

FIGURE 5.1 Definition of the partition coefficient P or D for the equilibrium distribution of a molecule between octanol/water and octanol/aqueous buffer, respectively.

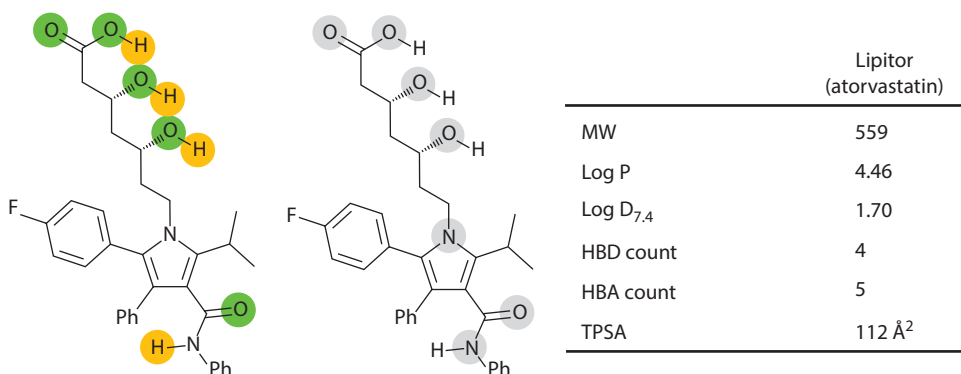


FIGURE 5.2 Physicochemical properties for atorvastatin. The atoms contributing to the number of HBD (orange), HBA (green), and TPSA (gray) are indicated.

known a priori but requires a computational analysis. Drawing tools such as ChemDraw are the most convenient tools to obtain the values for each of these descriptors directly from the chemical structure, but several public websites also offer these calculations for free. The fundamental properties are illustrated for the cholesterol-lowering drug Lipitor (atorvastatin) in Figure 5.2. The significantly lower $\log D_{7.4}$ value as compared to $\log P$ is a consequence of deprotonation of the carboxylic acid at physiological pH (7.4) and the accompanying higher hydrophilicity of the carboxylate anion.

Most commonly the assessment of drug-likeness is performed using guidelines, the original and most well-known of which is Lipinski's rule of five (Ro5). In the following we first discuss two of these rules of drug-likeness, and then turn our attention to a measure of the so-called molecular beauty based on scoring functions to avoid hard cutoffs.

5.2.1 THE LIPINSKI RULE OF FIVE (Ro5)

In 1997, Lipinski et al. reported a seminal paper in which they analyzed the physicochemical properties of drugs in a database of about 2500 orally active small molecules that had entered at least phase II clinical trials. From this analysis, the "Rule of five" (Ro5) was developed. The Ro5 owes its name to the fact that it is based on four essential physical properties, each of which is constrained by an upper value related to the number five ($MW \leq 500$, $\log P \leq 5$, $HBD \leq 5$, $HBA \leq 10$). Nine out of ten orally active small-molecule drug candidates that achieved phase II clinical status are found within these boundaries. This also applied broadly to oral small-molecule *drugs* as we shall learn later in this chapter. These physicochemical parameters are associated with acceptable aqueous solubility and intestinal permeability that are the essential first two steps toward oral bioavailability. Although it is termed the "Rule of five," it is in fact an "anti-rule" that states that it is unlikely that compounds with two or more "violations" can be orally absorbed. The Ro5 does not