# Solution chemistry, solubility and solubilization

### Solubility

Dissolution limited bioavailability is a very common problem in pharmaceutical development. The well-known adage "*like dissolves like*" is, I am sorry to say, not true. Well, it is true, but only for liquids. If the solute is a solid, then the solid properties of the solute play an often dominant role. Many drugs are hydrophobic, which makes them poorly soluble in water. But when we have a nightmarish solubility problem, one where the hydrophobic solute does not dissolve in water, but it does not dissolve in hydrophobic liquids either, then it is best to look at the solid instead of at the solvent.
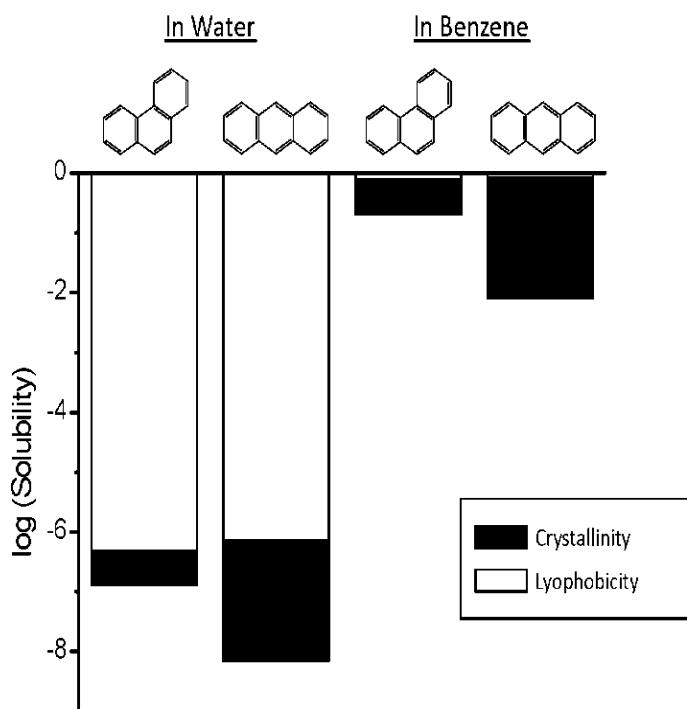
*like dissolves like*

Solubility of two isomers in the same solvent



and

in

0.81 mol%          20.7 mol%
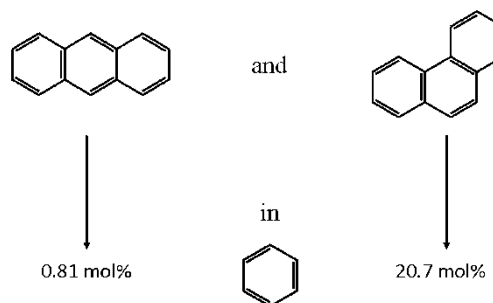
*like* 25.5 times different

## Solubility of Isomers of different symmetry



In Water          In Benzene

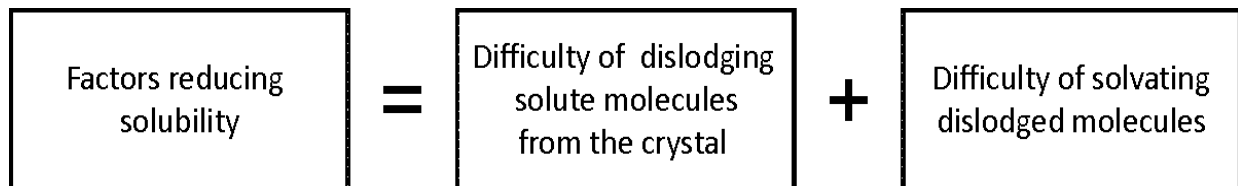log (Solubility)

■ Crystallinity
□ Lyophobicity

The phenanthrene-anthracene example is very informative because it makes it very easy to show an important point. The figure to the left shows the "magnitude" of the problem. It is a log scale, so that the solubility in benzene is about a million times higher than in water for each of the two compounds. This means that by solvent manipulation we can increase the solubility of these compounds a millionfold. If instead of phenanthrene and anthracene we had, say, drug A and drug B, could we solubilize drug B to the same level of drug A? The answer is no.

