

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:

$$\frac{dA}{dn} = \frac{2\bar{V}}{r} \quad (\text{Eq. 1})$$

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

Keyphrases □ Amphetamines, methoxylated—UV spectra correlated with hallucinogenic potency □ Hallucinogenic activity of methoxylated amphetamines—correlated with UV spectra □ Structure-activity relationships—methoxylated 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

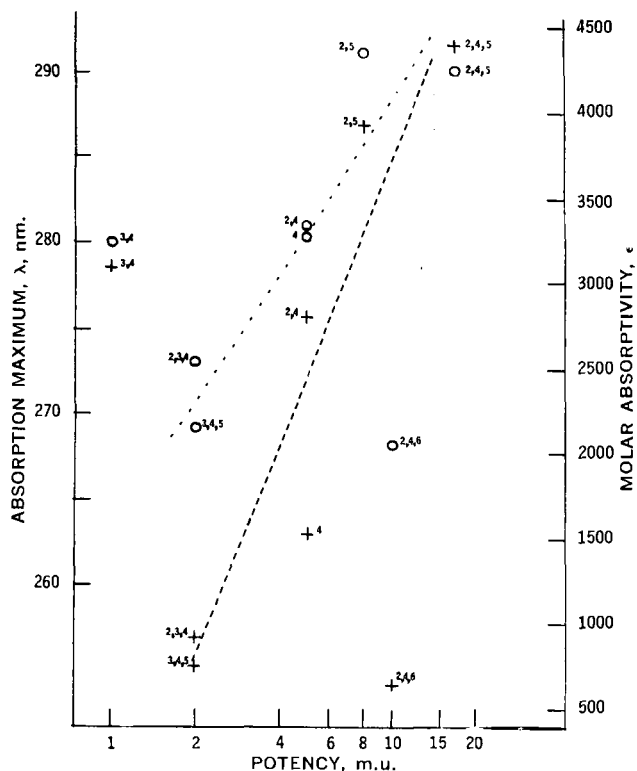


Figure 1—Log potency (m.u.) in humans versus UV absorption maximum, λ (nm.) (---○---), and log potency versus molar absorptivity, ϵ (---+---). The numbers adjacent to the points show the positions of methoxy group substitution on the benzene ring of amphetamine. Spectra were determined on the methoxyamphetamine hydrochloride in ethanol. If the 3,4-dimethoxyamphetamines and 2,4,6-trimethoxyamphetamines are neglected, the linear regression equations are expressed by:

$$\log \text{potency} = -9.96 + 0.0380 \lambda \quad (r = 0.94, F = 28.15, p < 0.01)$$

$$\log \text{potency} = 0.176 + 0.000213 \epsilon \quad (r = 0.94, F = 27.92, p < 0.01)$$

A significant correlation is not obtained if these apparently anomalous compounds are included in the regression analysis:

$$\log \text{potency} = -4.99 + 0.020 \lambda \quad (r = 0.42, F = 1.32, 0.1 < p < 0.5)$$

$$\log \text{potency} = 0.434 + 0.000091 \epsilon \quad (r = 0.33, F = 0.75, 0.1 < p < 0.5)$$

interactions could resemble those proposed in explaining the benzene-induced solvent shifts in the PMR spectra of polar solutes, where it is generally considered that the π -bonds of the aromatic ring interact with an electron-deficient region of the solute, perhaps forming a low energy 1:1 complex ($-\Delta H$ about 1–2 kcal./mole) (5).

Antun *et al.* (6) recently demonstrated a correlation between the degree of native fluorescence of methoxy-substituted amphetamines and their hallucinogenic potency but they noted that the activities of the 3,4-dimethoxyamphetamine and 2,4,6-trimethoxyamphetamine appeared to be anomalously low and high, respectively. Appropriate bands in the UV spectra of aromatic compounds are functions of the energy of the π -electrons. The π - π^* or local excitation band (7) of substituted benzenes results from the perturbation of the π -electrons to a more polar state. It seemed possible that a correlation between this electronic transition and the ease of formation of the excited π -state involved in the π -receptor complex might exist (despite the differences in the mechanisms involved), since the energy differences

of the two processes for a series of structurally similar compounds could well be different functions of the same variables.

Figure 1 shows our results for the UV spectra of eight methoxylated amphetamine hydrochlorides which we prepared and for which hallucinogenic activity data (expressed in the figure as log potency in mescaline units, m.u.) are available (8). The λ_{max} of the 4-methoxy and dimethoxy compounds is given as the center of a shallow trough in the absorption maximum, about 4 nm. wide. The relationship between λ_{max} and potency and between the molar absorptivity (ϵ) and potency are indicated by the graph lines. The lower energy of the π - π^* transition and the increased probability of it occurring (7) (λ_{max} correlates with ϵ for this series) appear to correlate positively with hallucinogenic potency. However, the activities of 3,4-dimethoxyamphetamine and 2,4,6-trimethoxyamphetamine are anomalous in the sense observed by Antun *et al.* (6), the degree of agreement in our work being similar to that presented by them.

The results seem to offer supporting evidence for the substrate-receptor model proposed (2).

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Effect of Levodopa upon Plasma Levels of 17-Hydroxycorticosterone

Keyphrases □ Levodopa—chronic treatment, effect on plasma levels of 17-hydroxycorticosterone, dogs □ 17-Hydroxycorticosterone plasma levels—effect of chronic levodopa treatment, dogs □ Plasma levels, 17-hydroxycorticosterone—effect of chronic levodopa treatment, dogs

Sir:

It has been observed that an intravenous single dose of levodopa (50 mg./kg.) inhibits the increase of 17-hydroxy corticosteroid in the adrenal vein of the dog in association with surgical stress (1). An effect mechanism