Figure 1—*Effect of temperature on the ratio of the solubility of microcrystalline griseofulvin, S, and crystalline griseofulvin, S_0. (See text for explanation.)*

interpretations have been referred to previously. No organic solid seems to have been investigated with any degree of precision. Qualitatively, however, it may be noted that heats of solution for fine particles have been measured for many salt systems and are found to be more negative than for large crystals [1]. The values of the interfacial energy per square centimeter, E^s ($E^s \approx H^s$ for condensed systems), found are quite appreciable. For sodium chloride, for example, the heats of solutions in water led to an interfacial energy estimate of 276 ergs/cm.^{2} [5] as compared to the interfacial free energy of 171 ergs/cm.^{2} in alcohol [6], suggesting that S^s is positive. These values compare reasonably well with the surface tension of 190 ergs/cm.^{2} for liquid sodium chloride measured at its melting point [7].

One system investigated rather thoroughly was fine magnesium oxide [8, 9]. From precise heats of solution and heat capacity measurements [8, 9] of coarse and fine crystals, it was found that at 298°K, the value of H^s was 1040 ergs/cm.^{2} whereas the value of G^s was 1000 ergs/cm.^{2}, again indicating a positive value of S^s and the overwhelming importance of H^s.

It seems, therefore, that in general the higher solubility of finely dispersed solids should be mainly due to enthalpy effects. Smolen and Kildsig [4] presented some solubility data for griseofulvin in support of their thesis that the increase in solubility of finely divided particles is entirely due to entropy changes. These authors, however, compared the gross heats of solution of coarse and fine crystals, about 8.6 kcal./mole, which is very large when compared to the expected *difference* of a fraction of a kcal. between the two heats of solution arising out of particle-size effects. This difference in the heat of solution, $\Delta (\Delta H)$, can be obtained from Eq. 1 by the usual manipulation in the form of a van't Hoff relation:

$$\frac{d \log (S/S_0)}{d(1/T)} = -\frac{\Delta (\Delta H)}{2.303R} \qquad \text{(Eq. 3)}$$

so that the relation of $\Delta (\Delta G)$, $\Delta (\Delta H)$, and $\Delta (\Delta S)$ in Eq. 4 can be investigated:

$$\Delta (\Delta G) = \Delta (\Delta H) - T\Delta (\Delta S) \qquad \text{(Eq. 4)}$$

Figure 1 shows the plot of log (S/S_0) for griseofulvin against $1/T$ from the data of Smolen and Kildsig [4]. The data scatter a great deal. By using a mean value of

log (S/S_0) = 0.178 when $1/T$ = 3.22 $\times$ 10^{-3}, three lines are drawn in the figure for three different values of $\Delta (\Delta H)$: (a) $\Delta (\Delta H)$ = 0 as suggested by Smolen and Kildsig [4] so that $\Delta (\Delta G)$ = $-T\Delta (\Delta S)$; (b) $\Delta (\Delta H)$ = $\Delta (\Delta G)$ so that $\Delta (\Delta S)$ = 0; and (c) $\Delta (\Delta H)$ = $2\Delta (\Delta G)$; i.e., $\Delta (\Delta S)$ is now negative and $\Delta (\Delta G)$ = $T\Delta (\Delta S)$. It is obvious that the data are at least as consistent with choices (b) and (c) as with (a) and that no firm conclusion can be derived from these data as regards the relative importance of surface enthalpy and surface entropy effects in the solubility of finely divided griseofulvin. Precise calorimetric measurements of heats of solution will probably be needed, as in the case of the inorganic systems, to establish the importance of $\Delta (\Delta H)$ and, therefore, H^s as compared to $T\Delta (\Delta S)$ and S^s. The solubility data clearly do not provide a sound basis for forsaking the well-established classical theory [1, 2] in favor of a mechanistic interpretation of the effect of particle sizes on solubility in terms of entropy changes alone [3, 4].

