y = vertical direction, cm
y_e = position where a light ray enters the electrolyte, cm
Y = dimensionless vertical distance, y/δ
z = distance from electrode leading edge in the flow direction, cm

Greek Letters

β = interfacial velocity gradients, s^{-1}
β_∞ = interfacial velocity gradient, $h/w \rightarrow 0$, s^{-1}
γ = interfacial concentration gradient, M/cm
δ = boundary layer thickness, cm
δ_N = Nernst boundary layer thickness, cm
ΔC = concentration difference, $C_b - C_s$, M
Δn = refractive-index difference $n_b - n_s$
η = similarity variable; see eq 5
θ = dimensionless concentration, $(C - C_s)/(C_b - C_s)$
λ = light wavelength, nm
ν = electrolyte kinematic viscosity, cm^2/s
τ = dimensionless time; see eq 29
ϕ = constant; see Table II

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Estimation of Entropies of Fusion of Organic Compounds

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The entropy of fusion for many drugs and molecules of intermediate size can be estimated in the following manner: (1) for rigid molecules, $\Delta S_f \simeq 13.5$ eu; (2) for long chain derivatives of such molecules, $\Delta S_f \simeq 13.5 \pm 2.5(n - 5)$ eu, where n is the number of flexible links in the chain. In most cases, these simple rules will provide an estimate of ΔS_f which is sufficiently accurate to obtain reasonable estimates of ideal solubility.

According to Hildebrand (1950, 1962), the ideal solubility of a crystalline substance can be calculated from a knowledge (or an estimation) of either T_m and ΔH_f or T_m and ΔS_f. Because melting points are easily determined, it is only necessary to estimate ΔH_f or ΔS_f in order to estimate the ideal solubility of existing compounds.

Although heat of fusion can be measured experimentally, it has not been found possible to estimate this parameter directly from considerations of chemical structure (Bondi, 1968). There are, however, several empirical relationships between entropy of fusion and structure in the literature (Bondi, 1968; Walden, 1908; Pirsch, 1937, 1956; Luttinghaus and Vierk, 1949). The first and most important of these is the Walden Rule (which is analogous to Troutons Rule for entropy of vaporization). Walden (1908) observed that the entropies of fusion for most organic compounds fall in a fairly narrow range about 13 eu. The data of Tsonopoulos and Prausnitz (1971) show, in agreement with Walden, that entropy of fusion tends to be nearly constant but 13.5 appears to be a better average value.

Pirsch (1937, 1956) observed a relationship between overall molecular shape and ΔS_f, with spherical molecules having the lowest values and highly elongated molecules having the highest values. More recently, Bondi (1968) attempted to calculate ΔS_f from molecular moments of inertia and empirical corrections for hydrogen bonding groups.

The entropy of fusion of long-chain molecules has been discussed by several workers (Bondi, 1968; Pirsch, 1937, 1956; Aranow et al., 1958; Garner et al., 1926; Bunn, 1955) who have shown that there is a regular increase in ΔS_f with increasing chain length. The above relationships will provide much of the basis for the calculations offered in this report.
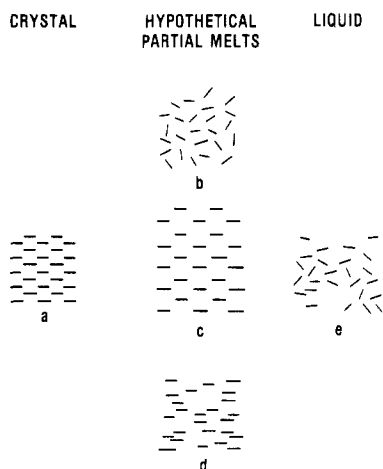
Figure 1. Schematic illustration of melting process: a, crystal; b, rotational melting; c, expansional melting; d, positional melting; e, liquid (complete melting).

Figure 2. Internal melting of flexible molecules: a, crystal; b, melt.

Entropy of Fusion

The most obvious difference between a crystal and its melt is the difference in their degrees of geometric order. The separation distance, packing arrangement, orientation, and conformation of molecules in a crystal are fixed within narrow limits, whereas in the liquid these parameters can vary over a much wider range of values.

