THE EFFECT OF FUNCTIONAL GROUPS ON THE ENERGETICS OF PARTITIONING OF PHENOLS BETWEEN LIPOSOMES AND WATER

J.A. Rogers, N. Anderson and S.S. Davis, Pharmacy Department, Nottingham University, Nottingham NG7 2RD, and ICI, Plant Protection, Jealott's Hill, Bracknell, Berks.

The permeability of membranes to drug molecules is determined by physical factors including partition coefficient (K_D) and diffusion coefficient. The resolution of the contributions of individual functional groups to the partition coefficients of parent molecules is now a well established approach to structure activity relationships. Furthermore the thermodynamics of partitioning can give insight into transport processes and their control; enthalpic (interactions) or entropic (structural changes) (Davis et al., 1974).

Liposomes have been widely studied as model membranes. They consist of lipid bilayers, either as multilayers arranged concentrically, or as single bilayers entrapping a volume of aqueous core. Liposomes can be used successfully to obtain partition data (Diamond & Katz, 1974). We have prepared dimyristoyl lecithin liposomes in the standard way and the partition of p-alkylphenols and p-halophenols into liposomes has been followed at eight temperatures. Linear relations between K_D and 1/T were obtained below and above the phase transition temperature of the phospholipid (T_C). The negative free energies of partition indicate that the alkylphenols favour the lecithin bilayers over the aqueous environment and the ease of accommodation increases with alkyl chain length (Table 1). Above T_C the partition process is enthalpy (ΔH) driven whereas below T_C it is entropy (ΔS) driven. The ΔH and ΔS contributions to the free energy of transfer of the p-halophenols from water to lecithin are much smaller than those for the p-alkylphenols. Halogen and alkyl substitution both increase K_D. The ΔH and ΔS of partition increase greatly on cooling through the transition temperature. In the crystalline state the hydrocarbon chains of the lecithin molecules are packed closely together. Insertion of a solute brings about considerable disruption of strong intermolecular forces between hydrocarbon tails and the breakdown of an ordered array. The changes in ΔH and ΔS take place in different directions and thereby compensate one another. Hence there is a small apparent change in ΔG above and below T_C.

Table 1. Thermodynamics of partition of p-substituted phenols into liposomes.

	methylphenol		ethylphenol		chlorophenol		bromophenol	
	18°	28°	18°	28°	15°	25°	15°	25°
ΔG ($kJmol^{-1}$)	-10.9	-13.5	-13.4	-15.9	-13.5	-13.7	-14.4	-14.0
ΔH ($kJmol^{-1}$)	8.8	-31.5	8.6	-38.9	10.3	-16.8	2.7	-30.7
ΔS ($Jmol^{-1}K^{-1}$)	67.6	-59.8	75.6	-76.6	82.4	-10.4	59.4	-56.2

Davis, S.S., Higuchi, T. & Rytting, J.H. (1974) Advan. Pharm. Sci. 4 : 73
Diamond, J.M. & Katz, Y. (1974) J. Memb. Biol. 17 : 69