

THEMODYNAMICS OF PARTITIONING - ABSENCE OF CONSTANT HYDROPHOBIC EFFECT OF INTRAMOLECULAR HYDROGEN BONDING

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It has been suggested (Leo, Hansch & Elkins. 1971) that intramolecular hydrogen bonding increases lipophilicity, through a reduction of polarity and hence reduced affinity for the aqueous phase. However, the data in Table 1 show that in some cases intramolecular hydrogen bonding actually reduces lipophilicity. The question therefore arises as to whether, in the calculation of partition coefficients, any a priori correction can be made for intramolecular hydrogen bonding.

Table 1. Thermodynamic parameters (mole fraction scale) of transfer of some phenols from water to 1-octanol

Substituent(s)	ΔG° (kJ mol ⁻¹)	ΔH° (kJ mol ⁻¹)	ΔS° (J mol ⁻¹ K ⁻¹)
2-Cl	-17.0	-8.4	+28.9
4-Cl	-18.6	-10.5	+26.9
2-CHO	-14.7	-3.7	+37.1
4-CHO	-13.3	-9.6	+12.4
2-COOH ^a	-18.0	-17.9	+0.6
4-COOH ^a	-13.9	-23.0	-30.4
2-NO ₂	-15.4	-2.5	+43.3
4-NO ₂	-16.1	-19.2	-10.3
2-NO ₂ -3-Me	-17.6	-12.8	+16.3
2-NO ₂ -6-Me	-20.0	+6.8	+89.8
2-Me	-5.3	+15.6	+70.1
4-Me	-3.6	+15.3	+63.4

^aAqueous phase at pH 1

From Table 1, the enthalpy of partitioning is less negative where intramolecular hydrogen bonding occurs; this is to be expected since less interaction with solvent is possible. ΔH° for salicylic acid is nevertheless highly negative, and this is undoubtedly due to the hydroxyl group still being available for solvation. Among the other 2-substituted phenols (except 2-methylphenol, which is included as a non-hydrogen bonded control) the enthalpy of partitioning decreases negatively as the expected strength of intramolecular hydrogen bonding increases. This is confirmed by the results for the methyl-substituted 2-nitrophenols; 3-methylation produces steric hindrance and thus weakens the intramolecular hydrogen bond, whereas 6-methylation gives rise to steric facilitation of the bond.

Table 1 also shows that, again with the exception of salicylic acid, the entropy of partitioning also increases as the expected strength of intramolecular hydrogen bonding increases. This is more probably related to the extent of the bonding, and hence to the overall polarity of the molecule; generally the more extensive the intramolecular hydrogen bonding, the less polar the molecule, the greater the extent of water structuring around the molecule, and therefore the greater the increase in entropy on transfer from water to octanol.

The above results make it clear that structural considerations affect both the enthalpy and entropy of partitioning markedly. Since log P represents the difference in enthalpic and entropic contributions to phase transfer, it is to be expected firstly that the effect of intramolecular hydrogen bonding upon log P will not be constant in different compounds, and secondly that the magnitude, and even the direction, of the effect will be difficult, if not impossible, to predict (cf. Rekker 1977).

Leo, A., Hansch, C., Elkins, D. (1971) Chem. Revs. 71: 525-616

Rekker, R.F. (1977) "The hydrophobic fragmental constant", Elsevier, Amsterdam, p.73

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