

# Solubility of Nonelectrolytes in Water: A Thermodynamic and Quantum Chemical Approach based on Dihydroxynaphthalene Derivatives

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The solubility of organic solids in water is a very important molecular property that affects their biological activity. A large number of pharmaceutically and environmentally relevant compounds is sparingly soluble.

The aim of our approach is to understand the elementary steps involved in the formation of a solution. On this basis we hope to find reasons explaining the poor solubility of a given compound. According to the Hess theorem, the direct formation of a solution can be replaced by a series of alternative processes leading to the same endpoint as the direct process. A first step in such a series may exist in the sublimation of the solid to be dissolved. In the next step cavities are formed in the solvent. They have to be large enough to take up the sublimated solute molecules, which are transferred into these cavities. In the last step the solute and solvent molecules rearrange to form a solvent shell around the solute.

Each of these steps is described thermodynamically by  $\Delta G$ ,  $\Delta H$  and  $\Delta S$  which can be determined by calorimetric or quantum chemical methods. If the energies of the changes of state are correctly determined and summed up, according to the Hess theorem the result must be zero.

The standard free energy of sublimation of a given compound is calculated from its vapor pressure. By means of its definition the corresponding standard free energy of solution is calculated from the solubility. The vapor pressure is determined by means of a static apparatus<sup>1</sup>. The standard free energy of solvation is calculated by the semiempirical, quantum chemical program AMSOL 6.6. The heat of solutions are determined by DSC-calorimetry by means of a special solution cell<sup>2</sup>.

It is the aim of our work to understand how the solubility of a compound depends on its structure. In the same way we study how the energies involved in the various alternative processes are determined by the structure of the molecules under study. For simplicity reasons we used the following naphthalene derivatives as model compounds: 1,3-, 1,6-, 1,7-, 2,7-Dihydroxynaphthalene, 4-Chloro-1-naphthol and 1-Naphthalenamine. In a previous work<sup>2</sup> 1- and 2-Naphthole and 2,3-Dihydroxynaphthalene were investigated under the same point of view. This group of molecules allows us to discuss the influence of the chemical nature of a substituent as well as its position in the molecule on their solubility and on the energies we determined for the various alternative processes. The discussion of these energies eventually allows to explain the poor solubility.

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<sup>1</sup> Sasse, K., Jose J., Merlin, J., Fluid Phase Equilibria 42, 1988, 287-304

<sup>2</sup> Kempf, G.: Thermodynamische und semiempirische Untersuchungen schwerlöslicher organischer Substanzen, Diss., Wuerzburg (2000)