For purposes of visualization, the melting process can be divided into four independent subprocesses: (1) expansional—the change in the average distance between molecules that usually occurs on melting and is evidenced by an increase in volume; (2) positional—the change from the ordered arrangement of molecular centers of gravity in the crystal to the randomized arrangement in the liquid; (3) rotational—the change from the ordered arrangement of the major axes of crystalline molecules to the randomly oriented arrangement in the liquid (This process is not applicable to spherical molecules); (4) internal—the change from the uniform conformation of flexible molecules of the crystal to the random conformation of such molecules in the liquid. (This process is not applicable to rigid molecules and thus to most drugs. It does become important, however, for long-chain molecules.) This strictly geometric interpretation of fusion provides an intuitive means of understanding the process in terms of molecular size, shape and interactions.

The first three subprocesses are illustrated schematically in Figure 1 and the fourth in Figure 2. Each of these submelting processes has associated with it a probability of occurrence and thus an entropy of occurrence. Since the probabilities are multiplicative, the entropies are additive

$$\Delta S_f = \Delta S_{exp} + \Delta S_{pos} + \Delta S_{rot}\ \Delta S_{int} \qquad (1)$$

it is possible to estimate the entropy of fusion from a consideration of the probabilities of the various processes.

Entropy of Expansion

The entropy of separation is similar in nature but smaller in magnitude than the entropy of vaporization. When a crystal melts there is usually, but not always, a slight increase in volume. The contribution to the entropy of fusion resulting from the change in free volume is calculated from the probabilities of finding a collection of liquid molecules in the crystal density. The volumetric probability is equal to the ratio of free volumes of the liquid and solid. The term free volume $V(f)$ as used here refer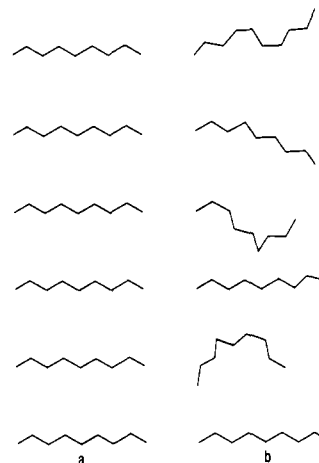s to the volume into which the centers of gravity of the molecules are free to move. It has also been called the fluctuation volume (Bondi, 1968). Therefore

$$P_{vol} = \frac{V(f)_{liq}}{V(f)_{solid}} \qquad (2)$$

and

$$S_f' = R \ln \frac{V(f)_{liq}}{V(f)_{solid}} \qquad (3)$$

Although the amount of expansion that occurs on melting and thus the entropy of expansion is largely dependent on molecular shape, it is usually found to lie between 1 and 3 eu. Compounds which are spherical or nearly spherical require very little expansion to attain free rotation and thus need expand only enough to allow for positional randomization of its molecules. Highly eccentric compounds, because of their greater space requirements for rotation, show much greater increases in volume on melting and consequently have higher expansional entropies of melting. Similarly, compounds, which, because of their shape, have high packing densities in the crystal, will have high entropies of expansion associated with melting.

Positional Entropy

The positional entropy of fusion as stated above is related to the probability of finding a collection of n molecules in the positions that are within the crystal lattice. This is analogous to the probability of finding 64 1-in. diameter checkers on an 8×8 in. checker board arranged so that the centers of all the checkers fall within a different square. The requirement that there are 64 checkers on a 64 in.^{2} surface and that there is no overlap of the checkers has been taken care of by the separation probability term. More sophisticated theoretical calculations of this type lead to calculated positional entropies of around 2 to 3 eu (Hirshfelder et al., 1937; Lennard-Jones and Devonshire, 1939).

The combined effects of separational and positional disorder can best be illustrated by the entropies of fusion observed for spherical molecules such as the inert gases, methane, etc. For these substances ΔS_f invariably falls between 2 and 4 eu. Since expansion on melting is minimal for these substances, the observed ΔS_f values can be regarded as being composed of primary ΔS_{pos}.

Rotational Entropy

In considering ΔS_{pos} for spherical molecules it is not necessary to be concerned with molecular orientation (since

Table I. Component Entropies of Fusion

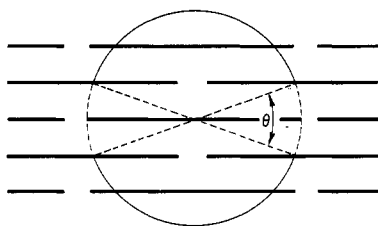| type of entropy | most likely values, eu | normal range of values, eu | |
		low	high
expansional	2	1	3
positional	2.5	2	3
rotational	9	7	11
total (rigid molecules)	13.5	10	17
internal	$2.5\,(n-5)$	(2.3–2.7)	$[(n-3)-(n-6)]$
total (flexible molecules)	$13.5 + 2.5(n-5)$		

Figure 3. Rotational freedom of crystalline molecule. Within the crystal, the rotation (libration) of a molecule is restricted by its nearest neighbors, whereas in the liquid it can rotate much more freely.

all orientations are equivalent for spherical molecules). However, in the case of nonspherical molecules (which includes nearly all drugs) the entropy associated with the change from a fixed orientation with respect to near neighbors in the crystal to the nearly random orientation of the liquid ΔS_{rot} is a major factor in determining the total entropy of fusion.

