Use of substituent constants in structure-activity relations and the importance of the choice of standard state

STANLEY S. DAVIS

The Pharmacy Department, University of Aston in Birmingham, Birmingham 4, U.K.

The value of the hydrophobic group substituent constant (π), calculated from logarithms of partition coefficients, is normally independent of the choice of the standard state used for the partition studies. However, in some cases e.g. when a partition coefficient for the intact molecule is taken as being equivalent to a π value, the choice of standard state is of utmost importance. It is suggested that π values may be additive on the mole fraction (thermodynamic partition coefficient) scale and not the molar scale as has been previously assumed. Consequently, some published π values may be in error.

The linear free energy approach to structure-activity relations developed by Hansch & Fujita (1964), Fujita, Iwasa & Hansch (1964) and Hansch (1969) using multiple regression analysis, has been a major advance in medicinal chemistry. The hydrophobic constant (π), that reflects the physico-chemical processes in the passage of the drug molecule across lipoidal compartments and its non-specific interaction with the receptor site, is calculated from partition coefficients (usually from the system 1-octanol–water).

In most studies π values are calculated according to the equation:—

$$\pi_x = \log K_{D(RX)} - \log K_{D(RH)} \quad \cdots \quad \cdots \quad \cdots \quad (1)$$

Where $K_{D(RX)}$ and $K_{D(RH)}$ are the partition coefficients of the substituted drug and the parent molecule. The partition coefficient as defined by the Nernst distribution law is the concentration of the solute in the oil phase divided by the concentration in the aqueous phase. However, concentration can be measured in a number of different ways and the molar (C) and mole fraction (x) scales have both been popular. The value of the partition coefficient will be concentration scale dependent.

In most studies on partition the standard state chosen is the hypothetical ideal unit molarity in each phase.

The molar partition coefficient (K_D^m) can be written as

$$K_D^m = C_o/C_w \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad (2)$$

The so-called 'thermodynamic' partition coefficient (K_D^x) has for reference state, in each phase, the hypothetical ideal mole fraction of solute such that

$$K_D^x = x_o/x_w \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad (3)$$

It is an easy matter to convert partition coefficients on the molar scale to the mole fraction scale and *vice versa* as:—

$$K_D^x/K_D^m = V_o/V_w \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad (4)$$

Where V_o and V_w are the molar volumes of the oily and aqueous phases respectively.

When π values are calculated according to equation (1) they will be independent of concentration scale because:—

$$\pi_x = \log K^m_{D(RX)} - \log K^m_{D(RH)}$$

$$= \log K^x_{D(RX)} - \log K^x_{D(RH)} \qquad .. \qquad .. \qquad (5)$$

The rearrangement of equation (5) has enabled Hansch to calculate with success the partition coefficients for a vast number of compounds:—

$$\log K^m_{D(RX)} = \log K^m_{D(RH)} + \pi_x$$

$$(\text{N.B.} \ \log K^x_{D(RX)} = \log K^x_{D(RH)} + \pi_x) \ .. \qquad .. \qquad .. \qquad (6)$$

Unfortunately this has been taken one step further and it has been suggested that equation 6 can be written simply as (Tute, 1971):—

$$\log K_D = \overset{n}{\underset{i}{\Sigma}} \pi \qquad .. \qquad .. \qquad .. \qquad .. \qquad (7)$$

That is the log of the partition coefficient is the sum of the π contributions for the constituent groups. This may be correct but what is the concentration scale of K_D?

The only detailed study on the absolute additivity of π values has been made by Currie, Lough & others (1966) and Delaney, Currie & Holmes (1969) for the partition system cyclohexane–water. They found that

$$\log K^m_D = \Sigma \pi - k \ .. \qquad .. \qquad .. \qquad .. \qquad .. \qquad (8)$$

Where k was an empirical constant equal to 1·3. On the basis that summing π values should be referred to the mole fraction concentration scale one would expect theoretically that

$$\log K^m_D = \Sigma \pi - 0·78 \qquad .. \qquad .. \qquad .. \qquad .. \qquad (9)$$

The constant found in the theoretical equation is lower than that found experimentally but it must be borne in mind that the systems studied by Currie and others were complex conjugated heterenoids and group values may be affected by group interaction, resonance effects and hydrogen bonding.

