, 9.5 and 93.2; chloroform, 9.3 and 86.6; nitrobenzene, 10.0 and 117.1; others as in Table III.

ferent solvents are given in Table V. These data were used to derive the two unknowns, solubility parameter and molal volume of cholesterol, by application of simultaneous equations (11) for solvent pair (Table VI). For each reference solvent, the mean value is listed at the end of the column. The relatively high δ derived from the more polar solvents is significant and needs explanation. In view of the accuracy and precision achieved in the measurement of densities in these solvents (Table V), we assume that the deviation of the experimental system from the theoretical model is minimal and cannot account for the differences among the reference solvents. There remains to be considered the reliability of the published values of δ and $(\partial E/\partial v)_T$ of the reference solvents. Solubility parameter data derived from ΔH^v are usually fairly reliable, but the energy–volume coefficient or internal pressure term, $(\partial E/\partial v)_T$, is a more problematic entity. Internal pressure values can be obtained through direct measurements of $(\partial P/\partial T)_V$, or indirectly by measuring the coefficient of expansion and isothermal compressibility. For most liquids, including some of those used in this study, the indirect and less reliable methods were used to derive the internal pressure values (19–21). Thus, the data derived from carbon tetrachloride and toluene are considered more precise than from the other solvents; the internal pressure of these two solvents had been measured directly.

The mean solubility parameter of cholesterol in the less polar solvents is 8.9, whereas the mean in the more polar ones is 9.1. The mean of means is 9.0 ± 0.1 cal$^{1/2}$ cm$^{-3/2}$ and v_2^0 is 390.81 ± 0.28 cm^3 mole^{-1}, as compared with a previous estimate (17) of 8.0 and 382.20, respectively.

The results for these compounds, all solid at room temperature, are summarized in Tables VII and VIII. The cholesteryl esters of straight-chain alkanoic acids deserve special consideration. If they are treated as a homologous series, a gradual decrease in δ with increasing length of the alkanoyl group, in analogy with the corresponding parent acids would be expected. But this is not the case. An attempt to relate $(-Ev)^{1/2}$ to the number of carbon atoms in the parent acid gave a poor correlation, $(-Ev)^{1/2} = 3.20 \pm 0.15 \, n, r^2 = 0.94$. The heptanoate ester has the highest δ value in the series, which then declines with either increasing or decreasing chain length. In this context, it should be recalled that compounds possessing liquid crystal properties exhibit unusual dependencies of their physical properties on chain length. The mesomorphic thermal transition of cholesteryl esters from cholesteryl formate to decanoate shows a similar, perhaps related dependency on chain length: the lower six members of the series exhibit only cholesteric mesophases, while the remaining members exhibit both smectic and cholesteric mesophases (22). Another example is offered by previous researchers (23) who observed a definite break at the butyl ester in the melting point and solubility profiles of a series of normal alkyl p-aminobenzoates. However, it has been noted (24) that the point of break in properties depends on the loading group, cholesteryl in the present case. In general, larger loading groups require more methylene units to offset their effect on crystal packing. While this generalization may explain the gradual decrease in cohesive energy density in the cholesteryl esters of longer chain than the heptanoate, it does not apply in the case of the lower esters, especially the butyrate which has an unusually low δ value. The emerging profile of δ with respect to chain length in this series may parallel the pattern of mesophase transitions mentioned earlier. In this respect, one must assume that some property of liquid crystal compounds persists into the isotropic phase. This is because the solubility parameter is an intensive property of matter, which, by definition, exists in the form of an isotropic liquid.

There remains to be considered the level of significance at which δ could be determined. This is an important issue in the context of drug distribution, because it can be shown that a hypothetical substrate (i.e., $\delta = 9.0$; $v_2^0 = 100$) will distribute at room temperature between two phases A and B (δ, 10.0 and 10.5, respectively) in a ratio of 0.81; the corresponding ratios for B having δ values of 10.6, 10.7, 10.8, are 0.77, 0.72, 0.68,

etc. From the preceding work, δ is calculated from values of partial molal volume that are significant to the second decimal point, and from solubility parameter and internal pressure data of the reference solvents, as published in the literature. Thus, the precision of the calculated δ values must reflect that of the published data.

In any case, a set of such values, generated by reference to a common set of solvents, must remain accurate enough to justify comparison between members, as given for the cholesteryl esters. In the present report, the values of δ for all reference solvents used were taken from a previous study (7). Data on $(\partial E/\partial V)_T$ were used as given for carbon tetrachloride, toluene (25); for chlorobenzene, nitrobenzene (Ref. 20) (given in kilobars (kbar), then transformed into cal$^{1/2}$ cm$^{-3/2}$ by multiplication by 1000/41.84); for chloroform (21), given at 20°, the data were transformed to 25° (19).

As a final check on the validity of the present procedure, the densitometric method was further applied to two reference compounds, as shown in Table IX. The values of the solubility parameter by the present method come very close to the values calculated from the heat of vaporization.

APPENDIX

For solids the solubility parameter of the solute, δ_2, and its molal volume, v_2^0, are derived by solving a set of two simultaneous equations:

$$\frac{\overline{V}_{s21} - V_{s2}^0}{V_{s2}^0} = \frac{(\delta_1 - \delta_2)^2}{P_{i1}} \qquad \text{(Eq. 13)}$$

$$\frac{\overline{V}_{s23} - V_{s2}^0}{V_{s2}^0} = \frac{(\delta_3 - \delta_2)^2}{P_{i3}} \qquad \text{(Eq. 14)}$$

where P_i stands for $(\partial E/\partial V)_T$, the internal pressure of two solvents 1 and 3, and the subscript 2 refers to the solute.

