

of 150 nM. According to the ligand–receptor X-ray structure, the binding displays a bidentate, charge-assisted hydrogen bond between the terminal glycerol hydroxyl groups and a glutamate side chain. Removal of the glycerol side chain as in analog **2.2** and replacement with a hydrophobic alkyl group increases the affinity to 1 nM (the minor modifications of the six-membered ring are not expected to influence the affinity significantly). An X-ray structure of the protein complex (**2.2**) shows that the glutamate side chain is folded back, opening up a large hydrophobic pocket as indicated in Figure 2.11.

2.3.5 ΔG_{vdW} : ATTRACTIVE AND REPULSIVE vdW INTERACTIONS

Nonpolar interactions between atoms may be calculated according to Equation 2.7. When the vdW energy is calculated and plotted as a function of distance (radius), it results in the energy curve shown in Figure 2.12. As evident from the figure, vdW interactions may be attractive as well as repulsive depending on the distance between the two interacting atoms/molecules. At short atom–atom distances, the vdW interaction is repulsive due to overlap of the electron clouds. The repulsion rises steeply with decreasing atom–atom distance in this region of the energy curve. When a part of the ligand clashes with atoms in the binding site, this steric repulsive vdW interaction is responsible for the often dramatic reduction in affinity which is observed. At a longer distance, there is a region of attraction between the atoms. This attraction is due to the so-called dispersion forces. These are basically of electrostatic nature and due to interactions between temporary dipoles induced in two adjacent atoms. For a single atom–atom contact, the strength of the interaction is small, ca. 0.2 kJ/mol. However, as the total number of such interactions may be large, the dispersion interaction may be significant in cases of a close fit between ligand and protein. Note also that E_{vdW} is inversely correlated to distance (r) to the power of 6

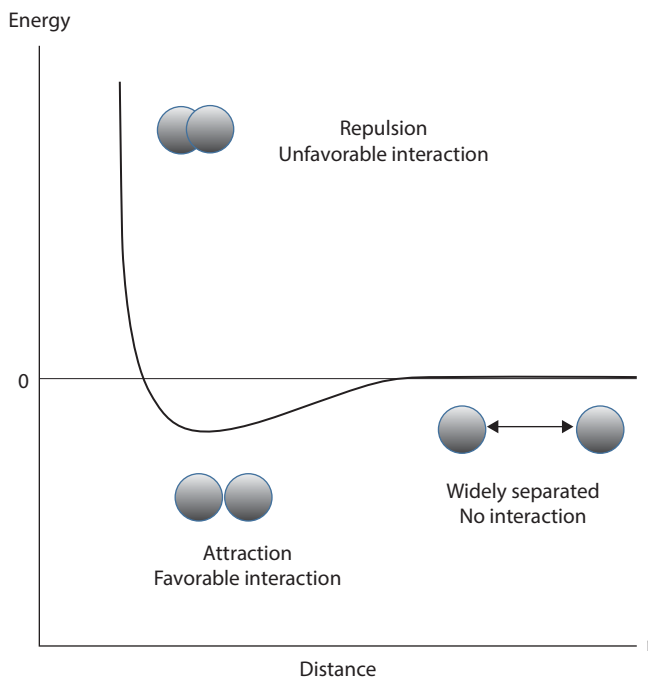


FIGURE 2.12 The van der Waals energy curve.