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.

REFERENCES

ATTWOOD, D. (1972). *J. Pharm. Pharmac.*, **24**, 751–752.
STEINER, R. F. (1952). *Archs Biochem. Biophys.*, **39**, 333–348.

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 cyclohehexane-water partition, as the following data (Saha, Bhattacharjee & others, 1963) show:

Compound	π
Phenol	0·00
o-Cresol	0·87
p-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:

Substituent(s)	π
3-Methyl	0·48
3-Ethyl	0·99
3-isoPropyl	1·40
3-t-Butyl	2·05
3,5-Dimethyl	0·80
3,5-Diethyl	1·56
3,5-Diisopropyl	2·36
3,5-Di-t-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

substitution. Such behaviour must be taken as a warning against the use of calculated partition coefficients in structure-activity studies.

REFERENCES

DRABER, W. (1973). Paper presented at First Internfitional Structure-Activity Conference, Prague, June 27–29.

LEO, A., HANSCH, C. & ELKINS, D. (1971). *Chem. Rev.*, **71**, 525–616.

SAHA, N. C., BHATTACHARJEE, A., BASAK, N. G. & LAHIRI, A. (1963). *J. Chem. Eng. Data*, **8**, 405–408.

Hydrophobic substituent constants from thin-layer chromatography on polyamide plates

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The use of reversed-phase chromatography for the determination of hydrophobic substituent constants is quicker and more convenient than is the determination of partition coefficients (Dearden & Tomlinson, 1972). However, difficulties are sometimes experienced during saturation of the plates with the stationary phase, and this procedure is also time-consuming. Draber, Buchel & Dickore (1972) showed that, within a given series of substituted triazinones, the use of polyamide plates gave R_M values that correlated well with log P (octanol–water). The polyamide itself acts as the lipophilic phase, and the plates can thus be used as received.

We have investigated whether the relation reported by Draber & others (1972) was general or not, by determining octanol–water partitition coefficients and R_M values of seventeen alkyl derivatives of paracetamol, and R_M values of twelve *p*-substituted acetanilides; partition coefficients of the latter compounds were taken from Dearden & Tomlinson (1971). The solvent used in the chromatographic work was water–acetone–dioxan, 2:1:1 by volume. Plates were Merck Polyamid 11 F254, 20 cm × 20 cm. Triazinone data were taken from Draber (1973). ΔR_M and π-values for all three series of compounds were plotted on the same axes, and with the exception of three compounds, which gave points slightly below the line, a good rectilinear correlation was obtained. The regression equation is:

$$\Delta R_M = 0{\cdot}027 + 0{\cdot}456\pi;\ n = 42,\ r = 0{\cdot}991,\ s = 0{\cdot}075,$$

where r is the correlation coefficient and s is the standard deviation. Thus the general validity of the relation is established for widely differing classes of compounds.

The points lying below the line represent *N*-methylacetanilide, 3,5-diisopropyl-4-hydroxy-acetanilide and 3,5-di-t-butyl-4-hydroxy-acetanilide. The hydrogen bonding ability of all of these compounds is low, due to either blocking or shielding of hydrogen bonding groups. This has a more marked effect on ΔR_M than on π because of the rigidity of the polyamide molecules, which cannot approach hindered groups on the solute molecules so closely as can octanol.

Polyamide may also be considered as a model protein, and in fact a better correlation is found between log K (binding constant to bovine serum albumin, Dearden & Tomlinson, 1970) and ΔR_M than between log K and π, for the *p*-substituted acetanilides:

$$\log K = 4{\cdot}381 + 0{\cdot}483\pi;\ n = 12,\ r = 0{\cdot}925,\ s = 0{\cdot}146$$

$$\log K = 4{\cdot}359 + 0{\cdot}939\Delta R_M;\ n = 12,\ r = 0{\cdot}981,\ s = 0{\cdot}076.$$

Thus the method may also be useful as a convenient way of determining a protein-binding parameter.