After rearrangement, the following quadratic equation is obtained:

$$a\delta_2^2 + b\delta_2 + c = 0 \qquad \text{(Eq. 15)}$$

where

$$a \equiv \frac{P_{i3}\overline{V}_{s23}}{P_{i1}\overline{V}_{s21}} - 1 \qquad \text{(Eq. 16)}$$

$$b \equiv 2\left(\delta_3 - \delta_1 \frac{P_{i3}\overline{V}_{s23}}{P_{i1}\overline{V}_{s21}}\right) \qquad \text{(Eq. 17)}$$

$$c \equiv \frac{P_{i3}\overline{V}_{s23}}{P_{i1}\overline{V}_{s21}}(\delta_1^2 + P_{i1}) - P_{i3} - \delta_3^2 \qquad \text{(Eq. 18)}$$

Table VII—Partial Specific Volumes ($\overline{V}_{s2}$) of Cholesteryl Esters in Two Reference Solvents, at 25°

Choles-teryl Esters	$\overline{V}_{s2}$ Carbon Tetrachloride			$\overline{V}_{s2}$ Toluene		
	cm³ g⁻¹	r^2	SE × 10⁵	cm³ g⁻¹	r^2	SE × 10⁵
Acetate	0.99845	0.99996	0	1.00172	0.99988	1
Propionate	0.99740	0.99981	1	1.00243	0.99982	1
Butyrate	1.00554	0.99984	1	1.01240	0.99991	1
Hexanoate	1.02041	0.99994	0	1.02433	0.99997	0
Hepta-noate	1.03220	0.99972	1	1.02918	0.99976	1
Laurate	1.05050	0.99977	1	1.04948	0.99974	1
Myristate	1.05130	0.99960	1	1.05501	0.99956	1
Palmitate	1.06078	0.99936	1	1.06201	0.99984	0
Stearate	1.06264	0.99968	1	1.06665	0.99974	1
Oleate	1.04773	0.99980	1	1.05717	0.99965	1
Chloride	0.98712	0.99970	1	0.99226	0.99998	0

[a] $n = 8$.

Table VIII—Molal Volumes (v_2^0), Partial Molal Volumes ($\bar{v}_2$), and Solubility Parameters (δ) of Cholesteryl Esters at 25° [a]

Cholesteryl Esters	v_2^0, cm^3 mole^{-1}	$\bar{v}_2$, cm^3 mole^{-1} Carbon Tetrachloride	Toluene	δ, cal$^{1/2}$ cm$^{-3/2}$
Acetate	427.54	428.04	429.49	8.3
Propionate	439.83	441.55	443.78	8.0
Butyrate	455.46	459.33	462.46	7.8
Hexanoate	493.77	494.69	496.60	8.2
Heptanoate	513.02	514.90	513.40	9.1
Laurate	597.12	597.72	597.12	8.9
Myristate	627.49	627.66	629.87	8.7
Palmitate	663.07	663.07	663.84	8.6
Stearate	692.81	694.04	696.66	8.2
Oleate	670.79	682.20	688.34	7.4
Chloride	398.19	397.02	401.98	8.0

[a] Derived from the data in Table VII by application of Eq. 11 for solvent pairs; solvent data as in Table III.

Table IX—Comparison Among Values of Solubility Parameter Determined by Various Procedures

Parameter	Method	Reference Compound Carbon Disulfide	Reference Compound Carbon Tetrachloride
v_2^0, cm^3 mole^{-1}	Present	60.63	97.10
	Ref. 6	60.7	97.1
$\bar{v}_2$, cm^3 mole^{-1} in carbon tetrachloride at 25°	present dilatometry (6)	62.36[a] 62.0	
In cyclohexane at 25°	present dilatometry (6)		97.46[b] 97.7
Solubility parameter, cal$^{1/2}$ cm$^{-3/2}$, calculated from $\bar{v}_2 - v_2^0)/\bar{v}_2$	present dilatometry (6)	10.1 10.1	8.7 8.9
From ΔH^v	Ref. 6	10.0	8.6

[a] $r^2 = 0.99890$. [b] $r^2 = 0.99980$.

The molal volume of the solute is given by:

$$v_2^0 = \frac{P_{i1}\bar{V}_{s21}M_2}{\delta_2^2 - 2\delta_2\delta_1 + \delta_1^2 + P_{i1}}$$ (Eq. 19)

As an example, the above was used to calculate values for δ_2 and v_2^0 for cholesterol by application to the data shown in Table V for the solvent pair nitrobenzene–toluene:

$$a = \frac{117.1 \times 1.01764}{83.0 \times 1.0100} - 1 = 0.42152$$

$$b = 2(10.0 - 8.9 \times 1.42152) = -5.30298$$

$$c = 1.42152\,(8.9^2 + 83.0) - 117.1 - 10.0^2 = 13.48403$$

$$\delta_2 = 9.04335 \to 9.0$$

$$v_2^0 = \frac{83.0 \times 1.01000 \times 386.66}{9.04335^2 - 2 \times 9.04335 \times 8.9 + 8.9^2 + 83.0} = 390.43$$

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