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Prediction of interfacial transfer kinetics. Reply to de Haan and Jansen

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In a series of three papers (Byron et al., 1980, 1981; Byron and Rathbone, 1984) we developed and tested a theory to describe the interfacial transfer kinetics of a series of drug homologues in a symmetrically stirred two-phase transfer cell (TPTC). The theory assumed constancy of aqueous and organic diffusion coefficients within the homologous series and required measurement or definition of some physicochemical variables describing the binary solvent system (viscosity, density, degree of self-association, molecular weight). The form of the non-linear dependence of the observed rate constant for solute transfer (sum of the forward and reverse first-order rate constants for partitioning) upon the partition coefficient, K_d, could be predicted. The theories provided a testable kinetic rationale for interfacial transfer studies performed in the TPTC.

In their recent paper on the influence of solvent properties on interfacial transfer, de Haan and Jansen (1986) make several statements about our work. In essence they state:

(1) "In the required calculations it is assumed implicitly that Eqn. 44 is valid.

$$\frac{k_{aq}}{k_{org}} = \left[\frac{\Psi_{aq} \cdot M_{aq}}{\Psi_{org} \cdot M_{org}}\right]^{1/3} \left[\frac{d_{aq}}{d_{org}}\right]^{-2/3} \left[\frac{\nu_{aq}}{\nu_{org}}\right]^{-5/6} \tag{44}$$

(2) Eqn. 44 can only be valid when $Rel_{aq} = Rel_{org}$.
(3) Because Rel_{aq} and Rel_{org} are not identical, it has to be concluded that the theory of Byron and Rathbone is not valid."

All the terms are as defined by de Haan and Jansen (1986). Although statement 1 is correct, statement 2 is wrong. For this reason and others which I describe below, readers of the de Haan and Jansen paper should be advised that statement 3, which declares our theory invalid, is itself incorrect.

The terms Rel_{aq} and Rel_{org}, as defined by the Netherlands researchers, can only be equal if the binary solvent system they refer to behaves identically to the hexane : water system which they use as reference. Neither Eqn. 44, nor our theories, require this as a prerequisite for validity. Our theories furthermore, were derived to describe interfacial solute transfer in a *symmetrically* stirred TPTC (Byron et al., 1981) and will produce erratic predictions if diffusivities vary within the solute series under investigation. The Netherlands group obtained their results in a cell with different stirring dynamics in each of the phases (their lower stirring blade is twice the size and at an angle of 90° to the upper) and show no evidence for effective constancy of diffusion coefficients throughout their series of analogues and homologues.

I have few practical objections to the TPTC theories proposed by de Haan and his colleagues. Indeed, their papers make a valuable contribution to this area. From a philosophical point of view,

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however, it is worth noting that their theories are difficult to test and offer no comprehensive explanation for the varied behaviour of S, the apparent first-order rate constant for partitioning, with K_d (Byron et al., 1981; Byron and Rathbone, 1984) in binary solvent systems with different association parameters, molecular weights, viscosities and densities. It should be emphasized that it is S which is measured while the forward and reverse rate constants (k_1^{obs}, k_2^{obs}; de Haan and Jansen, 1986) are data abstractions obtained by subdivision of S according to the value of the partition coefficient, K_d.

In our final paper on the subject of the TPTC (Byron and Rathbone, 1986) we report the effects of varying aqueous phase ionic strength and solute ionization upon transfer kinetics. In an octanol: aqueous system, solute transfer rates, even of non-ionized compounds, vary substantially with the ionic content of the aqueous phase. The content of the aqueous phases employed by the group from The Netherlands appears to be unreported. Nevertheless, they do state that octanol (which dissolves water; solubility increases with decreasing temperature) was washed with 1 N HCl and 1 N NaOH before use in their TPTC. Depending upon the reproducibility of this procedure, the stability of the aqueous: organic interface may vary owing to changes in the ionic content of the aqueous phase (Byron and Rathbone, 1986). Because of the difficulty in ensuring interfacial stability in the TPTC (Byron and Rathbone, 1986; de Haan and Jansen, 1986) we now employ a rotating diffusion cell (RDC) in our studies (Albery et al., 1976). This cell has a mechanically stabilized interface which is unaffected by solute ionization or the contents of the aqueous phase (Byron and Rathbone, 1986). Interfacial transfer kinetics in this RDC also conform to our theories.

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