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DISSOLUTION KINETICS OF SOME ALKYL DERIVATIVES OF ACETAMINOPHEN

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ABSTRACT

Intrinsic aqueous dissolution rates are shown to be better related to octanol-water partition coefficients than to aqueous solubilities, for six alkyl derivatives of acetaminophen. Aqueous solubilities are shown to relate surprisingly well to partition coefficients, but this is probably due to the very close structural similarity of the compounds investigated. The activation energy of dissolution does not vary greatly with lipophilicity, which suggests that the mechanism of dissolution is the same for all the compounds studied.

INTRODUCTION

The first step in the movement of the active ingredient of a solid oral dosage form towards the receptor site is dissolution in the aqueous medium of the gastro-intestinal tract. Most workers concerned with correlating biological potency with physico-chemical properties have neglected dissolution rate and solubility as parameters. Dearden, Collett and Tomlinson (1) showed that improved correlations could be obtained by the inclusion of

intrinsic dissolution rate (D), and Collett and Koo (2) found rectilinear relationships between log D and log P (P = partition coefficient) for benzoic acids and acetanilides. This perhaps explains why quantitative structure-activity relationships (QSARs) using only log P as a parameter can be successful for solid orally administered drugs.

Nonetheless, it is our view that dissolution rate, and perhaps solubility also, are important parameters in their own right in QSAR studies, and we have therefore examined in detail the dissolution behaviour of a series of derivatives of acetaminophen substituted in the aromatic ring by alkyl groups.

MATERIALS

Acetaminophen (British Drug Houses Ltd.) was recrystallised from aqueous ethanol until melting-point and spectrophotometric examinations showed it to be sufficiently pure. The derivatives were prepared by a modification of the method of Albert (3), as described elsewhere (4), and recrystallised from aqueous ethanol.

METHODS

Solubility

Aqueous solubilities were determined as 25^{o} by equilibrating excess of finely ground solid with solution. Concentrations were determined spectrophotometrically on a Hitachi-Perkin Elmer 139 instrument.

Dissolution rate

Flat-faced, non-disintegrating compacts were prepared using a pressure of 4.5 tonne.cm^{-2}. Compact diameter was 1.305 cm and

thickness ranged from 0.25 to 0.45 cm. Compacts were attached to the flattened end of a glass stirrer with Canada balsam, and the edges coated with hard paraffin wax (m.p. 56-60°) so that only one face of the compact was exposed.

The dissolution vessel was a 500 ml beaker containing 400 ml of water, externally thermostatted. The dissolution medium was stirred magnetically at 250 r.p.m. clockwise, and the compact was rotated anti-clockwise at 60 r.p.m., with the surface of the compact 5.6 cm below the liquid surface and 2.0 cm above the bottom of the beaker. Samples of 1 or 5 ml were taken every five minutes, and were replaced by fresh water. Analysis was carried out on the Hitachi-Perkin Elmer 139 spectrophotometer, with sample dilution if necessary. Dissolution appeared to obey zero-order kinetics in all cases, and the dissolution rates were determined for each compound at six temperatures from 20° to 50°.

RESULTS

Arrhenius plots of log D verses reciprocal absolute temperature gave good straight lines in all cases, from which the activation energies were calculated. The results are given in Table 1, as are aqueous solubilities.

DISCUSSION

Hansch, Quinlan and Lawrence (6) found good relationships between aqueous solubility (S) and octanol-water partition coefficient for organic liquids, but commented that the variation of lattice energy gave rise to poor correlations for solids. Yalkowsky (7) has recently attempted to correct for this by

