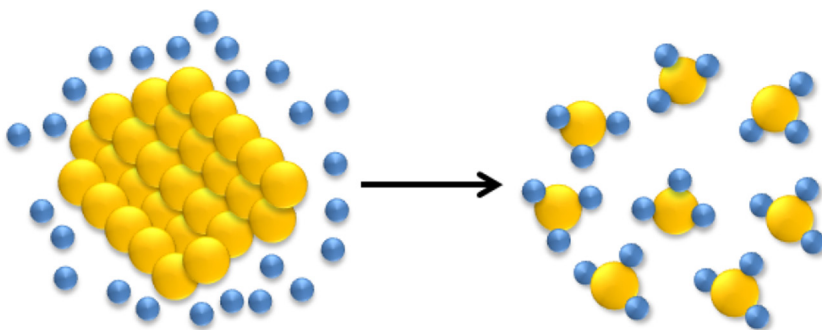


## Solubility

Solid tablets are the preferred method of oral delivery, so the first step in administering an oral therapeutic is dissolution of the compound in the fluids of the gastrointestinal tract. The solubility of a compound, the maximum concentration of compound attainable in a solution, is a critical aspect of oral delivery. Compounds that are not in solution are not readily absorbed by the body. No matter how potent and selective a compound may be, if it cannot be absorbed, it will not be able to reach its intended target and no therapeutic effect will be observed. In other words, compounds with low solubility are likely to have absorption issues and unlikely to become marketed drugs.

In essence, the process of dissolution of any material into a solvent requires that solvent molecules disrupt the interaction between the molecules that comprise the solid. These interactions are then replaced by interactions between the solvent molecules and the molecules of the dissolving compound (Figure 6.4). It stands to reason, therefore, that a compound's



**FIGURE 6.4** When a compound (yellow) dissolves in water (blue), the water molecules disrupt the interactions that stabilize the solid form of the material. The solubilized compound forms a favorable interaction with water.

aqueous solubility is a function of its ability to form energetically favorable interaction with water molecules as the solid material breakdown. There are a number of factors that can be manipulated in a given series of compounds to increase aqueous solubility. It has long been known, for example, that as the molecular weight of compounds within a given series increases, the aqueous solubility decreases. This is demonstrated by the change in solubility observed in 2-amino-imidazolidinone Kv1.5 blockers (1) and (2) (Figure 6.5). Extending the linker chain between the central imidazolidinone and the left-side benzene ring provides a relatively small increase in molecular weight, but that leads to a nearly 5 fold decrease in solubility.

It is also possible to manipulate the aqueous solubility of compounds in a given series by modifying the structures so that they are more polar in