THE VARIATION OF FORWARD AND REVERSE PARTITIONING RATE CONSTANTS WITH LIPOPHILICITY

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It is generally assumed that the rate constant of transfer of a solute from aqueous to non-aqueous solution is proportional to its partition coefficient, for solutes of similar structure at least (Davies, 1950). We measured forward (k_f) and reverse (k_r) partitioning rate constants between water and two separate non-aqueous solvents, octanol and chloroform, at 24°, for a series of five alkyl derivatives of paracetamol with a wide range of lipophilicity. Log k_f increased rectilinearly with log P initially (with gradient ≈ 1), but then reached a maximum and slowly decreased for highly lipophilic compounds. This is contrary to the predictions of Yalkowsky & Flynn (1973) and of Lippold & Schneider (1976) that the rate constant should attain a maximum value as lipophilicity increases. Clearly, the transfer becomes diffusion-limited at high lipophilicity, but the decrease in rate constant observed by us shows that diffusion rate constant cannot be assumed, as it was by Yalkowsky & Flynn (1973) and Lippold & Schneider (1976) to be independent of molecular weight. Similarly, the reverse rate constant tended towards a maximum as lipophilicity decreased; the range of lipophilicities covered did not permit us to determine whether there was a subsequent decrease at very low lipophilicities. The maximum rate constants found in each case reflected the viscosity of the medium relative to water; thus k_f (octanol) > k_r (octanol), and k_r (chloroform) > k_f (chloroform), which confirms diffusion as the maximum-rate limiting process.

As $P = k_f/k_r$ by definition, we calculated P for each compound and compared the calculated and experimentally observed values. For the chloroform-water system, calculated and observed values agreed closely. For the octanol-water system, however, we obtained:

$$\log P = 0.652 \log(k_f/k_r) + 0.371$$

$$n = 5,\ r = 0.996,\ s = 0.304$$

The gradient is significantly lower than unity at the 99.8% level. This suggests that k_r is too low, due perhaps to inadequate stirring of the octanol layer, although this was at the highest rate possible without a pronounced vortex being caused. It may be concluded that satisfactory transfer rate constants from viscous solvents cannot be obtained by this method.

Our study also enabled values of $k_f.k_r$ to be calculated, and we found that log $k_f.k_r$ varied approximately parabolically with lipophilicity, having a maximum value at around log P = 0. Thus the assumption of Penniston, Beckett & others (1969), in developing their model of drug partitioning behaviour, that $k_f.k_r$ is constant was not justified. However, we believe that our observation does not destroy the validity of their model, but simply alters slightly the parabolicity of the "structure-activity" curves generated.

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