TETRACYCLINE TRANSPORT ACROSS A LIPID BARRIER

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In apparent contradiction of the pH partition theory, the tetracyclines are moderately well absorbed from the gut. Three ionization sites of widely separated pKas ensure that the cationic, zwitterionic and anionic species are in relatively high concentration ratios with the unionized form such that it is unlikely that the neutral species contributes appreciably to drug transport.

Experimental procedures verified that partitioning of a series of tetracyclines varies with pH both in octanol and acetylated monoglycerides, a lipid solvent subsequently selected for transport studies. Maximum distribution values occurred in the pH region where a zwitterionic species predominates. Values are generally less than unity, although for pH >8.0 there was a sharp increase in lipid solubility of some tetracyclines.

Results from the rotating diffusion cell of Albery et al (1976) were used to analyse transport of tetracyclines in terms of diffusion and interfacial transfer components. A thin lipid-impregnated polycarbonate membrane provided the diffusion barrier. A commercially available preparation of acetylated monoglycerides was selected because it provided a stable lipid/water interface, yet transport occured over a time scale which ensured minimum tetracycline degradation.

The overall rate constants show positive correlation with partition coefficients at pH 5.6 for the series. A detailed study was made with demethylchlortetracycline (DMCT) and maximum transport rates were found at pH 5.6 and not at 8.3 as might have been expected.

Positive enthalpies were found for both bulk and interfacial transfer processes. Although there is considerable variation in the relative enthalpic contributions, the entropy values are comparatively small and for the interfacial transfers negative. The organic to aqueous interfacial transfer process is an exception where a large negative entropy is the sole contribution to the positive free energy change. Representative data for the bulk and interfacial kinetic processes are tabulated below for DMCT at pH 5.6 and 25°C.

CONSTANT	VALUE	ΔG kJ mol^{-1}	ΔH kJ mol^{-1}	ΔS kJ mol^{-1} ^{o}K^{-1}
K^{o}_{W}	0.367	2.48	27.44	0.084
k_{-I}	9.73×10^{-6}	*40.0	24.94	-0.05
k_{I}	2.651×10^{-5}	*37.5	0.00	-0.13

Key: K^{o}_{W} = bulk partition coefficient.
k_{-I} (m s^{-1}) aqueous → organic) interfacial rate constants *ΔG calculated
k_{I} (m s^{-1}) organic → aqueous) using a frequency factor of 10^{2} m s^{-1}.

Investigation of interfacial behaviour at pH values 3.0, 5.6, 7.4 and 8.3 indicated the formation of a viscous interfacial film which modified the pH dependent lowering of interfacial tension, especially at the two higher pH values. This phenomenon occurred at concentrations above 0.01% for all derivatives except oxytetracycline and tetracycline. Formation of a similar film may complicate interpretation of the kinetic data at pH 5.6 and possibly also accounts for the unexpectedly slow transport at pH 8.3 where partitioning is favourable.

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