

THERMODYNAMICS OF PARTITIONING - SOME CONSIDERATIONS OF INTRA-MOLECULAR HYDROGEN BONDING AND STERIC EFFECTS

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Intramolecular hydrogen bonding and steric effects are two factors that contribute to the non-additivity of hydrophobic substituent constants (π values) (Dearden & O'Hara 1975). As part of a study of such phenomena, we have investigated the thermodynamics of partitioning, in the octanol-water system, of the compounds shown in Table 1, using the probe method devised by Cantwell & Mohammed (1979).

Table 1. Thermodynamic parameters of transfer from water to 1-octanol

	ΔG° (kJ mol ⁻¹)	ΔH° (kJ mol ⁻¹)	ΔS° (J mol ⁻¹ K ⁻¹)
<u>o</u> -Hydroxybenzoic acid ^a	-12.9	-24.9	-41.1
<u>m</u> -Hydroxybenzoic acid ^a	-8.9	-21.1	-41.6
<u>p</u> -Hydroxybenzoic acid ^a	-8.9	-23.0	-48.0
<u>o</u> -Chlorophenol	-11.6	-8.9	+9.2
<u>m</u> -Chlorophenol	-13.9	-19.9	-20.6
<u>p</u> -Chlorophenol	-13.4	-15.3	-6.6
<u>o</u> -Methylacetanilide	-4.8	+6.5	+38.5
<u>m</u> -Methylacetanilide	-9.1	-5.7	+11.6
<u>p</u> -Methylacetanilide	-9.1	-5.5	+12.4

^aAqueous phase at pH 1.

The low aqueous solubility of o-hydroxybenzoic acid (0.18% w/v at 20° compared with 0.92% w/v at 18° for the meta-isomer (Handbook 1953)) indicates that its intramolecular hydrogen bond is more or less intact in aqueous solution; the remarkably similar values for both the enthalpy and entropy of partitioning of all the hydroxybenzoic acids thus indicate that the intramolecular hydrogen bond remains intact in octanol, and that the extent of solvation consequent upon transfer from water to octanol is not significantly affected by the presence of the intramolecular hydrogen bond. This may be because salicylic acid, even when intramolecularly hydrogen bonded, still has a free -OH group available for solvation.

A very different situation is observed with the chlorophenols. The aqueous solubilities of all three isomers are very similar (Handbook 1953), indicating that the o-isomer is not intramolecularly hydrogen bonded in water. Octanol being less polar than is water, the intramolecular hydrogen bond re-forms upon transfer, with a consequent reduction in solvation and hence a positive entropy change. One might have expected a larger negative enthalpy of transfer as a result of the intramolecular hydrogen bond's re-forming, but this is more than counterbalanced by the consequent loss of solvation capability.

Dearden & O'Hara (1978) reported an unusual partitioning effect of steric hindrance in o-substituted acetanilides; such an effect is clearly demonstrated by the positive enthalpy of transfer in o-methylacetanilide, and explained by the fact that in this compound the acetamido group is twisted out of the plane of the ring, loses conjugation and becomes less lipophilic (more polar) and is thus readily hydrated. Upon transfer the solvated water is released, leading to a positive enthalpy change and also to the very high positive entropy of transfer.

The above results emphasise the value of thermodynamic considerations in the interpretation of partitioning behaviour.

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