A similar situation will arise when the partition coefficient for the intact molecule is used as a π value.

Hansch (1971) may well be justified in proposing that

$$\pi \ \text{phenyl} \simeq \log K_D \ (\text{Benzene}) \qquad .. \qquad .. \qquad .. \qquad (10)$$

but are there fundamental reasons for selecting the molar scale at Hansch has done, rather than the mole fraction scale?

Mathematically equation (1) is a difference procedure, where any constant terms will disappear by subtraction. Equation (7) is an additive procedure that requires the addition of the unknown constant, i.e.

$$\log K^m_D = \overset{n}{\underset{i}{\Sigma}} \pi + k_m \qquad .. \qquad .. \qquad .. \qquad (11a)$$

$$\text{and} \ \log K^x_D = \overset{n}{\underset{i}{\Sigma}} \pi + k_x \qquad .. \qquad .. \qquad .. \qquad (11b)$$

Hansch and others have ignored the possibility of this 'additive' constant, and have assumed that equation (7) is correct. On the basis of this unjustified assumption they suggested that π values could be calculated by an alternative procedure to equation (1).

For example; Hansch & Anderson (1967):—

$$\pi_F = \log K^m_{D(C_5H_{11}F)} - \pi_{C_5H_{11}} \qquad .. \qquad .. \qquad .. \qquad (12)$$

where $\pi_{C_5H_{11}}$ is calculated by summing $5\pi_{CH_2}$ values.
Hansch, Steward & others (1968):—

$$\pi \text{ cyclohexyl} = \log K^m_D \text{ (cyclohexanol)} - \pi_{OH} \qquad .. \qquad .. \qquad (13)$$

$$\text{and } \pi \text{ phenoxy} = \log K^m_D \text{ (anisole)} - \pi_{CH_3} \qquad .. \qquad .. \qquad .. \qquad (14)$$

Lien (1970):—
π succinamide $= \log K^m_D$ (2-ethyl 2-phenyl glutaramide)

$$-(\pi \text{ ethyl} + \pi \text{ phenyl} + \pi \text{ 1/6 cyclohexane}) \qquad .. \qquad .. \qquad (15)$$

The π values on the right hand side of equations (12–15), [calculated in the usual way using equation (1)] will be concentration scale independent but the π values on the left hand side will depend on the concentration units of the partition coefficient. If one chooses to use $\log K^x_D$ instead of $\log K^m_D$ the derived π values will differ by an amount $\log (V_0/V_w)$—equal to 0·94!

It is interesting to note that when Hansch & Anderson (1967) calculated a number of π values using equation (12) they found that the values did not agree with π values obtained by equation (1) (Iwasa, Fujita & Hansch, 1965). Comparison of the two sets of values revealed an essentially constant difference. In order to explain this Hansch & Anderson (1967) resorted to a most complex theory of side-chain folding and inter-action of functional groupings with the benzene nucleus. Probably, a far more reasonable explanation of the 'surprising' constant difference is their choice of an unsuitable concentration scale and their assumption that π C_5H_{11} was simply the sum of 5 CH_2 groups. This ignores the well known difference between terminal CH_3 and mid-chain CH_2 groups (Némethy, Steinberg & Scheraga, 1963; Khrishnan & Freidman, 1969; Davis, 1973). However, this suggestion cannot be tested until an accurate group contribution for the methyl group has been determined. Unfortunately, this is not a simple procedure (Davis, 1973).

Free energy values based on the mole fraction concentration scale are larger than those based on the molar scale by an amount $2\cdot303$ RT $\log V_s$, where V_s is the molar volume of the solvent (Cratin, 1968). This means in effect that the value of the free energy, if expressed on the molar concentration scale, depends upon the molar volume of the solvent. The differences between thermodynamic quantities calculated on the two different concentration scales were first discussed by Gurney (1953) who divided values up into "unitary" (based on mole fraction concentration) and "cratic" (solvent effect) contributions. Kauzmann (1959) has shown that it is desirable to eliminate the rather arbitrary factor of differences due to concentration scale before trying to interpret the magnitude of thermodynamic changes in terms of the molecular structures present in solution.