Anthracene will be 25 times less soluble than phenanthrene in every solvent we care to try. The black portions of the bars are a property of the solid and are completely unaffected by the choice of solvent. The white part of the bars in the figure is labeled "Lyophobicity," that is to say, how much the solute "dislikes" the solvent. If the solvent is water, then lyophobicity=hydrophobicity, but if the solvent is benzene, for example, we see that the dislike of anthracene and phenanthrene for this solvent is, as expected, not there. Anthracene and phenanthrene both like benzene equally and very much - this is what is meant by "*like dissolves like.*"

The reason anthracene is 25 times less soluble is not that it dislikes benzene; but that it has a strong crystal that makes it difficult to dislodge the molecules from.

| Factors reducing solubility | = | Difficulty of dislodging solute molecules from the crystal | + | Difficulty of solvating dislodged molecules |

This is an extremely common problem during drug candidate selection, where we may have two or more drugs with remarkably similar structure but very different solubilities. There is so much we can do by solvent manipulation if we want to improve the bioavailability of a drug that is very poorly soluble and therefore dissolves very slowly. We need to add energy to that solid so that its crystal structure gets disrupted.

**Structural Effects on Solubility**

*What makes the solubility of two isomers like anthracene and phenanthrene so different?*

Even though they are chemically very similar, the two isomers have different symmetry. That gives them the ability to arrange into crystalline structures of different strength. It is something like having two jigsaw puzzles made with the same cardboard but different shape of cuttings, so that one pattern is more difficult to tear apart than the other. The different size of the black portions of the bars in the figure above is not the result of different intermolecular interactions in the crystals of anthracene or phenanthrene. It is the result of the different type of physical montage each can form. The more symmetrical a molecule, the stronger the crystal it can form. The reason is that it is easier for a symmetrical molecule to orient and align into a crystalline lattice than for a non-symmetrical one. This effect is easiest seen with benzene. If I take a molecule of benzene and rotate 60° clockwise, the result will look identical to the original position. I can do the 60° rotation six times with the same result. Then I can flip the benzene molecule so that the front is back and the back is front, and again, I have six possibilities to make the picture look identical. So benzene has a symmetry number ($\square$) of 12, because there are 12 indistinguishable ways I can rotate the same molecule. So a benzene molecule has 12 different ways of occupying the same "spot" in a benzene crystal. Benzene, by the way, has a strong crystal (high melting point) if we compare it with toluene, for example. Anthracene and phenanthrene have symmetry numbers of 4 and 2, respectively. So anthracene can form a stronger crystal. My view (*Org. Biomol. Chem.* 2004, 2, 2692-2699) is that in the ideal case, the solubilities of isomers of different symmetry are related to each other by a relationship of the following form:

$$\ln \frac{S_1}{S_2} = \frac{(2T_{m2} - T)}{T} \ln \frac{\sigma_2}{\sigma_1}$$

where *T* is the experimental temperature, *S* denotes solubility, $T_m$ is the melting point, and the subscripts 1 and 2 denote compounds **1** and **2**, respectively, and compound **2** has the higher symmetry ($\sigma_2 > \sigma_1$).

## Solvent Effect on Solubility

*What makes some solvent mixtures better than others for a given organic solute?*

When we use a water-cosolvent mixture to solubilize a drug, we have two sets of intermolecular interactions at play. The drug-water and drug-cosolvent interactions determine the overall solubilization behavior, as prescribed by the log-linear model. However, the water-cosolvent interactions have an important effect on the solubilization profile obtained. Water-cosolvent interactions actually contribute an additional effect to solubility that can be of significant magnitude compared with the reference value of the log-linear model. (*J. Pharm. Sci.* 2010, **99**, 293-302):

$$\log S_m = f_c \log S_c + f_w \log S_w + \sigma \left[ f_c^2 (\gamma_c - \gamma_w) + f_c (2\gamma_w - 2) - (\gamma_w - 1) \right]$$

If we know the solubility of the drug in pure water and in the pure cosolvent ($S_w$ and $S_c$, respectively), the log-linear model gives us the reference solubility as a function of the solvent composition (volume fraction of cosolvent, $f_c$). The activity coefficients of water and the cosolvent in the mixture ($\gamma_c$ and $\gamma w$, respectively), account for some "extra" solubilization observed. The figure to the right shows that the observed solubility of phenacetin in dioxane-water mixtures is considerably higher than expected from the log-linear model. Using the activity coefficients of the solvent mixture (free from drug), as shown in the equation above, shows how the deviation from the log-linear model is accounted for by the magnitude of the water-cosolvent interactions.