If the rotational entropy of fusion of all rigid molecules is assumed to be 7–11 eu, we would expect the total entropy of fusion to fall between 10 and 17 eu. (See Table I.) That this is the case for most compounds having melting points above 25 °C is obvious from the data in the literature (Aranow et al., 1958; Garner et al., 1926; Bunn, 1955). The near constancy of ΔS_f has been noted, but not explained by several early workers (Walden, 1908; Pirsch, 1937; Luttinghaus, 1949).

An intuitive justification of the nearly constant rotational entropy of fusion is based upon the following two assumptions. (1) In the crystal, the molecules with their centers of mass fixed (and accounted for by ΔS_{exp} and ΔS_{pos}) can "wobble" or librate to only a certain extent (say about 10° in the spherical coordinates ϕ and θ from their most stable position, after averaging over all axes). (2) In the liquid the individual molecules have nearly total orientational freedom and thus rotate freely in ϕ and θ.

The probability difference between these two different degrees of orientational freedom can be calculated by tracing the allowable positions of any point on the molecular surface. In a liquid molecule the chosen point will trace out a sphere about the center of mass, whereas in a crystal molecule it will only describe a segment of a sphere (see Figure 3). The size of the spherical segment with respect to the sphere is dependent only on the average values of ϕ and θ. (Free rotation in the liquid is assumed for mathematical convenience. It is not necessary for the applicability of the above approach.)

The area of a spherical segment obtained by a ±10° variation in θ and ϕ is 0.00754 times that of a sphere of the same radius. Thus, the probability of n molecules being oriented within the allowed limits for crystallinity is 0.00754^n and the entropy contribution is $-k \ln 0.00754^n$ or $-R \ln 0.00754$ or about 10 eu. Similarly, the entropy associated with $\theta = \phi = 20°$ is 7 eu. Although the actual values of θ and ϕ very likely will depend on the overall geometry of the molecules and their degree of interaction, the relative constancy of ΔS_f for rigid molecules suggests

Table II. Entropies of Fusion of Some Disubstituted Benzenes[a]

		CH₃	Cl	Br	NO₂	NH₂	OH	COOH
CH₃	ortho	13.2					12.4	12.8
	meta	12.4			11.4		9.0	9.8
	para	14.0		11.9	12.6	13.8	9.8	12.0
Cl	ortho		12.1		12.7		9.1	14.9
	meta		12.3		14.6		9.2	13.3
	para		13.1	13.3	14.0	13.8	11.1	15.0
Br	ortho			11.0	16.3		9.7	14.9
	meta			12.5	13.7			13.3
	para			13.5			10.5	15.0
NO₂	ortho				13.9	11.2	11.7	15.9
	meta				11.5	12.0	13.8	11.1
	para				15.1	14.6	15.0	17.2
NH₂	ortho							11.8
	meta							11.5
	para							10.8
OH	ortho						14.3	11.6
	meta						13.3	
	para						14.5	16.7

[a] All entropy values expressed in eu.

that the variation is not too large or that factors which inhibit rotation in the liquid also inhibit rotation in the crystal.

It has been proposed (Bondi, 1968) that hydrogen bonding groups such as OH and NH_2 allow association of liquid molecules and thus restrict free rotation of the liquid and that this results in a reduction in ΔS_f over the homomorphic CH_3 containing molecules. Analysis of the data in Table II suggests that this is not the case. The entropies of fusion of compounds which have no hydrogen bonding groups (left) are not significantly different from those of compounds having one (upper right) or two (lower right) hydrogen bonding groups. (Specifically o-, m-, and p-xylenes have nearly the same values as catechol, resorcinol, and hydroquinone, respectively.)

It is also evident from Table II that there is little systematic difference among ortho, meta, and para isomers. Evidently the increased symmetry of para isomers which would tend to decrease ΔS_{rot} is offset by their greater packing efficiency which tends to increase ΔS_{exp}.