TABLE 1

Substituent	M.p. (°C)	Solubility at 25° (mole fraction)	Intrinsic dissolution rate at 25° (mole.cm^{-2}.min^{-1})	Activation energy (kJ.mole^{-1})	Octanol-water partition coefficient[a]
H	171	1.667×10^{-3}	1.493×10^{-5}	47.87	2.05
2-CH_3	181	4.584×10^{-4}	2.958×10^{-6}	51.12	6.21
2,5-$(CH_3)_2$	181	1.748×10^{-4}	4.365×10^{-6}	38.17	3.95
2,6-$(CH_3)_2$	164	2.214×10^{-4}	2.042×10^{-6}	43.78	12.82
2,6-$(C_2H_5)_2$	146	5.301×10^{-5}	2.938×10^{-7}	44.68	74.8
2,6-$(CH(CH_3)_2)_2$	172	1.052×10^{-5}	5.321×10^{-8}	44.61	469

[a]Taken from ref.5

introducing melting-point as a parameter. The present results show, for solids, a remarkably good correlation between log S and log P:

$$\log S = -0.809 \log P - 2.806 \quad (1)$$

$$n = 6,\ r = 0.944,\ s = 0.280$$

This good correlation is probably due to the close structural similarity of the compounds; this is borne out by the fact that when the 2,5-dimethyl derivative (the only compound substituted adjacent to the acetamido group) is omitted, the correlation is much better (equation (2)).

$$\log S = -0.911 \log P - 2.574 \quad (2)$$

$$n = 5,\ r = 0.998,\ s = 0.069$$

Collett (8) has similarly found, for a series of p-substituted acetanilides, a good correlation between aqueous solubility and lipophilicity:

$$\log S = -1.28\pi - 1.30 \quad (3)$$

$$n = 9,\ r = 0.967,\ s = 0.205$$

Inclusion of melting-point (t) as a parameter did not improve the correlation of equations (1) and (2). For example, with all six compounds,

$$\log S = -0.854 \log P - 0.0073t - 1.523 \quad (4)$$

$$n = 6,\ r = 0.951,\ s = 0.304$$

Such a lack of improvement is perhaps not surprising in view of the small variation of melting-point amongst the compounds.

The intrinsic dissolution rate at 25° was found to be closely related to both solubility and partition coefficient:

$$\log D = 1.120 \log S - 1.616 \quad (5)$$

$$n = 6,\ r = 0.964,\ s = 0.264$$

$$\log D = -0.990 \log P - 4.655 \quad (6)$$

$$n = 6,\ r = 0.994,\ s = 0.106$$

Omission of the 2,5-dimethyl derivative greatly improved the correlation of log D with log S, although it did not significantly affect that of log D with log P. We are left with the conclusion that dissolution rate generally correlates better with partition coefficient that with solubility. Collett and

Koo (2) similarly found excellent relationships between log D and π; e.g. for 3-substituted benzoic acids:

$$\log D = -1.29\pi - 5.31 \quad (7)$$

$$n = 6,\ r = 0.980,\ s = 0.168$$

The results thus lend support to the suggestion made above that the log P term in many QSARs contains a dissolution rate factor, as well as a transport and a receptor-binding factor.

The dissolution rates given in Table 1, and used in equations (5) and (6), were calculated as being numerically equal to the slope of the plot relating amount dissolved from the compact with time. The Noyes-Whitney equation (9), however, gives:

$$\frac{dC}{dt} = k(C_s - C)$$

where k = dissolution rate constant

C = concentration at time t

C_s = saturation solubility.

Assuming sink conditions ($C < 0.1\ C_s$), which obtained during the present work, then $k = \text{slope}/C_s$. This correlates rather poorly with log P, as equation (8) shows:

$$\log k = -0.181 \log P - 1.849 \quad (8)$$

$$n = 6,\ r = 0.635,\ s = 0.219$$

Some improvement is again gained by omitting the 2,5-dimethyl derivative:

$$\log k = -0.104 \log P - 2.025 \quad (9)$$

$$n = 5,\ r = 0.812,\ s = 0.080$$

The very small coefficient of log P is noteworthy here. From equation (9), for a thousand-fold change of partition coefficient, k decreases only by a factor of two, and thus may be said to be almost independent of lipophilicity.

The activation energy of dissolution, calculated from the variation of D with temperature, is seen not to vary greatly with solubility or lipophilicity, which indicates that the mechanism of dissolution is similar for all the compounds examined.

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