schemes have been suggested in the literature and differ in their level of detail. The one used here is essentially as suggested by Williams (see Further Reading):

$$\Delta G = \Delta G_{transl+rot} + \Delta G_{conf} + \Delta G_{polar} + \Delta G_{hydrophob} + \Delta G_{vdW} \quad (2.5)$$

where

- $\Delta G_{transl+rot}$ accounts for the restrictions of translational movements (movements in x-, y-, and z-directions) and restrictions of rotations (about the x-, y-, and z-axes) of the "whole" molecule from the unbound to the bound state
- ΔG_{conf} is the difference in the conformational free energies between the unbound and bound states due to conformational restrictions in the ligand–protein complex
- ΔG_{polar} is the free energy change due to interactions of polar functional groups in the binding cavity of the protein
- $\Delta G_{hydrophob}$ accounts for the binding free energy due to the hydrophobic effect
- ΔG_{vdW} gives the difference in free energy due to van der Waals (vdW) interactions in the bound and unbound states

In the following sections, the different terms in Equation 2.5 and their magnitudes will be discussed in more detail and illustrated in terms of ligand–protein recognition.

2.3.1 $\Delta G_{TRANSL+ROT}$: The Freezing of the Overall Molecular Motion

In the "free" unbound state, both receptor and ligand are able to rotate and translate freely around in the aqueous solution. When bound in the cavity, the freedom of the ligand to tumble is lost because the small ligand will now have to follow the motions of the big protein. The loss of freedom is unfavorable in a thermodynamic sense and is a cost associated with ligand binding that must be overcome by the favorable binding forces to enable formation of a complex. The freezing or restriction of the motions of the ligand is a decrease in entropy resulting in a more negative ΔS and consequently a more negative $T\Delta S$. According to Equation 2.3, this results in a more positive ΔG. The magnitude of this free energy cost has been much debated in the literature. Explicit calculations show that it varies only slightly with molecular weight, but an important problem for the estimation of $\Delta G_{transl+rot}$ is that it depends on the "tightness" of the ligand–protein complex. A tighter complex leads to a greater loss of freedom of movement and thus to a more negative $T\Delta S$. Most estimates of $\Delta G_{transl+rot}$ range from 12 kJ/mol for a "loose" complex to 45 kJ/mol for a tightly bound complex. Whatever the exact magnitude of $\Delta G_{transl+rot}$ is in a particular case, it is a very significant energy to overcome by the favorable binding forces. Consider a ligand with an affinity (K_i) of 1 nM corresponding to ΔG of −53.4 kJ/mol at 310 K (Section 2.2). In order to end up with this free energy difference between the bound and unbound states, the favorable binding forces must produce not only 53.4 kJ/mol of ligand–protein binding energy but in addition 12–45 kJ/mol of free energy is required to compensate for the loss of entropy associated with binding. It should be noted that this free energy cost of ligand–protein association is always present and cannot be reduced by ligand design. However, the exact value of $\Delta G_{transl+rot}$ is only important for predictions of "absolute" ΔG values. To a first approximation it cancels out when comparing the affinities of different ligands to the same receptor.

2.3.2 ΔG_{CONF}: Conformational Changes of Ligand and Receptor

The restriction of motions that are accounted for in $\Delta G_{transl+rot}$ described in Section 2.3.1 refers to the "overall" motion of the molecule relative to its surroundings. However, there is an additional internal motion which is more or less frozen upon ligand binding. Most ligand molecules are flexible which means that in the aqueous phase outside the binding cavity, the ligand constantly undergoes conformational changes by rotation around single bonds. For example, the dihedral angle in a hydrocarbon chain alters between gauche and anticonformations resulting in a mixture of ligand