It is generally agreed that for the distribution of solutes between aqueous phase and organic solvent, the difference in unitary free energy (calculated from the thermo-

dynamic partition coefficient) can be considered to be approximately an additive function of the contributions for the constituent groups (Hersh, 1971; Mukerjee, 1967; Aveyard & Mitchell, 1969). Mole fraction concentration units are also the concentration scale of choice when comparing the effects of different organic solvents on partition as they provide a comparison of equal numbers of molecules (Aveyard & Mitchell, 1969; Mottola & Freiser, 1967). Therefore, it is our opinion that π values are more probably additive on the mole fraction (unitary free energy) concentration scale than on the molar scale and that values obtained as in equation (12) to (15) should be questioned. Alternatively, we may discover that the sum of π values may not be equivalent to a logarithm of the partition coefficient on either scale and equation (11b) with an unknown constant may be the true relation. This is the situation in chromatography where the R_M value (derived from R_F and related to the chromatographic partition coefficient) is an additive constitutive property such that

$$R_M = \Sigma \triangle R_M + k \quad .. \qquad .. \qquad .. \qquad .. \qquad (16)$$

Where k is a constant that depends on the chromatographic system. Until we are able to answer some of these questions, by undertaking detailed partition experiments, it would be wise to restrict the calculation of π values for structure-activity studies to equation (1).

REFERENCES

AVEYARD, R. & MITCHELL, R. W. (1969). *Trans. Faraday Soc.*, **65**, 2645–2653.

CRATIN, P. D. (1968). *Ind. Engng Chem.*, **60** (9), 15–19.

CURRIE, D. J., LOUGH, C. E., SILVER, R. F. & HOLMES, H. L. (1966). *Can. J. Chem.*, **44**, 1035–1043.

DAVIS, S. S. (1973). *J. Pharm. Pharmac.*, **25**, 1–12.

DELANEY, A. D., CURRIE, D. J. & HOLMES, H. L. (1969). *Can. J. Chem.*, **47**, 3273–3277.

FUJITA, T., IWASA, J. & HANSCH, C. (1964). *J. Am. chem. Soc.*, **86**, 5175–5180.

GURNEY, R. W. (1953). *Ionic Processes In Solution*, New York: McGraw Hill, p. 90.

HANSCH, C. (1969). *Acc. Chem. Res.*, **2**, 232–239.

HANSCH, C. (1971). In *Drug Design*, vol. 1, pp. 271–342. Editor: Ariens, E. J., New York: Academic Press.

HANSCH, C. & ANDERSON, S. M. (1967). *J. org. Chem.*, **32**, 2583–2586.

HANSCH, C. & FUJITA, T. (1964). *J. Am. chem. Soc.*, **86**, 1616–1626.

HANSCH, C., STEWARD, A. R., ANDERSON, S. M. & BENTLEY, D. (1968). *J. medl Chem.*, **11**, 1–11.

HERSH, L. S. (1971). In *The Chemistry of Biosurfaces*, vol. 1, pp. 349–376. Editor: Hair, M. L., New York: Dekker.

IWASA, J., FUJITA, T. & HANSCH, C. (1965). *J. medl Chem.*, **8**, 150–153.

KAUZMANN, W. (1959). *Adv. Protein Chem.*, **14**, 1–63.

KHRISHNAN, C. V. & FRIEDMAN, J. L. (1969). *J. Phys. Chem.*, **73**, 1572–1580.

LIEN, E. J. (1970). *J. medl Chem.*, **13**, 1189–1191.

MOTTOLA, H. A. & FREISER, H. (1967). *Talanta*, **14**, 864–869.

MUKERJEE, P. (1967). *Adv. Colloid Inter. Sci.*, **1**, 241–275.

NÉMETHY, G., STEINBERG, I. Z. & SCHERAGA, H. A. (1963). *Biopolymers*, **1**, 43–69.

TUTE, M. S. (1971). *Advances in Drug Research*, **6**, 1–77.