Internal Entropy

If the compound under consideration is not a rigid molecule as discussed above, it becomes necessary to account for the entropy that results from the greater conformational freedom of the liquid. In a crystal, a molecule is not only fixed in its position and orientation but is also fixed in its conformation. Fatty acids and other long-chain compounds, for example, are fully outstretched in the crystal but may be coiled to some extent in the liquid.

A compound having a long chain of n carbons will have $n-1$ carbon carbon bonds, $n-2$ C–C–C bond angles, and $n-3$ C–C–C–C twist angles (this is equal to the number of bonds about which there is free rotation of nonhydrogen

atoms). The bond lengths and bond angles are not affected to any great extent by melting, but the twist angles are. In the fully stretched conformations of most crystals these angles are invariably 180°. In the liquid state, other angles, especially 60 and 300°, are likely to be observed. If these three angles are assumed to be equally probable, then the probability of finding a fully outstretched chain in $(1/3)^{n-3}$. This corresponds to an idealized internal entropy of fusion of

$$\Delta S_{int} = R \ln (1/3)^{n-3} = R(n - 3) \ln (1/3) = -2.3(n - 3) \quad (4)$$

Heteroatoms in the chain, e.g., amide nitrogens, ether oxygens, and ester oxygens, are included in the value of n.

Actually, the values of $\partial \Delta S / \partial n$ most often observed experimentally are 2.3 eu/CH_2 for homologous series of orthorhombic crystal forming compounds and 2.7 eu/CH_2 for series that form monoclinic crystals. In the absence of specific information about the type of crystal formed, a value of 2.5 eu/CH_2 can safely be used for purposes of estimation.

It has been observed for a number of different series containing alkyl groups attached to large rigid moieties (Breusch, 1969; Ubbelohde, 1965; Yalkowsky et al., 1972) that the melting behavior characteristic of aliphatic compounds is not observed until there are at least 4 to 6 atoms in the chain. This is in agreement with our observation that short chains ($n \leq 5$), which are configurationally constrained by the rigid portion of the molecule, do not contribute appreciably to ΔS_{int}. Therefore, molecules with less than 5 chain atoms, as a first approximation, can be treated as rigid molecules. (The actual chain length required for the aliphatic chain to dominate the crystal forming properties is dependent upon the size and interaction ability of the nonhydrogen portion of the molecule. In alkylbenzenes, benzoates, and parabens, 5 chain atoms are required whereas in alkylnaphthalenes, 6 chain atoms are required.) For longer chains we can estimate the contribution to internal entropy by adding 2.5 $(n - 5)$ eu, where n is the total number of chain atoms (exclusive of protons).

The total entropy of fusion of a flexible or semiflexible molecule is calculated from the sum of the four partial entropies described above. Table III gives calculated and observed entropies of fusion for some nonrigid molecules. Attempts (Bondi, 1968; Pirsch, 1937, 1956) to provide more sophisticated and/or more accurate estimates of entropy of fusion than the above variation of Walden's Rule tend to be more cumbersome and not consistently more accurate than the following

$$\Delta S_f = 13.5 \text{ eu for rigid molecules} \quad (5)$$

and

$$\Delta S_f = 13.5 + 2.5(n - 5) \text{ eu for flexible molecules} \quad (6)$$

Table III. Calculated Entropies of Fusion of Some Alkyl-p-aminobenzoates at 37 °C

ester	mp, °C	ΔS_f, obsd	$n - 5$	13.5 + 2.5 $(n - 5)$
methyl	112	15.1[a]	0	13.5[a]
ethyl	89	13.1	0	13.5
propyl	74	14.6	0	13.5
butyl	56	17.8	1	16.0
pentyl	52	17.8	2	18.5
hexyl	61	25.2	3	21.0
heptyl	75	18.1	4	23.5
octyl	71	28.3	5	26.0
nonyl	69	31.4	6	28.5
dodecyl	82	41.5	9	36.0
hexadecyl	87	55.5	13	46.0

[a] All entropy values are expressed in eu.

The ideal solubility of many crystalline compounds can be estimated from the melting point and entropy of fusion as given by eq 5 and 6.

Because the above treatment is based on many assumptions and approximations, it cannot be expected to provide highly accurate solubility estimates for all compounds. It does, however, provide a very simple means of obtaining a reasonable estimate of ideal solubility from nothing more than the structure and melting point of the compound in question. If means were available for predicting melting point from chemical structure, this type of approach could be used for the design of compounds having desired solubility properties.

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