PARTITIONING RATE CONSTANT AS A PARAMETER IN QUANTITIVE STRUCTURE-ACTIVITY RELATIONSHIPS (QSARs)

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Many studies have shown that, within a series of congeners, biological activity correlates more or less well with partition coefficient. Any so-called "outliers" in such relationships are usually explained as anomalies due to, for example, specific receptor binding or metabolism, and attempts are often made to account for these effects by including steric, electronic or other parameters in the correlation.

It must be borne in mind, however, that partition coefficient is an equilibrium constant; as such, it is somewhat inappropriate for describing a biological response which is time-dependent (i.e. non-steady state). Most pharmacological testing is carried out following administration of a single dose, and response is usually measured at a fixed time after dosage. Under such conditions, it is the rate of partitioning, and not the partition coefficient, that will govern the concentration of drug at the receptor at a given time. It might be argued that since partition coefficient is the ratio of the forward and reverse partitioning rate constants, partition coefficient is a satisfactory parameter to use. However, it is known that some compounds have abnormal rates of partitioning (Elson 1978), whilst displaying normal or expected partition coefficients; such compounds could appear as outliers in QSARs.

We have therefore measured forward and reverse partitioning rate constants in the water-octanol system of a series of paracetamol derivatives for which we have already reported a QSAR (Dearden & O'Hara 1976). For the eight compounds examined, correlation of analgesic activity with octanol-water partition coefficient (P) gave:

$$\log(1/ED30) = -0.133 + 1.541 \log P - 0.829(\log P)^2 \quad (1)$$

$$n = 8 \quad r = 0.919 \quad s = 0.103$$

Correlation with the reverse (i.e. octanol to water) rate constant k_R (m^{-2} h^{-1}) gave an equation of almost identical significance:

$$\log(1/ED30) = -6.050 + 7.379 \log k_R - 2.050(\log k_R)^2 \quad (2)$$

$$n = 8 \quad r = 0.921 \quad s = 0.101$$

Correlation of biological activity with the forward rate constant k_F gave a poor correlation ($r = 0.601$); correlation with various combinations of k_F and k_R did not improve equation (2) significantly, although it is interesting to note that the use of $\log(k_F/k_R)$ (which is equivalent to $\log P$) gave a correlation coefficient of 0.931.

The fact that k_R correlates much better than does k_F with biological activity is possibly accounted for by the much wider range of the former ($\log k_R$ 1.309 - 2.299) than the latter rate constant ($\log k_F$ 2.439 - 2.904) and indicates that k_R is the predominant factor governing in vivo transport, in this series of compounds at least.

The fact that k_R does not correlate significantly better than does P with biological activity in this series of compounds probably means that none of the compounds has anomalous partitioning rate behaviour. Nonetheless, we commend the further investigation of partitioning rate behaviour as a possible parameter for the refining of quantitative structure-activity relationships.

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Elson, G. (1978) M.Sc. thesis, Univ. of Aston in Birmingham