

$\ln(\nu - \nu_e) = -kt + \ln(\nu_t - \nu_e)$ (1) where ν is the agglomerate population density (cm^{-3}) at time t (min), ν_e is the population density at equilibrium, ν_t is the initial flocculated population density and k is the first order constant (min^{-1}).

Differences in behaviour were observed between the finer particles ($<24 \mu\text{M}$) and the coarse. The bridging liquid level, R_p , required for good microagglomeration ranged from 6 to 50% for the former and from 65 to 122% for the latter. The rate constant for primary agglomeration was at least an order of magnitude less for the fine particles. Both of these differences may be explained by the much larger capillary cohesive forces acting in the agglomerates of very fine powders. In addition, a secondary agglomeration phenomenon was observed with the fine materials at long agglomeration times for R_p in the range 25 to 50%. This secondary process was 15 to 25 times faster than the primary agglomeration and, as was the case with all the experiments with coarser particles, ν_e approached zero. In contrast, ν_e had a large finite value for the fines at $R_p < 25\%$.

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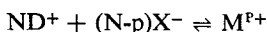
Self-association of some antihistamines in aqueous solution

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The self-association of the antihistaminic drugs, tripeleannamine HCl, thenyldiamine HCl, mepyramine maleate, pheniramine maleate, chlorpheniramine maleate and brompheniramine maleate in aqueous solution has been investigated by light-scattering methods. The scattering intensity, S_{90} , of these compounds was in excess of that calculated for unassociated monomers. No significant discontinuity in the concentration-dependence of S_{90} , attributable to a critical micelle concentration (cmc) could, however, be detected. This is in contrast to antihistaminic drugs based on the diphenylmethane nucleus (e.g. chlorcyclizine HCl, diphenhydramine HCl, diphenylpyraline HCl and bromodiphenhydramine HCl) which exhibited appreciable discontinuities in their physico-chemical properties at well defined critical micelle concentrations (Attwood, 1972).

Two possible models for the association of these drugs were investigated. In the 'closed association' model normally encountered in micellar systems, the cationic micelle M^{P+} is assumed to be formed by an all-or-none process from N monomers (D^+) and $(N-p)$ firmly bound anions (X^-).



The abruptness of the change in physical properties at the cmc decreases with decrease in N and in the equilibrium constant, k , of the micellization process. It was possible to simulate the light scattering plots of tripeleannamine, thenyldiamine and pheniramine assuming aggregation numbers of $N = 3$ and 4 and k values of 10^{10} and 10^{14} respectively. It was not, however, possible to reproduce the scattering plots of the remaining compounds using this model.

The 'open association' model assumes micellar growth by monomeric addition and predicts a continuous distribution of multimers of varying degrees of association. An analytical method proposed by Steiner (1952) was used to calculate equilibrium constants, K_N , for the formation of N -mer from $(N-1)$ -mer. Data were fitted using the polynomial

$$M_w/xm = 1 + 4k_2(xc/m) + 9k_2k_3(xc/m)^2 + \dots + N^2 \left(\prod_{N=2}^N k \right) \left(\frac{xc}{m} \right)^{N-1}$$

M_w is the apparent weight-average molecular weight, m is the monomer molecular weight and x is the mole fraction of monomer as derived by graphical integration of the light-scattering data. Theoretical curves could be generated using this model which satisfactorily reproduced the light-scattering behaviour of all compounds.

Attempts to detect a cmc by other physical methods also proved unsuccessful. It is suggested that the 'open association' model provides the most suitable description of the self-association of these systems.

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Ortho-Effects in structure-activity studies. Shielding of hydroxyl by alkyl groups

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Leo, Hansch & Elkins (1971) have commented that *o*-alkyl substitution in a phenol should shield the hydroxyl group and hence should make the compound more lipophilic. This is certainly the case in cyclohexane-water partition, as the following data (Saha, Bhattacharjee & others, 1963) show:

<i>Compound</i>	π
Phenol	0.00
<i>o</i> -Cresol	0.87
<i>p</i> -Cresol	0.58
2,6-Xylenol	1.70
3,5-Xylenol	1.04

We find a very different effect when the solvent pair is octanol-water, in a series of alkyl derivatives of paracetamol (4-hydroxy-acetanilide), as the following table shows:

<i>Substituent(s)</i>	π
3-Methyl	0.48
3-Ethyl	0.99
3-isoPropyl	1.40
3- <i>t</i> -Butyl	2.05
3,5-Dimethyl	0.80
3,5-Diethyl	1.56
3,5-Diisopropyl	2.36
3,5-Di- <i>t</i> -butyl	2.87

The π -value for 3-methyl is close to the value of 0.51 reported by Draber (1973) for 3-methylacetanilide, and the value for 3-ethyl is about twice this; the 3-isopropyl value is rather less than three times the methyl value, as branching tends to lower π (Leo & others, 1971). The rather high 3-*t*-butyl value may reflect some shielding of the lone pair of the oxygen of the hydroxyl group. There is no indication of the entropic lowering of π proposed by Leo & others (1971).

A striking phenomenon occurs on 3,5-dialkyl substitution in paracetamol, for the π -values are in each case appreciably lower than twice the corresponding monoalkyl π -value. Part of this effect may be entropic, but we suggest that it is produced largely by shielding. In contrast to cyclohexane-water partition, both octanol and water compete for the hydroxyl group; if this group is shielded, then water, being a much smaller molecule than is octanol, can more readily gain access, so that the partition coefficient is lower than expected. The effect is particularly marked in 3,5-di-*t*-butylparacetamol, for the partition coefficient of that compound is lower by a factor of 13.5 than the value predicted from mono-*t*-butyl