CALCULATION OF THE PARTITION COEFFICIENT OF AN UNSTABLE COMPOUND USING KINETIC METHODS

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A stirred transfer cell (Gordon and Sherwood,1954) has been used containing equal volumes of light liquid paraffin and an aqueous phase at 37° C to demonstrate the feasibility of calculating the partition coefficient of an unstable compound by kinetic analysis.

Cyclohept-2-eneone (CHP) was chosen as a model solute. It is a neutral molecule as a function of pH and should therefore have a single pH-independent value for its oil:water partition coefficient, P.It is sufficiently stable in water to determine P. Moreover, as a cyclic α,β unsaturated ketone, CHP undergoes H⁺-ion catalysed hydration. The model system chosen is shown as Scheme I

$$c_{1p} \xrightarrow{k_{1p}} c_{1} \xrightarrow{k_{12}} c_{2} \xrightarrow{\text{Scheme I}}$$

which represents first-order transfer of a compound between the aqueous phase (C_1) and the organic phase (C_2) of a transfer cell and simultaneous, but reversible, first-order loss to a degradation product (C_{1p}) in the aqueous phase. Theory predicts that the value of P, which would be observed were the compound stable $(\mathsf{P} = \mathsf{C}_2^{\infty}/\mathsf{C}_1^{\infty})$, should equal the ratio $\mathsf{k}_{12}/\mathsf{k}_{21}$. The values of k_{12} and k_{21} were determined in the transfer cell at $37^{\mathsf{O}}\mathsf{C}$ in the absence of degradation using water as the aqueous phase and stirring at either 50 or 100 rpm. The solute was introduced into the aqueous phase and its disappearance monitored as a function of time until equilibrium was attained. Final values of C_1 (C_1^{∞}) agreed with those predicted from non-kinetic partitioning studies. The first-order rate constants k_{1p} and k_{p1} for hydration of CHP in 0.1 N HCl saturated with light liquid paraffin were determined at $37^{\mathsf{O}}\mathsf{C}$ in the

Partitioning with simultaneous hydration was then studied using O.1 N HCl and light liquid paraffin in the transfer cell stirred at 50 and 100 rpm. Data were analysed by nonlinear regression (Metzler, 1969) based on an equation derived for $\rm C_1$ as a function of time. The values for $\rm k_{12}$ and $\rm k_{21}$ from these experiments are compared to the independent estimates in Table 1.

absence of the organic phase.

Table 1. Comparison of the rate constants k_{12} and k_{21} (hours $^{-1}$) for distribution of CHP under stable and unstable conditions.

Stable conditions		Simultaneous loss			
k ₁₂	k ₂₁	P	k ₁₂	k ₂₁	k ₁₂ /k ₂₁
		1.7	0.163	0.105	1.6
	k ₁₂ 0.168	k ₁₂ k ₂₁ 0.168 0.098	k ₁₂ k ₂₁ P	k ₁₂ k ₂₁ P k ₁₂ 0.168 0.098 1.7 0.163	k ₁₂ k ₂₁ P k ₁₂ k ₂₁ 0.168 0.098 1.7 0.163 0.105

The agreement between the nonlinear estimates for k_{12} , k_{21} and those determined independently demonstrates that the biexponential loss of solute from the aqueous phase in a system described by Scheme I may be analysed for k_{12} and k_{21} . This allows for the calculation of P, the partition coefficient in the absence of degradation, as the ratio k_{12}/k_{21} .

Gordon, K.F., & Sherwood, T.K. (1954). Chem. Eng. Prog., (Symposium Series), 50, 15. Metzler, C.M. (1969). "NONLIN". The Upjohn Co., Kalamazoo, Mich., U.S.A.

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