

THE THERMODYNAMICS OF PARTITIONING OF ALKYL PHENOLS

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The importance of hydrophobicity in drug absorption, drug binding and receptor site interactions is well known. The hydrophobicity of a solute is given by its partition coefficient (K_D) between water and some suitable organic solvent. Usually the choice of solvent is n-octanol, based on the unjustified assumption that this solvent is a good model for lipoidal biological phases. Davis et al (1974) have argued that a less polar, inert solvent, such as cyclohexane, would be more suitable from a thermodynamic standpoint. K_D is a free-energy related term and it can be resolved into the appropriate enthalpy and entropy terms by studying its temperature dependence. In the present work, data derived in this way for various phenolic compounds partitioned in the octanol-water and cyclohexane water systems, have been compared with similar data for model biological membranes (liposomes). K_D values for the simple two phase systems were obtained using the AKUFVE system (Davis et al 1976) over the temperature range 15-35°C. Dimyristoylphosphatidylcholine liposome-water partition coefficients were obtained using the method described by Rogers and Davis (1980). All partition values were obtained below the phase transition temperature of the liposomes. The results (Table) indicate that the ΔH and ΔS of transfer for the phenols between water and liposomes are positive at 22°C and the process is entropy controlled. A similar situation holds for the cyclohexane-water system with ΔH and ΔS both positive, however the derived values are very much smaller. In contrast, for the octanol-water system, ΔH and ΔS are both negative and indicate an enthalpy controlled mechanism.

The results indicate that there is probably no 'ideal' water-organic solvent system, which resembles the biological membrane in every respect. Partition coefficients derived for the liposome water system might well yield useful information more relevant to the actual biological situation.

Table Thermodynamics of partitioning of alkyl phenols at 22°C.

	ΔG kJmole ⁻¹	ΔH kJmole ⁻¹	ΔS Jmole ⁻¹ K ⁻¹	Dominating Process
<u>Liposome</u>				
p cresol	-13.3	+119.02	+448.0	entropy
p ethylphenol	-14.8	+ 80.84	+324.5	entropy
p propylphenol	-15.5	+ 31.11	+157.1	entropy
<u>water/cyclohexane</u>				
phenol	+3.15	+ 13.59	+ 35.35	enthalpy
p cresol	+0.63	+ 12.25	+ 39.39	entropy
p ethylphenol	-2.57	+ 10.78	+ 45.20	entropy
<u>water/octanol</u>				
phenol	-8.36	- 26.65	- 61.95	enthalpy
p cresol	-11.18	- 12.44	- 4.24	enthalpy

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