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The Kelvin Equation and Solubility of Small Particles

Sir:

It was recently proposed (1, 2) that the increased solubility of small particles is due primarily to a larger entropy of solution for fine particles as compared to

coarse ones. I believe that this interpretation of the small-particle phenomenon is incorrect for the reasons given below. In this discussion, any of the problems associated with the application of the Kelvin equation to solids, rather than liquids, will be omitted.

It was hypothesized that the enthalpy of solution is independent of particle size (1, 2). However, the surface enthalpy (or energy, which is nearly the same for surfaces), h, exists and generally has a positive value larger than the surface tension (3). The enthalpy of a mole of material is $\bar{H} + hA$, where $\bar{H}$ is the molar enthalpy and A is the area. If one had two samples of material, each containing a mole but with one having a much larger surface area, it is apparent that their enthalpy would be different. This would necessitate a difference in the heats of solution for the two samples, which would be contrary to the above hypothesis. It may be a small difference, however, since surface properties are generally of much less magnitude than thermodynamic properties involving phase changes.

Experimental evidence apparently supporting the above hypothesis was presented as a van't Hoff plot of the relative solubilities of microcrystalline and crystalline griseofulvin (1). An alternative to the van't Hoff plot is a plot of log solubility *versus* log temperature, for which the slope is equal to the entropy of solution divided by the gas constant (4). Plotting the data given in *Reference 1* by this method yields lines as parallel as those presented as evidence (1) and implies that the entropy of solution is also independent of particle size. The obvious conclusion then is that the free energy of solution is independent of particle size, which is in direct conflict with the data and the Kelvin equation. In the derivation of the van't Hoff equation, there is no consideration of surface properties, so it would seem inappropriate to apply it directly in this case.

It was argued that a molecule within a crystal is at a state of maximum randomness because of a uniformity of forces acting on the molecule and, further, that molecules at a surface have a relatively lower entropy because of the unbalance of forces; hence, an increased entropy of solution for surfaces was thought to exist (1, 2). Actually, the opposite is true. The high degree of order in a crystal gives it an entropy that is low relative to a liquid or gaseous state. Molecules brought to the surface experience a certain freedom or randomness which gives rise to an entropy increase (5). If anything, this would indicate a decreased change in entropy for molecules leaving a surface and entering the solution as compared to molecules dissolving from within the particle.

A two-step sequence was proposed to describe the entropy change upon dissolution. A ratio of the number of subsurface molecules exposed to the number of molecules dissolved was included to account for the geometry of the particles undergoing dissolution (1, 2). While the entropic factor has already been adequately discussed, a comment on the second point is in order. The consideration of this arbitrary ratio is superfluous since in the derivation of the Kelvin equation, which may be found in any surface chemistry text, the critical relationship is the differential change in area with a differential change in the number of moles transferred

from a flat region to a small spherical particle:

$$\frac{dA}{dn} = \frac{2\bar{V}}{r} \tag{Eq. 1}$$

where n is the number of moles, $\bar{V}$ is the molar volume, and r is the radius of the particle. Implicit in dA/dn is the fact that for each layer of molecules removed from the surface, there is a smaller number of molecules in the succeeding layer exposed. This term is the very essence of the Kelvin equation. As the particle becomes progressively smaller, dA/dn becomes increasingly important. The product of surface tension and dA/dn gives the molar free energy change which gives rise to the increased vapor pressure or solubility.

In summary, as indicated by the Kelvin equation, the important factors in the small-particle phenomenon are the surface (or interfacial) tension and the particle size. Surface enthalpy and surface entropy both exist and are related to surface tension through the usual thermodynamic relationships.

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Correlation between Potency and UV Spectra of Hallucinogenic Amphetamines

Sir:

Recent work has shown that the energy of the highest occupied (π) molecular orbital correlates with the hallucinogenic potency of methoxylated amphetamines (1–4). Higher energies are associated with greater potency, although the 4-methoxy and 2,4,6-trimethoxy compounds are anomalously active by this analysis, which necessarily ignores such variables as steric effects and metabolic processes (2). Kang and Green (2, 3) suggested that the ease of perturbability of the π-electrons allows the formation of a low energy, reversible, π-molecular complex with a brain receptor. Such