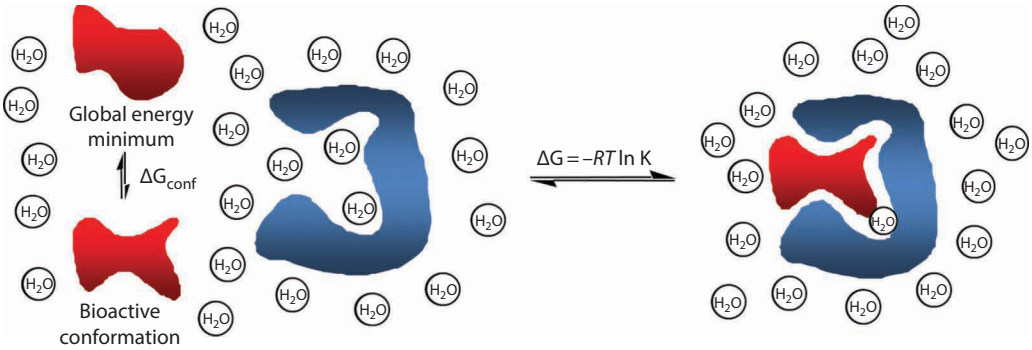

FIGURE 2.2 The equilibrium determining the affinity of a ligand.

Before the ligand can bind to the receptor it may have to change its conformation and so may the receptor. Water also plays an important role in the binding process and a change in the network of water molecules surrounding ligand and receptor may occur as illustrated in Figure 2.2.

The free energy difference is related to the equilibrium constant K by

$$\Delta G = -RT \ln K \tag{2.1}$$

where

R is the gas constant (8.315 J/K/mol)
T is the temperature in kelvin
K is (complex)/(ligand) × (receptor)

A higher affinity is the result of the equilibrium in Figure 2.2 being pushed toward the receptor–ligand complex on the right. This implies a larger positive value of K and, thus, a larger negative value of ΔG. In medicinal chemistry, the affinity of a ligand is most often given as an inhibition constant K_i or by an IC_{50}-value which is the concentration of an inhibitor that is required to displace 50% of the specific binding of a radioactively labeled ligand in a radioligand binding assay. Since $K = 1/K_i$, the free energy difference in terms of K_i can be written as

$$\Delta G = RT \ln K_i \tag{2.2}$$

The ΔG term can be dissected into an enthalpic component (ΔH) and an entropic component (ΔS) according to

$$\Delta G = \Delta H - T\Delta S \tag{2.3}$$

A higher affinity (a more negative ΔG) corresponds to a smaller value of the inhibition constant K_i (most often given in nM or μM). A K_i of 1 nM corresponds to a ΔG of −53.4 kJ/mol at 310 K and a K_i of 1 μM to −35.6 kJ/mol. Furthermore, using Equation 2.2 it can be calculated that an increase in ΔG by 5.9 kJ/mol corresponds to a 10-fold loss in affinity (10-fold increase in K_i). An example of the size of this energy in terms of molecular structural change is shown in Figure 2.3. A conformational change of the ethyl group in ethylbenzene from a perpendicular conformation